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Chettinad
Hospital & Research Institute

Department of General Medicine

CHETMEDICON - 2017

RECENT ADVANCES IN HEMATOLOGICAL ABNORMALITIES AND MANAGEMENT

(RAHAM)

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MEDICAL JOURNAL

Contents

Editorial

On behalf of the General Medicine department I am very proud to write the editorial for this edition of Chettinad Health City Medical Journal, on the occasion of our fourth annual conference Chetmedicon-2017. The theme of the conference is "Recent Advances in Hematology And their Management (RAHAM)". The issue has five review articles on the practical aspects of hematology apart from the latest developments in this field. In addition the abstracts of papers and posters presented in conference have been included in the issue.

Though there is a progressive decrease in the incidence of Iron deficiency anemia, it still remains the most common cause of anemia. Children and the women in reproductive age group population are affected world-wide, especially in the developing countries. In their article "An overview of iron deficiency anemia" the authors have described in detail about the causes, and elucidated the evidence based management of the condition.

Generally hemoglobinopathies are described as congential disorders due to defect in the quality (Sickle cell anaemia) and quantity (thalassemia) of the globin chains of hemoglobin. But these disorders can also manifest as acquired disorders as in myelodyplastic syndrome and certain hematological malignancies. In the article, "Acquired hemoglobin disorders", the authors discuss the changes in hemoglobin which may lead to high or low affinity to Oxygen;and have also elaborated on acquired globin chain disorders.

Pancytopenia is not a primary disease entity but it is only a laboratory diagnosis. It is a manifestation of varying disorders ranging from bone marrow failure to peripheral sequestration and destruction of formed elements of blood. A systematic approach is needed to find out the etiology for an appropriate management. In their article "Pancytopenia: a physician's perspective" the authors have analyzed in detail the various aspects of pancytopenia.

AIHA (autoimmune hemolytic anemia) poses to be a disease of diagnostic challenge and a physician's night-mare. Unless there is an awareness, this uncommon entity goes undiagnosed with high morbidity. The authors of "AIHA" have elaborated the approach to the diagnosis and treatment of the condition in this issue.

Clonal proliferation of B cells leading to abnormal immunogobin production ends up in various plasma cell disorders. Often the patients with these conditions are asymptomatic, requiring a battery of investigations to classify and treat. The authors have highlighted the approach to the diagnosis and the management of plasma cell disorders in the article "An overview of plasma cell disorders".

I hope this issue may revise and enrich your knowledge in the hematological disorders.

Dr.Rajasekaran. D

Section Editor

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Review Article

Autoimmune Hemolytic Anemia

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Abstract

Autoimmune hemolytic anemia (AIHA) is caused by autoantibodies that react with Red Blood Cells. It is an uncommon entity. Even being a well-recognized entity for so many years, there are lot of difficulties regarding its diagnosis and therapies used for treatment. There are different types of autoimmune hemolytic anemia like warm antibody hemolytic anemia, cold agglutinin disease/paroxysmal cold hemoglobinuria and mixed type. The warm antibodies react at temperatures ≥37°C and cold agglutinin disease/ paroxysmal cold hemoglobinuria react at <37°C. Usually the hemolysis is extravascular. The positive direct antiglobulin (direct Coombs) test establishes the diagnosis and may suggest the cause. Treatment is usually cause dependent and includes corticosteroids, splenectomy, IV immune globulin, immunosuppressants and withdrawal of drugs.

Key Words: Autoimmune hemolytic anemia, AIHA, Autoantibodies, Warm Antibody, Cold Antibody, Mixed AIHA.

Introduction

Autoimmune hemolytic anemia (AIHA) is a group of disorders characterized by an impairment of the immune system which produces auto-antibodies (auto erythrocytes antibodies AEA), that act against one's own red blood cells considering it as foreign substance to the body. The main feature in immune related RBC injury is decreased RBC survival in-vivo along with confirmation of host antibodies that react with heterologous RBCs. AIHA can be primary or idiopathic and secondary. Secondary AIHA could be due to infections, autoimmune diseases, lymphoma or lympho-proliferative disorder and drugs[1]. To establish these antibodies, the test used is direct antiglobulin test (DAT), also known by another name as Coombs test. A negative Coombs test does not exclude AIHA[2,3].

Etiopathogenesis

I. Warm-autoantibody (WA) type: autoantibody maximally active at body temperature (37°C)
A. Primary or idiopathic warm AIHA
B. Secondary warm AIHA
1. Associated with lymphoproliferative disorders (e.g., Hodgkin disease, CLL, lymphoma)
2. Associated with certain nonlymphoid neoplasms (e.g., ovarian tumors)
3. Associated with the rheumatic disorders, particularly SLE
4. Associated with certain chronic inflammatory diseases (e.g., ulcerative colitis)
5. Associated with ingestion of certain drugs (e.g., -methyldopa)
II. Cold-autoantibody (CA) type: autoantibody optimally active at temperatures <37°C
A. Mediated by cold agglutinin
1. Idiopathic (primary) chronic cold agglutinin disease
2. Secondary cold agglutinin hemolytic anemia
a. Postinfectious (e.g., Mycoplasma pneumoniae or infectious mononucleosis)
b. Associated with malignant B cell lymphoproliferative disorder
B. Mediated by cold hemolysins
1. Idiopathic (primary) paroxysmal cold hemoglobinuria (very rare)
2. Secondary
a. Donath-Landsteiner hemolytic anemia, usually associated with an acute viral syndrome in chidren(relatively uncommon)
b. Congenital or tertiary syphilis in adults (very rare)
III. Mixed cold and warm autoantibodies
A. Primary or idiopathic mixed AIHA
B. Secondary mixed AIHA
1. Associated with the rheumatic disorders, particularly SLE
IV. Drug-immune hemolytic anemia
A. Hapten or drug adsorption mechanism
B. Ternary (immune) complex mechanism
C. True autoantibody mechanism

Table 1 - Classification of Hemolytic Anemia as a Result of Immune Injury[4]

AIHA = Autoimmune hemolytic anemia; SLE = Systemic lupus erythematosus, CLL = Chronic Lymphocytic Leukemia

Warm antibodies

The destruction of red blood cells in hemolytic anemia is due to the presence of autoantibodies, mediated by immunoglobulins mainly IgG, IgM, or IgA which may depend upon on the complement. These auto-antibodies generally react at temperature of 37˚C and cause warm AIHA[5]. The activation of complement continues till the emergence and establishment of membrane attack complex (MAC) which leads to hemolysis[6]. Very rarely these warm auto-antibodies can be IgM related but it is not detected in the serum; it

combines with the RBCs, activates the complement and separates from the membrane leaving only the complement[6-9].

When the RBCs are coated with IgG along with or without complement (C3c, C3d), the phagocytosis takes place by Fc gamma receptor in the spleen, whereas if it is coated only with the complement (C3c, C3d) without IgG, it is eliminated by complement-receptor phagocytosis in the liver(extra vascular hemolysis)[6]. In primary AIHA the only aberrant auto-antibody is anti erythrocyte auto antibody and it is specific for single RBCs membrane that is small range of auto- reactivity. In secondary AIHA(due to lymphoma, CLL(chronic lymphocytic leukemia), or SLE) the auto antibody are usually formed due to latent defect in immune system. The auto-antibodies formed secondary to drug is usually reversible on withdrawal of the drug[4].

Cold antibodies

IgM auto-antibodies(usually monoclonal) are pentameric antibodies which after fixing with complement causes intravascular hemolysis and to a small extent C3d mediated extra-vascular hemolysis. These antibodies react at low temperature with optimal effect at 4˚C[5-7].

The thermal range of IgM auto-antibodies is from 0˚C- 34˚C and those antibodies which react at temperature close to physiological temperature are the most harmful and cause severe form of AIHA[6,7]. These auto-antibodies are usually confirmed by positive DAT. Sometimes DAT could be positive for both IgG and high titres of C3d which shows that patient is having mixed type AIHA. In few cases DAT is negative and the patients present with severe form of disease which is refractory to treatment and has worst outcome[10-12]. These are usually IgM associated warm autoantibodies which can be tested by dual direct agglutination test(DDAT)[13]. At this juncture, it is worth mentioning Donath-Landsteiner autoantibody, which is a biphasic cold hemolysin, causing complement-mediated hemolysis and contributes to paroxysmal cold hemoglobinuria which is common in children and very rare in adults[1,14].

Epidemiology

Hemolytic anemia represents approximately 5% of all anemias. Acute AIHA is relatively uncommon disease, with an incidence of 1-3 cases/100,000 population per year[15]. The prevalence of Cold agglutinin disease is 14 per million population[16]. The incidence of mixed autoimmune hemolytic anemia (both warm and cold) is approximately 1 in 80,000; and the occurrence of cold agglutinin disease is 1 in 300,000[16,17]. Warm AIHA although a rare disease, can affect any age from infancy to old age but mostly common over the age of 40years with peak incidence at the age of 70 years[4]. Not much is known about cold agglutinin disease, few reports say that it is more common in male children and female adults[2,17,18].

Diagnosis

The diagnosis of AIHA is mainly made by clinical presentation, lab findings and immune hematological diagnosis.

Clinical features of warm antibody associated AIHA

The features of warm AIHA are similar to that of any other hemolytic anemia. Usually the first presentation is jaundice along with other signs of anemia. These patients usually have mild to moderate splenomegaly. Those who presents with acute AIHA have severe anemia developing in short duration along with other profound features of anemia including hepatosplenomegaly, hyperapnea, tachycardia and even heart failure[2,19]. Whenever a patient presents with sudden onset anemia, jaundice and splenomegaly, suspect AIHA and search for the causes and mechanisms in such cases.

Clinical features of cold antibody AIHA

The patient with cold agglutinnin AIHA(CA-AIHA) usually presents as chronic hemolytic anemia with or without jaundice. Some patients also complain of dark coloured urine due to hemoglobinuria which represents intravascular hemolysis. On exposure to cold, they develop acrocyanosis and veno-occlusive features of fingers, toes and tip of nose because of blockage of micro-circulation by lysed RBCs. Skin ulceration is uncommon. There could be additional features of other underlying diseases like respiratory involvement in mycoplasma pneumonia and splenomegaly in lymphoproliferative disorders[20-22]. In paroxysmal cold hemoglobinuria, the patient develops features after exposure to cold.

Drug induced Immune Hemolytic Anemia

The presentation of drug induced AIHA is variable. Drugs whose auto reactivity depends upon hapten/drug adsorption (like penicillin) and autoimmunity (like methyldopa); and present with mild to moderate hemolysis. Other drugs like cephalosporins or quinidine whose autoimmunity depends upon ternary complex mechanism present as sudden and severe hemolysis with hemoglobinuria. Sometimes patients may present with acute renal failure.

Laboratory findings

Severity of presentation of AIHA is variable. In warm AIHA, the compensated hemolytic anemia usually shows reticulocytosis. In some cases AIHA is associated with auto immune thrombocytopenia when it known as Evans syndrome. In CA-AIHA, the patient presents with mild to moderate anemia, the hematocrit is low but not less than 15%. There is sudden decrease in hematocrit in patients with paroxysmal cold hemoglobinuria during an attack. The presentation of drug induced hemolytic anemia is almost similar to Warm AIHA and the peripheral smear may reveal polychromasia, spherocytyosis (unless proved otherwise it is taken as immune hemolytic anemia), RBCs fragments, nucleated RBCs and sometimes erythrophagocytosis by monocytes.

Next important is the presence of indirect hyper-bilirubinemia with only modest increase in total bilirubin and presence of urobilinogen. The level of haptoglobin is low and LDH level is usually increased, but if normal does not rule out hemolytic anemia. Fig 1 represents an algorithm for approach to AIHA.

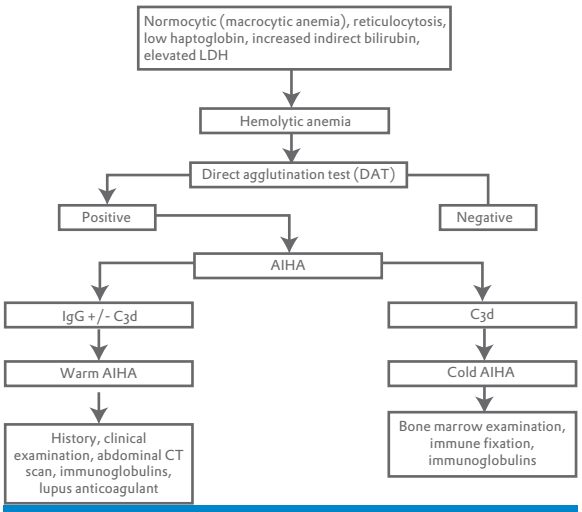


Fig 1 : Approach to Autoimmune hemolytic anemia (AIHA)

Immunohematological diagnostics

The diagnosis of AIHA and drug immune hemolytic anemia depends upon the detection of auto antibodies against RBCs. Direct and indirect antiglobulin test (Coomb's test) are done to demonstrate non-agglutinating red cell antibodies (indirect antiglobulin test, IAT) or sensitized red cells (direct antiglobulin test, DAT)[22-24].

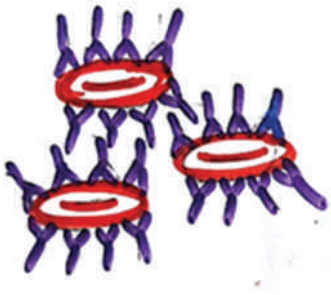
There are three possible designs for direct antiglobulin test for AIHA and drug induced hemolytic anemia: one is RBCs coated with only IgG, second is RBCs coated with IgG and complement components, and third is RBCs coated with complement components without detectable immunoglobulin.

Reaction pattern and type of injury based on IgG and complement is shown in table 2.

IgG alone	i) Warm antibody autoimmune hemolytic anemia ii) Drug-immune hemolytic anemia: hapten drug adsorption type or autoantibody type.
Complement	i) Warm antibody autoimmune hemolytic anemia with subthreshold IgG deposition. ii) Cold aggltinnin disease. iii) Paroxymal cold hemoglobinuria iv) Drug-immune hemolytic anemia: ternary complex type
Both IgG and Complement	i) Warm antibody autoimmune hemolytic anemia ii) Drug-immune hemolytic anemia: autoantibody type (rare)

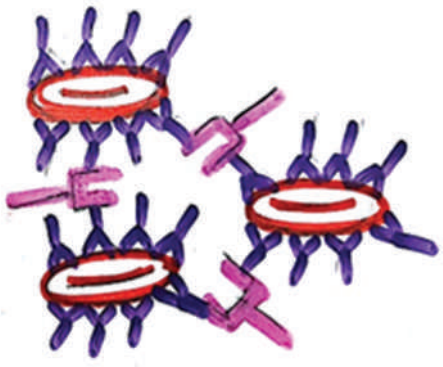
Table 2 - Reaction pattern and type of injury based on IgG and complement

Direct antiglobulin test (DAT) tests the presence of in vivo antibodies. On the addition of polyspecific anti-human globulin reagent to RBCs, the RBCs agglutinate and the test is considered as positive[27,28]. Sometimes when the suspicion of AIHA is strong and the DAT is negative, the test should be repeated with anti-IgA, anti-IgM, anti-IgG, anti-C3c and anti-C3d separately, because the poly-specific anti human globulin contains only IgG, and C3d[26,29]. If still the DAT remains negative, one should look for spherocytes in peripheral smear. When the DAT is positive with the polyspecific anti-human globulin reagent further testing with monospecific reagent is required to differentiate the type of auto-antibody whether it is IgM, IgG, IgA, C3c, or C3d (Fig 2). If antibody is negative and complement deposition is noticed, then one should think of CA-AIHA(IgM), WA-AIHA(IgM, IgA), or bithermic antibodies. Such situation warrants further laboratory investigations to ascertain the presence of either IgM or IgA[5].



Patient erythrocyte coated with auto antibodies

serum directed to human IgG or complement C3c/d



agglutination patient erythrocytes

Fig 2 : : Direct antiglobulin test (DAT)[5]

Indirect antiglobulin test (IAT) is used

1) as a workup (intensive diagnostic study) of a transfusion reaction that has ABO incompatibility.
2) as a part of workup during a pregnancy that has Rh incompatibility.

In IAT (Fig 3), the patients serum consisting of auto or alloantibodies is mixed or incubated with labeled or non-labeled recipient blood or tested RBCs. In the second step, after washing the incubated sample to remove the excess immunoglobulin, the polyspecific anti-human globulin reagent directed against both IgG and C3d is added to the sample. If antibodies are present in the patients serum, it will get attached to RBCs and after addition of reagent, the RBCs will agglutinate indicating positive results. This is an in-vitro test and IgG are incomplete antibodies. If patient's serum contains IgM antibodies, there is agglutination soon after adding test RBCs and the result is positive (Fig 4). The differences between DAT and IAT are outlined in Table 3.

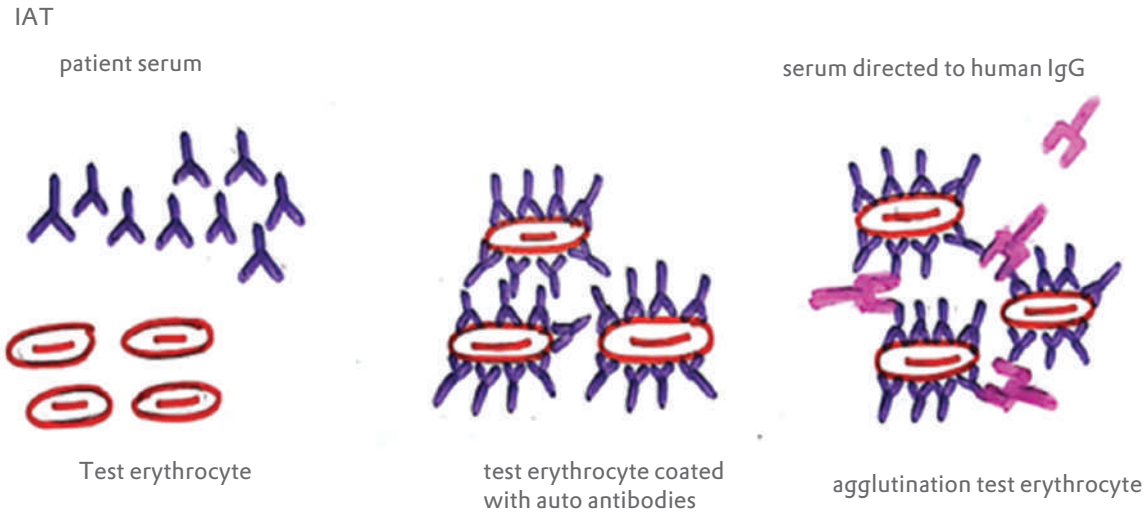


Fig 3 : Indirect Antiglobulin test (IAT)

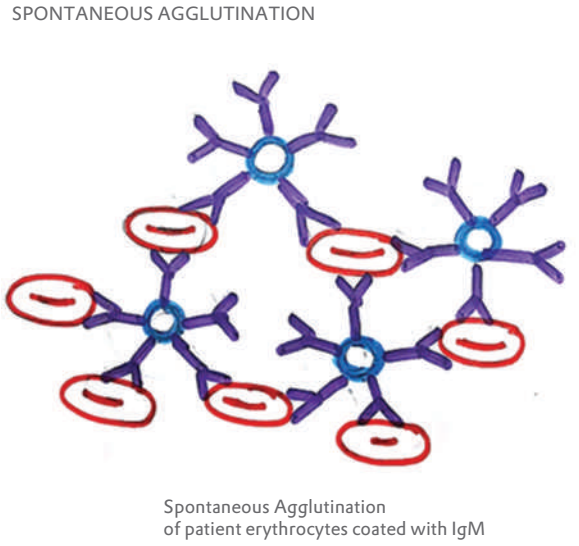


Fig 4 : : IAT in the presence of IgM antibody

Direct	Indirect
Direct coombs test detects the presence of the antibodies attached to the surface of the red blood cells	Indirect coombs test detects the antibodies present in the serum which are not bound to the red blood cells.
This type is more commonly used	Indirect Coombs test are performed rarely
Direct coombs test is important to diagnose autoimmune hemolytic anemia.	Indirect coombs test is important for prenatal testing for pregnant women prior to blood transfusion
Direct coombs test can detect in vivo antigen-antibody interaction.	Indirect coombs test can detect in vitro antigen-antibody interactions.

Table 3 - Difference between Direct and Indirect Coombs Test[30]

Treatment

General

Blood transfusion- In general blood transfusion shall always be avoided as far as possible. If it is required and/or unavoidable, blood with least incompatibility should be selected and patients serum should be thoroughly checked for alloantibody which, if present, can lead to critical hemolytic transfusion reactions especially in patients with pregnancy and those who have received previous blood transfusion. If the patient is a non pregnant woman or in men without any prior history of tranfusion, the chances of alloantibody are almost nil and they can go with transfusion after appropriate matching[31]. For other cases, from the point of patient safety one has to go ahead with phenotyping for other subclasses of Rh, Kell,Kidd, Duffy, Ss[12,32-35]. In emergencies and resource limited situations, it is worth to consider the usage of transfusion set with filters.

Treatment of WA-AIHA

First line therapy

Corticosteroids

The first line of treatment for WA-AIHA (primary) is corticosteroid (prednisolone). Algorithm for steroid treatment is shown in Fig 5. Approximately 20% of patient with WA-AIHA show complete remission with steroid and 10% show no or minimal response[36,37]. All patients with steroid therapy should receive suplementation of vitamin D, bisphosphonates, calcium and folic acid. In those who are unresponsive to initial therapy, secondary causes like malignant tumor, ovarian teratoma(benign), inflammatory bowel disease(mainly ulcerative colitis) and warm IgM AIHA should be considered[40].

Second line therapy

Patients who require more than 15mg of steroid/day and/or refractory to initial steroid treatment are candidates for second line regimen[2,38]. There are many options for second line treatment with somewhat proven efficacy. The two options are Splenectomy and Rituximab. Algorithm for treatment of steroid refractory WA-AIHA is given in Fig 6.

