AUTOIMMUNE HEMOLYTIC ANEMIA ITS NATURAL HISTORY AND MANAGEMENT

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SYNOPSIS

Autoimmune hemolytic anemia (AIHA) is a clinical syndrome characterized by an uncompensated hemolytic state that develops as a result of the failure of immune self-recognition. Three thermal reactive red cell autoantibodies are recognised of which the warm-reacting type is the most common. Despite its variable clinical course, the mainstay of AIHA therapy consists of the suppression of autoantibody production by corticosteroids, failing which alternate therapeutic modalities consisting of splenectomy or immunosuppressive therapy are undertaken.

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is made up of a heterogenous group of acquired hemolytic disorders. The common denominator is the shortened survival of the erythrocyte as a result of red cell autoantibodies. The differences in the thermal characteristics of these antibodies allow AIHA to be classified into the warm, cold and biphasic types.

Warm-reacting autoantibodies associate with red blood cells (RBCs) optimally at 37°C. They are the most common of the 3 types and are usually IgG immunoglobulins. Occasionally they may be IgA and rarely IgM (1). The cold-reacting antibody is seldom active at 37°C but binds RBCs with increasing affinity as the temperature is lowered towards 0°C. It is an IgM immunoglobulin. It may arise in the wake of a viral infection or mycoplasmal pneumonia in which case the hemolytic process is transient, or less commonly in a spontaneous form, the idiopathic cold agglutinin disease, where chronic hemolysis with high titres of the antibody is observed. The rarest of the autoimmune hemolytic syndromes, but the first to be recognized and described is paroxysmal cold hemoglobinuria (PCH). It is caused by a biphasic antibody known also as the Donath-Landsteiner antibody. It is an IgG immunoglobulin which at temperatures below 20°C in the presence of complement, fixes itself firmly to the RBC. Hemolysis occurs only when the temperature returns to 37°C. PCH is characterized by acute intermittent massive hemolysis with hemoglobinuria. The majority of cases occur in children following certain viral infections such as measles, mumps or influenza. Rarely it is associated with congenital syphilis (1).

The cold and biphasic types AIHA are not a significant clinical problem in the tropics as the ambient temperature is never sufficiently close to the thermal requirements of these antibodies. The purpose of this paper is to review the natural history and management of the warm type AIHA. A case report is included to emphasize its unpredictable course and to illustrate the ramifications of its therapy.

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CASE REPORT

A 30 year old Chinese woman was admitted to the University Department of Medicine, Singapore General Hospital on 7 July 1980 for investigation of severe anemia. A week prior to admission she fainted during school assembly. In the ensuing week she experienced giddy spells and generalized fatigue. The past medical history revealed that she was mildly anemic during her pregnancy and was given 2 units of blood after the delivery of a term infant 9 months earlier. Her health otherwise was normal. There was no personal or family history of chronic anemia. Her menstrual periods were light and she had no bleeding tendency. Until the week prior to admission she was preoccupied as a schoolteacher and housewife.

On admission she was afebrile. She was noted to be extremely pale and mildly icteric. The pulse rate was 120 per minute and the blood pressure was normal. An ejection systolic murmur was heard at the aortic area. Bruit over both orbits were noted. The liver, spleen and lymph nodes were not enlarged. She was conscious and rational. The neurological examination was normal.

The hemoglobin was 3.7 gm/dl with a reticulocyte count of 51% (normal is less than 3%). The peripheral blood film showed moderate anisocytosis with increased numbers of spherocytes. The total white cell count was 14,200/cu mm and platelet count 285,000/cu mm. The prothrombin and partial thromboplastin times were normal. The erythrocyte sedimentation rate was 3 mm in the first hour. The direct Coomb's test (DCT) was strongly positive. The indirect (unconjugated) bilirubin was 5.1 mg/dl, blood urea and serum creatinine were both normal. The antinuclear factor and lupus erythematosus cell (LE) preparations (x3) were negative. The glucose-6-phosphate-dehydrogenase (G-6-P-D) enzyme was normal.

