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President's Column


Prof. Dr. Samina Naeem

Assalam o Alikum ! With the spring blooming in Lahore, the new executive committee has taken the office. I take the opportunity to extend warm greetings to all my colleagues. My predecessors Gen. (Retd) Suhaib Ahmad and Brig. Nadir Ali were very dynamic and energetic. I want to thank them for their sincere efforts to keep up the high standards of this prestigious forum.

The regular publication of Haematology Updates by Prof. Khalid Hassan is a great contribution for haematology. The long awaited haematlogy text book is also on the way. We are indebted to him for his tireless efforts for making it all come true. He has very kindly agreed to continue as the editor of these publications. I request all the haematologists to make a sincere effort to contribute their articles for the next issues of Haematology Updates.

Our colleagues and the budding haematologists are an asset for us. They are our future. It is of utmost importance to have them all registered as members of PSH. This will not only strengthen our society but will also give us a sound standing in the medical community. Although already mentioned in our meetings, I would like to emphasize again that all the activities regarding haematology should be under the umbrella of PSH. Activities planned individually should bear the logo of PSH. Your cooperation in this regard will be highly appreciated.

There is hustle and bustle as the excitement for general electoral process is still in the air. Due to current situation of our country it is our responsibility to act wisely for its betterment. Let's hope and pray to Allah the almighty that there is smooth transition of power and the present situation of insecurity and power scarcity be over. Ameen.

With warm regards,

Prof.Dr.Samina Naeem

ACADEMICS

Autoimmune Haemolytic Anemia: A Brief Review

Contributed by Dr. Humera Rafiq DCP, MPill, FCPS and Prof. Dr.Samina Naeem MPhill, FCPS. Chairperson, Department of pathology, King Edward Medical University, Lahore.

Autoimmune haemolytic anaemia (AIHA) is a relatively rare disease. Correct diagnosis is extremely important and dependent on proper comprehension of the pathophysiology and the knowledge of laboratory tests to be performed. The growths in knowledge of the scientific basis of disease and consequent advances in the practice of medicine that have taken place in the past century have been truly remarkable. According to Crosby (1952), William Hunter of London in 1888, was the first to use the term 'haemolytic' to denote an anaemia caused by excessive blood destruction. Later in France Widal etal (1908a) and Le Gendre & Brulé (1909) reported autohaemoagglutination as a striking finding in some cases of ictère hémolytique acquis. At about the same time, Chauffard & Trosier (1908) and Chauffard & Vincent (1909) described the presence of haemolysins in the serum of patients suffering from intense haemolysis. These observations suggested that abnormal immune processes, i.e. the development of auto-antibodies damaging the patients' own erythrocytes, played a part in the genesis of acquired haemolytic anaemia. These were followed by the classic observations of Donath & Landsteiner (1904) and Eason (1906) on the mechanism of haemolysis in paroxysmal cold haemoglobinuria.

Autoimmune hemolytic anemia (AIHA) is defined as an increased destruction of erythrocytes due to the presence of anti-erythrocyte autoantibodies (AEA). It is usefully classified into warm-antibody and cold-antibody type immune haemolytic anemia, according to whether the patient is forming (warm) antibodies which react (perhaps optimally) at body temperature or (cold) antibodies which react strongly at low temperatures (e.g. 4°C) but progressively less well as the temperature is raised. Both warm and cold autoantibodies can co exist in some patients.Thus the clinical syndrome suffered by the patient depends not only on the amount of antibody produced but also on its temperature requirement. The etiology behind AIHA is likely to be the result of disrupted immune self-tolerance, or due to autoantibodies induced nonspecifically and transiently during microbial infections. A defective immune self-tolerance may be either due to a central defect during lymphocyte development, or due to a peripheral defect involving down-regulation of activated mature T and B cells.