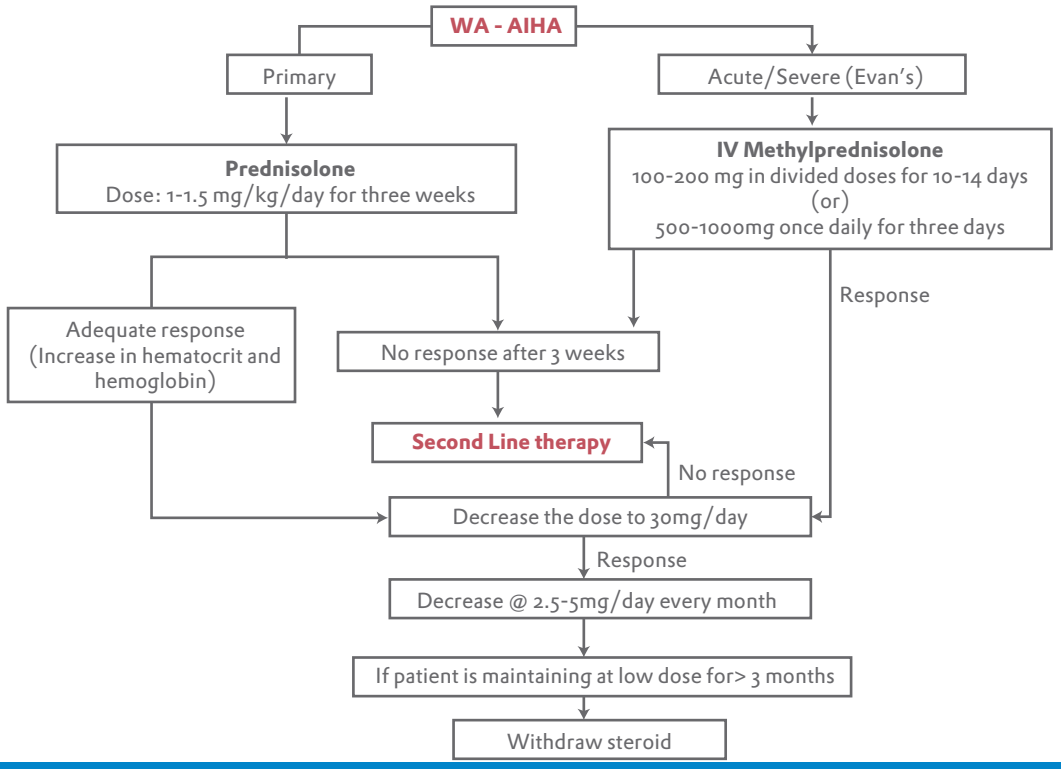


Fig 5 : : Algorithm for treatment of WA-AIHA with corticosteroids[36-40]

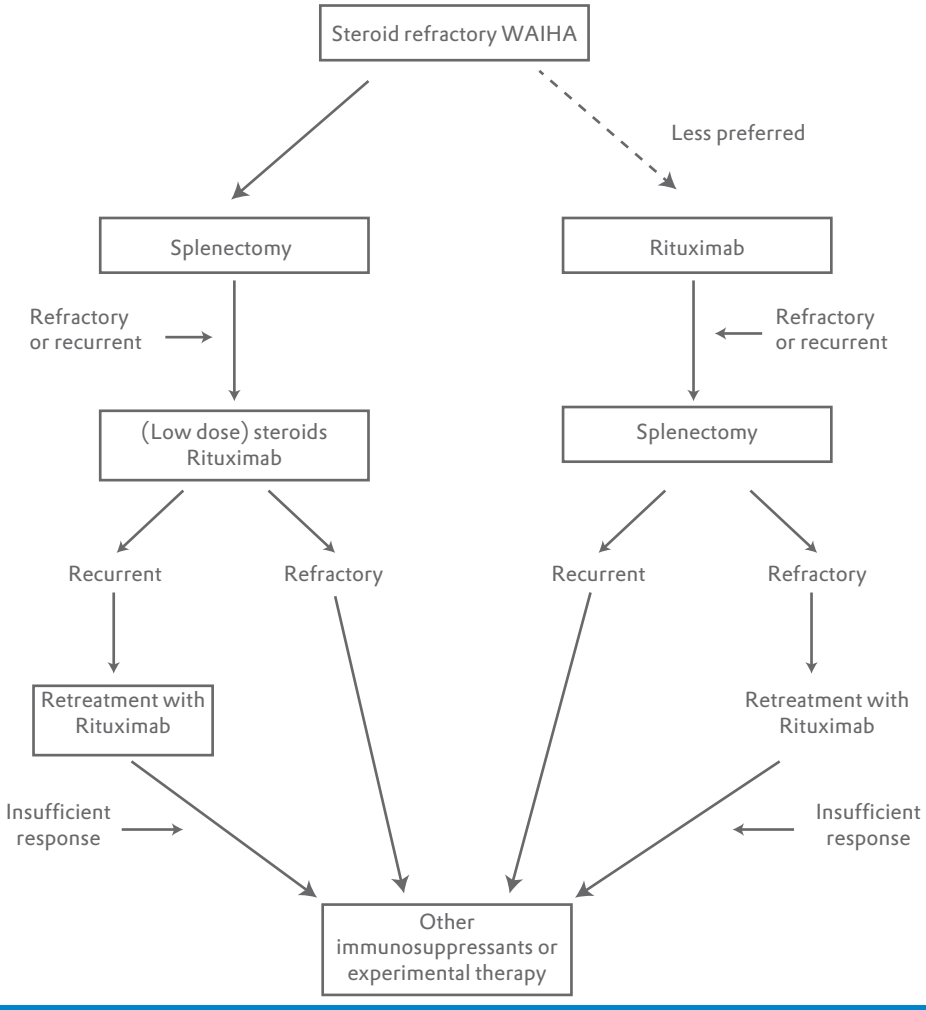


Fig 6 : Treatment of steroid refractory WA-AIHA

Splenectomy

Most accepted second line regimen is splenectomy, but available data on duration of complete or partial remission after splenectomy are less. The factors favouring this regimen are better initial response and interim effectiveness. Long remission was noticed among those patients who underwent splenectomy with or without steroid therapy[41,42]. The remission is approximately 38-82% depending upon the percentage of secondary cases which are less responsive[43]. With the laparoscopic approach there is lesser chance of perioperative complications like pulmonary embolism, abscess, bleeding etc. Patients should be vaccinated against encapsulated organisms such as Pneumococcus, Meningococcus, and H.influenzae. The mortality rate after splenectomy is more in children as compared to adults[44]. The cure rate is approximately 20%.

Rituximab

It is a monoclonal anti-CD20 antibody which acts on B lymphocytes. It also shows good short term efficacy and is usually given in a dose of 375mg/m^2 in 4 doses for 4 weeks(1^{st} day, 8^{th} day, 15^{th} day, 22^{th} day). The actual response rate is not known. It is efficacious in both warm and cold AIHA with complete response rate of about 54-60%[45]. If the patient is on steroid , they are advised to continue the same until the response with rituximab has started. It shows good response when used as a monotherapy or in combination with other drugs like steroid, immunosuppresant, interferon α, irrespective of previous treatment[46]. It is highly responsive in patients with Evans syndrome. As such the drug is safe, and the long term side effects are progressive multifocal leukoencephalopathy. It is contraindicated in patients with untreated hepatitis B infection. Usually it is used in patients who refuse splenectomy or in whom the splenectomy is contraindicated.

Immunosuppressants

Azathioprine (dose 100 to150mg/day) and Cyclophosphamide(100mg/day) can also be considered as second line therapy with response rate of 40-60%[1,38]. Cyclosporine has also showed good response in patients with refractory warm AIHA[47]. Only limited data is available for Mycophenolate mofetil which also showed good response in few studies.

Other modalities

Danazol, a synthetic anabolic steroid given with or after prednisolone is good for initial response, but less effective in refractory or relapse cases[48]. Intravenous IG alone or in combination with corticosteroid is used mostly in children because of relatively less side effects. Plasmapheresis is used in warm AIHA in both children and adults in cases where steroid and transfusion are not able to control anemia on temporary basis.

Miscellaneous options

High dose Cyclophosphamide(50mg/kg/day for 4 days) along with GM-CSF have shown to be effective in highly refractory cases of WA-AIHA. Alentuzumab an anti CD52 antibody and Ofatumumab, an anti CD20 antibody are also under trials.

Treatment of secondary AIHA

In SLE, the treatment is same as primary AIHA. For patients with CLL, prednisolone is the first choice (also in fludarabine associated AIHA). In active CLL, additional chemotherapeutic agents (Chlorambucil, R-CVP) and in refractory cases, rituximab and splenectomy are indicated. For Non Hodgkins Lymphoma, chemotherapy with or without rituximab may give a sustained response.

Treatment of CA-AIHA

Cold AIHA are usually secondary in nature and associated with lympho-proliferative disorders like IgM associated monoclonal gammopathy. The treatment is usually reserved for symptomatic cases. In asymptomatic cases, it may be moderately helpful to keep the extremities warm to avoid symptoms[49]. Transfusion can be safely done in these patients by taking needed precautions such as keeping the patient warm. The use of steroids and splenectomy are not much useful and discouraged nowadays[49,50]. The era for the treatment of CA-AIHA has changed after the introduction of rituximab. The drug is helpful in treatment because it is specifically directed against B-cell clone which is the culprit in many patients[49,50]. The patients who are refractory to one or two courses of rituximab, a combination of rituximab and fludarabine (40mg/m^2 on 1^{st} and 5^{th} day) have shown high response rate and long duration of remission[51,52]. Cold AIHA secondary to infection is usually self limited and treating the underlying cause is sufficient.

Paroxysmal cold hemoglobinuria(PCH) is generally known to occur with Donath Landsteiner antibody of IgG type, pointing against the P blood group system. Though PCH was previously associated with syphillis, it is now associated with other viral and bacterial infections. This is also a self limiting condition but may sometimes need treatment with steroids and transfusion.

Conclusion

AIHA is a well known hematological condition, whose clinical features, pathophysiology and diagnosis have been extensively described in literature. The discovery of Rituximab has remarkably improved treatment outcomes of AIHA.

References

1) Petz LD, Garratty G. The serologic investigation of autoimmune hemolytic anemia. In: Petz LD, Garratty G (Eds). Immune hemolytic anemias. 2nd ed. Philadelphia: Churchill Livingstone; 2004; 201-30.

2) Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol. 2002; 69(4):258–71.

3) Packman CH, Leddy JP. Drug-related immune hemolytic anemia. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ (Eds). William's hematology. 5th ed. New York: McGraw-Hill; 1995:691–704.

4) Engelfriet CP, Overbeeke MA, von dem Borne AE. Autoimmune hemolytic anemia. Semin Hematol. 1992;29(1):3–12.

5) Zeerleder S. Autoimmune haemolytic anaemia - a practical guide to cope with a diagnostic and therapeutic challenge. Neth J Med. 2011; 69(4):177-84.

6) Arndt PA, Leger RM, Garratty G. Serologic findings in autoimmune hemolytic anemia associated with immunoglobulin M warm autoantibodies. Transfusion. 2009;49(2):235–42.

7) Packman CH. Hemolytic anemia due to warm autoantibodies. Blood Rev. 2008;22(1):17–31.

8) Dacie J. Auto-immune haemolytic anaemia [AIHA]: pathogenesis. In: Dacie J (Edr): The Haemolytic Anaemias. Vol. 3. London, Churchill Livingstone, 1992: 392-451.

9) Kurlander RJ, Rosse WF, Logue GL. Quantitative influence of antibody and complement coating of red cells on monocyte-mediated cell lysis. J Clin Invest. 1978;61(5):1309–19.

10) Barcellini W, Fattizzo B, Zaninoni A, Radice T, Nichele I, Di Bona E, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. Blood. 2014;124(19):2930–6.

11) Fattizzo B, Zaninoni A, Nesa F, Sciumbata VM, Zanella A, Cortelezzi A et al. Lessons from very severe, refractory and fatal primary autoimmune hemolytic anemias. Am J Hematol. 2015;90(8):E149–51.

12) Arndt PA, Leger RM, Garratty G. Serologic findings in autoimmune hemolytic anemia associated with immunoglobulin M warm autoantibodies. Transfusion. 2009;49(2):235–42.

13) Bartolmas T, Salama A. A dual antiglobulin test for the detection of weak or nonagglutinating immunoglobulin M warm autoantibodies. Transfusion. 2010;50(5):1131–4.

14) Berentsen S. How I manage cold agglutinin disease. Br J Haematol. 2011;153(3):309–17.

15) Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol. 2002; 69(4):258-71.

16) Berentsen S, Bo K, Shammas F, Myking A, Ulvestad D. Chronic cold agglutinin disease of the 'idiopathic' type is a premalignant or low-grade malignant lymphoproliferative disease. APMIS. 1997;105(5):354–62.

17) Dacie J, The auto-immune haemolytic anaemias. The Haemolytic Anaemias. 3rd ed. Edinburgh, United Kingdom: Churchill Livingstone; 1992. Vol 3.: 210-362.

18) Sokol RJ, Booker DJ, Stamps R. Erythropoiesis: Paroxysmal Cold Haemoglobinuria: A Clinico-Pathological Study of Patients with a Positive Donath-Landsteiner Test. Hematology. 1999. 4 (2):137-64.

19) Packman CH, Leddy JP. Aquired hemolytic anemia due to warm-reacting autoantibodies In: Williams WJ, Beutler E, Erslev AJ, Lichtman MA, (Eds).Hematology New York: McGraw-Hill, Inc.1990. 666–75.

20) Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. Blood. 2013;122 (7):1114-21.

21) Prabhu R, Bhaskaran R, Shenoy V, G R, Sidharthan N. Clinical characteristics and treatment outcomes of primary autoimmune hemolytic anemia: a single center study from South India. Blood Res. 2016;51(2):88–94.

22) Berentsen S, Randen U, Tjnnfjord GE. Cold agglutinin-mediated autoimmune hemolytic anemia. Hematol Oncol Clin North Am. 2015;29 (3):455-71.

23) Darrell J. Triulzi, M.D.Indirect and Direct Antiglobulin (Coombs) Testing and the Crossmatch. Transfusion medicine Updates October 2000. http://www.itxm.org/tmu/tmu2000/tmu10-2000.htm (accessed on 08/10/2013)

24) Coombs RR, Mourant AE, Race RR. A new test for the detection of weak and incomplete Rh agglutinins. Br J Exp Pathol. 1945. 26:255-66.

25) Silberstein LE, Cunningham MJ. Autoimmune hemolytic anemias. In: Hillyer CD, Silberstein LE, Ness PM, Anderson KC, Roback JD (Eds). Blood Banking and Transfusion Medicine: Basic Principles and Practice. 2nd Edition. Philadelphia: Churchill Livingstone; 2007. 557-70.

26) Roback JD, Combs MR, Grossman BJ, Hillyer CD. AABB Technical Manual. 16th ed. Bethesda: AABB; 2008.

27) Segel GB, Lichtman MA. Direct antiglobulin ("Coombs") test-negative autoimmune hemolytic anemia: a review. Blood Cells Mol Dis. 2014:52(4):152-60.

28) Roback JD, Barclay S, Hillyer CD. An automatable format for accurate immunohematology testing by flow cytometry. Transfusion 2003;43(7):918–27.

29) Chaplin H Jr. Clinical usefulness of specific antiglobulin reagents in autoimmune hemolytic anemias. Prog Hematol 1973;8:25–49.

30) Bass GF, Tuscano ET, Tuscano JM. Diagnosis and classification of autoimmune hemolytic anemia. Autoimmun Rev 2014;13(4-5):560-4

31) Schonewille H, de Vries RR, Brand A. Alloimmune response after additional red blood cell antigen challenge in immunized hematooncology patients. Transfusion. 2009;49(3):453-7.

32) Go RS WintersJL, Kay NE. How I treat autoimmune hemolytic anemia. Blood 2017;129(22);2971-9.

33) Valent P, Lechner K. Diagnosis and treatment of autoimmune haemolytic anaemias in adults: a clinical review. Wien Klin Wochenschr. 2008; 120(5-6):136-51

34) Eyster ME, Jenkins DE Jr: Erythrocyte coating substances in patients with positive direct antiglobulin reactions: Correlation of G globulin and complement coating with underlying diseases, overt hemolysis and response to therapy. Am J Med 1969:46(3):360-71.

35) Shirey RS1, Boyd JS, Parwani AV, Tanz WS, Ness PM, King KE. Prophylactic antigen matched donor blood for patients with warm autoantibodies: An algorithm for transfusion management. Transfusion 2002:42(11):1435-41.

36) Naithani R, Agrawal N, Mahapatra M, Kumar R, Pati HP, Choudhry VP. Autoimmune hemolytic anemia in children. Pediatr Hematol Oncol. 2007;24(4):309–15

37) Gupta V, Shukla J, Bhatia BD. Autoimmune Hemolytic Anemia. Ind J Ped. 2008;75(5):451–4

38) Lechner K, Jager U. How I treat autoimmune hemolytic anemias in adults. Blood. 2010;16(11):1831–8

39) Dussadee K, Taka O, Thedsawad A, Wanachiwanawin W. Incidence and risk factors of relapses in idiopathic autoimmune hemolytic anemia. J Med Assoc Thai. 2010;93(Suppl 1):S165–S170

40) Alberto Z, Wilma B. Treatment of autoimmune hemolytic anemias. Haematologica. 2014; 99(10): 1547–54.

41) Serrano J. Autoimmune hemolytic anemia. Review of 200 cases studied in a period of 20 years (1970-1989). Sangre (Barc).1992;37(4):265-74.

42) Coon WW. Splenectomy in the treatment of hemolytic anemia. Arch Surg.1985;120(5):625-8.

43) Akpek G, McAneny D, Weintraub L. Comparative response to splenectomy in Coombs-positive auto-immune hemolytic anemia with or without associated disease. Am J Hematol. 1999;61(2):98–102.

44) Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. J Infect. 2001;43(3):182–6.

45) Barcellini W, Zanella A. Rituximab therapy for autoimmune haematological diseases. Eur J Intern Med. 2011;22(3):220–9.

46) Peñalver FJ, Alvarez-Larrán A, Díez-Martin JL, Gallur L, Jarque I, Caballero D, et al. Rituximab is an effective and safe therapeutic alternative in adults with refractory and severe autoimmune hemolytic anemia. Ann Hematol. 2010(11);89:1073–80.

47) Barros MM, Blajchman MA, Bordin JO. Warm autoimmune hemolytic anemia: recent progress in understanding the immunobiology and the treatment. Transf Med Rev. 2010;24(3):195–210.

48) Ahn YS. Efficacy of danazol in hematologic disorders. Acta Haematol 1990;84(3):122–9.

49) Berentsen S, Tjønnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune hemolytic anemia. Blood Reviews. 2012;26(3):107–15.

50) Schreiber AD, Herskovitz BS, Goldwein M. Low-titer cold-hemagglutinin disease. Mechanism of hemolysis and response to corticosteroids. N Engl J Med. 1977;296(26):1490–4.

51) Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. Blood. 2013;122(7):1114–21.

52) Berentsen S, Randen U, Vagan AM, Hjorth-Hansen H, Vik A, Dalgaard J, et al. High response rate and durable remissions following fludarabine and rituximab combination therapy for chronic cold agglutinin disease. Blood. 2010;116(17):3180–4.

Review Article

Plasma Cell Disorders

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Abstract

Plasma cell disorders are monoclonal neoplasm due to underlyng clonal plasma cell or B cell. This is a group of disorders that comprise of multiple myeloma, Waldenstrom's macroglobulinemia, amyloidosis and heavy chain disease together called monoclonal gammapathy. Immunoglobulins or its fragments secreted by these neoplastic plasma cells cause clinical manifestations. Protein electrophoresis identifies the presence of these monoclonal proteins whereas immunofixation identifies the fragments like heavy or light chain and clonality, flow cytometry identifies the cell type. Treatment modalities with drugs and stem cells are focused to prolong survival by reducing tumour load and its effects.

Key Words: Plasma Cell Disorders, Multiple Myeloma, Amyloidosis, Monoclonal Gammapathy

Introduction

Plasma cell disorder is a group of disorders characterised by uncontrolled proliferation of a single clone of immunoglobulin secreting terminally differentiated B cells or so called plasma cells . Also the immunoglobulins or its fragments produced are identical or homogenous, they produce discrete spike called Monoclonal (M) protein or paraprotein during electrophoresis. Pathophysiological effects of paraproteins are as follows : Raised serum globulin level, hypoalbuminemia, hyponatremia, dilutional anemia, raised ESR, rouleaux in blood flow, hyperviscosity, interference with platelet function and coagulation pathway, peripheral neuropathy, proteinuria, renal failure, amyloidosis and cryoglubulinemia .

Conditions included under plasma cell disorder are multiple myeloma, Waldenstrom's Macroglobulinaemia, amyloidosis, heavy chain diseases and monoclonal gammopathy of undermined significance (Table 1) and Plasmocytoma (medullary / extramedullary), Plasma cell leukemia, Immunoglobulin light chain amyloidosis, Osteosclerotic multiple myeloma, B-cell lymphocytic neoplasms, other neoplastic conditions like Chronic Lymphocytic Leukemia, Chronic Myeloid Leukemia, Carcinoma breast, colon and non–neoplastic conditions like cirrhosis, sarcoidosis, autoimmune disorders, skin diseases like lichen myxedematosus, necrobiotic xanthogranuloma.

CLASSIFICATION OF MONOCLONAL PROTEINS		
Laboratory finding		
Clinical implication	Non-IgM monoclonal proteins	IgM monoclonal proteins
Premalignant or undetermined	IgG, IgA, light chain, and other MGUS	IgM MGUS other lymphoproliferations
intermediate	SMM(Smoldering multiple myeloma)	Smoldering macroglobulinemia
Malignant	Active MM Plasma cell leukemia	Waldenstrom macroglobulinemia or other lymphoprliferative disorders

Table 1 - Classification of monoclonal proteins[1]

As far as the pathogenesis is concerned there is an interaction between plasma cells and their microenvironment –bone marrow stroma cells through adhesion molecules belonging to Beta-1 integrin family and vascular cell adhesion molecules respectively. This micro environment provides a sanctuary for plasma cells by promoting proliferation and blocking apoptosis leading to disease progression and drug resistance. Reduction of this interaction stops the cell growth and its replication which is of benefit to patients[2].

Clinical Approach

Appropriate diagnosis can be obtained by taking a detailed history and by doing physical examination. Multiple myeloma patients present with features of renal failure, hypercalcaemia (lethargy, weakness, depression and confusion), hyperviscosity (headache, fatigue, shortness of breath, visual disturbance, ataxia and somnolence), bone pain or fractures, lytic lesions (Fig 1,2), skin infiltration, polyneuropathy. Presence of dyspnea, hepatomegaly, edema, macro-glossia and entrapment neuropathy invoke the possibility of amyloidosis[3-5].

In **Waldenstrom's Macroglobulinemia** there may be features of hyperviscosity causing recurrent epistaxis and bleeding from mouth and gum, lymphadenopathy, hepatosplenomegaly and anemia .

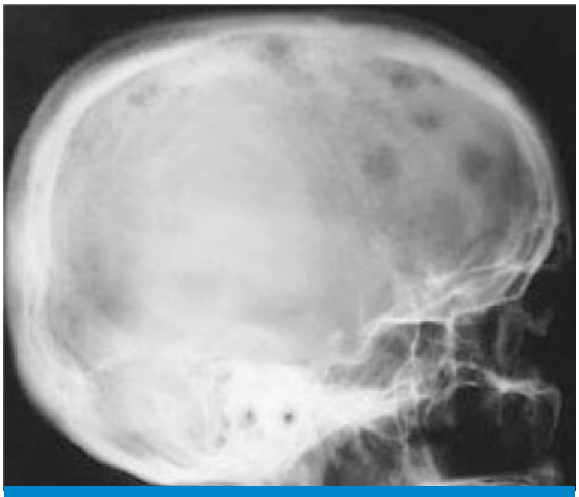


Fig 1 : Lytic lesions - skull

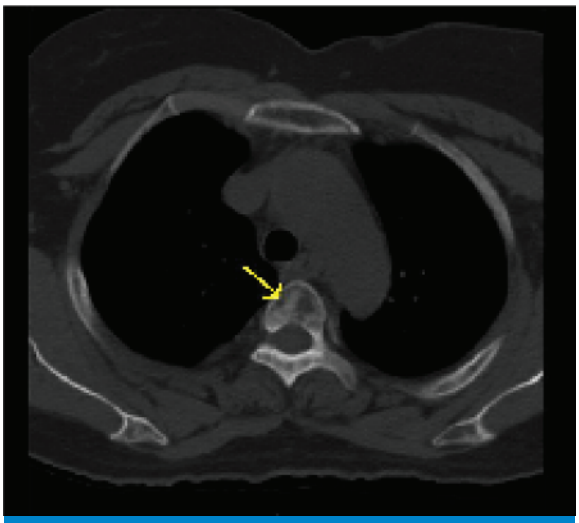


Fig 2 : Lytic lesions in Vertebra

POEMS syndrome includes Polyneuropathy, Organomegaly, Endocrinopathy (hypogonadism, hypothyroidism, diabetes mellitus, adrenal dysfunction), M-protein and skin changes (hyperpigmentation, acrocyanosis, hypertrichiosis, multiple haemangiomas).

Gamma heavy chain disease manifests as lymphadenopathy, hepatosplenomegaly, anemia, weakness and a peculiar symptom of palatal edema causing respiratory compromise due to involvement of Waldeyers nodes. Patients with **Alpha** heavy chain disease manifest with weight loss, chronic diarrhea, malabsorption due to mesentric adenopathy. Patients with **Mu** heavy chain disease present with hepatosplenomegaly, lytic bone disease, cast nephropathy due to light chain proteinuria .

Investigations

Complete blood count and differential peripheral blood film - Anemia is due to plasma volume expansion with paraproteinemia, infiltration of bone marrow and cytotoxic drugs. Leucopenia is due to cytotoxic drugs . Because of Rouleaux formation blood grouping may be difficult .

Chemistry including calcium, creatinine - Increased calcium and creatinine may be seen in Multiple myeloma due to renal insufficiency. **Serum protein Electrophoresis and Immunofixation :** Used to identify type of monoclonal protein either light or heavy chain[6], **Nephelometric quantification of immunoglobulin :** Used to measure serum immunoglobulin, **24 hrs Urine collection for electrophoresis and immunofixation** To quantify urinary light chains .

