International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

AN UPDATED ON APLASTIC ANEMIA

Nur Hoda Dewan

Department of Internal Medicine, Advance Medicare hospital and research center, Birgunj, Nepal, 44600

ABSTRACT

Aplastic anemia is the name commonly used to describe the syndrome of marrow hypoplasia with pancytopenia. This disorder is associated with a variety of etiologic agents and, most probably, with several different pathogenic mechanisms. The incidence in higher in asian population than others. Radiation, toxins such as benzene, drugs such as nonsteroidal anti-inflammatory agents, chloramphenicol, alcohol, chemotherapeutic alkalyting agent can all cause aplastic anemia. Bone marrow confirms the diagnosis when alternative etiology for pancytopenia is not present. Immunosuppressive therapy is the treatment for aplastic anemia patient's ineligible for transplantation.

INTRODUCTION

Aplastic anemia is a rare disorder characterized by suppression of bone marrow function resulting in progressive pancytopenia.[1] This disorder is associated with a variety of etiologic agents and most probably, with several different pathogenic mechanisms. A trigger-related abnormal T cell response facilitated by some genetic predisposition has been postulated as the pathogenetic mechanism leading to the overproduction of bone marrow-inhibiting cytokines. Patients may present along a spectrum, ranging from being asymptomatic with incidental findings on peripheral blood testing to having life-threatening neutropenic infections or bleeding.

Epidemiology:

Aplastic anemia is a rare disorder, with an incidence of approximately 1.5 to 7 cases per million individuals per year.[2,3] The incidence of aplastic anemia varies globally, with a disproportionate increase in incidence seen among Asian populations, with rates as high as 8.8 per million individuals per year.[4] There appears to be a bimodal distribution, with incidence peaks seen in young adults and in older adults[5].

Etiology:

Although there are many things that can cause bone marrow failure, the most common cause of true aplastic anemia is rarely precisely determined. Radiation, toxins such as benzene, drugs such as nonsteroidal anti-inflammatory agents, chloramphenicol, alcohol, chemotherapeutic alkalyting agent can all cause aplastic anemia. Infiltration of the marrow with infection such as tuberculosis or cancer such as lymphoma can cause pancytopenia but this not truly aplastic anemia. Aplastic anemia can be caused by hepatitis, HIV, CMV, Epstein Barr virus or Parvo virus B19 in immunocompromised patients. Aplastic anemia can be mistaken for a condition called myelodysplastic syndrome. In this group of disorders, the bone marrow produces new blood cells, but they're deformed and underdeveloped. The bone marrow in myelodysplastic syndrome is sometimes called hyperplastic — meaning that it's packed with blood cells. But some people with myelodysplastic syndrome have empty marrow that's difficult to distinguish from aplastic anemia.

Autoantigens:

A few putative antigens have been teased from screening antibodies in patients' sera against a peptide library (by expression of genes in fetal liver or leukemic-cell lines). Kinectin, a widely expressed protein, bound to antibodies from about 40% of aplastic patients.[6] Another antigen that bound to antibodies, in a smaller minority of marrow failure patients, was diazepam-binding related protein-1, an enzyme essential in the oxidation of unsaturated fatty acids and broadly distributed in tissues.[7] The relevance of these autoantibodies to a cellular pathophysiology of aplastic anemia is unclear. For kinectin, reactive cytotoxic T cells could be generated in vitro and inhibited human hematopoietic colony formation, but antikinectin T cells were not found in patients. For diazepam-binding related protein-1, a putative T-cell epitope derived from this protein could stimulate cytotoxic T cells obtained from one patient, and T-cell precursors with peptide-binding activity were present in 2 cases.

Clinical presentation:

Patients most commonly presents with bleeding from thrombocytopenia but may present with the combination of the findings associated with deficiency with all three cell lines. Fatigue from anemia and infection from neutropenia may also occur. The clinical presentation may give a clue to the presence of pancytopenia but is not sufficient to determine a true aplastic anemia by clinical manifestation alone. The absence of a classical association such as benzene, radiation, chloramphenicol would certainly not exclude the diagnosis of aplastic anemia. The most common single etiology is idiopathic.