Warm AEA are generally IgG but sometimes IgA and/or IgM are also present. The surface bound IgG is recognized by Fcγ receptors of cells of the monocyte-macrophage phagocytic system, preferentially in the spleen and liver, resulting resulting in uptake and destruction of IgG-opsonized erythrocytes. In chronic cold agglutinin disease cold-activated immunoglobin M (IgM) and complement (C3d) coat RBCs and trigger hemolysis mainly in liver. Paroxysmal cold hemoglobinuria (PCH) is a rare disease induced most often by postviral Donath-Landsteiner autoantibody at cold temperatures.

The reported incidence of AIHAs varies from 1: 100,000 in the general population per year to1:300,000. Warm AIHA is the most common 50-70%, chronic cold agglutinin disease makes up 16-32% and paroxysmal cold hemoglobinuria occurs rarely, in perhaps 1% of all AIHAs. Warm AIHA affects people of all ages, but its incidence increases with age and peaks in

midlife. Chronic cold agglutinin disease predominates among patients in their 50s and 60s. Paroxysmal cold hemoglobinuria is usually a disorder of children or young adults; spontaneous remission occurs in most children. More women than men suffer with warm AIHA and chronic cold agglutinin disease.

A wide spectrum of cases are idiopathic, however a long list of secondary causative factors is also present. Most commonly encountered causes of warm AIHA include lymphoproliferative disorders (e.g.NHL, CLL; collagen vascular/autoimmune diseases e.g.SLE; and HIV infection. Less common causes include Evans' syndrome and certain antineoplastic drugs (e.g. cladribine and fludarabine). Rarer causes include Immunologic diseases such as agammaglobinemia, hypogammaglobulinemia, dysglobulinemias, immune deficiency syndromes, monoclonal gammopathy of undetermined significance (MGUS)and gastrointestinal diseases, including ulcerative colitis. Cold agglutinin disease can be secondary to infections with Epstein-Barr virus, Mycoplasma pneumoniae, and infectious mononucleosis and lymphoproliferative disorders, such as NHL, CLL and Waldenström macroglobinuria. Certain medications, including alpha-methyldopa, high-dose penicillin, and few second and third generation cephalosporins can lead to chronic cold agglutinin disease. Paroxysmal cold hemoglobinuria is usually secondary to viral infections (particularly in children and young adults), which produce the Donath-Landsteiner antibody.

Hallmark findings of AIHA include anemia (normocytic or macrocytic) with elevated reticulocyte count in the absence of blood loss; a positive direct antiglobulin test with a broad-spectrum antibody against immunoglobulin and complemet; and spherocytes or RBC aggregates on the peripheral blood smear. So The diagnosis of AIHA is usually straightforward and made on the basis of the above laboratory findings as well as low serum haptoglobin levels, elevated LDH level, increased indirect bilirubin level.

However, there are pitfalls, particularly in secondary cases, because all of the typical laboratory findings of AIHA may not be present in all the cases. In this situation two points of information are of utmost importance.

(1) The type of antibody involved. The type of antibody can be identified with the use of monospecific antibodies to IgG and C3d. When the red cells are coated with IgG or IgG plus C3d, the antibody is usually a warm antibody (warm antibody AIHA). When the red cells are coated with C3d only, the antibody is often but not always a cold antibody. For definite diagnosis of a cold antibody AIHA (CAIHA), the cold agglutinintiter should be markedly elevated (1:512). In some cases of direct antiglobulin test negativity,(IgM warm antibodies, cold antibodies with low titers, or Donath-Landsteiner antibodies), diagnosis maybe difficult, and the expertise of an immune-hematologic laboratory is required.

(2) Whether the AIHA is primary or secondary. For the diagnosis of secondary AIHA a careful history including information of the onset (acute or insidious), history of infections, information of recent transfusions, exposure to drugs or vaccination, signs of immune disease (arthritis), and general clinical condition are helpful. The exclusion of a drug-induced hemolytic anemia is particularly important, because stopping the drug is the most effective therapeutic measure in this situation. A clinical examination (to rule out lymphadenopathy, splenomegaly) is obligatory. The need for additional investigations must be determined by history, clinical findings and the type of antibody. Routine work-up relevant for treatment decisions may include abdominal examination by computed tomographic scan (to search for splenomegaly,

abdominal lymphomas, ovarian dermoid cysts, renal cell carcinoma), quantitative determination of immunoglobulins, a search for a lupus anticoagulant in case of warm antibodies, or a bone marrow examination and a search for clonal immunoglobulins (immune fixation) in case of cold antibodies.