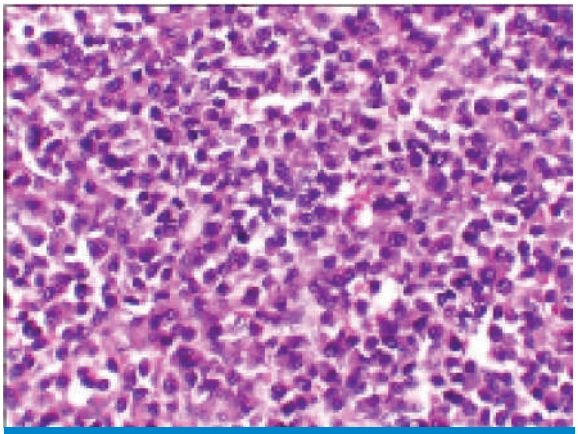


Fig 3 : Sheets of plasma cells

Bone marrow aspirate / Biopsy to assess for plasma cell morphology (Fig 3), proliferation rate, immunophenotyping[7] (to identify aberrant phenotyping markers), cytogenetic analysis[8] (provides evidence of clonality, confirms specific diagnosis, prognostic information, indicates whether neoplasm is therapy induced or not).

FISH (Fluorescence In situ Hybridization): Uses labelled oligonucleotide probe that binds to specific DNA sequences. Performed in the plasma cells from the bone marrow aspirates to identify chromosomal abnormality. Locus specific probes detect oncogenes and tumour suppressor genes. Centromeric probes detect monosomy and trisomy as well as to study two genes involved in specific translocation or other rearrangements.

Radiological skeletal bone survey : Chest and bone radiographs to identify lytic lesions. CT is used to detect bone defects. **MRI** reveals extent of bone marrow infiltration, cord or root compression in patients with pain syndrome. **PET** to assess disease activity.

BETA - 2 Microglobulin, CRP (C-reactive protein), LDH (lactate dehydrogenase): Serum levels of Beta 2 microglobulin (the light chain of HLA class 1 glycoproteins) correlates with tumor mass. **Measurement of free Monoclonal light chain, Multiparameter Flow Cytometry.** It is performed in the peripheral blood to confirm the presence of clonal circulating plasma cells[9].

PCR / RT PCR : Used in detection of rearrangements of immunoglobulin heavy and light chain loci and TCR loci. It provides evidence of clonal disorder, if a monoclonal rather than an oligoclonal or polyclonal pattern is detected. The advantage here is only small amount of DNA is required, no need for dividing cells .

Differential Diagnosis

Monoclonal Gammapathy Of Unknown significance: Most of the patients with this disorder remain asymptomatic and there is no evidence of end organ damage . MGUS have <3g/dl monoclonal proteins and <10% bone marrow plasma cells. Progression to myeloma is 1 % per year[10]. **Smoldering multiple myeloma (SMM):** Usually asymptomatic or presents with mild anemia. Diagnostic criteria of >10% clonal bone marrow plasma cells and M protein >3 gm/dl and <4.5 gm/dl is seen in SMM. Around 10 to 20 % patients with SMM progress to myeloma in a year[11]. Stringent follow up and and bone marrow evaluation is mandatory. **Multiple myeloma:** Features are hypercalcaemia, renal insufficiency, anemia, bone disease (CRAB criteria) and underlying clonal plasma cell disorder. Bone diseases manifest in the form of lytic lesions, severe osteoporosis, compressive features, bacterial infections, extra medullary plasmacytoma or associated amyloidosis[12]. **Amyloidosis :** Presentations depend upon the organ invloved. Patients with restrictive cardiomyopathy presents with dyspnoea, chest pain and renal disease patients may have proteinuria and hypoalbuminemia. Liver disease patients will have hepatomegaly with elevated alkaline phosphatase. In nervous system invlovment patient presents with peripheral neuropathy and postural hypotension. Constipation and diarrhea are the clinical manifestation in patients with gastrointestinal involvement .

Special forms of plasma cell disorders

Plasma cell leukemia : Characterised by >20 % peripheral blood plasmocytosis. It presents in two forms, one as de novo leukemic phase and other form is leukemic phase occurring with myeloma. **Solitary Plasmacytoma of bone :** It occurs usually on the vertebral column, <10% plasma cell infiltration in bone marrow sampling . No evidence of end organ damage. The most common symptom at diagnosis is pain.

Extramedullary plasmacytoma : It arises outside the bone marrow and involves upper respiratory tract or gastrointestinal tract. Treatment of choice is local radiotherapy. **Non–secretory Multiple Myeloma :** This form is difficult to diagnose, clonality is usually assessed by immunophenotyping. **IgM Multiple myeloma:** Definitive diagnosis is arrived by immunophenotype of infiltrating cells and detection of osteolytic lesions. It is a differential diagnosis for waldenstrom macroglobulinemia. **Osteosclerotic myeloma (POEMS syndrome) :** Presents with M protein, Polyneuropathy and osteosclerotic lesion. Other features not in the acronym are pleural effusion, thrombocytosis, ascites and edema.

Treatment

Multiple Myeloma

Therapeutic measures are focused on preventing early mortality and to prolong survival by rapid cytoreduction and intervening end organ complications.

Therapy is influenced by patient's age and comorbidities. Treatment includes 3 to 6 cycles of induction therapy followed by autologous stem cell transplantation and if needed consolidation/maintenance therapy.

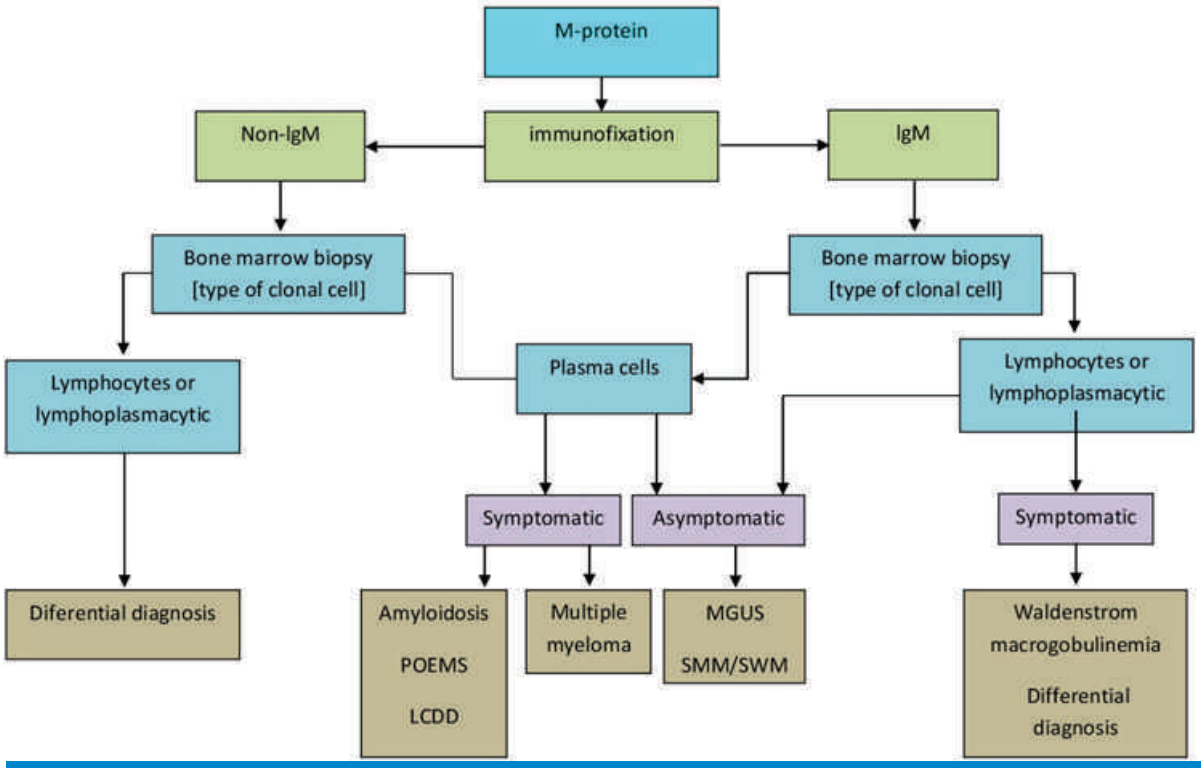


Fig 4 : Diagnostic Algorithm

LCDD - Light chain deposition disease, SMM - Smoldering multiple myeloma

Gold standard regimen for young and newly diagnosed patients is VAD combination (Lenalidomide, bortezomib, dexamethasone).

Most studies favour treatment with Lenalidomide and dexamethasone due to safety profile in patients more than 70 years who are unfit for transplant.

Stem cell based therapy along with drug combination during induction phase showed only modest benefit but not curative compared to drug alone therapy.

Randomized studies in consolidation phase show prolonged progression free and high overall response rates with high dose melphalan therapy with stem cell support compared to standard dose therapy. Tandem transplant i.e two successive high dose melphalan therapy with hematopoetic stem cell support may be valuable in patients with high risk cytogenetics.

Maintenance phase is aimed at prolonging the duration of response after transplantation and remission. Nontransplant patients treated with Lenolidamide, Melphalan, Prednisolone in induction phase and receives Lenalidomide for maintenance are at the risk of second primary malignancy as benefit outweighs the risk. Patients with high risk cytogenetics after transplant are benefited with Lenalidomide and Bortezomib combination therapy[13,15].

Relapse cases may respond to 1) Lenalidomide and or Bortezomib combined with dexamethasone or 2) Combination of Bortezomib and doxarubicin.

In refractory cases, thalidomide or high dose Melphalan and stem cell therapy can be used if not initiated earlier.

Second generation proteosome inhibitor Carfilzomib and immunomodulator agent Pomalidomide may be used in refractory and relapsed cases.

Supportive measures address issues like anemia which is treated with erythropoitin and haematinics. Hypercalcemia is treated with bisphosphonates, Plasmapheresis is used for hyperviscosity syndrome, Calcium and vitamin D is given for bone strengthening. Patients presenting with pain and collapsed vertebra are treated with surgical interventions like kyphoplasty and vertebroplasty .

Waldenstrom's Macroglobulinemia

Treatment is initiated in symptomatic patients with worsening anemia, hyperviscosity symptoms. Significant efficacy is achieved with Bortezomib and Bendamustine. Fludarabine and cladribine are also highly effective single agents. Frail elderly patients are treated with single agent Rituximab (anti-CD20) or oral Fludarabine.

Poem's Syndrome

Neuropathic symptoms resolve after local radiotherapy for plasmacytoma.High dose therapy and stem cell transplantation may be useful for selective patients .

Heavy Chain Disease

Gamma heavy chain disease - Symptomatic patients can be treated with either combination chemotherapeutic agents or with rituximab. **Alpha** heavy chain disease is treated with antibiotics and combination chemotherapy. **Mu** heavy chain disease is treated similar to Chronic lymphocytic leukemia.

Conclusion

Plasma cell dyscrasias are a heterogeneous group of disorders either present as asymptomatic condition with high potential for transforming to malignancy or as more aggressive form at presentation itself . Clinical presentation may be due to the clone itself or the properties of the secreted Immunoglobulin. Because of this various mode of presentation a systematic approach which includes earliest diagnosis of clinically significant condition is needed to avoid unnecessary testing and treatment.Therapy is largely directed (if indicated) at reducing the underlying clone.

References

1) Dispenzieri A, Lacy MQ, Kumar S. Multiple myeloma. Greer JP, Arber DA, Glader B, List AF, Means RT Jr, Paraskevas F, Rodgers GM, Foerster J, (eds.). (2014). Wintrobe's Clinical Hematology. (13th Edition). Lippincott Williams & Wilkins. 98: 2030-2031

2) Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e.New York, NY: McGraw-Hill; 2012: 713.

3) Myeloma of bone. PathologyOutlines.com website. http://www.pathologyoutlines.com/topic/bonemyeloma.html.

4) Scott JF, Reichert B, Merati M, Honda K, Cooper KD. Resident Rounds: Part III - Case Report: Metastatic Multiple Myeloma. 2015; 14(12): 1485

5) Samanthula H, Deshpande DP, Parvathaneni V. Primary systemic amyloidosis. J NTR Univ Health Sci. 2013;2(2):138-41

6) Mark T1, Jayabalan D, Coleman M, Pearse RN, Wang YL, Lent R et al. Atypical serum immunofixation patterns frequently emerge in immunomodulatory therapy and are associated with a high degree of response in multiple myeloma Br J Haematol. 2008 Dec; 143(5): 654–60.

7) Robillard N, Wuilleme S, Moreauet P. Immunophenotype of Normal and Myelomatous Plasma-Cell Subsets. Front Immunol. 2014; 5: 137.

8) Rajan AM, Rajkumar SV. Interpretation of cytogenetic results in multiple myeloma in clinical practice; Blood cancer J. 2015; 5(10): e 365

9) Dispenzieri A, Lacy MQ, Kumar S. Multiple myeloma. Greer JP, Arber DA, Glader B, List AF, Means RT Jr, Paraskevas F, Rodgers GM, Foerster J, (eds.). (2014). Wintrobe's Clinical Hematology. (13th Edition). Lippincott Williams & Wilkins. 98: 2018

10) Raja KR, Kovarova L, Hajek R.Review of phenotypic markers used in flow cytometric analysis of MGUS and MM, and applicability of flow cytometry in other plasma cell disorders Br J Haematol.May;149(3):334-51.

11) Berenson JR1, Anderson KC, Audell RA, Boccia RV, Coleman M, Dimopoulos MA et al. Monoclonal gammapathy of undetermined significance: A consensus statement. Br J haematol. 2010; 150(1): 28-38.

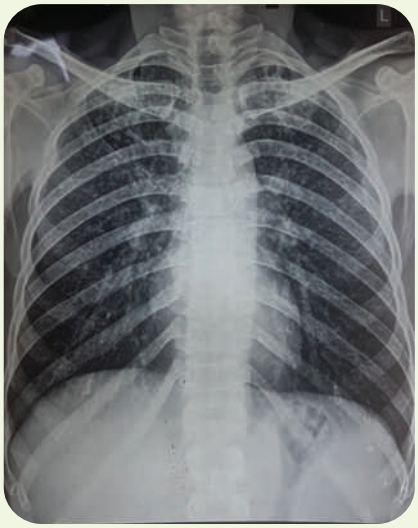
12) Kyle R, Budi F,Rajkumar S. Management of monoclonal gammopathy of undetermined significance and Smoldering multiple myeloma. Oncology 2011;25(7):578-86.

13) Palumbo A, Anderson K, Multiple myeloma. N Engl J Med. 2011; 364(11) : 1046 -60

14) Palumbo A, Cavallo F, Gay F. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma. N Engl J Med. 2014; 371(10): 895-905

15) Attal M, Lauwers-Cances V, Hulin C. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Eng J Med. 2017; 376(14): 1311-20.

Image Challenge - 1



Clue: 18 year old boy living in a hostel, presented with low grade fever, weight loss for 45 days.

- Answer in page : 92

Review Article

Pancytopenia - A Physician's Perspective

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Abstract

Pancytopenia is a one of the challenging disorder to the treating physician due to its diverse etiologies. It may be due to bone marrow failure syndromes, malignancies, infections or side effect of drugs, and it is also noted in hypersplenism. These patients may present without any symptoms and diagnosed during routine blood investigations or may present with symptoms of thrombocytopenia, anemia and leucopenia. The workup for pancytopenia is often quite extensive and includes a detailed clinical history, meticulous physical examination, and appropriate laboratory investigations in relation to the clinical scenario. Bone marrow examination helps to find out the underlying condition causing pancytopenia. Treatment of the pancytopenia includes supportive care for infections, bleeding and symptomatic anemia until the patient receives definite and/or curative treatment which depends upon the etiology.

Key Words: Pancytopenia, Hypersplenism, Aplastic Anemia, Myelofibrosis

Introduction

Pancytopenia is one of the commonest hematological conditions encountered by the practitioners in their day to day practice. It is characterized by reduction in cell counts of all three lineages of the blood leading to anemia, leucopenia and thrombocytopenia[1,2].

The causes of pancytopenia being quite varied result in diagnostic dilemma. Cytotoxic therapies, including myeloablative radiation therapy and chemotherapy, are common and predictable causes of pancytopenia in patients being treated for malignancies; pancytopenia outside this setting, can be very challenging. Evaluation of patient begins with exhaustive history including but not limited to drug intake, exposure to toxins, family history and febrile illness; followed by meticulous physical examination and detailed investigations including bone marrow evaluation in most cases. All the cases of pancytopenia require a thorough approach to find out the cause.

There are no universally accepted guidelines for the management of pancytopenia. The treatment depends upon the underlying etiology. The main goal is to provide supportive care including broad spectrum antibiotics along with blood and blood components especially in patients with fever and bleeding till they receive treatment for the basic disease causing pancytopenia.

Definition

As pancytopenia is a not a disease by-itself, there is no clear cut definition that exists for it. However, this disorder can be defined by simultaneous presence of low counts of all three cell lines i.e. leukocytes, erythrocytes, and platelets in the peripheral blood as compared to age and sex adjusted normal range for healthy population. Therefore it is a combination of anemia, leucopenia and thrombocytopeina. (Hemoglobin < 13.5gms in males or 11.5gms in females, WBC count $<4*10^9$/L and platelet count $<150*10^9$/L).

Severe pancytopenia is defined as absolute neutrophil count <500/mm, platelet count < 20,000/mm, corrected reticulocyte count < 1%,which was initially proposed to assess the severity of severe aplastic anemia[3].

Etiopathogenesis

As pancytopenia is a laboratory finding, and not a particular diagnosis, it has a broad differential diagnosis. On one hand it may be the only manifestation of an easily treatable disease like B12 deficiency but on the other hand it may be the striking feature of a life threatening condition like leukemia[4].

The pathophysiological mechanisms to explain pancytopenia can be simplified by dividing the causes into two broader categories. Most often it is caused by decreased production of multiple cell lineages from primary dysfunction of marrow or the stem cells. Rarely it is caused by destruction or sequestration of cell lines in the periphery. Sometimes, the same disease produces pancytopenia by overlapping the mechanisms. Hypersplenism is the commonest cause for pancytopenia without primary deficits in the marrow or the stem cells. Causes and classification of pancytopenia is stated in Figure 1.

Bone marrow failure state is characterized by presence of pancytopenia or single lineage disorder resulting from defective hematopoiesis. The disorders which produce bone marrow failure syndromes with pancytopenia include aplastic anemia, myelodysplasia, and myelophthisis. These disorders have normocytic and normochromic anemiaon peripheral smear with an inappropriately low reticulocyte count.

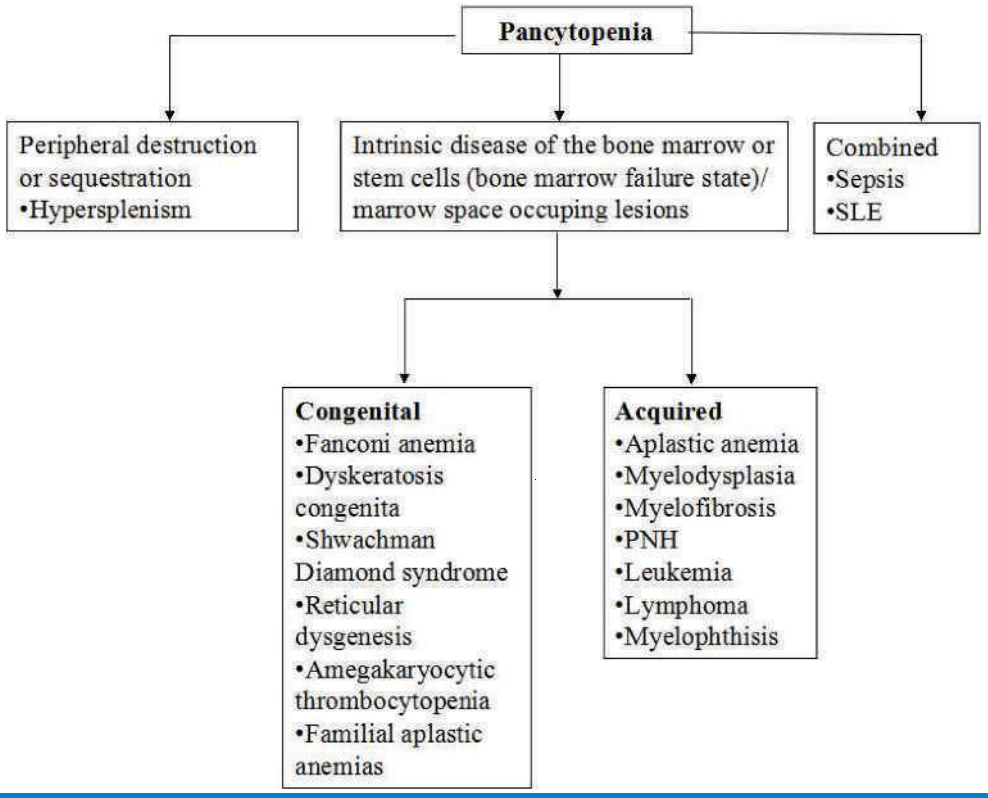


Fig 1 : Causes and classification of pancytopenia

Aplastic anemia is defined as pancytopenia with hypocellular marrow in the absence of abnormal infiltrate or increased fibrosis[5]. The disorder can result from both inherited and acquired causes or it may be iatrogenic[6]. The causes of acquired aplastic anemia is summarized in Table 1.

The most common congenital cause for pancytopnia is Fanconi's anemia. It is an autosomal recessive disorder which is characterized by congenital developmental anomaly, progressive pancytopenia, and an increased risk of malignancy. Dyskeratosis congenita is an another inherited bone marrow failure disorder which is defined by triad of nail changes, oral leukoplakia, and a reticulated skin rash[7].

Bone marrow failure with resultant pancytopenia may result from exposure to radiation or chemicals (benzene). Exposure to benzene is associated with aplastic anemia, acute leukemia, and blood and marrow abnormalities[6].

The other causes of pancytopenia include acute leukemias (aleukemic leukemia), advanced stages of chronic leukemias. High grade lymphomas and myeloma can also produce pancytopenia. The mechanisms of marrow failure in these diseases can be related either due to active suppression of normal haematopoiesis or bone marrow infiltration by the abnormal cells.

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic and debilitating disorder which most frequently presents in early adulthood. It is an unique clinical syndrome which is characterized by the triad of hemolytic anemia, pancytopenia, and thrombosis[8].

Myelodysplastic syndrome is a heterogeneous group ofhematologic disorderscharacterized by cytopenias of any individual or all cell lines associated with abnormal appearing cellular marrow[6]. It is due to mutation in haematopoietic stem cells which results in defective differentiation and maturation of cells. It is more common in elderly population with increased risk (20-25%) of developing acute myeloid leukemia.

Myelofibrosis is characterized by replacement of the normal bone marrow by fibrous material. It can occur as a primary hematologic disease (myelofibrosis or myeloid metaplasia). Secondary myelofibrosis (myelophthisis) can occur as a response to invading tumor cells (usually an epithelial cancer of breast, lung, or prostate origin or neuroblastoma), infections (mycobacterium tuberculosis, mycobacterium avium, fungi, and HIV), and in sarcoidosis. Is appears to the be final common pathway of chronically overstimulated marrow as occurs in essential thrombocytosis, polycythemia vera and chronic myeloid leukemia[6].

Aplastic anemia was first diagnosed in a pregnant female. It can recur during successive pregnancies. It resolves after delivery or with spontaneous or induced abortion. Idiopathic aplastic anemia is a diagnosis of exclusion[7].

