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Severe Fatigue: Could It Be Aplastic Anemia?

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Case Study

Mr. X, a single, 55-year-old administrative assistant, presented to his family practice clinic with a complaint of fatigue. He was previously healthy and enjoyed walking his dog in his free time.

Mr. X reported that he was easily fatigued and often short of breath. He said that it was difficult to walk several blocks. Mr. X also reported a low-grade fever and suspected that he had an upper-respiratory infection, but he did not seek medical treatment for those symptoms. He has had some bruising on his extremities and colleagues have told him that he looks pale. Mr. X, however, denied any headaches, lightheadedness, dizziness, chest pain, or palpitations.

A general examination revealed an obese, afebrile, normotensive white male. No oral lesions, mucosal bleeding, or cervical lymphadenopathy were noted. Respiratory and cardiovascular examinations were unremarkable. Mr. X's liver and spleen were not enlarged and no bruising or petechiae were noted.

A complete blood count (CBC) with differential was ordered. Mr. X's hemoglobin was 6.4 g/dl, white blood cell count was 3.1 k/ul, and platelets were $6,000 \times 10^9/L$.

Treatment Plan

Mr. X was admitted to the hospital for evaluation and treatment of severe anemia. A bone marrow biopsy was remarkable for a severely hypoplastic marrow with 5% cellularity. Very few megakaryocytes were present with no definite dysplastic changes. A flow cytometry also was done and did not reveal any evidence of a lymphoproliferative disorder. A cytogenetic study was normal. Mr. X was evaluated by a hematology consultant and given a provisional diagnosis of aplastic anemia (AA). The hematologist ordered red blood cell and platelet transfusions. Mr. X also was started on prednisone. His CBC rose to a hemoglobin level of 11.8 g/dl, white blood cell count to 3.8 k/ul, and platelets to $16,000 \times 10^9/L$. Mr. X was then discharged from the hospital with a referral to a specialty oncology center for further evaluation.

A repeat CBC was obtained at the oncology center and revealed a white blood cell count of 1.93 k/ul, hemoglobin of 9.1 g/dl, platelet count of $3,000 \times 10^9/L$, and absolute neutrophils of 0.12 K/ul. Diagnoses of AA or hypoplastic myelodysplastic syndrome were considered. A repeat bone marrow biopsy was done and revealed a paucicellular (5%) bone marrow with panhypoplasia. Flow cytometric analysis reported no evidence of lymphoproliferative disorder. Cyto-genetic testing revealed a normal male karyotyping. Additional testing favored an AA diagnosis. Mr. X decided to be treated with antithymocyte globulin (ATG) in combination with cyclosporine (CsA). Mr. X was given the combination of rabbit-derived ATG (r-ATG) plus CsA and received steroid prophylaxis for serum sickness. Mr. X was supported with platelet and blood transfusions during the first week after treatment and started to have hematologic improvement eight weeks after ATG treatment. About 60% of patients respond at three or six months after initiation of ATG, so Mr. X was ahead of the curve (Rosenfeld, Follman, Nunex, & Young, 2003). His siblings were human leucocyte antigen-typed, but no match was found. Mr. X's options, in the event of relapse, included more ATG treatment, which would be with the horse form based on high response rates after first relapse (60%–70%), or a matched-unrelated donor allogeneic bone marrow transplantation if a suitable donor is found

Discussion

AA is a bone marrow failure disorder characterized by pancytopenia (a significant decrease in blood cells and platelets) and a hypoplastic (appearance of fat cells and very few hematopoietic cells) bone marrow. Although rare, AA can be life threatening and, if untreated, is associated with a high mortality rate (Young, Scheinberg, & Calado, 2008). The curative approach for patients with severe and very severe forms of AA is bone marrow transplantation. However, this option is only available to about 30% of patients (Maciejewski & Risitano, 2005). Factors that limit this option include comorbidities such as diabetes mellitus, hypertension, advanced age, and limited human leucocyte antigen-matched donors.