The triad of severe anemia, marked reticulocytosis and strongly positive DCT led to a prompt diagnosis of AIHA. Subsequent investigations revealed the autoantibody to be an IgG, warm, nonspecific panagglutinin. The patient was treated with high dose prednisolone (60 mg/day). On the second hospital day she developed a high fever (temperature 40°C) and became irrational. Clinically there was no obvious focus of infection. Blood and urine cultures subsequently were reported to be sterile. The chest x-ray was normal. It was felt that her fever was related to the brisk red cell destruction and that her mental confusion was due to a combination of the high fever and cerebral anoxia, the latter caused by the severely depressed hemoglobin level (3.4 gm/dl on the second hospital day). Under the usual circumstances blood transfusion is not undertaken in patients with AIHA because of the risk of inducing intravascular hemolysis and acute renal shutdown. The administration of corticosteroid is specifc and effective for the treatment of this disorder. However, if the hemoglobin is so low, as in our patient, as to produce cerebral symptoms or cardiac failure, then the infusion of packed cells under close observation may be a life-saving measure. Our patient was given 2 units of packed cells with close monitoring to prevent intravascular hemolysis. The fever subsided after the first unit of packed cells and the mental state returned to normal after the second. Subsequent to this her clinical course was one of steady improvement with a rising hemoglobin and reduction in the reticulocyte count (Fig. 1). She was discharged on 4 September 1980 (8 weeks after admission) on 10 mg of prednisolone a day.

When reviewed in the Outpatient Department 2 weeks later, it became apparent that the dose of prednisolone (10 mg/day) was inadequate. She remained refractory even after increasing the dose of prednisolone to 40 mg daily. Splenectomy was offered to her but she turned it down. Azathioprine therapy (100 mg/day) was then instituted with

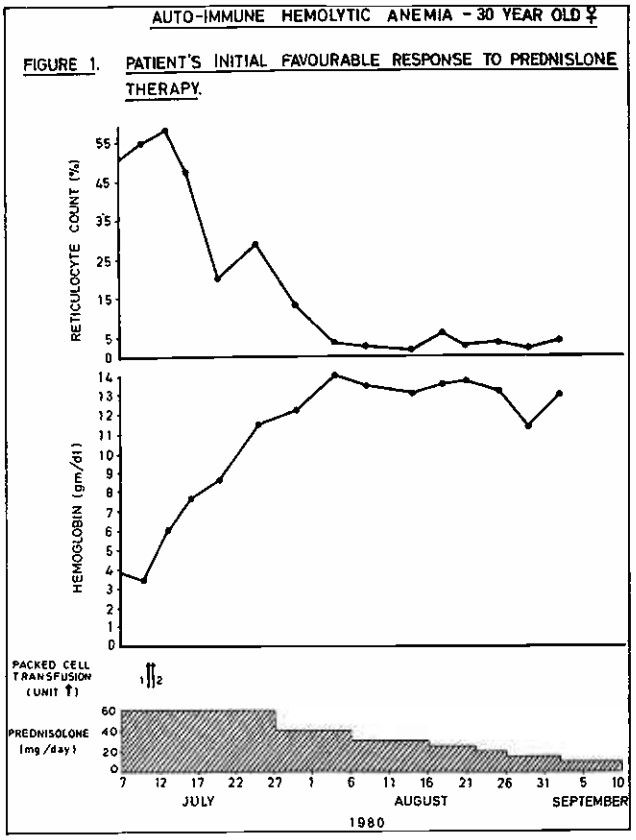

Figure 1. Patient's initial favourable response to prednisolone therapy.