Pathophysiology:

In most cases aplastic anemia is an immune mediated disease. Cellular and molecular pathways have been mapped in some detail for both effector (T lymphocytes) and target (hematopoietic stem and progenitor) cells. Exposure to specific environmental precipitants, diverse host genetic risks factors and individual difference in the characteristics of the immune response likely account for the disease's infrequency, variation in its clinical behavior and patterns of responsiveness to the treatment.

Immune mediated T cell destruction of the marrow:

An immune mechanism was inferred decades ago from the recovery of hematopoiesis in patients who failed to engraft after stem-cell transplantation, when renewal of autologous blood-cell production was credited to the conditioning regimen. Also suggestive was that the majority of syngeneic transplantations in which bone marrow was infused without conditioning failed.[8]

Hematopoiesis:

Immune attack leads to marrow failure. "Anhematopoiesis" was inferred from the empty appearance of the marrow at autopsy by the earliest observers of the disease. The pallor of the modern biopsy core or empty spicules of an aspirate, few or no CD34 cells on flow cytometry, and minimal numbers of colonies derived from committed progenitors in semisolid media all reflect the severe reduction in hematopoietic cells that defines the disease. Stem-cell "surrogate"—really correlative—assays, LTC-ICs,[9] or cobblestone forming cells,[10] which measure a primitive infrequent and quiescent multipotential progenitor cell, also show marked deficiency, and from the product of the low percentage of marrow cellularity and the scant numbers of LTC-ICs per mononuclear cell, suggest that only a small percentage of residual early hematopoietic cells remains in severely affected patients at presentation.

Clonal evolution:

Clinically, aplastic anemia may coexist or appear to evolve to other hematologic diseases that are characterized by proliferation of distinctive cell clones, as in paroxysmal nocturnal hemoglobinuria (PNH) or myelodysplasia.

PNH: Fifty percent or more of patients at presentation with pancytopenia have expanded populations of PNH cells, easily detected by flow cytometry due to the absence of glycosylphosphatidylinositol-linked membrane proteins, the result of somatic PIG-A gene mutations.[11]

MDS: Stereotypical patterns of aneuploidy develop in a minority of patients over time: monosomy 7 or trisomy 8 is most characteristic.[12]Trisomy 8 is MDS with many immune abnormalities that resemble aplastic anemia. Patients respond to immunosuppressive therapies, and oligoclonal T-cell expansions are usually present.[13]

Diagnosis:

Pancytopenia on a CBC is the first test. Bone marrow confirms the diagnosis when alternative etiology for pancytopenia is not present. In other words, the marrow is empty of almost all precursor cells as well as evidence of primary or metastatic cancer, infection or fibrosis. The marrow is hypoplastic and fat filled with no abnormal cells.

Treatment:

Bone marrow transplantation should be carried out whenever the patient is young and healthy enough to withstand the procedure and the donor is available. Allogenic transplant cures up to 80-90% of the patient under 50. Immunosuppressive therapy is the treatment for aplastic anemia patient's ineligible for transplantation.[14] This is a combination of anti thymocyte globulin, cyclosporin and prednisone. Outcomes of immunosuppressive therapy are related to patient age: 5-year survival of more than 90% of children has been reported in recent German,[15] Japanese,[16] and Chinese[17] trials, compared with about 50% survival for adults older than 60 years in the collective European experience.[18] The role of hematopoietic growth factors as adjunct to treatment in these patients is unclear. HGF include both hematopoietic colony stimulating factors, i.e. granulocyte colony stimulating factor (G-CSF) and granulocyte-monocyte colony stimulating factor (GM-CSF), and erythropoiesis stimulating agents, i.e. erythropoietin (EPO).