Drugs are the commonest cause for many hematologic disorders, affecting white cells, red cells, platelets, and the coagulation system[9], but less well recognized. They induce pancytopenia either by predictable (dose dependent manner) or by unpredictable manner (idiosyncratic). The drugs that are commonly implicated are listed in Table 2. They cause bone marrow suppression by three different mechanisms which

Secondary	
Radiation	
Drugs and chemicals	
Regular effects	
Idiosyncratic reactions	
Viruses	Epstein-Barr virus (infectious mononucleosis)
	Hepatotropic viruses
	Parvovirus B19 (transient aplastic crisis, PRCA)
	Human Immunodeficiency Virus
Immune diseases	Eosinophilic fasciitis
	Hyperimmunoglobulinemia
	Large granular lymphocytosis (LGL)
	Thymoma/ Thymic carcinoma
	Graft versus host disease in immunodeficiency
Paroxysmal nocturnal hemoglobinuria (PNH)	
Pregnancy	
Idiopathic	

Table 1 - Causes of acquired aplastic anemia[6]

Cytotoxic drugs
Chloramphenical
NSAIDs
Chloroquine
Colchicine
Anticonvulsants (hydantoins, carbamazepine)
Heavy metals (gold, arsenic, bismuth and mercury)
Antithyroid drugs (methimazole, methylthiouracil,propylthiouracil)
Carbonic anhydrase inhibitors (acetazolamide and methazolamide)
Sulfonamides
Antidiabetes drugs (tolbutamide, chlorpropamide),
Antihistamines (cimetidine, chlorpheniramine)
d-Penicillamine

Table 2 - Drugs implicated for pancytopenia

include direct toxicity, metabolite-driven toxicity, and immune-mediated[10].

Several underlying mechanisms have been described for pancytopenia induced by infections[11,12]. One of the commonest cause for infection related pancytopenia is sepsis. Sepsis and the ensuing systemic inflammatory response, can cause cytopenias[13]. The postulated mechanisms include consumptive coagulopathy, hypersplenism, and release of inflammatory mediators which suppress the marrow. The second explanation for infection induced pancytopenia is due to the effect of viral infections. Any viral illness can be associated with transient bone marrow suppression due to direct damage of the haematopoietic precursor cells. But commonly implicated viral illness includes HIV, parvovirus B19, EBV, CMV, and hepatotropic viruses (A, B, and C)[14,15].

Abnormal immune response which follows some infections, can destroy the precursor cells in the marrow or blood cells in the periphery which results in pancytopenia

Infection can also lead to hematophagic histiocytosis which is characterized by increased macrophage activity and phagocytosis of blood cells and precursors. Viral infections are most commonly involved (EBV, CMV, Measles, HHV-8, HIV), but virtually any other infectious agent can precipitate this syndrome like TB, brucella, salmonella, malaria, leishmaniasis and fungal infection[16,17].

Microorganisms that infect endothelial cells (e.g. rickettsia, babesia) may produce pancytopenia as part of a generalized vasculitis. Tropical infections like malaria, visceral leishmania can produce hypersplenism and resultant pancytopenia[18]. Finally infections may lead to pancytopenia by replacement of the marrow by infectious organisms such as mycobacterial infections and fungal infections like histoplasmosis[19,20].

In SLE, pancytopenia commonly results from an immune mediated bone marrow failure, myelofibrosis, vasculitis with bone marrow necrosis, excessive peripheral cells destruction and macrophage activation syndrome[21,22]. Sometimes it may be secondary to drugs used for treatment of SLE or resulting from infections.

One of the commonest extra medullary cause for pancytopenia is hypersplenism. It is characterized by splenomegaly, cytopenia(s), normal or hyperplastic bone marrow, and a response to splenectomy. The cytopeniasresult from increased destruction of the blood cells secondaryto reduced flow of blood through enlarged and congested cords(congestive splenomegaly) or to immune-mediated mechanisms[23]. The size of the spleen does not correlate well with severity of cytopenias. The causes for hypersplenism include portal hypertension (cirrhosis of liver, extra hepatic portal obstruction), tropical splenomegaly (hyperreactive malarial splenomegaly and visceral leishmaniasis), lymphomas or rarely idiopathic[24].

Clinical manifestations

The clinical features depends upon both of the underlying disease process as well as relate to the blood cell lineages affected. Patients with mild pancytopenia are often asymptomatic and in most instances it goes unnoticed unless complete blood count is ordered for some other reason. Or the patients can present with life threatening infection or catastrophic bleeding manifes

tations. Symptomatic pancytopenia is more common in patients with primary dysfunction of the bone marrow or the stem cells.

The symptoms are attributable to anemia, leucopenia, and/or thrombocytopenia. As the platelets have shorter half life, symptoms of thrombocytopenia appears first. Mucocutaneous bleeding is is the most common early symptom; a complaint of days to weeks of epistaxis, easy bruising, oozing from the gums, hematuria, menorrhagia, and sometimes petechiae will have been noticed. Massive hemorrhage is unusual with thrombocytopenia, but even small amounts of bleeding in the central nervous system can result in catastrophic intracranial or retinal hemorrhage.

Anemia develops slowly because red blood cells have longest half life compared to white blood cells and platelets. The symptoms depends on the rapidity of development of anemia and those include lassitude, weakness, shortness of breath, and a pounding sensation in the ears.

Infection is an unusual first symptom in pancytopenia due to bone marrow failure as compared to agranulocytosis. The features include pharyngitis, anorectal infection which respond poorly to antibiotics. Patients may develop overwhelming sepsis without any focal sign of infection, with malaise and fever being the only clinical features.

Evaluation

The need for detailed work-up should be based on the clinical scenario. Mild pancytopenia in patients with a recent viral illness or following drug exposure and who are clinically stable, less likely require further investigations. Similarly, pancytopenia in the midst of sepsis rarely need extensive evaluation unless the peripheral smear shows immature cells. But these patients need repeat blood counts to demonstrate resolution of cytopenias.

Initial evaluation of pancytopenia starts with proper history, followed by examination (Table 3) and then finally moving on to laboratory investigations (basic hematological, biochemical, radiological, and histopathological investigations as needed). A simplified approach to pancytopenia is given in Figure 2.

Clinical features	Clinical findings
Age	Petechiae and ecchymoses
Bone pain	Retinal hemorrhage
Fever	Blood in the stools and abnormal vaginal bleeding
Night sweats	Pallor
Malaise, weight loss	Fever
Bleeding from any site	Oral candidiasis, pharyngeal exudates (neutropenia)
Treatment history	Lymphadenopathy, organomegaly (hematological malignancy)
Alcohol intake	
Dietary history	Bone tenderness (leukemia)
Occupational exposure	Gingival hypertrophy
Joint pain, rash, photosensitivity and recurrent fetal loss	Cafe au lait spots and short stature (Fanconi's anemia)
Family history	Peculiar nails, reticulated skin hyperpigmentation and leukoplakia (dyskeratosis congenita)
Early graying (telomerase defect)	

Table 3 - Initial evaluation of pancytopenia: clinical features and findings

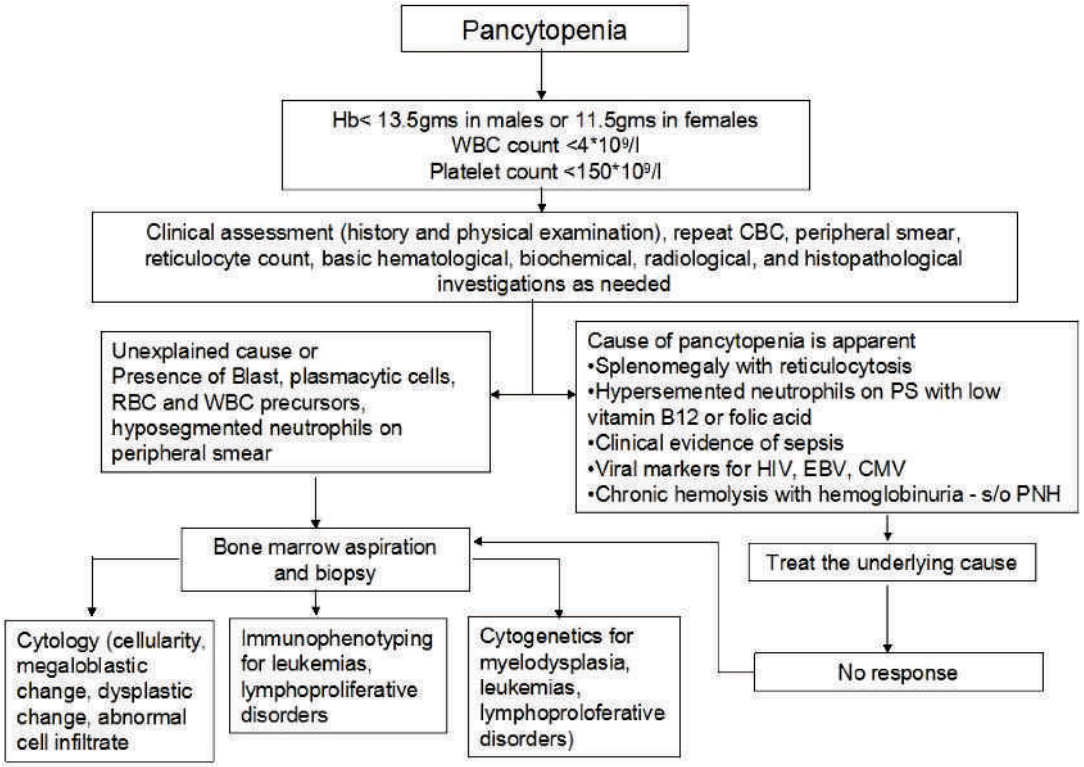


Fig 2 : Approach to Pancytopenia

All patients with pancytopenia have to be subjected to complete blood counts (CBC), reticulocyte count and a peripheral blood examination. CBC will show that all 3 cell lines are decreased. The reticulocyte counts will be decreased in bone marrow failure due to ineffective production of the cells by the marrow whereas it is more in cases when pancytopenia is secondary to the peripheral destruction of the cells. Peripheral smear may show anisopoikiliocytosis (prominent in myelofibrosis), RBC and WBC precursors, Howel-Jolly bodies (megalioblastic anemia and myelodysplastic syndromes [MDS]), giant platelets (hypersplenism and MDS), toxic granules of the neutrophils (infections), hypogranulation of the neutrophils (MDS), hypersegmentaion ((megaloblastic anemia) or hyposegmented (MDS) , blasts (acute leukemias, myelofibrosis, aleukemic leukemias) and plasmacytic cells (multiple myeloma). Increase in ESR is noted in infections and mutiple myeloma.

In addition to basic hematological investigations most of the patients need liver function test, coagulation profile, fibrinogen, D-dimer, serum B12, folate levels, serum direct antiglobulin test, viral markers for hepatitis, serology for EBV, CMV and HIV, serum ferritin and triglycerides (elevated in hemophagocytic lymphohistiocytosis) and antinuclear antibodies (ANA).

In hypersplenism, increased reticulocyte production index reflects increased marrow production of red cells, although the value may be less due to increased sequestration of reticulocytes in the spleen. Blood and bone marrow culture for leishmaniasis, ELISA for leishmaniasis and serum titers of IgM malarial antibody shall be carried out in patients with suspected tropical splenomegaly.

Bone marrow examination (both aspiration and biopsy) is almost always indicated for evaluating the cases of pancytopenia unless the cause is otherwise apparent (e.g., hypersplenism, deficiency of vitamin B12 or folate, sepsis or autoimmnue diseaes). Bone marrow examination permits to assess the cellularity (decreased-indicate decreased production of blood cells, normal or increased-indicate ineffective production or increased destruction or sequestration of blood cells). The classification pancytopenia based on bone marrow cellularity is shown in Table 4. This also helps to examine the cytology (megaloblastic change, dysplastic change, abnormal cell infiltrates, haemophagocytosis, and infection [e.g., Leishman-Donovan bodies, malarial parasites, tuberculosis and fungal infection]), immunophenotyping (leukemias, lymphoproliferative disorders) and cytogenetics (myelodysplasia, leukemias, lymphoproloferative disorders). It also permits examination of histology and evaluation for cellular infiltration, blasts, features of MDS (e.g., abnormal localization of immature precursors) and reticulin stain (fibrosis)[25,26].

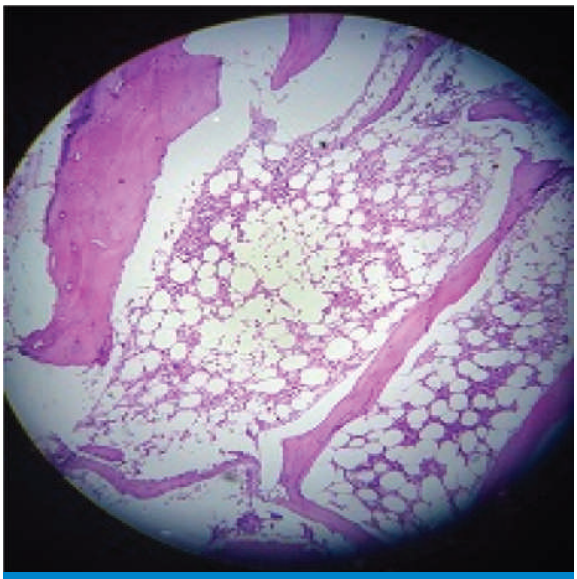


Fig 3 : Bone marrow showing aplastic anemia

Pancytopenia with hypocellular bone marrow	Pancytopenia with Cellular Bone Marrow	
	Primary bone marrow diseases	Secondary to systemic diseases
Acquired aplastic anemia	Myelodysplasia	Hypersplenism
Constitutional aplastic anemia (fanconi anemia, dyskeratosis congenita)	Paroxymal nocturnal hemoglobinuria (PNH)	B12 and folate deficiency
Some myelodysplasia	Myelofibrosis	Overwhelming infection
Rare aleukemic leukemia	Some aleukemic leukemia	Alcohol
Some acute lymphoid leukemia	Bone marrow lymphoma	Tuberculosis
Some lymphomas of the bone marrow	Hairy cell leukemia	Systemic lupus erythematosus
		Brucellosis
		Sarcoidosis
		Leishmaniasis

Table 4 - Classification of pancytopenia based on bone marrow cellularity[6]

In patients with splenomegaly, to find out the cause ultrasound abdomen or CT abdomen can be performed. X-ray chest may reveal evidence of tuberculosis, fungal infection, tumor masses. When metastatic bone infiltration is suspected, search shall be made for primary malignancy.

Management

The management includes identification and reversal of the underlying cause with appropriate and adequate supportive care until normal counts are restored. However, the treatment of underlying etiologies are not considered here owing to space constraints.

Life threatening infections, catastrophic bleeding and symptomatic anemia are much more common among patients with pancytopenia due to intrinsic diseases of the bone marrow or stem cells.

Supportive care[6]

First and the most important, is treatment of infections. Infection in the presence of severe neutropenia must be treated aggressively by early initiation of empirical broad-spectrum parenteral antibiotics, usually ceftazidine or a combination of an aminoglycoside, cephalosporin, and semisynthetic penicillin. Specific foci of infection should be sought by careful physical examination and by imaging studies. Vancomycin should be added in patients with indwelling catheter. Persistent fever spikes indicate fungal infection and warrants treatment with antifungal drugs. For overwhelming and refractory infection, granulocyte transfusions using G-CSF–mobilized peripheral blood can be tried. Growth factors or G-CSF analogues, such as filgrastim, may be used to boost WBC counts once a presumptive diagnosis is made. Use of nonabsorbable antibiotics for gut sterilization and total reverse isolation do not improve the outcome as compared to simple measures like hand washing.

Platelet transfusions are indicated for the treatment of bleeds caused by thrombocytopenia as well as prophylactically once or twice weekly to maintain the platelet count >10,000/µL (bleeding from the gut increases precipitously at counts <5000/µL). Major problem related to platelet transfusions is the development of a refractory state caused by alloimmunisation. This can be minimized by use of single donors to reduce exposure and physical or chemical methods to diminish leukocytes. HLA matched platelet transfusions are quite effective in patients refractory to random donor products. Oral estrogens or nasal follicle-stimulating hormone/luteinizing hormone (FSH/LH) antagonists are given to suppress menstruation. The drugs which inhibit platelet function like aspirin should be avoided.

Anemia should be corrected with packed red blood cell transfusion to maintain hemoglobin value >7 gms/dl. If patients have underlying cardiac or respiratory disease, hemoglobin should be maintained above 9 gms/dl. For those patients who are likely to need repeated transfusion, use of leukoreduced products is recommended as it reduces febrile transfusion reactions, CMV transfer, and alloimmunization, as they are crucial in reducing complications of the further transfusions. Similarly, the use of irradiated blood to destroy donor lymphocytes and prevent transfusion-associated graft versus host disease (GVHD) is recommended. In patients with bone marrow failure 2 units of blood is given every 2 weeks, which will replace normal losses. In patients with repeated transfusion, who have a reasonable expectation of survival iron chealtors, deferoxamine and deferasirox should be given after every fiftieth transfusion.

Hematopoietic stem cell transplantation (HSCT) using allogeneic donor has been attempted successfully in some cases.

Conclusion

Pancytopenia is a laboratory finding which may indicate a constellation of underlying etiologies. Some of these are self limiting, while others may require exhaustive investigation and aggressive treatment. A systematic approach to pancytopenia will guide the treating physician towards appropriate therapy.

References

1) de Gruchy GC: Pancytopenia, aplastic anemia. De Gruchy's clinical hematology in medical practice, 5th edition. In: Firkin F, Chesterman C, Penington D, Rush B (Eds). Berlin, Germany: Blackwell Science, 1989;119-36.

2) Naseem S, Verma N, Das R, Ahluwalia J, Sachdeva MS, Marwaha RM. Pediatric patients with bicytopenia/pancytopenia: Review of etiologies and clinico-hematological profile at a tertiary care center.Indian Journal of Pathology and Microbiology.2011;54(1):75-80

3) Camitta BM, Storb R, Thomas ED. Aplastic anemia: pathogenesis, diagnosis, treatment and prognosis.N Engl J Med1982; 306(11): 645-52

4) Bunch C. Bone marrow failure. Medicine International 1995;10: 495-9

5) Gewirtz AM, Hoffman R. Current considerations of the etiology of aplastic anemia .Crit Rev Oncol Hematol. 1985 (1);4:1–30

6) Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. Harrison's Principles of Internal Medicine, 19e Vol1.New York, NY: McGraw-Hill; 2015

7) Brodsky RA, Jones RJ. Aplastic anemia. Lancet 2005;365(9471):1647–56

8) Young NS. Paroxysmal nocturnal hemoglobinuria: current issues in pathophysiology and treatment. Curr Hematol Rep. 2005;4(2): 103-9

9) Aksoy M, Erdem S, Dincol G, Bakioglu I, Kutlar A. Aplastic anemia due to chemicals and drugs: a study of 108 patients. Sex Trans Dis 1984;1(4 Suppl): 347-50.

10) Young NS, Maciejewski J. The pathophysiology of acquired aplastic anemia. N Engl J Med 1997;336(19):1365–72

11) Jenkins G, Williams JD (Eds) Infection and Haematology. 1994. Butterworth-Heinemann, Oxford, UK

12) Wickramashinghe S.N. (ed) Haematological Aspects of Infection. Bailliere's Best Practice and Research in Clinical Haematology 13 (2), June 2000. Bailliere Tindall, London, UK

13) Garewal G, Marwaha N, Marwaha RK, Das KC. Bone marrow necrosis and pancytopenia associated with gram negative septicemia. Indian Pediatr 1991; 28(1):79-81

14) Young NS, Mortimer P: Viruses and bone marrow failure. Blood 1984; 63:729-37.

15) Ajlouni, K, Doeblin, TD. The syndrome of hepatitis and aplastic anaemia. British Journal of Haematology. 1974;27(2):345–55

16) Reiner A, Spivak J. Hemophagocytic histiocytosis: a report of 23 new patients and a review of the literature. Medicine 1988;67(2):369-88

17) Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 1998;12(2):435-44

18) Perrin LH, Mackey LJ, Miescher P A. The hematology of malaria in man. Semin Hematol 1982; 19(2):70-82

19) Zamorano J, Tompsett R. Disseminated Atypical Mycobacterial Infection and Pancytopenia. Arch Intern Med. 1968;121(5):424-7

20) Hunt BJ, Andrews V, Pettingale KW. The significance of pancytopenia in miliary tuberculosis. Postgraduate Medical Journal. 1987;63(743):801-4

21) Schur P H, Berliner N. Hematological manifestations of systemic lupus erythematosus in adults. USA: Up To Date; 2012.

22) Bashal F. Hematological Disorders in Patients with Systemic Lupus Erythematosus. The Open Rheumatology Journal. 2013;7:87-95

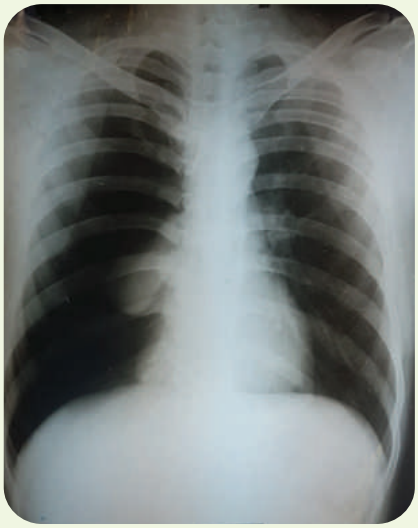
23) Jandl JH Aster RH. Increased splenic pooling and the pathogenesis of hypersplenism. Am J Med Sci. 1967;253:383–98

24) Dameshek W. Hypersplenism. Bull NY Acad Med. 1955;31(2):113–36

25) Bashawri LA. Bone marrow examination. Indications and diagnostic value. Saudi Medi J. 2002;23(2):191-6

26) Trewhitt KG. Bone marrow aspiration and biopsy: Collection and interpretation. Oncol Nurs Forum 2001;28(9):1409-15

Image Challenge - 2



Clue: 45 year old smoker with breathlessness and hemoptysis

- Answer in page : 93

Review Article

Iron Deficiency Anemia: An Overview

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Abstract

Iron deficiency anemia (IDA) is the leading cause of anemia worldwide, which causes significant morbidity. In this evidence based review, the etiology of IDA, guidelines on screening, most useful diagnostic tests, and the role of various modalities of treatment have been elaborated. Timely diagnosis and appropriate management of IDA are crucial especially in developing countries.

Key Words: Anemia, Iron Deficiency, Screening, Intravenous Iron, Oral Iron, Blood Transfusion

Introduction

Anemia affects almost a quarter of the world's population and iron deficiency is the commonest cause[1]. Other causes include megaloblastic anemia due to Vitamin B12 and folate deficiency. This review summarizes the etiology, screening, diagnosis of nutritional anemia with special importance to the management of anemia related to the deficiency of iron. Evidence based guidelines have been discussed and the levels of evidence with grades of recommendation are shown in Table 1.

Grades of Recommendation	
A	Supported by, at least, two level I investigations
B	Supported only by one level I investigation
C	Supported only by level II investigations
D	Supported by, at least, one level III investigation
E	Supported by level IV or V Evidence
Evidence Levels	
Level I	Randomized trials; great sample size; clear results; low risk of alpha (false-positive) or beta(false-negative) errors
Level II	Randomized trials; small sample size; uncertain results; moderate to high risk of alpha (false-positive) or beta(false-negative) errors
Level III	Nonrandomized, contemporaneous controls
Level IV	Nonrandomized, historical control and experts opinion
Level V	Case series; without control subjects and experts opinion

Table 1 - Grades of recommendation and levels of evidence[2]

Iron deficiency anemia (IDA)[3,4]

Iron deficiency affects both men and women and prevalence of anemia increases with age[3]. Anemia decreases the increases costs of health care by retarding the capacity to work[4]. Iron deficiency is known to be associated with fatigue, cognitive dysfunction, infertility, restless leg syndrome (RCS) and overall reduced quality of life, all of which can be easily reversed with early and appropriate iron therapy[5-11]. Conditions of the gastrointestinal tract such as hook worm infestation, inflammatory bowel disease, malignancy and celiac disease are notorious for causing IDA. Comorbidities such as chronic kidney disease (CKD) and chronic heart failure (CHF) also increase the risk of anemia and iron deficiency. In turn, iron deficiency in CHF is associated with increased risk of death, irrespective of the level of hemoglobin. It is also associated with increase in platelet count, with consequent risk of thrombosis and embolism.

Etiology

The commonest cause of iron deficiency anemia in India is worm infestation. Iron deficiency anemia also occurs in premenstrual women due to normal uterine bleeding with inadequate nutrition or abnormal uterine bleeding. In developing countries, anemia is due to diminished RBC production due to low iron stores, decreased iron intake, impaired absorption, increased iron demand and excessive loss. The causes are represented in Table 2.