Epidemiology

Acquired AA is a rare disease. In the Western world, the incidence is about two cases per million per year but is actually about two- to three-fold higher in Asia (Young et al., 2008). The Thai National Heart Lung and Blood Institute's Aplastic Anemia Study conducted in Bangkok, Thailand, and in a rural region of northeastern Thailand, showed the incidence at four cases per million and six cases per million, respectively (Issaragrisil et al., 2006). Environmental factors, such as benzene and pesticides, are implicated in a small etiologic portion. On the other hand, an infectious etiology also is suggested by associated exposures to unbottled water, zoonotic infections, and animal fertilizers (Young et al.; Issaragrisil et al.). The peak occurrences of AA are in young adults and in adults aged 50–70 years. No significant difference exists between men and women in the incidence of AA (Marsh et al., 2003).

Clinical Presentation

The most common presenting symptom for patients with newly diagnosed AA is progressive fatigue. Other accompanying or presenting symptoms may include infections related to neutropenia and bruising, petechiae, increased menstrual flow for female patients, and gum bleeding related to thrombocytopenia. On physical examination, signs of pallor, petechiae, and bruising may be observed. The spleen is not generally enlarged and lymphadenopathy is uncommon.

Pathophysiology

The pathophysiologic mechanisms of AA are still unknown. Current theories support an immune mediated mechanism, first suggested in 1970 when Mathe et al. noticed the recovery of autologous bone marrow production in patients with AA where partially matched engrafting failed (Young & Maciejewski, 1997). In the study, patients were given anti-lymphocyte globulin as an immunosuppressant drug before undergoing transplantation. Antilymphocyte globulin is an immunoglobulin derived from the plasma of horses inoculated with human lymphocytes (Young & Maciejewski). Mathe et al. believed that antilymphocyte globulin treatment was the reason for the recovery of marrow function. In AA, T-cell lymphocytes, particularly the cytotoxic T-cell subset, actively target and destroy hematopoietic stem cells. Various in vitro models have been created to help explain the mechanism of T cell mediated cytotoxicity. T cells bearing a Th1 profile, which express and secrete interferon- γ , are thought to inhibit hematopoiesis (Sloand et al., 2002; Young et al., 2008). Solomou, Keyvanfar, and Young (2006) studied T-bet, a transcription factor that binds to the interferon- γ promoter region and is critical for Th1 polarization. Their data suggested that T-bet was upregulated in AA patients, resulting in increased interferon- γ levels. Interferon- γ , in combination with tumor necrosis factor, depletes hematopoietic stem cells (target cells) by their effects on the mitotic cycle (Young & Maciejewski). The two cytokines induce the expression of the Fas receptor on CD34 cells and potentiate cytokine-mediated hematopoietic suppression (Maciejewski, Selleri, Anderson, & Young, 1995) (see Figure 1). What triggers the cytotoxic T cells in AA is still unknown. However, damage induced by chemicals, drugs, viruses, or antigens may be behind its activation (Schrier, 2007). Another important observation in AA is that about 33% of patients have shortened telomeres in their white blood cells. Telomeres are specialized structures located at the end of a chromosome that are involved in the replication and stability of a chromosome. Shortening of telomeres is attributed to mutations in components of the telomerase complex and resulting to hypoproliferative hematopoietic stem cells (Young et al., 2008)

Diagnosing Aplastic Anemia

AA is suspected when a patient presents with peripheral blood cytopenia and a hypocellular bone marrow. Based on the degree of hypocellularity, part of the differential diagnosis should include hypocellular myelodysplastic syndrome (MDS).

According to Schrier (2007), the bone marrow is profoundly hypocellular with a decrease in all blood elements and the remaining hematopoietic cells are morphologically normal. The morphologic appearance of the remaining cells in the bone marrow is very important as dysplastic features may point more toward a diagnosis of hypocellular MDS. In addition, the

presence of excess and abnormal blasts or abundant megakaryocytes is not compatible with the AA diagnosis (Maciejewski & Risitano, 2002).

Severity of AA serves as the most important determinant of whether to proceed with treatment or not. Schrier (2007) categorized the various forms of AA (see Table 1). The differential diagnosis of a hypocellular bone marrow in the setting of pancytopenia includes AA and hypoplastic MDS. The presence of myeloid dysplasia, excess blasts, karyotypic abnormalities, and micromegakaryocytes may help establish an MDS diagnosis.

Mr. X had an absolute neutrophil count of 120 per mcl, platelet counts of $3 \times 10^9/L$, and bone marrow biopsy with 5% cellularity. He met the criteria for very severe AA and warranted urgent treatment. Cytogenetic analysis, if done, usually reveals a normal chromosomal profile in patients with AA, which was the case with Mr. X.