consequent good response (Fig. 2). Normal hemoglobin and reticulocyte count were maintained with a combination of azathioprine and prednisolone, the latter was tapered slowly to 10 mg/day. The disease relapsed in February 1981. Reinstitution of high dose prednisolone (60 mg/day) failed to gain control of the hemolytic process. Splenectomy was undertaken on 31 March 1981. Earlier on, red cell survival study (using ^{51}Cr tagged RBC's) confirmed a shortened survival with a T½ ^{51}Cr of 15 days (normal T½ ^{51}Cr is 25-33 days) and the same study disclosed the presence of preferential splenic red cell sequestration. As expected from these results, splenectomy was followed by a dramatic recovery in the hemoglobin level and normalization of the reticulocyte count (Fig. 3). The hemoglobin rose to 14 gm/dl and the reticulocyte count dropped below 3% on the fourth postoperative day. She was discharged home eight days following splenectomy. Unfortunately her response to splenectomy was short-lived. The hemoglobin level and reticulocyte count remained normal throughout April and the first three weeks of May. She relapsed following a viral infection and was readmitted to hospital on 21 May 1981. She responded after a latency period of 3 weeks to prednisolone and cyclophosphamide. Currently she feels well as the dose of prednisolone is being slowly reduced.

DISCUSSION

The incidence of warm AIHA is approximately 1 per 75-80,000 population (2). Unlike cold AIHA which typically affects the middle-aged and the elderly and unlike PCH which involves the pediatric age group, warm AIHA occurs at any age. In Dacie's series of 125 patients the age distribution ranged from 5 months to 78 years (3). There is no racial predisposition for or protection from AIHA. Although almost all the literature on AIHA concerns patients living in temperate countries, Lie-Injo and Pillay (4) reported its occurrence in Malaysia as early as 1964.

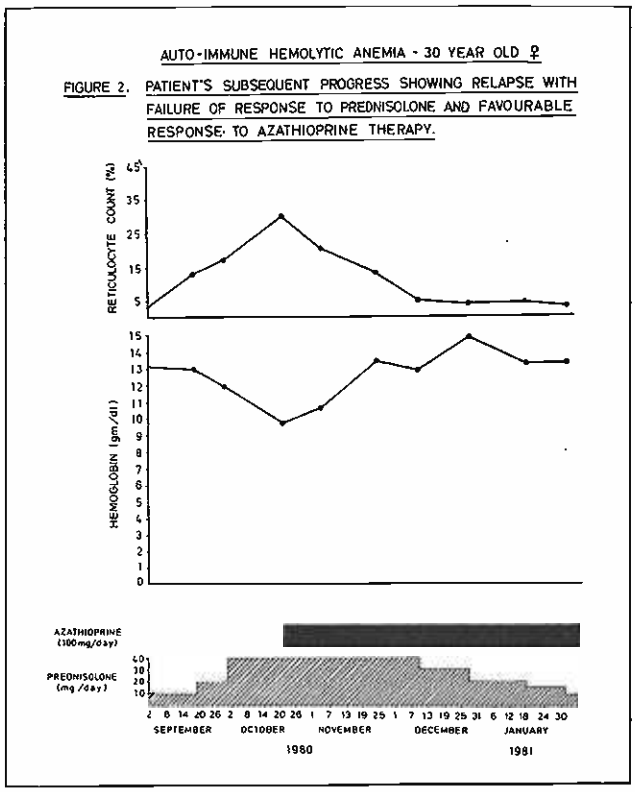

Figure 2. Patient's subsequent progress showing relapse with failure of response to prednisolone and favourable response to azathioprine therapy.