There are 4 stages of iron deficiency anemia[3]:

Stage I : Moderate depletion of iron stores

Stage II: Severe depletion of iron stores

Stage III: Iron deficiency

Stage IV: Iron deficiency/dysfunction and anemia

In premenstrual women	In men and post-menopausal women
Normal uterine bleeding with inadequate nutrition	Long term aspirin and NSAID use
Abnormal uterine bleeding	Peptic ulcer disease
Thyroid disorders	H.pylori infection
Polycystic ovary syndrome	Esophageal and colonic cancer
Uterine fibroids	Celiac disease
Hyperprolactinemia	Gastric antral ectasia
Endometrial hyperplasia	Bacterial overgrowth
Drugs such as anti-psychotics and anti-epileptics	Gastrectomy, intestinal resection
	Angio dysplasias

Table 2 - Causes of Iron Deficiency Anemia[4,5]

Screening of patients for iron deficiency[6-8]

1. Screening during pregnancy (C)
2. Children at one year of age (C)
3. Men and post menopausal women need not be screened but may be evaluated when iron deficiency anemia is present (C)
4. Screening for celiac disease in adults with IDA (C)
5. CDC recommends screening of children from low income families at 9 and 12 months of age.
6. CDD recommends screening of preterm and low birth weight babies before six months of age
7. A meta analysis has shown that in neonates in whom cord clamping was delayed for up to two minutes after birth, there was a diminished risk of low iron stores in these infants up to six months.
8. Babies breastfed exclusively for beyond four months and weaning without iron fortified formulas need to be screened.

Diagnosis

WHO criteria[3]

Anemia is defined as a hemoglobin concentration below 13g/dl in men over 15 years; below 12 g/dl for non pregnant women over 15 years, and below 11g/dl in pregnant women. In pregnancy hemoglobin level less than 11g/dl in first or third trimester, or less than 10.5 g/dl in second trimester is considered as anemia. A maternal hemoglobin less than 6g/dl has been associated with poor fetal outcome including death.

Hemoglobin levels may vary according to age, race, smoking status, people living in higher altitudes and participants in endurance sports. The age related variation in hemoglobin and mean corpuscular volume (MCV) is represented in Table 3.

Diagnosis of iron deficiency anemia[7]

One of the simple and informative tests in the diagnosis of anemia is the complete blood count. It can be used to determine the Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCV), and mean corpuscular

Age	Hemoglobin level		Mean corpuscular volume (MCV)	
	Mean (g/dl)	Diagnosis of anemia	Mean	Diagnosis of microcytosis
3-6 months	11.5	9.5	91	74
6-24 months	12	10.5	78	70
2-6 years	12.5	11.5	81	75
6-12 years	13.5	11.5	86	77
12-20 years female	14.0	12	90	78
12-20 years male	14.5	13	88	78
20-59 years		13.7	90	80
60 years and above		13.2	90	80

Table 3 - Age related variation in hemoglobin and MCV[9]

hemoglobin concentration (MCHC) all of which are reduced in IDA (microcytic, hypochromic RBCs). However, it should be noted that normocytic erythrocytes may be seen in upto 40% of patients with IDA. Hence iron deficiency should still be considered in all cases of anemia unless the MCV is more than 95fl, since at this level MCV has a sensitivity of 97.6%. It is not uncommon to find dual deficiency anemia (combination of IDA and macrocytosis) resulting from deficiency of multiple nutrients or use of some medications. In this condition, although MCV may normal,peripheral smear will reveal both micro and macrocytic RBCs. A wide red cell distribution width (RDW) should arouse a suspicion of IDA combined with macrocytic anemia.

The most accurate test for the diagnosis of iron deficiency anemia is serum ferritin level since it effectively reflects iron stores. Serum ferritin below 15ng/ml is diagnostic of IDA. Nevertheless, if the cut-off is increased to 30ng/ml the sensitivity increases from 25 to 92% while retaining a specificity of 98%. At this juncture, it should be mentioned that ferritin is also an acute phase reactant which can be elevated in chronic inflammatory states as well in certain

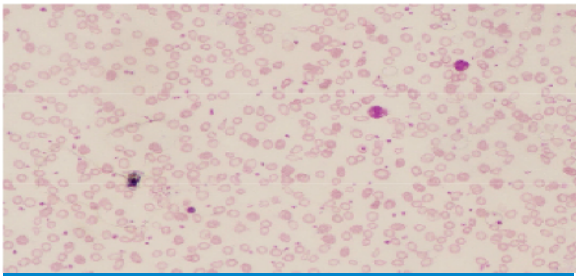


Fig 1 : Peripheral smear showing microcytic hypochromic RBCs

infections.Patients with chronic inflammation should be suspected of having iron deficiency anemia if their ferritin level is less than 50ng/ml, and in such patients ferritin level equal to or greater than 100ng/ml virtually excludes iron deficiency. Additionally, C-reactive protein measurements serve to confirm that raised ferritin level may be due to inflammation.

For patients with no inflammatory states and in whom ferritin level is indeterminate 31-99 ng/ml, further tests is warranted to determine the iron status. In iron deficiency, seum iron will be low, with increased TIBC (total iron binding capacity). Other tests of value include transferrin level,soluble transferrin receptor, erythrocyte protoporphyrin testing or bone marrow biopsy with iron staining.

Soluble transferrin receptor (sTfR) level is elevated only in IDA and is unaltered in inflammatory states, thereby identifying concomittant IDA in patients with chronic disease. sTfR and sTfR/log ferritin index (<1) can also be used.

The heme precursor RBC protoporphyrin accumulates in the absence of adequate iron stores. The gold standard in the diagnosis of IDA is the absence of stainable iron in bone marrow biopsy specimens.

Transferrin saturation (TfS) signifies the amount of iron available for erythropoeisis. A TfS below 20% and ferritin level below 30ng/ml are indicative of IDA. For example, in patients with inflammatory bowel disease, ferritin level less than 100ng/ml with TfS<30%; In chronic kidney disease, ferritin level less than 500ng/ml with TfS<30% and in congestive heart failure, ferritin level less than 100ng/ml with TfS<20% are indicative of iron deficiency.

	Key recommendations	Grade of recommendation
1	Anemia should be defined according to the lower limit of normal range of the concerned laboratory	B
2	Presence of iron deficiency should prompt investigation irrespective of the level of anemia.	B
3	A lower the hemoglobin level increases the likelihood of a serious underlying pathology	B
4	In the absence of chronic inflammation, infection or hemoglobinopathy RBC indices are reliable indicators of iron deficiency	A
5	Serum ferritin is the most useful test for IDA	A

Table 4 - Summary of key recommendations for iron deficiency anemia

Management[10]

Aim

After discovering any underlying cause, the aim of treatment should be to restore the hemoglobin concentration and RBC indices to normal, and replenish iron stores.

Iron therapy

Intestinal iron absorption is limited. Maximal absorption of oral iron is between 20 to 25% and is reached in the late stages of iron deficiency. Latent iron deficiency and iron deficiency anemia correspond to absorption rates of nearly 10% and 13% respectively. Healthy males and females absorb iron at the rate of 5% and 5-6% respectively.

Calculation of iron deficit

In iron deficiency, dose of iron required is calculated by certain formulae:

Ganzoni formula[11]:

Total iron deficit in mg =

[Body weight in kg x (target Hb - actual Hb in g/dl)] x 0.24]+ 500mg for body iron stores.

Patients with more severe anemia of Hb<7g/dl may need additional 500mg of elemental iron. Treatment of iron deficiency without anemia can be undertaken with 500-1000 mg of elemental iron. Iron deficit may be corrected either in the form of oral or intravenous iron therapy.

Poor compliance and non adherence to oral iron therapy are due to unpleasant dose dependent gastrointestinal side effects in nearly 50% of patients. Normal range of oral iron administration is between 100 to 200 mg of elemental iron per day, however IDA can be treated even with lower doses of 15-20 mg of elemental iron per day by oral administration, which may improve compliance. The GI effects of oral iron may be minimized by giving iron during meals, but the rate of absorption falls below 40%. Proton Pump inhibitors, chronic atrophic gastritis, vagotomy or recent gastrectomy reduce oral absorption. The different forms of oral iron, their formulations, content of

Form of Oral iron	Formulation	Elemental iron	Adult dose/day
Ferrous sulphate	325 mg tablet	65 mg	1 tablet thrice daily
Ferrous fumarate	324 mg tablet	106 mg	1 tablet twice daily
Ferrous gluconate	300 mg tablet	38 mg	2-3 tablets, 2-3 times a day
Dose in children: 3mg/kg/day up to 60mg/ day			

Table 5 - Oral iron therapy

elemental iron and dose in adults and children are summarized in Table 5.

Intravenous iron[12,13]

When uptake through the gut is impaired in conditions such as celiac disease, autoimmune gastritis, past gastric or duodenal resection, the efficacy of oral iron may be poor.Further, oral iron therapy may not be able to keep up with ongoing blood loss as in menorrhagia/ gastrointestinal bleeding, or in non-compliance with oral iron medication. Under these circumstances, intravenous iron is very effective. The main disadvantage of IV iron is its cost. Although safety of IV iron preparations has been a concern, a review by the US food and drug administration database from 1998-2000 showed that the cumulative risk of adverse reactions by all IV formulations (except high molecular weight iron dextran) is quite low (1 in 200,000). Intravenous formulations are solutions for infusion, and dose is based on the patient's weight and expected change in hemoglobin level. The various preparations of IV iron available are shown in Table 5.

IV iron formulation	Iron concentration
Sodium ferric gluconate	12.5 mg/ml
Iron dextran	50 mg/ml
Iron sucrose	20 mg/ml
Ferumoxytol	30mg/ml
Ferric carboxy maltose	50 mg/ml

Table 6 - Intravenous iron formulations

Blood transfusion in IDA[14-16]

1. Patient's clinical condition and symptoms should determine whether there is a need for blood transfusion, since there are no established guidelines on the level of hemoglobin below which transfusion is beneficial.

2. In pregnancy a hemoglobin less than 6g/dl warrants transfusion as there may be resultant abnormal fetal oxygenation with fetal distress, reduced amniotic fluid volume, fetal cerebral vasodilation and consequent fetal death.

3. In the event of transfusion, 2 units of packed RBCs should be given initially and later clinical scenario should be assessed for further management.

4. Transfusion may be considered for patients have cardiovascular compromise due to active bleeding or myocardial injury, and as a last resort when other treatment modalities have failed.

5. In the presence of significant underlying cardiovascular disease, transfusionmay have to be done at higher levels of Hb(<8g/dl).

6. Intravenous iron should be supplemented whenever transfusions are given in order to prevent the need for subsequent transfusions.

Follow up and monitoring

The hemoglobin level raises by 2g/dl within 4-8 weeks of therapy., and depending on the severity of deficiency, normalization of hemoglobin may take up to 3 months, and further longer to replenish body iron stores. Therefore, another hemoglobin value should be obtained at 12 months. The first marker to increase in the first few weeks of transfusion is serum ferritin. However, it does not correlate with body iron stores and estimation of ferritin may be beneficial only 8-12 weeks after the end of treatment. On the other hand, iron overload should also be avoided in patient requiring recurrent transfusions, and this may be reflected by a TfS exceeding 50%. Patients who do not respond to IV iron therapy should be given Erythropoeitin stimulating agents in addition, and the target Hb should not exceed 12g/dl.

Conclusion

Iron deficiency anemia is one of the easily treatable causes of anemia. Early detection, evaluation for the underlying etiology, screening in the appropriate population at risk is essential. Initiation and continuation of treatment through various modalities including oral and intravenous iron as well as blood transfusions should be the mainstay of management.

Reference:

1) Short MW, Domagalski JE. Iron deficiency anemia: evaluation and management. Am Fam Physician. 2013;87(2):98-104.

2) Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Developing clinical guidelines. West J Med. 1999; 170(6):348-51,

3) WHO UNICEF UNU Iron deficiency anaemia: assessment, prevention and control, a guide for programme managers Geneva, World Health Organization, 2001.

4) Johnson-Wimbley TD, Graham DY. Diagnosis and management of iron deficiency anemia in the 21st century. Therap Adv Gastroenterol. 2011;4(3):177–84

5) B. Benoist, E. McLean, I. Egli, and M. Cogswell, Worldwide Prevalence of Anaemia 1993–2005: WHO Global Database on Anaemia, WHO, Geneva, Switzerland, 2008

6) Ioannou, G.N, Spector, J, Scott K, Rockey D.C. Prospective evaluation of a clinical guideline for the diagnosis and management of iron deficiency anemia. Am J Med.2002; 113(4), 281–7

7) Goddard AF, James MW, McIntyre AS, Scott BB, British Society of Gastronterology. Guidelines for the management of iron deficiency anaemia. Gut. 2011;60(10):1309–16.

8) Centers for Disease Control and Prevention Recommendations to prevent and control ID in the United States. MMWR. 1998;47:1–29

9) Robert D. Baker, Frank R. Greer Diagnosis and Prevention of Iron Deficiency and Iron-Deficiency Anemia in Infants and Young Children (0–3 Years of Age) The Committee on Nutrition Pediatrics. 2010; 126 (5): 1040-50

10) Ajmera, Akash V, Shastri, Ghanshyam S, Gajera, Mithil J, et al. Suboptimal Response to Ferrous Sulfate in Iron-Deficient Patients Taking Omeprazole American Journal of Therapeutics.2012; 19(3):185-9.

11) Ganzoni A. M. Intravenous iron-dextran: therapeutic and experimental possibilities. Schweizerische Medizinische Wochenschrift. 1970;100(7):301–3.

12) Maslovsky I. Intravenous iron in a primary-care clinic. Am J Hematol. 2005; 78(4):261–4

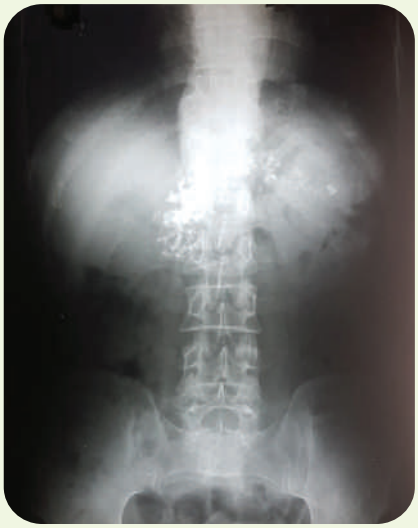
13) Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol. 2004; 76(1):74–8

14) Murphy MF, Wallington TB, Kelsey P, Boulton F, Bruce M, Cohen H et al. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the clinical use of red cell transfusions. Br J Haematol. 2001;113(1):24–31

15) Hebert PC, Wells G, Blajchman MA. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999; 340(6):409–17

16) Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK et al. Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2012;157(1):49–58

Image Challenge - 3



Clue: 27 year old lady with diabetes whose sugars were highly fluctuant

- Answer in page : 94

Review Article

Acquired Hemoglobin Disorders

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Chettinad Health City Medical Journal 2017; 6(2): 77 - 79

Abstract

Hemoglobin is made of Heme and globin and disorders of hemoglobin can be due to abnormality in either one of them. More than 1000 genetic mutations have been identified to cause hemoglobin disorders. Mutations can affect heme molecule and cause disorders like Methemoglobinemia. Mutations affecting globin chains are called Hemoglobinopathies and can be quantitative (thalassemia) or qualitative (sickle cell Anemia) .Hemoglobin disorders are mostly inherited and only a few are acquired. In this article we discuss about the structure of heme and globin molecules, abnormalities that can occur in them and review about Acquired Heme and Globin disorders. Acquired heme disorders are Methemoglobinemia and Sulfhemoglobinemia and an example for acquired globin disorder is alpha thalassemia.

Key Words: Acquired hemoglobin disorder, Methemoglobinemia, α Thalassemia, Sulfhemoglobinemia, Myelodysplastic syndrome

Introduction

Hemoglobin is a spherical molecule present within RBC and is made of 4 heme and 4 globin chains and it carries oxygen.

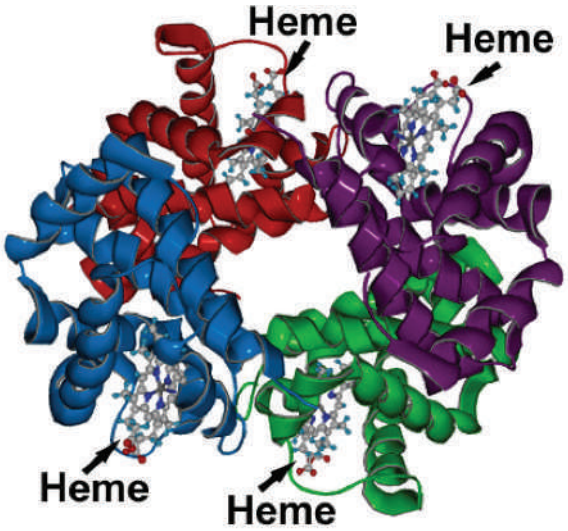

Fig 1 : Structure of Hemoglobin (Figure Courtesy Wikipedia)

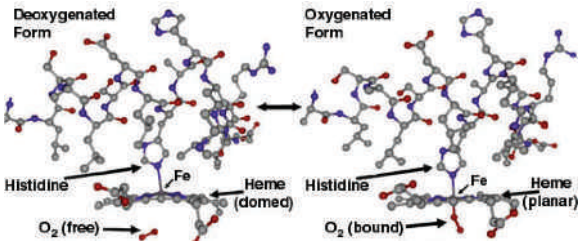

Fig 2 : Binding of iron with O2 and globin chains

Each heme has 1 iron in the center of protoporphyrin. This iron attaches to Oxygen (O_2) on one side and to globin chain on the other side through the histidine aminoacid of the globin chain. Each iron binds to 1 molecule of oxygen, so 1 hemoglobin molecule can carry 4 molecules of Oxygen. This binding of iron with oxygen is reversible.

Abnormalities that can occur in Heme Molecule

Heme exists in 2 states, Oxy state also called R state (Relaxed State) when iron binds with Oxygen and Deoxy state also called T state (Tense State) when iron gives up oxygen[1]. Iron in heme exists normally as ferrous form. When oxygen attaches to the ferrous iron of 1 heme group, conformational change occurs in the surrounding globin chains. This change in shape makes it easier for the other three heme groups to become oxygenated. This enhancement in the ability of hemoglobin molecule to bind more oxygen is called "cooperative binding"[1]. But if ferrous form is converted to ferric form it results in methemoglobinemia where oxygen affinity is altered leading to poor oxygen delivery to tissues. Similarly when sulfur binds to heme and produces sulfated heme, oxygen affinity is altered.

Abnormalities that can occur in Globin chains

Normal hemoglobin has 4 globin chains in the form of a tetramer. There are 4 different globin chains alpha, beta, gamma and delta. A tetramer is formed by combination of 2 of these chains, in dimers. Normal adult hemoglobin (HbA) has 2 alpha and 2 beta chains ($\alpha_2\beta_2$), while fetal hemoglobin (HbF) has 2 alpha and 2 gamma chains ($\alpha_2\gamma_2$) and second adult type (HbA2) has 2 alpha and 2 delta chains ($\alpha_2\delta_2$). A tetramer formed of such a dimer combination makes it more stable. But when a tetramer is formed of 4 monomers

of same chain called homotetramer as in Thalassemias, the tetramer becomes unstable and forms inclusions within RBCs.

Also, synthesis of globin chains is controlled by multigene clusters. Multigene clusters in chromosome 16 control alpha chain synthesis and multigene clusters in chromosome 11 control beta chain synthesis. In addition, there are also regulator genes which control the expression of these globin genes. Mutations in these multigene clusters or in the regulator genes cause thalassemia. Thalassemia occurs because of quantitative defects in globin chains. Thalassemias can be alpha or beta thalassemia. Mutations causing beta thalassemia are mostly point mutation while mutations causing alpha thalassemia are mostly deletion mutations[2].

Acquired Heme disorders

Under this we discuss Methemoglobinemia and Sulfhemoglobinemia

Methemoglobinemia

It is a disorder in heme molecule. In this disorder, ferrous form (Fe2+) of iron is oxidised to ferric form (Fe3+) and Hemoglobin becomes Methemoglobin. When iron in one of the four heme molecules is converted to ferric form, certain conformational changes occur in the heme group increasing the affinity of the remaining heme for Oxygen. So they bind more O2 and also do not give O2 to tissues causing tissue hypoxia. Methemoglobin thus formed gives a slate grey colour to the blood and resembles cyanosis (Pseudo cyanosis).

Normal Methemoglobin level is 0 - 2%. When methemoglobin level is > 10%, there is cyanosis and when levels go > 30% it leads onto cerebral and cardiovascular hypoxic symptoms. These hypoxic symptoms and cyanosis also do not respond to supplemental oxygen. Though these patients are cyanotic, Oxygen saturation (SaO2) and Partial pressure of Oxygen (PaO2) are normal, this is the most important clue for differentiating from other causes of cyanosis. Methemoglobin is best diagnosed by spectrophotometer and gas chromatography. Methylene blue by reducing ferric iron to ferrous iron is the treatment of choice.

But not all patients with Methemoglobinemia respond to treatment with Methylene blue. Methemoglobinemia can be congenital or acquired. Congenital Methemoglobinemia is a rare autosomal recessive disorder occurring due to mutation in gene controlling the production of Nicotinamide Adenine Dinucleotide Hydrogen (NADH) Cytochrome b5 reductase enzyme (the enzyme which helps in reducing Ferric iron to ferrous iron)causing a deficiency in this enzyme[3]. This congenital form does not respond to treatment with Methylene blue.

On the other hand, Acquired Methemoglobinemia is a more common disorder. This occurs on exposure to oxidising agents present in drugs or toxins. Common drugs causing it are Sulphonamides, Sulphasalazine, Dapsone, Chloroquine, Primaquine, Nitroglycerine, Phenytoin and Sodium valproate . These drugs oxidize the ferrous form to ferric form producing Methemoglobin. Such hemoglobin also becomes denatured and form inclusions within RBC called Heinz bodies. This leads to hemolysis. Methemoglobinemia also can occur in sepsis where Nitric Oxide (Oxidising agent) levels are high. Acquired methemoglobinemia responds to treatment with Methylene blue. Methylene blue absorbs the O2 attached to Ferric form and the Nicotinamide Adenine Dinucleotide Dehydrogenase (NADH) present within RBC reduces Ferric to ferrous form of iron. So NADH is required for the conversion. Dextrose infusion is also given for increasing NADH production within RBC through Glycolytic pathway[3].

Sulfhemoglobinemia

This is also a heme disorder. Here sulfur atom is incorporated into protoporphyrin ring forming sulfated heme. Once formed, sulfated hemoglobin persists throughout the RBC life span and this conversion is irreversible. This creates a conformation change in the other heme molecules decreasing their oxygen affinity. This is unlike methemoglobinemia where there is marked increase in O2 affinity.

Sulfhemoglobinemia is less common, milder and less symptomatic disease than methemoglobinemia but the cyanosis colour is bluer[4]. This occurs commonly with exposure to sulpha drugs and environmental pollution. In some it occurs in combination with methemoglobinemia and is called sulfmethemoglobinemia. This occurs because many oxidising agents causing methemoglobinemia have sulfur atoms and sulfur also get incorporated. This combination is less toxic than pure methemoglobinemia as the O2 affinity is less and so oxygen delivery to tissues is facilitated. Normally, the bluish discolouration with sulfhemoglobinemia occurs when sulfhemoglobinemia level is > 0.5 gm%. Level required by Methemoglobin to produce similar cyanosis is > 1.5 gm % and for deoxyhemoglobin to produce is > 5 gm%. Like Methemoglobinemia, Sulfhemoglobinemia is also diagnosed by spectrophotometer or gas chromatography. No specific treatment is available as sulfur binds to heme irreversibly and levels will fall only with the death of the affected RBCs[4].