Prognosis

Patients with severe AA have an unfavorable prognosis if not treated: 70% or higher mortality rate within one year (Young, 1995). Aside from the severity, the prognosis also is affected by patient age. A study by Tichelli et al. (1999) looked at the effectiveness of immunosuppressive therapy in 810 patients with AA from 1974–1997 (Schrier, 2008; Tichelli et al.). The survival rate varied inversely and significantly with age. The five-year survival rate was 72%, 57%, and 50% for age groups of 49 years and younger, 50–59 years, and 60 years and older, respectively. The prognosis is clearly influenced by advancing age.

Treatment

The approach to treating patients with AA depends on the severity of the blood counts. Patients with AA who are independent of transfusions may be monitored on a regular basis and may not actually require drug intervention. This group of patients also may be offered supportive care or outpatient treatment with anabolic steroids and/or low-dose steroids or CsA (Bacigalupo, 2007). However, immunosuppressive therapy or bone marrow transplantation prove to be the best options for patients with severely depressed counts. Patients 20 years or younger with very severe AA are candidates for first-line transplantation (Bacigalupo), whereas older patients, because of other comorbidities, are not ideal for bone marrow transplantation and are best treated with immunosuppression. Although its exact mechanism is still unclear, horse-derived ATG (h-ATG) is the only drug currently approved by the U.S. Food and Drug Administration for the treatment of AA (Young et al., 2008). H-ATG preparations contain a variety of antibodies recognizing human T-cell epitopes and directed against activated T cells or activation antigens (Young et al., 2008). H-ATG is cytolytic and induces lymphocyte depletion by complement-dependent cell lysis (Mueller, 2007). The use of ATG in the treatment of aplastic anemia has yielded superior survival rates when compared with supportive care (Young, Calado, & Scheinberg, 2006). The response rate to h-ATG alone ranges from 70%–80% with a five year survival of 80%–90% (Rosenfeld et al., 2003). Although ATG appears to be superior to CsA as a single agent, the combination of both drugs provides better results (Maciejewski & Risitano, 2005).

The standard combination therapy for severe AA is ATG plus CsA. Two forms of ATG (h-ATG and r-ATG) are available. R-ATG may be more potent because it induces prolonged

lymphopenia (Young et al., 2008). However, no available data exist from clinical trials comparing the two forms. The usual dose of h-ATG is 20 mg/kg per day for four days, r-ATG is 3.5 mg/kg per day for five days (Maciejewski & Risitano, 2005). Both are given by IV infusion over a period of at least six hours. CsA usually is initiated at 12–15 mg/kg divided into twice daily dosing after day 4 or 5 and given for at least six months and tapered thereafter. No regimen exists as to when and how fast the tapering should be done (Bacigalupo, 2007). Steroids also are part of ATG treatment to prevent the development of serum sickness, one of ATG's adverse effects.

Based on clinical trials listed in Table 2, the average overall response rate for h-ATG plus CsA is 60%–70% with a 20%–30% relapse rate among respondents (Young et al., 2008). Patients who have relapsed can be treated with a trial of CsA alone and, if counts are not responding, another course of ATG can be initiated (Maciejewski & Risitano, 2005). R-ATG can be used if h-ATG was initially used. This second treatment with ATG plus CsA usually has comparable response rates of 50%–60% (Young et al., 2008). However, in some cases, AA can evolve into other bone marrow failure disorder like MDS and the management will eventually be changed.

The addition of granulocyte–colony-stimulating factor as a support for immunosuppressive therapy in patients with AA can improve neutropenia but failed to increase the survival rate after five years of follow up (Gluckman et al., 2002). Efforts also have been made to find an effective third immunosuppressive (i.e., sirolimus, androgens, or mycophenolate mofetil) agent to the ATG plus CsA combination to achieve an even higher response rates. However, outcomes were not impressive (Young et al., 2008).

Daclizumab was found to improve both blood counts and transfusion requirements for patients with moderate AA who require transfusions. (Maciejewski & Risitano, 2005). Daclizumab is an immunosuppressive humanized monoclonal immunoglobulin G antibody to interleukin-2 receptor that is expressed on the surface of activated lymphocytes.