In the era of evidence-based medicine it is difficult to give trials so treatment of patients of AIHA is still essentially experience-based. There is no formal consensus on the definition of complete (CR) or partial (PR) hematologic remission and refractoriness. The primary goal of treatment is to keep the patient clinically comfortable and to prevent "hemolytic crises" with the use of medical interventions with the lowest possible short- and long-term side effects. The mainstay of treatment of newly diagnosed primary WAIHA is glucocorticoids (steroids). According to accepted recommendations treatment is started immediately with an initial dose of 1 mg/kg/d prednisone (PDN) orally or methylprednisolone intravenously. This initial dose is administered until a hematocrit of greater than 30% or a hemoglobin level greater than10 g/dL is reached. If this goal is not achieved within 3 weeks,second-line treatment is started because further improvement with steroid treatment is unlikely.

If a patient is refractory to the initial corticosteroid treatment, a diagnostic re evaluation with regard to a possible underlying disease should be made. Patients with malignant tumors, benign ovarian teratomas, or with warm IgM antibodies are often steroid-refractory.With regard to the decision for a second-line treatment classify patients in 3 categories: (1) patients who are refractory to initial steroids and those who need more than 15 mg/d PDN as a maintenance dose are absolute candidates for a second-line therapy;(2) patients who need between 0.1 mg/kg/d and 15mg/d PDN should be encouraged to proceed to a second-line treatment; whereas(3) patients with PDN requirement of 0.1 mg/kg/d or less may do well with long-term low-dose PDN. Second line treatment includes splenectomy,immunosuppressive drugs like cyclophosphamide and azathioprine, androgens, immunoglobulins, plasmapheresis and antiCD20(rituximab).

The crucial decision to be made in management is whether the patient immediately needs transfusions. This is an individual decision and depends on the speed of development and severity of anemia, the type and cause of hemolytic anemia and the age and clinical condition of the patient. Because in WAIHA the antibody is directed against blood group antigens, no truly matched blood transfusions are possible, but red cells can be safely given if alloantibodies are excluded.

The following guidelines can be helpful:

In women without history of pregnancy and/or previous transfusions and in nontransfused men the risk of alloantibodies considered as almost absent, allowing for transfusion of only ABO- and RhD matched red cells in urgent cases.

In other patients an extended phenotyping with respect to Rh subgroups (C,c,E,e),Kell, Kidd, and S/s with the use of monoclonal IgM antibodies is performed, and compatible red cell concentrates should be selected for transfusion.

In critical cases transfusions should not be avoided or delayed because of uncertainty in matching. Even a small amount of transfused blood can be life-saving. In patients with CAIHA transfused blood must be pre warmed with the use of commercial warming coils.

A brief account on management of emergency cases is given below:

Immediate action:

If severe anemia is suspected as indicated by extreme pallor, somnolence, obtundation, tachycardia, breathlessness at rest, postural hypotension or angina, hospitalization should be advised for potential transfusion.

- Order complete blood count and start intravenous line

- Draw blood for type and cross-match
- If patient's hemoglobin is low (<4g/dL), pulmonary edema is present, or cardiac or cerebral function is threatened, this is a medical emergency and transfusion is necessary
- If cross-match is problematic, transfuse best possible match; transfused RBCs will not hemolyze faster than the patient's own RBCs
- If rare aplastic crisis is suspected (hemoglobin low, reticulocyte count near zero) advise hospitalization for potential transfusion as this is a medical emergency.

Urgent action

- A hematocrit of <20, rapidly developing anemia, declining functional status, or evidence of end-organ damage requires urgent action
- Admit patient to hospital for observation and potential transfusion
- Evaluate patient for underlying infection and medication history.