Acquired Globin disorders

Here we discuss about 2 acquired alpha thalassemias namely Alpha Thalassemia with Mental Retardation (ATR) and Alpha Thalassemia associated with Myelodysplastic Syndrome (ATMDS)

Introduction to Thalassemia

Thalassemias are genetic disorders occurring due to deficiency of globin chains and are generally inherited. Alpha thalassemia occurs due to deficiency or absence of alpha chains & beta thalassemia occurs due to deficiency or absence of beta globin chains. 4 genes in chromosome 16 control the production of the 2 alpha chains of which 2 genes are from maternal side and 2 from paternal side. Also, of the 2 genes in chromosome 11 which control the production of the 2 beta chains, 1 gene comes from each parent.

Beta thalassemias are of 2 types - beta thalassemia major (when both beta genes are affected) and beta thalassemia minor (when one beta gene is affected). Alpha thalassemias are of 4 types. When 1 of the 4 alpha genes is affected it is called α+ thalassemia, when 2 alpha genes are affected it is called αo thalassemia. When 3 alpha genes are affected its HbH disease and when all 4 alpha genes are affected it is called Hb Bart's. In Hb H, the remaining globin chains are beta while in Hb Bart's, all 4 globin chains are γ type (γ tetramer) and γ chains have high affinity for oxygen and so fetus develops hypoxia, hydrops fetalis occurs and the condition is incompatible with life. All these thalassemias are congenital.

Acquired Alpha Thalassemia (also called acquired Hb H disease)

While thalassemias are nearly always inherited, it can also be rarely acquired. Most of the acquired alpha thalassemia develops in patients with Myelodysplastic syndrome (MDS) and a few have been reported in patients with aplastic anemia. Such acquired mutations can occur in the alpha gene clusters or other in the regulatory genes which control the expression of alpha globin chains. 2 regulator genes have been found , one called HS - 40 (Hypersensitive Site - 40), present in the same chromosome 16 as alpha globin gene clusters but present more upstream and the other ATRX gene (Alpha Thalassemia mental Retardation X - linked gene) present in the X chromosome[5].

Alpha Thalassemia associated with Mental Retardation (ATR)

This occurs due to an acquired mutation in ATR – 16 gene (mutation in chromosome 16) or in ATR - X gene (mutation in X chromosome)[6]. The affected children with any of these 2 mutations have alpha thalassemia with mental retardation and facial abnormalities. ATR – X gene phenotype are all male. They might also have cardiac, renal, skeletal and genital abnormalities[6].

Alpha thalassemia associated with Myelodysplastic Syndrome (ATMDS)

This also occurs due to mutation in ATRX gene. Certain MDS patients develop this mutation causing alpha thalassemia. When alpha thalassemia develops in MDS patients, the usual peripheral smear picture of MDS changes from predominantly macrocytic RBC to microcytic hypochromic RBC[7]. In addition HbH inclusions also develop within RBCs. As mutation is in ATR- X gene, these MDS patients are mostly Males and their median age of onset is 68 years. When MDS transforms into leukemia these thalassemic RBCs disappear.

Conclusion

Few diseases which we think can only be congenital, can also occur be acquired. Site of mutation can be different but the phenotype resembles the inherited ones. Among the acquired globin disorder, alpha thalassemia is well characterised and its occurrence with MDS is well documented.

References

1) Structural Biochemistry / Hemoglobin [Internet]. en.wikibooks.org. Available from: https://en.wikibooks.org/wiki/Structural_Biochemistry/Hemoglobin

2) Forget BG, Bunn HF. Classification of the Disorders of Hemoglobin. Cold Spring Harb Perspect Med. 2013;3(a01684):1–12.

3) Rehman HU. Methemoglobinemia. West J Med. 2001;175(3):193–6.

4) Constance M, Park RLN. Sulfhemoglobinemia. N Eng J Med. 1984;310(24):1579–84.

5) Steensma DP, Higgs DR, Fisher CA, Gibbons RJ. Acquired somatic ATRX mutations in myelodysplastic syndrome associated with α thalassemia (ATMDS) convey a more severe hematologic phenotype than germline ATRX mutations. Blood. 2004;103(6):2019–27.

6) Gibbons RJ. Alpha Thalassemia, Mental Retardation and Myelodysplastic Syndrome. Cold Spring Harb Perspect Med. 2012;2(a011759):1–15.

7) Steensma DP, Gibbons RJ, Higgs DR. Acquired alpha thalassemia in association with myelodysplastic syndrome and other hematologic malignancies. Blood. 2005;105(2):443–53.

Abstracts - Oral Papers

A Study on Correlation Between Serum Uric Acid Levels and Target Organ Damage In Hypertensive Patients

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Chettinad Health City Medical Journal 2017; 6(2): 80

Abstract

Introduction: Studies show that serum uric acid (SUA) plays a role in cardiovascular morbidity in general population as well in hypertensives, type2DM and cardiac or vascular diseases. Independent role of SUA as a risk factor is debate for decades. Pathophysiological mechanisms are cardiovascular damage at cellular and tissue level by proliferation of vascular smooth cells, stimulation of inflammatory pathway and possibly by platelet activation. SUA proved to be a better marker also for endothelial dysfunction.

Aims and Objectives: To evaluate the correlation between SUA and the presence of preclinical target organ damage in hypertensive population.

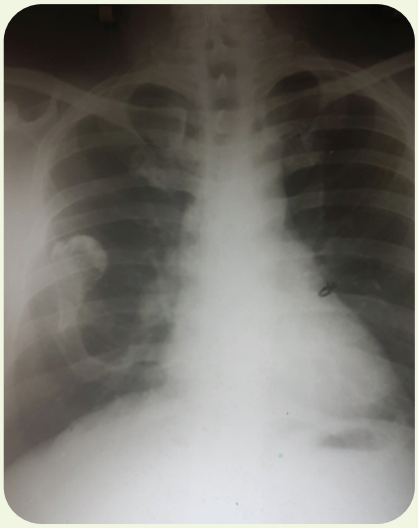
Materials and Methods: The study was conducted in 100 patients attending medicine outpatient department as a cross sectional study.Target organ damage was assessed by microalbuminuria (30-300mcg/mg creatinine) and fundus examination. Hyperuricemia was defined as SUA>7mg/dl in males and >6mg/dl in females. Statistical analysis was done using chi-square and two sample T test and data analysed by SPSS software.

Results: Microalbuminuria correlated significantly with serum uric acid level (p value <0.01) but retinopathy did not correlate significantly with serum uric acid (p=0.217)

Conclusion: Serum uric acid levels are related to target organ damage in hypertensive patients. Further studies are needed regarding benefit of uric acid lowering therapy in hypertension.

Key Words: Uric acid, Hypertension, Microalbuminuria

Image Challenge - 4



Clue: Patient came for a routine pre-employment check up

- Answer in page : 95

Study of Oral Glucose Tolerance Test in Chronic Liver Disease

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Chettinad Health City Medical Journal 2017; 6(2): 81

Abstract

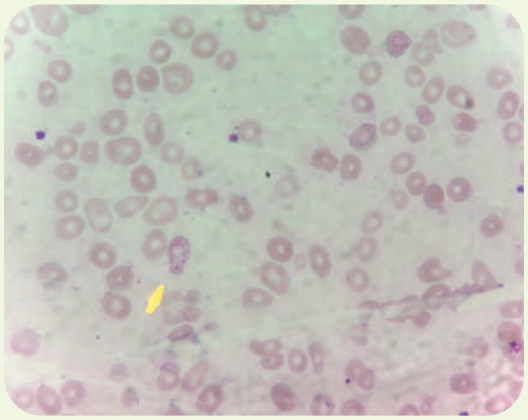
Introduction: The liver plays a key role in blood glucose control. In presence of cirrhosis of liver, the metabolic homeostasis of glucose is impaired. Diabetes mellitus in cirrhosis may be subclinical, since fasting glucose may be normal. Hence post-prandial blood glucose level by oral glucose tolerance test may be a simple indicator of liver disease.

Materials and Methods: 50 patients with cirrhosis of liver were included in this study, after getting informed consent. Diabetics, pregnant women, drugs and diseases causing hyperglycemia were excluded. OGTT was performed and correlated with Child Pughs scoring system.

Results and Conclusion: In this study of OGTT in chronic liver disease, diabetes mellitus was detected in 8% of patients -hepatogenous diabetes; and impaired glucose tolerance in 40%, thus showing abnormal glucose homeostasis in 48% of patients overall. Impaired glucose tolerance was seen in 77% of patients in Child Pughs category B. This indicates that as the liver disease advances, diabetes becomes clinically manifest. Hepatogenous diabetes can be considered as a marker for liver function deterioration. Hence in patients having advanced chronic liver disease (Child Pughs category B), OGTT may be done to assess the severity of liver disease.

Key words: Chronic liver disease, Glucose homeostasis, Oral glucose tolerance test, Child-Pugh score

Image Challenge - 5



Clue: Identify the abnormality on the peripheral smear

- Answer in page : 96

A Study of Serum Iron and Serum Ferritin Levels in Chronic Renal Failure

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Chettinad Health City Medical Journal 2017; 6(2): 82

Abstract

Objective: Aim of this study was to observe serum iron and serum ferritin levels in patients with chronic renal failure.

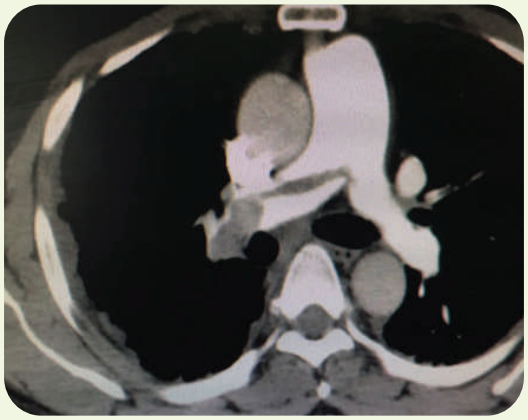
Methods: 50 patients with chronic renal failure were selected for study, irrespective of their age, sex, clinical profile and etiology, and they were subjected to serum iron and serum ferritin levels.

Results: In this study 14 (28%) patients had serum iron levels less than the lower limit of normal range among which 11(22%) were males and 3(6%) were females. 12 (24%) patients had serum ferritin levels less than the lower limit of normal of which 6 patients were on hemodialysis. The mean serum iron for the 29 patients on oral iron supplementation was 58.76 mcg/dL, whereas the mean serum iron for the 21 patients on IV Iron supplementation was 68.38 mcg/dL.The mean serum ferritin for the 29 patients on oral iron supplementation was 118.34 ng/ml whereas the mean serum ferritin for the 21 patients on IV iron supplementation was 311.76 ng/ml.

Conclusion: Intravenous iron supplementation was found to be more beneficial than the oral iron supplementation in all CRF patients irrespective of whether the patient was on hemodialysis or on medical management, in treating iron deficiency associated with anemia of chronic renal failure.

Key words: Chronic kidney disease, Iron, Ferritin

Image Challenge - 6



Clue: Elderly male with sudden onset of dyspnea in the background of significant weight and appetite loss.

- Answer in page : 87

A Study on Serum Magnesium Levels and Its Correlation With Microvascular Complications In Type 2 Diabetes Mellitus

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Chettinad Health City Medical Journal 2017; 6(2): 83

Abstract

Introduction: Diabetes mellitus is a metabolic disorder which results from defect in insulin secretion or action and leads to several micro and macrovascular complications. Minerals such as magnesium play an essential role in glucose homeostasis and low levels of serum magnesium have been found to be associated with micro and macrovascular complications in diabetes.

Aims and Objectives: To assess the level of serum magnesium levels in Type 2 DM patients and to correlate serum magnesium concentration with microvascular complications in Type 2 DM .

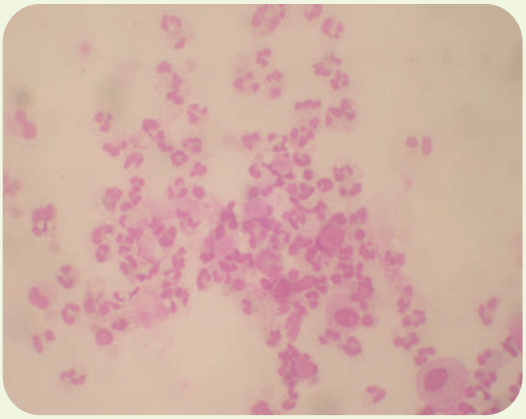
Materials and Methods: 105 patients presenting to the outpatient department or admitted in the general medicine ward were subjected to clinical examination and investigated for FBS,PPBS,HbA1C and serum magnesium levels. Microvascular complications were assessed using urine spot PCR for nephropathy, Toronto clinical scoring system for neuropathy and fundus examination for retinopathy. Statistical analysis was done using appropriate methods and p value<0.05 was considered statistically significant.

Results: Of the 105 patients included in the study, mean age was 56.92 years with 48.6% males and 51.4% females. Mean serum magnesium level was 1.965±0.177 mg/dl. Mean duration of diabetes was 8.53 years. Among the patients with low magnesium levels, 8.6% had diabetic retinopathy,15.2 % had diabetic neuropathy and 14.3% had diabetic nephropathy. Correlation between hypomagnesemia and all three microvascular complications were statistically significant (p<0.001).

Conclusion: Patients with longer duration of diabetes had low magnesium levels and hypomagnesemia was significantly associated with microvascular complications.

Key words: Diabetes, Magnesium levels, Microvascular complications, Macrovascular complications

Image Challenge - 7



Clue: A known case of SLE, came with progressive abdominal distension. Examination showed ascites. Paracentesis was done, and cytological examination of the ascitic fluid showed: Identify the abnormal cell.

- Answer in page : 88

Case Series of Unusual Presentations of Tuberculosis

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Chettinad Health City Medical Journal 2017; 6(2): 84

Abstract

Introduction: Tuberculosis is a multisystem disease with numerous complications. We hereby present four cases of unusual presentations and complications of tuberculosis that presented to our institute.

Case profiles:

1) 50-year-old male presented with fever, lymphadenopathy and cough. Radiological evaluation showed features of lung secondaries with primary focus in liver. Biopsy was suggestive of nonspecific granulomatous disease with pleural fluid analysis suggestive of Tuberculosis. Patient treated with antituberculous (ATT) drugs and had resolution of lesions

2) 24-year-old male diagnosed as sputum positive Tuberculosis outside developed transverse myelitis secondary to tuberculosis. Treated with Methylprednisolone and switched to oral steroids with continuation of ATT. Patient had resolution with regain of normal function.

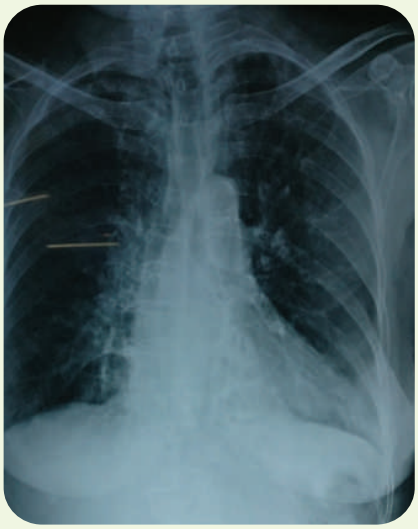
3) 19-year-old male presented with fever of one-month duration and bilateral ankle and knee arthritis and effusion came to our institute with right pleuritic pain. Pleural fluid analysed and diagnosed as TB with rheumatological manifestations - Poncets Disease after thorough work up. He was started on ATT and oral steroids and complaints resolved.

4) 45-year-old male presented with acute respiratory distress on ventilator support for 3 weeks in outside hospital. He was diagnosed as pulmonary tuberculosis by bronchoscopy, started on ATT and weaned off ventilator.

Conclusion: Tuberculosis has a wide spectrum of organ involvement and the presentation is not always straight-forward. High degree of suspicion and thorough work up is required to diagnose tuberculosis. Judicious and appropriate use of steroids is indicated in complications due to tuberculosis.

Key words: Tuberculosis, Unusual presentation, ARDS, Poncets disease, Transverse myelitis

Image Challenge - 8



Clue: 75 year old lady with clinical features suggestive of bronchiectasis

- Answer in page : 89

A Cross Sectional Study of Cardiovascular Changes in Chronic Liver Disease

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Chettinad Health City Medical Journal 2017; 6(2): 85

Abstract

Introduction and aims: Cirrhosis is associated with several hemodynamic changes like hyperdynamic circulation, increased cardiac output, increased heart rate and decreased systemic vascular resistance which are collectively called cirrhotic cardiomyopathy. The measurement of circulating levels of cardiac biomarkers may aid in the diagnosis. Early diagnosis and management of cirrhotic cardiomyopathy is essential to reduce morbidity. The aim of this study was to evaluate the cardiac biomarkers in CLD, and correlate them with severity of liver disease.

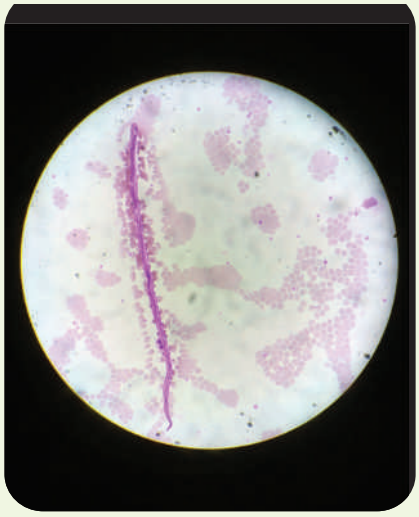
Study Design: 50 adult patients diagnosed with chronic liver disease were subjected to detailed history, examination, preliminary tests, and cardiac markers namely Troponin I, CKMB and NT pro BNP were performed. The Child Pugh and MELD scoring were done in these patients to assess the liver disease severity and compared with the cardiac markers.

Results: Mean age was 46.48 years, 84% subjects were male and 68% had history of alcohol intake. Troponin I was elevated in 24% of study subjects. There was a positive correlation between troponin I and increasing severity of liver disease as evidenced by Child Pugh score ($p< 0.001$) and MELD ($p= 0.015$). NT pro BNP levels also showed a statistically significant positive correlation with severity of the liver disease.

Conclusion: Troponin I proved to be a significant marker of myocardial injury in chronic liver disease patients. Elevated NT pro BNP may probably be due to fluid overload state related to liver disease. Therefore patient needs close monitoring for myocardial injury as there is demonstrable rise in cardiac markers with increasing severity of liver disease.

Key words: Chronic liver disease, Cardiac biomarkers, Child Pugh score, MELD score

Image Challenge - 9



Clue: 22 Year old lady presented with fever with rigors. What is the abnormality in Peripheral smear?

- Answer in page : 91

A Comparative Study of Knowledge and Awareness about Dietary Modifications in Kidney Disease Among Medical Interns and Final Year Undergraduates

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Chettinad Health City Medical Journal 2017; 6(2): 86

Abstract

Introduction : Dietary factors may have an effect on the progression of kidney disease and its complications. Among CKD patients, over-nutrition results in sodium and volume overload, hyperkalemia, hyperphosphatemia, and accumulation of toxic metabolites of protein degradation. Under-nutrition, on the other hand, exacerbates the risk for malnutrition and wasting. Appropriate dietary interventions may have an effect on clinical outcomes in the CKD population and awareness regarding this is essential right from the undergraduate level.

Aims and Objectives: To assess the knowledge about dietary modification in kidney disease among the medical interns and final year undergraduates.

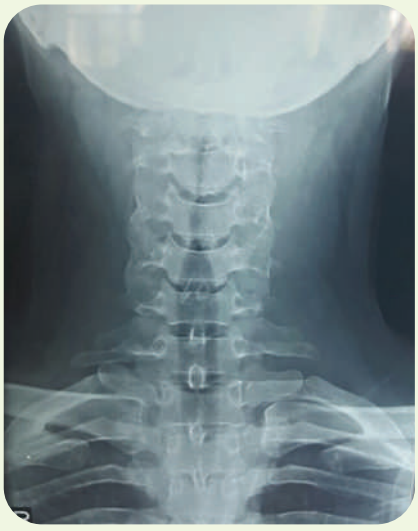
Methodology: 100 interns and 100 final year undergraduates from a university teaching hospital in semi-urban South India were given a set of questions related to dietary modifications in kidney disease patients. Each individual's score was calculated and the total mean score of 100 interns and 100 final year undergraduates was taken. The scores of both interns and final year undergraduates were compared using appropriate statistical methods. Performance in each question was also individually assessed.

Results: The mean score of final year Under Graduates was 48.12% whereas mean score of interns was 60.71% (p value 0.24). There was no statistically significant difference overall.However the knowledge about individual questions in the questionnaire varied between the two groups. The interns had better knowledge about the type of protein intake ($p<0.001$) and awareness of salt restriction tended to be more among interns ($p=0.07$). However undergraduates seemed to have better knowledge regarding dietary modifications for CKD related bone disease.

Conclusion: The overall knowledge between the two groups was similar and there is a definite need for improving the knowledge about dietary modification in kidney disease. Focused teaching may help in practical application of theoretical knowledge.

Key words: Chronic kidney disease, Dietary modifications, Knowledge, Undergraduates, Interns

Image Challenge - 10



Clue: 24 year old male came with breathlessness after consuming sea food

- Answer in page : 90

Prevalence of Rheumatological Disorders in Diabetes Mellitus

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Chettinad Health City Medical Journal 2017; 6(2): 87

Abstract

Introduction : Diabetes mellitus is associated with several musculoskeletal manifestations. We intended to study the most common rheumatological manifestations in our study group.

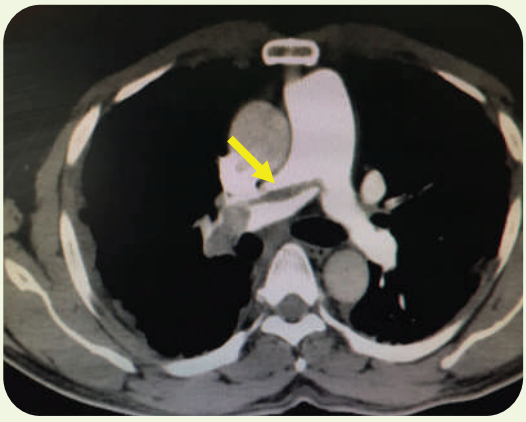
Materials and Methods: It is a cross sectional observational study for a period of 15 months. 174 out patients and stable in patients aged over 18 yrs, known diabetics were included in the study. Patients with renal osteodystrophy, rheumatoid arthritis, secondary osteoarthritis, history of trauma related musculoskeletal deformities and who have undergone surgery for musculoskeletal deformities were excluded.

Results: Of the 174 patients studied, age was less than 50 years in 78 patients (44.8%). Male population was 60 (34.5%). Duration of diabetes was less than 5 years in 36 patients (20.7%). Osteoarthritis was found in 77 patients predominantly involving knee (44.30%), periarthritis shoulder was present in 44 cases (25.3%), neuroarthropathy was found in 29 cases (16.66%), Diffuse idiopathic skeletal hyperostosis (DISH) was found in 11 patients (6.3%), chieroarthropathy was found in 1 case (0.5%), others included cervical spondylosis and lumbar spondylosis induced restricted mobility.

Conclusion: Several rheumatic conditions are more prevalent or caused by the long term metabolic consequences of diabetes mellitus. Poor glycemic control and increased BMI had an adverse effect on the incidence of musculoskeletal disorders.

Key words: Diabetes, Rheumatological Manifestations, Periarthritis, DISH

Image Challenge - 6



Answer: Filling defect in the Right main pulmonary artery - pulmonary embolism secondary to gastric adenocarcinoma

Prevalence of Dilated Cardiomyopathy in Chronic Alcoholics: A Prospective Study

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Chettinad Health City Medical Journal 2017; 6(2): 88

Abstract

Introduction : The incidence of dilated cardiomyopathy appears to be increasing and is associated with significant morbidity and mortality. The aim of this study was to determine the prevalence of dilated cardiomyopathy in chronic alcoholics.

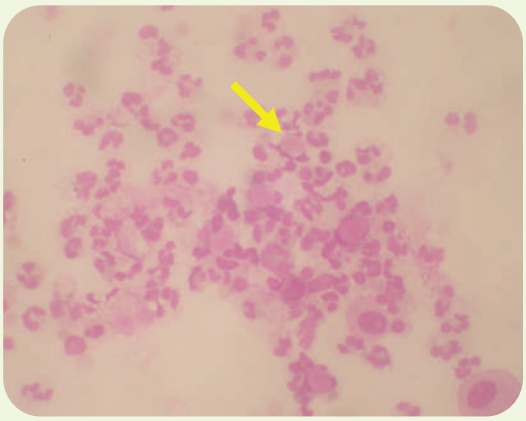
Materials and Methods: 50 patients who were fulfilling the inclusion and exclusion criteria were evaluated by history,physical examination, ECG and Echocardiography.