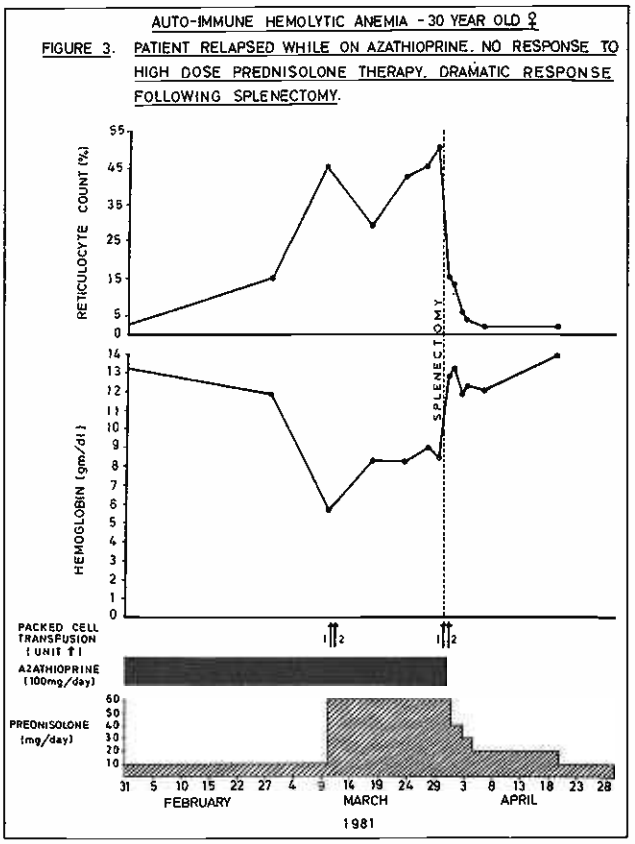

Figure 3. Patient relapsed while on azathioprine. No response to high dose prednisolone therapy. Dramatic response following splenectomy.

The classification of AIHA is based on the presence or absence of associated disease states. It is termed primary or idiopathic if it occurs without any underlying clinical conditions. When associated with diseases such as systemic lupus erythematosus or lymphoproliferative disorders, or when drugs are implicated, a secondary type of AIHA is recognized. Dacie (3) and Dausset et al (5) reported an occurrence of approximately 70% of the idiopathic variety while Pirofsky (6) noted an unusually low occurrence of less than 20%. The discrepancy between these reported figures reflects the changing concept of what are to be considered as significant associated diseases and the duration of patient follow-up. It is well known that AIHA can herald the appearance of some other underlying immunologically mediated disorder months or years in advance. This knowledge should alert the clinician to be on the constant look-out for the eventual presence of associated diseases in the so called "idiopathic" patients. The term primary or idiopathic becomes obsolete eventually in the majority of such cases. Our patient has to date no clinical evidence of associated connective tissue or lymphoproliferative disorders. Time will reveal if she is truly idiopathic.

The presentation of AIHA is highly variable. The symptoms may be divided into 3 basic groups. Symptoms of anemia, such as pallor, weakness, dyspnoea, syncope and at times mental confusion, occur in 90% of patients. Those related to hemolysis (jaundice and rarely hemoglobinuria) occur in about 20%. The third group of nonspecific symptoms (fever, anorexia, weight loss) occurs in 30-40% of patients (2). These complaints usually develop insidiously over days, weeks or months, although acute hemolytic crisis may occasionally be the mode of presentation particularly in children (6). Pirofsky observed that hepatosplenomegaly and lymphadenopathy were quite common in his series of 230 patients (2). Splenomegaly was noted in more than 50% of patients, hepatomegaly in about 45% and enlarged nodes in 34%. These figures reflect the large number of his patients with underlying lymphoid malignancies. In the strictly idiopathic group (44 out of 230 patients) only 23% had clinical evidence of reticuloenthelial proliferation. Our patient presented with the classical symptom complex of AIHA but did not have either hepatosplenomegaly or lymphadenopathy.

Complications of AIHA relate in part to the hemolytic process and in part to the therapy. Severe refractory anemia is often complicated by intractable heart failure particularly in the elderly patients. Cerebral anoxia giving rise to bizarre mental changes or mimicking cerebrovascular accident is another serious complication of a very low hemoglobin. Rarely, thrombophlebitis with fatal embolization occurs in AIHA patients. Longterm therapy with corticosteroids or immunosuppressive agents is associated with risks of infection. These complications are responsible for the mortality in the idiopathic group. Patients with secondary AIHA succumb more often to their underlying associated diseases than to these complications.