Allogeneic bone marrow transplantation is the only curative option for qualified patients with favorable results. For matched-sibling bone marrow transplantation, survival rates may be as high as 77% (Horowitz, 2000) and even higher in pediatric populations. Survival rates of 80%–90% are achievable in pediatric populations (Young et al., 2008); therefore bone marrow transplantation should be offered as a first therapeutic option (Maciejewski & Risitano, 2005). However, the outcome for matched/unrelated donor is not as impressive. The five-year survival rate for patients 20 years or younger was 44%, between 21–40 years was 35% (Horowitz). Issues with graft-versus-host disease, opportunistic infections, and failure to engraft were the major limiting factor for matched-unrelated donor allogeneic transplantation.

Conclusion

After his initial treatment with ATG and CsA, Mr. X had a two-year period of remission. His blood counts, drawn every three months after ATG plus CsA therapy, showed normal indices. At the two-year point, Mr. X noted an increase in his fatigue. His CBC revealed a

deterioration in the blood count. He received a transfusion of red blood cells and then a repeated cycle of AGT plus CsA, which improved his fatigue. Because of his age and lack of a human leucocyte antigen compatible family donor for stem cell transplantation, Mr. X received repeated cycles of ATG plus CsA over the next three years. Overall, Mr. X has stated that his quality of life is “pretty good.” He is able to keep up his activities of daily living, fish twice a week, and watch his favorite game shows on television. His physicians have informed him that he may need to consider an unrelated donor bone marrow transplantation in the future if he cannot attain a long-term remission from immunosuppressive therapy.

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Figure 1. Therapeutic Algorithm for Aplastic Anemia

Note. From “Aplastic Anemia: Management of Adult Patients,” by J.P. Maciejewski and A.M. Risitano, 2005, American Society of Hematology Education Program, 1, p. 116. Copyright 2005 by the American Society of Hematology. Adapted with permission.

Table 1

Categories of Aplastic Anemia

APLASTIC ANEMIA TYPE	CHARACTERISTICS
Moderate	Diagnosed when aplastic anemia fulfills the criteria for aplastic anemia based on bone marrow cellularity but does not fulfill criteria of severe aplastic anemia based on cytopenia. Requires persistent moderately depressed counts over six months or more
Severe	Characterized by a marrow biopsy showing less than 25% of normal cellularity or a marrow showing less than 50% normal cellularity in which fewer than 30% of the cells are hematopoietic and at least two of the following occur: absolute reticulocyte count less than 40,000 per mcl, absolute neutrophil count less than 500 per mcl, platelet count less than $20 \times 10^9/L$
Very severe	Same characteristics as severe aplastic anemia with the addition of an absolute neutrophil count less than 200 per mcl

Note. Based on information from Maciejewski & Risitano, 2005; Schrier, 2007.

Table 2**Intensive Immunosuppression (Antithymocyte Globulin Plus Cyclosporine) for Severe Aplastic Anemia**

STUDY	N	MEDIAN AGE (YEARS)	RESPONSE (%)	RELAPSE (%)	CLONAL EVOLUTION (%)	SURVIVAL (%)
Frickhofen et al., 2003	84	32	65	19	8	58 at 11 years
Bacigalupo et al., 2000	100	16	77	12	11	87 at 5 years
Rosenfeld et al., 2003	122	35	61	35	11	55 at 7 years
Kojima et al., 2000 ^a	119	9	68	22	6	88 at 3 years
Scheinberg et al., 2006 ^b	104	30	62	37	9	80 at 4 years

Note. Only studies of more than 20 enrolled patients are tabulated. Responses to immunosuppressive therapy are usually partial; blood counts may not become normal, but transfusions are no longer required and the neutrophil count is adequate to prevent infection. Relapse is usually responsive to further immunosuppressive therapies. Clonal evolution is to dysplastic bone marrow changes and/or cytogenetic abnormalities.

Note. From "Current Concepts in the Pathophysiology and Treatment of Aplastic Anemia," by N.S. Young, R.T. Calado, and P. Scheinberg, 2006, *Blood*, 108(8), p. 2513. Copyright 2006 by the American Society of Hematology. Reprinted with permission.

^aWith androgens and with or without granulocyte–colony-stimulating factor

^bWith mycophenolate mofetil