Results: Out of 50 chronic alcoholics studied, 10 patients were found to have dilated cardiomyopathy. Out of these 10 patients, 8 were found to have cardiac failure, 8 were found to have atrioventricular valvular regurgitation. Conduction disturbances were noted in most of the cases. Patients in the age group of 50 to 60 years who were chronic alcoholics showed high prevalence of dilated cardiomyopathy.

Conclusion: In this study it was observed that 20 % of patients who consumed alcohol regularly for a period of more than 20 years were found to have dilated cardiomyopathy.

Key words: Alcohol, Dilated cardiomyopathy, Prevalence

Image Challenge - 7



Answer: LE cells in the ascitic fluid

A Study of the Incidence and Factors Associated with Bleeding in Critically Ill Medical Patients on Pharmacological Prophylaxis for DVT.

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Chettinad Health City Medical Journal 2017; 6(2): 89

Abstract

Introduction : Deep vein thrombosis is a frequent cause of preventable illness and death in hospitalized patients.

Aim: Aim was to study the incidence of bleeding in critically ill patients receiving anticoagulation for DVT and identify factors associated with bleeding.

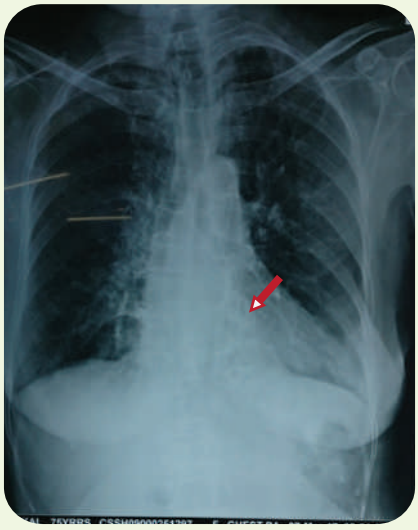
Methods: This study included 490 patients admitted in critical care receiving DVT prophylaxis. Patients requiring therapeutic heparin, pregnant women and patients at risk for bleeding diathesis were excluded. Patients were followed up throughout the course of hospitalization; investigations, treatment and clinical course including complications were recorded. Outcome was categorized as presence or absence of bleeding. These patients were further analyzed for identification of risk factors.

Results: The study included 490 patients, 282 males and 208 females. The incidence of bleeding in critically ill medical patients on prophylaxis for DVT was 5.9% (29 patients). Incidence of major bleeding was 1.6% and that of minor bleeding was 4.3%. The incidence of bleeding in study population receiving enoxaparin was 5.8% and those receiving unfractionated heparin was 7.3%. Bleeding along with other causes such as sepsis, shock, multi organ dysfunction syndrome [MODS] and CAD were major contributors of death in these patients. Risk factors for bleeding with anticoagulant therapy include older age, female sex, anemia, diabetes, hypertension, presence of cancer, alcoholism, prior stroke/intracerebral hemorrhage, concomitant use of antiplatelets, NSAIDs, steroids.

Conclusion: The incidence of bleeding in critically ill medical patients on DVT prophylaxis was 5.9% and patients with identified risk factors need to be monitored closely for bleeding, in order to reduce mortality.

Key words: Bleeding, DVT prophylaxis, Heparin, Critically-ill patients

Image Challenge - 8



Answer: Retrocardiac collapse with bronchiectasis

Study of Lipid Profile In Anemia

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Chettinad Health City Medical Journal 2017; 6(2): 90

Abstract

Introduction : Anemia is reported to be associated with lowering in all lipid sub-fractions. The study was conducted to study the clinical features of anemia, effect of anemia on lipid profile & effect of severity and type of anemia on lipid profile.

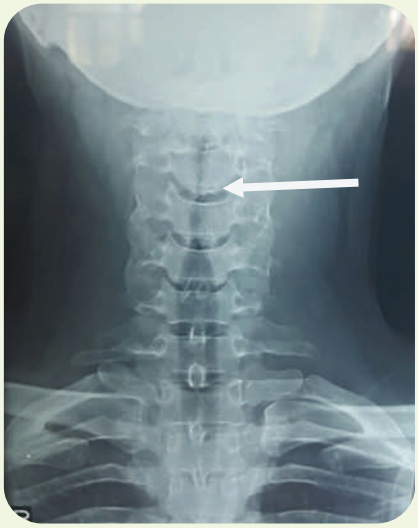
Methods: The data for this study was collected from patients who presented to VMMC Hospital. 100 anaemic and 100 non-anaemic age and sex matched controls underwent clinical assessment and relevant investigations including lipid profile estimation.

Results: Cases younger than 50 years were found to be more likely to have severe anemia. Fatigue and pallor were the most common clinical features. The mean total cholesterol (132.2 ± 29.0 vs 173.4 ± 20.3, P<0.01), HDL (31.0 ± 6.7 vs 38.8 ± 7.1, P<0.01), LDL (79.7 ± 25.0 vs 110.1 ± 16.6, P<0.01), VLDL (21.6 ± 6.3 vs 24.5 ± 6.2, P<0.01) and Triglyceride (108.1 ± 31.3 vs 122.5 ± 30.6, P<0.01) levels, along with TC/HDL (4.4 ± 0.8 vs 4.6 ± 0.7, P<0.05) and LDL/HDL (2.6 ± 0.7 vs 2.9 ± 0.6, P<0.01) ratios were significantly decreased in cases compared to controls. There was a larger reduction in mean total cholesterol, HDL, LDL, VLDL and triglyceride levels, along with TC/HDL and LDL/HDL ratios with increasing severity of anemia (P<0.05). Type of anemia did not have significant effect on the lipid levels (P>0.05).

Conclusion: Anemia is associated with significant hypocholesterolemia, with lowering in all lipid sub-fractions, the extent of hypocholesterolemia being proportional to severity of anemia. Further studies are required to study the long term effect of anemia on developing the risk of atherosclerosis, and effect of treatment of anemia on lipid levels and cardiovascular morbidity and mortality.

Key words: Anemia, Lipid profile, Hypocholesterolemia, Severity

Image Challenge - 10



Answer: "Steeple Sign" in airway edema

A Meta-Analysis to Assess the Effect of Vitamin D supplementation on level of Blood glucose in Prediabetes

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Chettinad Health City Medical Journal 2017; 6(2): 91

Abstract

Objective: To systematically review and Meta analyze the selected randomized controlled trials (RCT) on effect of vitamin D supplementation on level of fasting blood glucose in pre-diabetes

Methods: **Design:** Systematic review and meta-analysis of randomized controlled trials.

Data Sources: PubMed/MEDLINE, Science Direct, Indian Citation Index, International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/) to identify unpublished studies, Google Scholar, Grey Literature and hand search were used and selected the study on randomized controlled trail from inception to December 2016.

Eligibility criteria for study selection: The eligible studies were randomised/ double blind/placebo/controlled trials. Vitamin D in the form of D3 (Cholecalciferol) or D2(Ergocalciferol), supplemented alone or in combination with calcium; dose and duration of supplementation; reported serum 25(OH) D and Fasting Plasma Glucose at the beginning and end of the intervention were considered.

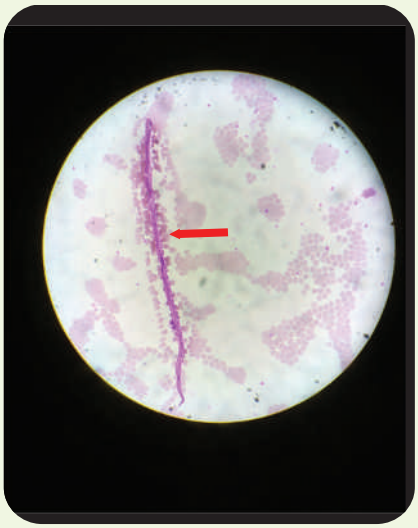
Data Extraction and Synthesis: Reviewer collected the data and assessed the quality of the study by using Jadad score. The standardized mean difference was derived to assess the effect of vitamin D supplementation on Fasting blood glucose. Random Effect Model was followed to assess the meta-analysis and represented in Forest plot for comparison of Vitamin D vs Placebo or without supplementation on Fasting blood glucose.

Results: Meta analysis of pooled data of 1828 subjects in 11 RCT was done. The pooled significant mean difference on effect of vitamin D supplementation on fasting blood glucose was -2.01mg/dl; (95%CI, -3.23 to -0.79; I2=97%). The results showed that there was a small improvement in fasting blood glucose among vitamin D group compared with placebo or control group.

Conclusion: Larger randomized controlled trials are needed to assess the effect of oral supplementation of cholecalciferol on blood glucose.

Key Words: Meta analysis, Vitamin D, Level of blood glucose, Prediabetes.

Image Challenge - 9



Answer: Microfilariasis

Role of BNP As A Screening Tool To Identify Asymptomatic Cardiac Disease In Type 2 Diabetic Patients

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Chettinad Health City Medical Journal 2017; 6(2): 92

Abstract

Introduction : Adults with diabetes have two to fourfold greater risk for dying from CVD compared to non-diabetics.Our objective of this study is how far BNP value will be useful in early detection of Left Ventricular Dysfunction (LVD) and ischemia without subjecting the patients to TMT and Echo.

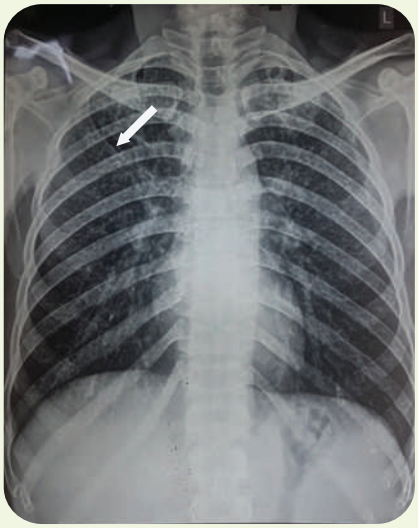
Materials and Methods: This study was conducted in the Department of Medicine VMMC,Karaikal. Total number of patients included in this study were 77.This study was a cross sectional study and aimed to assess the diagnostic role of serum BNP level in asymptomatic type 2 diabetic patients for LV dysfunction.

Results: Among 77 patients 28 had sub-clinical LVD identified by a 2D echo and in these patients NT pro BNP was performed. NT pro BNP (>600 pg/ml) could predict diastolic dysfunction at a sensitivity of 64 % and with a negative predictive value of 73% (p<0.001).Hence BNP could be used effectively as a screening tool to identify diastolic dysfunction.

Conclusion: We conclude that single measurement of NT pro BNP at the diabetic OPD can provide important information about their cardiac status.

Key words: BNP, Screening tool, LV dysfunction

Image Challenge - 1



Answer: Miliary Tuberculosis

Study of High Sensitivity C-Reactive Protein In Chronic Obstructive Pulmonary Disease Among Smokers

Raqib Abbas N*, Premnath V*, Chelluri Anil Kumar*, Sankar R N K*, Ganesan C**
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Chettinad Health City Medical Journal 2017; 6(2): 93

Abstract

Introduction : In patients with COPD, systemic inflammation, in addition to local airway inflammation, contributes to pulmonary and extra-pulmonary complications of the disease. Systemic inflammation can be determined with markers of inflammation such as hsCRP, interleukins and TNFα. Among these markers, hsCRP is as an important one. This study aims to evaluate the hsCRP in smokers with COPD.

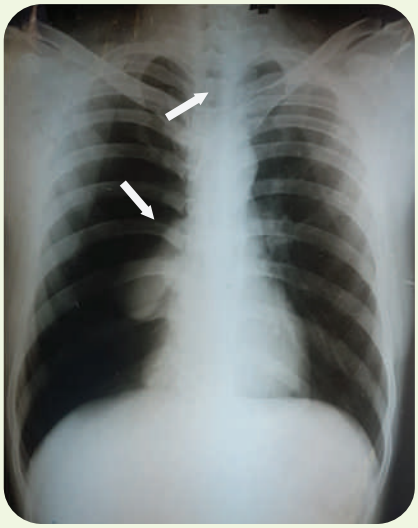
Materials and Methods: 80 cases were selected for the study after applying the inclusion and exclusion criteria. Pulmonary function test was done using the spirometer in the department of thoracic medicine and post bronchodilator values after 20 min of salbutamol nebulisation were recorded. Based on FEV1 % predicted value patients were classified into stages based on GOLD guidelines. The hs-CRP was measured by nephalometric method using the turbox analyzer. Other parameters such as BMI, ESR, polymorph percentage, pack years of smoking were recorded.

Results: Serum hsCRP levels were significantly higher in patients with COPD which correlated with pack years of smoking and stages of COPD according to GOLD criteria. FEV1 coef ESR= (-.1846), hsCRP= (-.2784) with significant p value <0.05.

Conclusion: Hs-CRP has been found to be significantly elevated with increasing severity of COPD. Polymorph percentages, ESR are not significant markers of inflammation in COPD. Physicians need to approach COPD as a multi system disease and identify patients with the associated co-morbidities of COPD vis-à-vis the extra pulmonary manifestations of COPD.

Key words: COPD, hs-CRP, ESR, Inflammatory markers

Image Challenge - 2



Answer: Right sided pneumothorax without mediastinal shift

Estimation of Prostate Specific Antigen in Metabolic Syndrome- A Study in South Indian Male Population

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Chettinad Health City Medical Journal 2017; 6(2): 94

Abstract

Introduction: Prostate specific antigen (PSA) is a protease that is produced by secretory epithelial cells lining the prostate ducts in response to androgen receptor activation. Interactions between body adiposity and steroid hormone metabolism, the inflammatory response, or insulin regulation, are sufficient to affect PSA expression.

Aim: The purpose of this study was to determine the role of prostate specific antigen in Indian males and to assess its correlation with insulin resistance in metabolic syndrome.

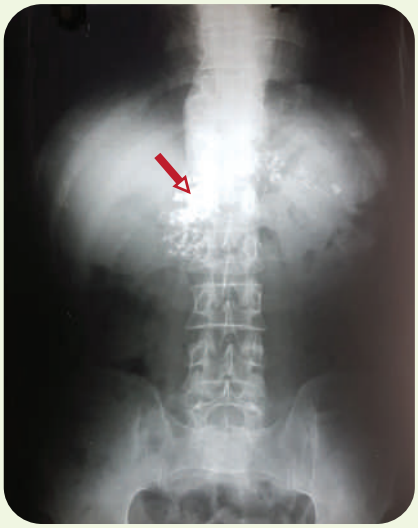
Materials and Methods: For this study, 62 male subjects of 40-65 years having metabolic syndrome were chosen. Body mass index, fasting blood sugar, serum prostate specific antigen, serum fasting insulin and insulin resistance were analyzed using multivariate regression analysis and ANOVA.

Results: There was no statistically significant difference between body mass index and prostate specific antigen, body mass index and insulin resistance, prostate specific antigen and triglyceride, prostate specific antigen and high density lipoprotein, and prostate specific antigen and fasting blood sugar.

Conclusion: There was no statistical significant difference between the various parameters like age, fasting blood sugar, triglyceride, high density lipoprotein, insulin levels and body mass index with PSA thereby indicating that there was no correlation between prostate specific antigen levels and metabolic syndrome.

Key words: Prostate specific antigen, Metabolic syndrome, South India

Image Challenge - 3



Answer: Calciific pancreatitis

Organophosphate Poisoning - Predictors of Requirement of Ventilator - A Prospective Study

Shameer Hakkim*, Nikil Sam Varghese*, Sheju Jonathan*, Muthukumaran **
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Chettinad Health City Medical Journal 2017; 6(2): 95

Abstract

Introduction : Acute Organophosphate (OP) poisoning is one of most frequent poisoning encountered in casualty in which majority of cases are suicidal attempts. The aim of this study was to determine the predictors of respiratory failure and ventilator requirement in patients with organophosphate poisoning

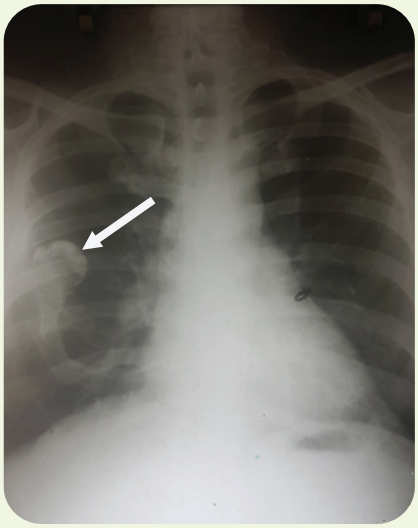
Material and Methods : 167 patients who were admitted with OP poisoning and fulfilling the inclusion and exclusion criteria were evaluated by physical examination and assessed on the requirement of ventilator support with ABG.

Results : Out of 167 patient enrolled in the study, 70 required assisted ventilation of which 35 patients required ventilator support within 24 hours of poisoning. 23 patients had complications of pneumonia and 12 had intermediate syndrome.

Conclusion : In this study, we found that greater time duration for institution of specific treatment, low level of sensorium at admission, grade 3 severity of poisoning, increased requirement of PAM, high initial atropine requirement for atropinization, presence of pneumonia and CVS collapse and low serum cholinesterase activity were predictors of respiratory failure.

Key words: Organophosphate poisoning, Respiratory failure, Ventilator, Risk factors

Image Challenge - 4



Answer: Exostosis of the rib

Validating the Fatty Liver Index For Prediction of Hepatic Steatosis in Patients Attending Tertiary Care Hospital in South India

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Chettinad Health City Medical Journal 2017; 6(2): 96

Abstract

Introduction : Non alcoholic fatty liver disesase(NAFLD) is the most common chronic liver disease in the western world and has now turned its expression towards the developing nations. The fatty liver index(FLI), which is an algorithm based on waist circumference, triglyceride, BMI and gamma-glutamyl-transferase(GGT), was initially developed in Italy to detect fatty liver, needs to be validated in our population.

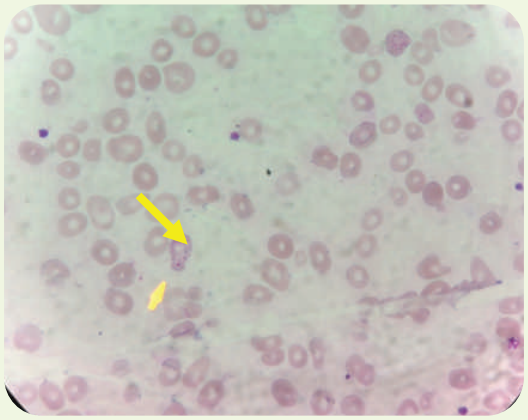
Materials and Methods: The case control study included 160 patients aged 18 to 75 years of age, attending medicine OP, ward and gastroenterology clinic. Anthropometric and biochemical features were collected by a standard protocol. NAFLD was diagnosed by abdominal ultrasonography.The accuracy and cut-off point of the FLI to detect NAFLD were evaluated by Area under the receiver operator characteristic curve (AUROC) and the maximum Youden index analysis respectively.

Results: AUROC of the FLI was 0.773(95% confidence interval:0.701-0.836) p<0.001, and its each individual component: waist circumference 0.772(0.698-0.834) p<0.01, BMI 0.757(0.683-0.821) p<0.001, triglyceride 0.518(0.438-0.598) p<0.694,and GGT 0.592(0.512-.066) p<0.038. The optimal cut-off point of the FLI for diagnosing NAFLD was 60 with maximal Youden Index of 0.41, achieving a sensitivity of 62.5% and a specificity of 78.7%. FLI diagnosed NAFLD patients had worse metabolic characteristics than USG diagnosed NAFLD patients.

Conclusion: FLI could accurately identify NAFLD in the studied population. Attention should be paid to the control of metabolic parameters in the management of NAFLD.

Key words: NAFLD, Fatty liver index, Prediction, Hepatic steatosis, South Indian

Image Challenge - 5



Answer: Basophilic stippling

Abstracts - Posters

An Unusual Case of Adrenal Mass Presenting as Ganglioneuroma

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Chettinad Health City Medical Journal 2017; 6(2): 97

Abstract

An adrenal mass can be found as a part of an evaluation for a specific complaint related to adrenal pathology or an incidental finding on imaging (incidentaloma). Most masses are either adenomas, malignantmetastasis, carcinoma or pheochromocytomas and hence warrant evaluation.

Our patient, a 29 year old male with nocomorbidities , presented with mild right hypochondrial pain for almost a year and acute gastroenteritis for 2 days.USG revealed a right suprarenal mass 12.7x 9 x12.2 cm.CECT Abdomen showed central necrosis and non visualization of the adrenal gland; features suggesting adrenal tumor ganglioneuroma/cortical carcinoma.Hormonal workup and 24 hour metanephrine test was normal.USG guided biopsy revealed ganglioneuroma. Patient was planned for adrenalectomy.

Adrenal ganglioneuromas are rare, hormonally silent tumors which can resemble malignancies.Careful evaluation by endocrine tests ,imaging and histological examination is essential for a definitive diagnosis.

Key words: Adrenal mass, Ganglioneuroma, Incidentaloma

A Case Report of Mixed Autoimmune Hemolytic Anaemia

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Chettinad Health City Medical Journal 2017; 6(2): 97

Abstract

Mixed autoimmune haemolytic anemia (AIHA) is defined by the presence of both warm and cold auto antibodies with incidence of approximately 0.2 per 100,000 in 11–20 years age group. We report a 15 year old girl who presented with easy fatiguability and breathlessness on exertion for 3 months. Clinically she had severe pallor, mild icterus and hepatosplenomegaly with direct coomb's test being positive for both IgG &IgM with complement C3d. Peripheral smear showed polychromasia and fragmented RBCs. Since all workup for secondary causes of mixed AIHA were found to be negative, she was diagnosed as idiopathic mixed AIHA. She responded well to short course of glucocorticoid therapy. We present this case for its rarity.

Key words: Mixed AIHA, Pediatric, Idiopathic

Rare Presentation of Melioidosis-Bilateral Pneumothorax with Pneumatoceles

Allen D'Silva*, Jayannan Jayasenan*, Vasanthi Natarajan**, Ali Karnam**, Ashok Kumar Das***,
* Postgraduate **Associate Professor ***Professor, Department of General Medicine, Pondicherry Institute of Medical Sciences, Pondicherry, India.

Corresponding author - Allen D'Silva (allendsilva04@gmail.com)

Chettinad Health City Medical Journal 2017; 6(2): 98

Abstract

Melioidosis is a life threatening infectious disease. This disease usually develops in immunocompromised host. Acute melioidosis with pulmonary complications usually presents as consolidation with nodules and abscesses. 48-year-old diabetic smoker and alcoholic , presented with fever ,breathlessness, swelling on the right side of neck for 5 days. Chest xray showed bilateral reticular shadows and he was intubated. Further xrays revealed multiple small pneumatoceles and subsequently developed bilateral pneumothorax. Blood and neck aspirate grew B. pseudomallei. Melioidosis is a very rare emerging disease in India. Acute pulmonary melioidosis, although a rare disease, should be kept in mind by clinicians. The development of pneumatoceles is a very rare entity in the manifestations of melioidosis with only a few case reports available.

Key words: Melioidosis, Pulmonary manifestation, Pneumothorax

Sucralfate Enema In Hemorrhagic Colitis For Abrus Precatorius Poisoining - A New Dimension In Treatment

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Abstract

Abrus precatorius poisoning is one of the common means of suicide in rural India. Consumption of crushed seeds is lethal. Hemorrhagic gastroenteritis with erosions, hemolysis, acute renal failure, hepatotoxicity are common manifestations.20 year female presented with alleged history of 20 crushed seeds of Abrus precatorius seeds and complaints of diffuse, colicky pain abdomen and complaints of passage of blood in stool. Patient was started on Sucralfate Enema and Hydrocortisone enema, and Supportive management with which she improved drastically. Sucralfate enema and Hydrocortisone enema can be utilized as newer life-saver in patients with hemorrhagic colitis of patients with Abrus precatorius poisoning.