Summary

- The diagnosis of AIHA must meet two criterias: evidence of hemolysis (anemia plus elevated reticulocyte count in the absence of blood loss); and evidence of RBC autoantibodies/complement (usually indicated by a positive direct Coombs test). Note: the direct Coombs test is falsely negative in a small percentage of AIHA
- Though usually idiopathic, AIHA is commonly associated with infection, autoimmune disease, lymphoproliferative disorders, and some drugs
- Warm AIHA and cold agglutinin disease are more common among adults over age 40, in whom the diseases are usually chronic and relapsing; PCH, a rare disorder occurring most commonly in children, usually resolves on its own
- Medical intervention is usually not necessary in many patients who present with a mild hemolytic anemia; therapy becomes necessary when anemia is significant.

About PSH and PSH conference

As per constitution of PSH and results of PSH elections 2013 the new office bearer team for 2013-2014 are as follow

President:	Professor Dr Samina Naeem
President Elect:	Maj Gen Muhammad Ayyub
Secretary/treasurer:	Dr Humera Rafiq

Members Executive Counsel

Army	1.Brig Nadir Ali 2. Brig Jalil Anwar
Islamabad	Dr Lubna Naseem
Punjab	1. Dr Nisar Ahmed 2. Dr Javed Asif 3. Dr Shahida Mohsin
Sindh	1.Dr Muhammad Nadeem 2.Dr Mahadev Harani
Khyber Pakhtoonkhawa	Dr Akhtar Zarin Khattak
Balochistan	Dr Muhammad Luqman

OBITUARY

On December 10 2012 we lost our great Professor and senior haematologist Dr Mohsin Anvery. He was born in 1942 and graduated from DOW medical college in 1963.He got the degree of MRCPath from UK and worked in St. George teaching Hospital London. He also worked as Head of Department in Gulf states and examiner in CPSP. He was a dedicated teacher and a renowned scholar. It was a great loss for the nation and haematology community in particular. May Allah Almighty give courage to the family to bear this grief and bless him and rest his soul in Jannat Ul Firdous.

PSH NEWS

1st Joint Conference of PAP/ 15th PSH conference

1st Joint Conference of PAP/ 15th PSH conference was held on 7th-9th Dec 2012 in Islamabad. The conference was a big success with many national and international participants .There were 5 workshops on topics of Molecular haematology, Morphology, Transfusion Medicine, General haematology and Data analysis with interpretations of Forensic DNA.

The venue of conference was Convention Center Islamabad on 7th and 8th Dec, last day (9th Dec) of conference was in Barian Murree. Many interesting and knowledge imparting lectures were given by leading haematologists namely Dr.Tahir Shamsi, Dr Bushra Moiz, Maj Gen Muhammad Ayyub, Brig Saleem Ahmed Khan and Dr. S. M. Irfan followed by discussions. Many research papers were also presented by trainees and doctors from all leading centres in Pakistan.

Activities at Lahore chapter of PSH

Local chapter of PSH Lahore has been active as like previous year and regular monthly meetings are being held in different institutions. The year started in January by a meeting in Shaukat KhanumMemorial Cancer Hospital & Research Centre followed by another meeting in Allama Iqbal Medical College in February. Later PSH meetings were hosted by Sheikh Zayed Hospital , University Of Health Sciences and Children's Hospital & ICH in March, April and May respectively. Unusual interesting cases and presentations were discussed and participants benefited from mutual discussions and knowledge imparted to them.

Forthcoming National events

1. Education Day on Chronic Myeloid Leukaemia
   18 May 2013 at 8.30 AM to 5.00 PM. Venue: Amina Feroz Auditorium NIBD
2. CME on Anti Coagulation Therapy
   Wednesday, May29, 2013 at 3:00-5:00 pm Venue: AKU Auditorium, AKUH
3. Public awareness program on "Anemia"
   Last week of May. Venue:Liaquat National Hospital.
4. Seminar on "Leukemia and Lymphoma"
   Last week of June. Venue:Liaquat National Hospital.