REFERENCES

1. Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. *Blood.* 2006;108:2509-2519.
2. Vaht K, Göransson M, Carlson K, et al. Incidence and outcome of acquired aplastic anemia: real-world data from patients diagnosed in Sweden from 2000–2011. *Haematologica*. 2017;102:1683-1690.
3. Incidence of aplastic anemia: the relevance of diagnostic criteria. By the International Agranulocytosis and Aplastic Anemia Study. *Blood.* 1987;70:1718-1721.
4. Ohta A, Nagai M, Nishina M, et al. Incidence of aplastic anemia in Japan: analysis of data from a nationwide registration system. *Int J Epidemiol.* 2015; 44(suppl_1):i178.
5. Passweg JR, Marsh JC. Aplastic anemia: first-line treatment by immunosuppression and sibling marrow transplantation. *Hematology Am Soc Hematol Educ Program.* 2010;2010:36-42.
6. Hirano N, Butler MO, von Bergwelt-Baildon MS, et al. Autoantibodies frequently detected in patients with aplastic anemia. Blood. 2003;102: 4567-457
7. Feng X, Chuhjo T, Sugimori C, et al. Diazepambinding inhibitor-related protein 1: a candidate autoantigen in acquired aplastic anemia patients harboring a minor populatoin of paroxysmal nocturnal hemoglobinuria-type cells. Blood. 2004; 104:2425-2431.

8. Hinterberger W, Rowlings PA, HinterbergerFischer M, et al. Results of transplanting bone marrow from genetically identical twins into patients with aplastic anemia. Ann Intern Med. 1997;126:116-122.
9. Hirano N, Butler MO, von Bergwelt-Baildon MS, et al. Autoantibodies frequently detected in patients with aplastic anemia. Blood. 2003;102: 4567-4575.
10. Schrezenmeier H, Jenal M, Herrmann F, Heimpel H, Raghavachar A. Quantitative analysis of cobblestone area-forming cells in bone marrow of patients with aplastic anemia by limiting dilution assay. Blood. 1996;88:4474-4480
11. Young NS. Paroxysmal nocturnal hemoglobinuria: current issues in pathophysiology and treatment. Curr Hematol Rep. 2005;4:103-109.
12. Maciejewski JP, Selleri C. Evolution of clonal cytogenetic abnormalities in aplastic anemia. Leuk Lymphoma. 2004;45:433-440.
13. Sloand EM, Fuhrer M, Risitano A, et al. Preferential suppression of trisomy 8 versus normal hematopoietic cell growth by autologous lymphocytes in patients with trisomy 8 myelodysplastic syndrome. Blood. 2005;106:841-851.
14. Gurion R, Gafter-Gvili A, Paul M, Vidal L, Ben-Bassat I, Yeshurun M, Shpilberg O, and Raanani P. Hematopoietic growth factors in aplastic anemia patients treated with immunosuppressive therapy systematic review and meta-analysis. Haematologica 2009; 94:712-719.
15. Fuhrer M, Rampf U, Baumann I, et al. Immunosuppressive therapy for aplastic anemia in children: a more severe disease predicts better survival. Blood. 2005;106:2102-2104
16. Kojima S, Hibi S, Kosaka Y, et al. Immunosuppressive therapy using antithymocyte globulin, cyclosporine, and danazol with or without human granulocyte colony-stimulating factor in children with acquired aplastic anemia. Blood. 2000;96: 2049-2054
17. Fang JP, Xu HG, Huang SL, Chen C, Huang K. Immunosuppressive treatment of aplastic anemia in Chinese children with antithymocyte globulin and cyclosporine. Pediatr Hematol Oncol. 2006; 23:45-50.
18. Tichelli A, Socie´ G, Henry-Amar M, et al. Effectiveness of immunosuppressive therapy in older patients with aplastic anemia: The European Group for Blood and Marrow Transplantation Several Aplastic Anaemia Working Party. Ann Intern Med. 1999;130:193-201