Key words: Abrus precatorius, Hemorrhagic colitis, Sucralfate enema, Hydrocortisone enema

Osteonecrosis in Adolescent Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is characterized by malignant transformation of lymphoid progenitor cells and accounts for only 20 percent of acute leukemias in patients above 15yrs of age. Osteonecrosis is one of the most common therapy-related complications but it can also be seen in early stages of bone marrow infiltration. Here we report a 18 year old male who was diagnosed as a case of osteonecrosis as the initial presentation of ALL, based on bone marrow biopsy findings of undifferentiated blasts, erythroid hyperplasia, myelonecrosis with Grade 3 Reticulin stain and positive Maissons trichrome stain. IHC showed CD34, Tdt, CD10, CD20 positive markers. Osteonecrosis seems to be a predominant problem in children and adolescents diagnosed with acute lymphoblastic leukemia, where lymphoblasts are known to have bone-resorbing effects. Better understanding of non-therapy-related risk factors is needed to improve prediction, management, and, preferably, prevention of this sequelae.

Key words: Osteonecrosis, Acute lymphoblastic leukemia, ALL, adolescent

Hemolytic Disease of Fetus and Newborn Due to Anti-d Successfully Managed with Intra-uterine Transfusions: A Case Report

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Abstract

Anti-D is still the cause of most severe Hemolytic Disease of Fetus and Newborn (HDFN). A 23yr old female G4P3L2A0D1, presented at 28 weeks of gestation with severe fetal anemia. Her immunohematological work up showed blood group B Negative and revealed the causative antibody to be anti-D with a titre of 1:64. For fetal anemia, two episodes of IUT were performed successfully with fresh, leukocyte reduced and irradiated PRBC, 2 weeks apart. The cord sample taken at that time revealed the blood group as B Positive with Direct Coomb's test (DCT) giving 4+ reaction. In view of increasing anti-D titres at 36 weeks, pregnancy was terminated by caesarian section. The neonate was healthy and no features of HDFN were noted in the postnatal period. This case report highlights the fact that, HDFN can be successfully managed during antenatal period, provided there is timely planned intervention by the team of obstetrician and transfusion medicine specialist.

Key words: HDFN, Intra uterine transfusion, Anti-D

A Rare Case of Renal Failure

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Abstract

Light chain deposition disease (LCDD) is an extremely rare condition caused by deposition of monoclonal light chain in the basement membrane. These light chains are produced by a small (less than 10% bone marrow plasma cells) yet extremely dangerous clone. As opposed to Light chain amyloidosis (AL), light chain is kappa in approximately 80% of patients. Renal involvement is a constant feature. Restrictive cardiomyopathy and cirrhosis can occur as an extra renal LCDD. We present a 56 year old male recently diagnosed hypertensive, who presented with elevated creatinine and nephrotic range of proteinuria. Renal biopsy revealed kappa light chain deposition, lambda and congo red were negative. Serum free light assay confirmed kappa light chain disease. Patient was initiated on treatment with Injection Bortezomib 2mg and Dexamethasone along with anti-hypertensives. Light Chain Deposition Disease is a rare plasma cell disorder that has to be differentiated from multiple myeloma and amyloidosis.

Key words: Light Chain Deposition Disease, Hypertension, Nephrotic Proteinuria, Amyloidosis

A Rare finding in Cirrhosis Liver with Portal Hypertension: Cruveilhier Baumgarten Syndrome

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Abstract

A 30 year old male patient who was a chronic alcoholic came with complaints of bilateral pedal edema, breathlessness and massive ascites. On examination there was distended paraumbilical vein with venous hum on auscultation, and investigations showed liver cirrhosis with portal hypertension. This was also proved with Doppler. Thus we report a rare finding known as Cruveilhier Baumgarten syndrome.

Key words: Cirrhosis, Portal hypertension, Venous hum, Cruveilhier Baumgarten syndrome

Adult-Onset Still's Disease

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Abstract

Adult-Onset Still's Disease (AOSD) is a rare systemic autoinflammatory disease and is a diagnosis of exclusion. A 22 year old male presented with fever, high grade associated with left knee pain, sore throat for 2 weeks. On examination, erythematous rash was seen in trunk. Investigations revealed neutrophilic leukocytosis and elevated ESR. Other preliminary reports were normal. He continued to have fever spikes after 72 hours of antibiotics with sterile cultures. ASO titre, RA factor, ANA profile, ANA-IF, ANCA profile were negative, CRP was elevated. Ferritin levels were high. Bone marrow aspiration and biopsy ruled out hematological malignancy. PET-CT scan ruled out occult malignancy/ infection. Possibility of Adult-Onset Still's Disease was suspected since he fulfilled Yamaguchi's criteria for AOSD. He was started on steroids, following which fever subsided and counts normalized. He was afebrile during follow up. In the presence of unrelenting fever spikes, non infective causes such as AOSD should be considered.

Key words: Adult onset Still's disease, Yamaguchi criteria, Pyrexia of unknown origin

Ralstonia Bacilli - A Silent Killer

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Abstract

Ralstonia species is a new genus that includes former members of Burkholderia species. Ralstonia pickettii was considered as the only representative of clinical importance among Ralstonia species. We report a 70 year male, with hypertension, chronic kidney disease, chronic liver disease and hypothyroidism who presented with pancytopenia and fever. Bone marrow culture revealed gram negative bacilli- Ralstonia bacilli sensitive to Inj.Meropenem. His counts improved after a course of the antibiotic. Infections with Ralstonia bacilli mostly affect immunocompromised individuals. The most important feature is the ability of Ralstonia to pass through both 0.45- and 0.2-mm filters that are used for the terminal sterilization. Thus early detection of Ralstonia allows specific anti-microbial treatment with removal of infected indwelling catheter which is associated with a favorable outcome.

Key words: Ralstonia, Immunocompromised, Chronic kidney disease

A Rare CNS Disorder

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Chettinad Health City Medical Journal 2017; 6(2): 102

Abstract

Marchiafava bignami syndrome is a demyelinating disorder of corpus callosum. It is one of the rare complications of chronic alcoholism and malnutrition. The usual presentations are seizures, dysarthria, coma, dementia, hemiparesis and slowing of movements. Here we present such a case of a 29 year old alcoholic male, who presented with recurrent seizures. MRI disclosed demyelination, swelling, and necrosis of the corpus callosum with extension toward the subcortical white matter. Diagnosis of Marchiafava Bignami syndrome was made and patient was started on intravenous thiamine, antiepileptics and high doses of vitamin supplementations, with which he symptomatically improved.

Key words: Marchiafava Bignami syndrome, Corpus callosum demyelination, Chronic alcoholism

A Case Series of Pulmonary Nocardiosis

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Chettinad Health City Medical Journal 2017; 6(2): 102

Abstract

Nocardiosis is an uncommon Gram-positive bacterial infection caused by aerobic Actinomycetes in the genus Nocardia. Nocardiosis is typically regarded as an opportunistic infection, but approximately one-third of infected patients are immunocompetent. We report 3 cases of nocardiosis in various presentations which were deadly 1) pneumonia in old pulmonary tuberculosis patient which was treated 2) pneumonia with co-existing influenza A virus, 3) complete collapse with consolidation in an immunocompetent patient.

Key words: Nocardiosis, Immunocompetent, Pneumonia, Pulmonary Manifestation

An Unusual Case of Reccurrent Dysphagia

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Chettinad Health City Medical Journal 2017; 6(2): 103

Abstract

Papillary carcinoma thyroid (PCT) is one of the common histology of thyroid carcinoma. It usually presents early but occasionally may be detected only after pulmonary metastasis has occurred. We report a rare case of PCT with lung metastasis who presented with dysphagia without other symptoms of thyroid primary.

Key words: Papillary carcinoma thyroid, Dysphagia, Pulmonary metastasis

Co-existence of Tuberculosis in Malignant Lymph Nodes- A Report of Two Rare Cases

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Chettinad Health City Medical Journal 2017; 6(2): 103

Abstract

The synchronous occurrence of tuberculosis in malignant lymph nodes is quite rare. Here, we entail two patients with nodal tuberculosis, one coexisting with Diffuse Large B Cell Lymphoma(DLBCL) and another metastatic adenocarcinoma.

Case 1: A 38 year old male presented with fever and generalized lymphadenopathy. FNA of cervical lymph node, performed twice, was non-diagnostic. Hence a biopsy was done, revealing multiple necrotic foci surrounded by large atypical lymphoid cells positive for CD20 and EBV-LMP. Stain for AFB highlighted a high bacillary load. A relook at the FNAC smear showed negative images of AFB. Hence a diagnosis of DLBCL with mycobacterial lymphadenitis was offered.

Case 2: A 60 year old male presented with unilateral cervical lymph node enlargement. Biopsy of cervical lymph node revealed caseating epithelioid granulomas along with clusters of malignant epithelial cells positive for CK20 and negative for p63 and AFB. A diagnosis of metastatic adenocarcinoma with tuberculous lymphadenitis was provided. Workup for primary was advised.

The aforementioned cases are portrayed because of their rarity and to emphasise that necrosis in a malignant lymph node need not pertain to the malignancy per se but be because of coexistent infectious etiology such as tuberculosis.

Key words: Tuberculosis, Malignant lymph nodes, Co-existent TB and malignancy

A Rare Cause of Recurrent Quadriplegia

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Abstract

A middle aged woman presented to our hospital with recurrent episodes of quadriplegia. On evaluation, she was diagnosed to have recurrent hypokalemic episodes which recovered with treatment. On further evaluation she was found to renal loss of potassium due to distal renal tubular acidosis, which was confirmed by Wrong and Davies test. Renal tubular acidosis is an important cause of hypokalemia and should be considered in the differential diagnosis of patients presenting with recurrent hypokalemic quadriparesis.

Key words: Hypokalemic paralysis, Renal tubular acidosis, Wrong and Davies test

A Rare Congenital Heart Disease in an Adult

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Abstract

We report a female patient aged 50 years with complaints of palpitations and severe breathlessness of class III-IV to our hospital casualty. On examination her pulse rate was high with irregularly irregular rhythm and raised JVP; on palpation a systolic thrill was present. On auscultation a continuous high pitched murmur in left sternal border with Carvallo's sign was present. Her ECG showed Atrial fibrillation (AF) with high ventricular rate. Hence she was treated for AF in CCU and after stabilization she was taken up for ECHO that showed atrial septal defect of OS type with rheumatic mitral stenosis and moderate tricuspid regurgitation. She was further followed up with our Cardiologist. This rare presentation of Atrial fibrillation with murmur and ECHO showing features of ASD (OS TYPE) with rheumatic mitral stenosis was found to be Lutembacher's Syndrome.

Key words: Atrial fibrillation, ASD, Mitral stenosis, Lutembacher syndrome

Double Trouble Anemia

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by the clonal expansion of blood cells with hemolytic picture. It frequently occurs during clinical the course of acquired aplastic anemia and should be considered in patients with aplastic anemia who develop hemolysis or venous thrombosis. We report 67 year old male patient previously diagnosed to have aplastic anemia (AA), who presented with severe anemia in failure. His investigations revealed pancytopenia, with unconjugated hyperbilirubinemia, elevated LDH and reticulocytosis. His serum haptoglobin levels were very low; all features being consistent with intravascular hemolysis. He was subsequently found to have evolved into PNH. Therefore he was diagnosed as a rare case of PNH-AA syndrome.

Key words: Aplastic anemia, Paroxysmal nocturnal hemoglobinuria, PNH-AA syndrome

An Enigmatous Genital Lesion - A Surprise Finding

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Abstract

In the modern era, where sexually transmitted infections (STI) are decreasing, we report a case of secondary syphilis in a young boy. A 17 year old boy came with the complaints of genital discharge and ulcers in the genitalia for 1 week. Dark field microscopy of the discharge showed treponemes. RPR was done in dilutions along with TPHA where RPR was positive in >1:32 dilutions and TPHA was positive in >1:5120 dilutions. Patient was given a single dose of Inj.Benzathine Penicillin 24 lakh units and had resolving lesions after 9 days. Final diagnosis was Syphilis D'emblee with Prozone Phenomenon. This case is reported to emphasize that all dermatology patients, even children, unmarried or married adults, if in doubt should be screened for STI.

Key words: Syphilis, STI, Genital lesions, Prozone phenomenon

Case Report on Acute Undifferentiated Leukemia with Myelofibrosis

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Chettinad Health City Medical Journal 2017; 6(2): 106

Abstract

Acute Undifferentiated Leukemia (AUL) does not express any markers specific for either lineage. Before categorizing leukemia as undifferentiated, it is necessary to perform immunophenotyping with a comprehensive panel of monoclonal antibodies. As AUL is a diagnosis of exclusion and is very rare, the morphology of leukemic cells in AUL is also not specific. Here we report a rare case of AUL with an unusual morphology. The prognosis of AUL patients is generally considered as poor and the exact significance of AUL morphology is difficult to assess, because only a few cases of AUL have been reported in literature.

Key words: Leukemia, Acute undifferentiated, Myelofibrosis

A Rare case of Immunodeficiency diagnosed during Upper Gastro Intestinal Endoscopy

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Abstract

Common variable immunodeficiency (CVID) is defined as hypogammaglobulinemia with normal B cell phenotype and recurrent episodes of infection. A 25-year-old male presented with dyspeptic symptoms since 2 months with history of recurrent respiratory tract infections. Patient's general, systemic examination and routine investigations were unremarkable. He underwent upper G.I.endoscopy which showed numerous polyps in second part of duodenum extending to third part of duodenum ,multiple biopsies were taken. Patient underwent colonoscopy to rule out Familial Adenomatous Polyposis, however colonoscopy was normal. Histopathology of duodeneal biopsy revealed nodular lymphoid hyperplasia with absence of plasma cells. As there is a known association between nodular lymphoid hyperplasia and immunodeficiency, total immunoglobulins were sent which were significantly low(IgG= 290mg/dl, IgA<26.2mg/dl and IgM 22.6 mg/dl). Patient was diagnosed as CVID and advised treatment with intravenous immunoglobulin (IVIG). High index of suspicion is required in evaluating multiple polyps with histopathology picture of nodular lymphoid hyperplasia.

Key words: Immunodeficiency, Duodenal Polyp, Lymphoid Hyperplasia, Upper Gastrointestinal Scopy

A Case of Acute Pancreatitis in a Patient with SLE

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Chettinad Health City Medical Journal 2017; 6(2): 107

Abstract

Systemic lupus erythematosus (SLE) is an autoimmune systemic disorder that can affect most organs or systems and frequently involves the joints, skin and kidneys. Acute pancreatitis in SLE is rare. We report a patient with newly diagnosed SLE who developed acute pancreatitis.

Key words: SLE, Pancreatitis

A Rare Case of Acute Flaccid Paralysis

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Abstract

Tick paralysis is a preventable cause of illness and death that,when diagnosed promptly, requires simple low cost intervention (tick removal). In India, the discovery of the tick -borne viral disease, Kyasanur Forest Disease (KFD) in 1957 marked a milestone in the history of tick studies .The typical presentation is a prodrome followed by the development of an unsteady gait, and then ascending, symmetrical, flaccid paralysis. Early cranial involvement is a feature ,particularly the presence of both internal and external ophthalmoplegia. Neurophysiological studies reveal low-amplitude compound muscle action potentials with normal motor conduction velocities, normal sensory studies and normal response to repetitive stimulation. We report a case of a 21 year old male initially evaluated for acute flaccid paralysis and later diagnosed with tick paralysis.

Key words: Tick paralysis, Acute flaccid paralysis, Kysanur forest disease

An Unusual Cause of Pulmonary Hypertension - Isolated Partial Anomalous Pulmonary Venous Connection (PAPVC)

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Abstract

Isolated partial anomalous pulmonary venous connection (PAPVC) has been implicated as a cause of pulmonary arterial hypertension (PAH), however this condition is often overlooked in the diagnostic work up of patients with PAH. We report a case of 36 year old female who presented with exertional dyspnea and fatigue conforming to NYHA class II. CT-PA revealed isolated PAPVC without left-to-right shunts. Physicians who diagnose and treat adult patients with PAH should also consider PAPVC, particularly in cases with volume or pressure overloaded right cardiac chambers and in cases that cannot be explained presence of left to right shunt lesions.

Key words: PAPVC, Pulmonary hypertension, Congenital Heart Disease.

A Case of Hyperkinetic Movement Disorder – Hemichorea – Hemiballism – Nonketotic Hyperglycemia Induced

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Chettinad Health City Medical Journal 2017; 6(2): 108

Abstract

Nonketotic hyperglycemic hemichorea – hemiballismus is a rare presentation of diabetes mellitus which should be considered in any patient with sudden onset movement disorder. Hemichorea – hemiballism occurring in diabetes mellitus owing to non – ketotic hyperglycemia is a rather benign condition with a good prognostic outcome once the hyperglycaemia is recognised early and corrected. We report a case of a 60 year old post menopausal female, a hypertensive and diabetic, not compliant with treatment, who presented with upper limb hemichorea and lower limb hemiballism which was nonketotic hyperglycaemia induced.

Key words: Hyperglycemia, Movement disorder, Hemichorea, Hemiballism

A Rare Case of Peutz - Jeghers Syndrome

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Chettinad Health City Medical Journal 2017; 6(2): 109

Abstract

Peutz-Jeghers syndrome is a rare autosomal dominant disorder with variable inheritance, characterized by hamartomatous polyps in the gastrointestinal tract presenting as intussusceptions, gastric outlet obstruction, hematochezia or malena along with pigmented mucocutaneous lesions. Its incidence is approximately 1 in 25,000 to 300,000 births. We report a case of a 17 year old boy who presented with severe anemia and mucosal hyperpigmentation, in whom Computed Tomography abdomen revealed adynamic jejuno-jejunal intussusception; Endoscopy and colonoscopy demonstrated multiple polyps in the entire Gastro-intestinal tract and biopsy showed multiple hamartomous polyps. Patient was started on oral iron supplementation and blood transfusion. He was planned for genetic analysis and endoscopic sub mucosal resection and at present is doing symptomatically well. Hence a young patient presenting with a clinical constellation of anemia with muco-cutaneous pigmentation and hamartomous polyp possibility of this syndrome should be suspected.

Key words: Peutz-Jeghers Syndrome, Hamartomatous Polyps, Anemia, Muco-Cutaneous Pigmentation

A Rare Case of Facial Palsy

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Chettinad Health City Medical Journal 2017; 6(2): 109

Abstract

Vein of Galen malformations are rare anomalies that constitute only 1% of all intracranial malformations. However they represent 30 % in pediatric age group. A rare case of facial palsy with left sided cerebellar involvement presented to us, the cause being Vein of Gallen. In order to understand its valid clinical presentations, knowledge has to date back to its embryology. During the third phase of intrinsic vascularization, the median prosencephalic vein has to regress, failure of which will result in aneurysmal malformation. With newer techniques, it has been increasingly diagnosed in prenatal period. In adults the presentations can vary depending on its mass effects. It almost never bleeds. Continuing developments in diagnostic and interventional aspects have radically changed the management of these cases.

Key words: Facial nerve palsy, Vein of Gallen.

A Rare Case of SLE With Auto Immune Hemolytic Anemia Mixed Type

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Chettinad Health City Medical Journal 2017; 6(2): 110

Abstract

Immune mixed Haemolytic Anaemia is defined as presence of both warm and cold auto antibodies against patient's own RBC diagnosed by Monospecific Direct Antiglobulin Test. We present a 54 year old female with anemia and hepatosplenomegaly. Investigations showed hemolytic anemia in the presence of both warm and cold auto antibodies along with complement C3, reactive ANA and Ds DNA. Hence diagnosed as a case of mixed autoimmune haemolytic anaemia due to systemic lupus erythematosus. The patient was started on Methylprednisolone, and had an uneventful course with regression of hepato-splenomegaly and maintenance of Hb levels above 7.2g/dl.

Key words: Autoimmune haemolytic anemia, Warm and cold antibodies, Mixed, SLE

A Rare Case of Myotonia In An Adult

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Chettinad Health City Medical Journal 2017; 6(2): 110

Abstract

We came across a male patient of age 50 years with complaints of difficulty in walking for past 15 years. On examination he has myotonia that manifested as impaired relaxation of the muscle following a contraction, and spastic gait. There was sustained contraction of the muscle on direct percussion, and also showed signs like percussion myotonia, grip myotonia and tongue napkin sign. He also had typical 'hatchet facies', frontal baldness, mild mental retardation, dysarthria, proximal muscle wasting with distal limb weakness. Ophthalmology examination revealed bilateral cataracts. ECG showed arrhythmias and ECHO revealed cardiomyopathy. Serum CK levels were elevated. EMG showed typical 'dive-Bomber' effect. He was further followed up with our neurologist. Thus he was diagnosed as a rare case of myotonia dystrophica in adult.

Key words: Myotonia dystrophica, EMG

Chronic Myelogenous Leukemia With Nodal T - Lymphoid Blast Crisis - A Case Report

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Chettinad Health City Medical Journal 2017; 6(2): 111

Abstract

Chronic Myelogenous Leukaemia (CML) is a myeloproliferative neoplasm that often terminates in a phase of blast crisis. Blast crisis is diagnosed when 20% or more blasts are present in the peripheral blood or bone marrow or there is an extramedullary blast proliferation. In approximately 70% of the cases the blast lineage is myeloid, while 20-30% cases are lymphoid. Further, almost 95% of lymphoid blast crises are of B cell phenotype. Here we describe a rare case of lymph nodal T- lymphoid blast crisis in a patient of CML. Primary presentation of CML with nodal blast crisis is rare. Rarer is the blast crisis being of T cell lineage. We wish to highlight the diagnostic issues of lymph node enlargement in a case of CML with blast crisis.

Key words: Chronic Myelogenous Leukaemia (CML), T-lymphoid blast crisis, Lymphadenopathy

Case of Disseminated Tuberculosis With Pulmonary Thrombus

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Chettinad Health City Medical Journal 2017; 6(2): 111

Abstract

Tuberculosis is a dominant public health problem worldwide with India contributing to more than one fourth of the global disease burden. A wide variety of complications are seen but haematological complications are rare. We are reporting a rare case of a 30 year old male with disseminated tuberculosis with pulmonary thrombus masked by leptospirosis.

Our case emphasizes that patients with disseminated tuberculosis are at risk of developing hematological complications and superadded infection. Awareness of this condition with early intervention is the key to successful outcome. Therefore these patients should be closely followed up for early detection of likely complications.

Key words: Tuberculosis, Pulmonary thrombus, Leptospirosis

Troublesome Trio - IntraCardiac Mass in Progressive Pulmonary Thrombo-Embolism with Resistant Thrombocytopenia

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Abstract

Thrombocytopenia due to intracardiac mass is uncommon in clinical practice. Only a few cases of intracardiac mass causing thrombocytopenia have been reported in medical literature. We report a case of progressive pulmonary thromboembolism (PTE) in a 51 year old female patient with intra cardiac mass in the setting of severe thrombocytopenia. A possible explanation for thrombocytopenia would be mechanical shearing stress by the intracardiac mass acting on platelets. The management of PTE in resistant thrombocytopenia probably due to intracardiac mass can be quite challenging.

Key words: Intracardiac mass, thrombocytopenia, Pulmonary thromboembolism

A Rare Case of Renal Coloboma Syndrome with Underdiagnosed Multiple Congenital Anomalies

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Abstract

Renal coloboma syndrome (RCS) is an autosomal dominant condition characterized by optic nerve dysplasia, often described as a coloboma along with renal hypodysplasia. Cardiac anomalies are seldom reported in this syndrome. A 28 year old male presented with complaints of palpitations of two months duration. On examination, he had microcornea, with iris coloboma in his right eye. Auscultation revealed a loud A2 in all areas, and ECHO confirmed the diagnosis of bicuspid aortic valve with a small Patent ductus arteriosus. Ultrasound of the abdomen revealed bilateral shrunken kidneys. Thus he was diagnosed as a rare case of renal coloboma syndrome associated with cardiac anomaly.Physicians diagnosing renal coloboma syndrome should also rule out any underlying cardiac anomalies.

Key words: Bicuspid aortic valve, Renal coloboma, Cardiac anomalies

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