Forthcoming International Events

- International Conference on Hematology and Blood Disorders Raleigh, USA will be held in Sept 23-25.2013. For further info please contact **http://www.omicsgroup.com /conferences/hematology-blood-disorders-2013/**
- American Society of Hematology (ASH) ASH 2013: 55th Annual Meeting & Exposition December 7-10th 2013.New Orleans, Louisiana, USA, June 2013.
- 2013 Stem Cells Discussion Forum: Working Towards Clinical Application, 6th Jun 2013London, United Kingdom.
- European Haematology Association 18th Congress 2013 Thu 13th Jun 2013 to Sun 16th Jun 2013Stockholm, Sweden.
- Haematocon 2013, the 54th annual conference of ISHBT (Indian Society of Haematology and Blood Transfusion) being organized at Hotel Taj Mahal Palace, Mumbai, 7th to 10th November 2013.

About PSH

Pakistan society of Haematology (PSH) was officially registered in August 1998. Pakistan Society of Hematology (PSH) is a non-political, non – sectarian Govt registered organization consisting of hematologists of Pakistan. PSH promotes the advancement of hematology including transfusion medicine, through encouragement of research, improvement of teaching & technical methods, organization of scientific meetings, publication of scientific material, and is affiliated with other National & International organizations. PSH also provides forum for the persons practicing hematology and transfusion medicine to discuss problems and to formulate agreed viewpoints at National and International forum. Membership. (1) Members: MBBS or equivalent plus post graduate qualification in hematology/transfusion medicine and show evidence of active work in hematology during the last three years including the period spent in training for post graduate examination in hematology/transfusion medicine. (2). Associate members: Those who possess the prescribed for a member but not completed three years of active work in hematology (3). Junior members: Registered students of postgraduate training in hematology/transfusion medicine for at least one year. (4). Corporate members: Those with MBBS qualification and have keen interest in hematology, and become members on payment of Rs 5000 per annum. They will not be eligible for vote or contest of any office.

Haematology Conferences: The first haematology annual conference was held in 1998 at Hotel PC Rawalpindi, arranged by Rawalpindi Chapter. It was decided that annual conference will be held regularly, and will be hosted by all chapters turn by turn. This year 16th PSH conference will be arranged by Lahore chapter. Those who witnessed the 1st conference know how great and encouraging the event was. From first conference to date the enthusiasm, unity, friendship, and co-operation among the haematologist has grown tremendously. I am sure many of us are not aware how it was achieved. I assume it was not possible without tolerance, sacrifice and devotion of our founders. Following are few milestones in the history of PSH:

1. 1991, 22nd November: First meeting of proposed PSH was held at Hotel PC, Lahore attended by Dr Muhammad Khurshid , Brig (now Lt Gen Retd) Muhammad Saleem, Dr Khalid Zafar Hashmi, Dr Naseem Siddiqui, and Dr Abdul Hayee. Meeting was held in presence of Dr A V Hoffbrand of Royel Free Hospital, UK
2. Initially society was named as Pakistan Society of Haematology/Blood Transfusion later on Pakistan Society of Haematology/oncology/Blood Transfusion and finally Pakistan Society of Haematolgy (PSH)
3. 1996: general body meeting at Peshawar: Elections
   a. President: Lt Gen Muhammad Saleem
   b. VP: Professor Muhammad Khurshid
   c. Secretary: Dr Khalid Hassan
   d. Coordinator: Col(now Maj Gen retd) Masood Anwar
4. 1998 April: Affiliation of PSH with International Society of haematology
5. 1998 Aug: PSH registration with Govt of Pakistan
6. 1998 October: 1st PSH conference
7. Presently the society comprises of 223 members, held 15 annual conferences and > 80 workshops/technical sessions

Dear Colleagues

We request you to join us in newsletter by sending your comments, short communications, case reports, issues of national interest, new developments in your departments, and scientific activities in your institutes. Your contribution is the back bone of this newsletter. It is requested that report/write up should be brief and concise. For information, suggestions, and correspondences please e-mail to: humerarafiqsheikh@hotmail.com In case you are a member and you are not receiving mails from us please update your postal and e address urgently. You can find us at www.psh.org.pk

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