The prognosis of AIHA is dependent on the presence or absence of associated serious diseases. Secondary AIHA carries the prognosis of the underlying disease. The impact of modern therapy on the prognosis of the idiopathic group is still uncertain. Allgood (7) reported a 28% mortality rate in 1967. More recently Worlledge (8) released the figure of 14% in her series of 85 cases followed for periods of up to 7 years. The most optimistic figure came from the Mayo Clinic (9) giving a mortality rate of 9% at one year follow-up.

Despite the fact that AIHA has been a well defined clinical entity for almost 4 decades and a considerable volume of literature has been published in regard to its clinical characteristics, pathogenesis, etiology and serology, only a limited number of publications have reported investigations into the therapy of this disorder. Most of these represent the personal, anecdotal experiences of investigators and contain considerable variation in drug

formulation utilized, dosage regimens, criteria of response and indications for alternate treatment modalities. A lack of controlled clinical trials renders comparative evaluation of reported response rates impossible. Since the initial report by Dameshek (10), corticosteroids have remained the mainstay of therapy for AIHA. Prednisone or prednisolone has replaced ACTH and cortisone, being considerably cheaper and equally effective. The administration of large doses (60 mg/day) of prednisone or prednisolone to patients with AIHA usually results in prompt and dramatiac reduction in red cell destruction by 7 days (6). The lack of any improvement within 3 weeks implies refractoriness to steroid treatment and consideration must be seriously given for an alternate therapeutic modality namely splenectomy or immunosuppressive therapy.

80% of patients with idiopathic AIHA respond favourably to steroids compared with 60% of those with the secondary form (11). 20% of all patients achieve a complete remission and 40% require maintenance of 5-20 mg of prednisolone daily. There does not appear to be any predictive value from the initial serologic findings (such as the degree of DCT positivity or specificity of the autoantibody) and response to steroid therapy.

The onset of response to treatment is frequently heralded by a transient paradoxical rise in the reticulocyte count. This is soon followed by a gradual rise in hemoglobin and fall in the reticulocyte count (Fig. 1). Once the patient achieves normalization of hematological status the dose of steroid has to be gradually reduced with close monitoring of the reticulocyte count and hemoglobin level. Sudden cessation of therapy or too rapid a reduction in dose usually results in a prompt relapse as illustrated in our patient (Fig. 2). It is quite safe to reduce the dose to the equivalent of 30 mg/day of prednisolone over a 4 — 6 week period. Subsequent reduction must be more gradual in 5 mg decrement over a 3 month period to a dose of 10 mg/day. Finally an attempt must be made to withdraw all therapy in the stable patient over another 3 month period. Relapse of the disease using this type of regimen is usually gradual and readily recognized prior to the development of serious degrees of anemia (11). In the event of a relapse, the steroid dosage should be increased and a more gradual reduction attempted.

Unlike the corticosteroid popularity, the usefulness of immunosuppressants as a first line drug in the treatment of AIHA awaits further clarification. Steroid-failed patients are generally offered splenectomy. Where there are no medical contraindications to surgery, splenectomy is the alternate modality of treatment for AIHA. The hesitancy over the use of immunosuppressants is related to the lack of knowledge of the side effects of longterm use of these cytotoxic agents. Reports of their use are based on small numbers of patients over short periods of follow up (8), (12), (13). In view of the limited experience with immunosuppressants they are used only in splenectomy failures or in patients in whom splenectomy is contraindicated.

Success following splenectomy is predictable if radioisotopic confirmation of splenic sequestration of red blood cells is obtained prior to surgery (14). Approximately 75% of patients respond to splenectomy (8). Of the remaining 25%, a large proportion will respond if given prednisolone again or immunosuppressive therapy. A word of caution is that there is increasing evidence that splenectomized adults are as prone to pneumonia and septicemia by heavily encapsulated bacteria as children (15), (16), (17), (18), (19), (20), (21), (22). The need, therefore, for continuing long term (perhaps lifetime) follow up of all AIHA patients cannot be overemphasized.

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