Clinical Presentation and Management of Hemolytic Anemias

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The hallmark of hemolysis is shortened red blood cell survival in the peripheral blood. Hemolysis results in anemia only when bone marrow cannot keep up with the rate of red cell destruction. Even though anemia is very commonly observed in most cancer patients, hemolytic anemias are rather rare.

In hemolytic disorders, the normal life span of erythrocytes in the peripheral blood of 120 days is substantially shortened because of red cell destruction. As a compensatory mechanism, there is increased red blood cell (RBC) production by the bone marrow. Under normal conditions, the bone marrow can increase its capacity for RBC generation severalfold in response to anemia.[1] Shortening of RBC life span does not lead to anemia until a relative bone marrow failure follows with an inability of the marrow to keep up with the loss. Proportional increases in both destruction and generation of RBCs can result in compensated hemolysis without significant anemia. Some of the earliest observations of hemolysis have been the visualization of red-pink urine in patients with such rare conditions as paroxysmal cold hemoglobinuria, march hemoglobinuria, or paroxysmal nocturnal hemoglobinuria (PNH).

Classification and Pathogenesis

Hemolytic anemias can be categorized as acute or chronic, inherited or acquired, by the site of hemolysis (intravascular or extravascular), or by the location of the abnormality responsible for the hemolysis (intrinsic or extrinsic to the red cell). The distinction between inherited and acquired is probably the most useful clinically. Most intrinsic defects are inherited, and most extrinsic ones are acquired. Exceptions to this rule are few and include paroxysmal nocturnal hemoglobinuria (acquired intrinsic RBC defect), and G6PD deficiency (inherited intrinsic defect that depends on an extrinsic factor such as drugs to become evident).

Inherited intrinsic RBC disorders can be due to impairments in membrane structure, glycolytic pathway, glutathione metabolism, hemoglobin structure, or other rare enzyme defects. The acquired hemolytic anemias can be divided into antibody induced, physical injury related, or due to infection, physical agents, chemical agents, hypophosphatemia and liver disease.

The site of hemolysis may be intravascular, in which case the erythrocyte is destroyed in the circulation, or extravascular, in which case the red cell destruction occurs within macrophages in the spleen, liver, or bone marrow (see Table 1). Intravascular hemolysis is typically severe and results from mechanical damage to the red cell due to prosthetic valves, the presence of fibrin within the vasculature (microangiopathic hemolytic anemia), or thermal injury to the erythrocytes from serious burns; infections or toxins, such as Clostridium perfringens bacteremia, severe falciparum malaria, or certain snake venoms; or complement-mediated damage to red cells, as with paroxysmal nocturnal hemoglobinuria, ABO-incompatible blood transfusions, and cold agglutinins.

Intravascular hemolysis liberates hemoglobin into the bloodstream, where it binds to haptoglobin. The haptoglobin/hemoglobin complex is then removed by the liver. A reduced serum haptoglobin level is one of many findings in intravascular hemolysis, but it also occurs in extravascular hemolysis. When the amount of free hemoglobin in the circulation exceeds the binding capacity of haptoglobin, it makes the plasma pink and is filtered through the kidneys. The urine may become red, and proves positive for blood upon dipstick testing in the absence of erythrocytes on urine microscopy. The renal tubular cells, which reabsorb some of the hemoglobin and convert it to hemosiderin, are shed into the urine. Iron stains of urinary sediment demonstrate the hemosiderin within these renal tubular cells and confirm ongoing or recent intravascular hemolysis, even when hemoglobin has become undetectable in the plasma or urine.

Most hemolytic disorders are extravascular. The causes of extravascular hemolysis include infections, drugs, or immunologic processes; red cell membrane defects, such as hereditary spherocytosis; erythrocyte metabolic defects, such as deficiencies in pyruvate kinase or G6PD; and
hemoglobin structural defects, such as sickle cell anemia or hemoglobin C. Another classification of hemolytic anemias distinguishes between disorders intrinsic to the red cell, generally hereditary, and those extrinsic to the red cell, generally acquired. The intrinsic disorders include abnormal hemoglobins, such as HbS or HbC; enzyme defects, such as deficiencies in G6PD; and membrane abnormalities, such as hereditary spherocytosis or elliptocytosis. The extrinsic abnormalities are immunologic—alloantibodies, such as those associated with ABO incompatibility; autoantibodies, as in warm (IgG) or cold (IgM) antibody hemolytic anemias; drug-induced antibodies; mechanical factors, such as trauma from prosthetic valves or fibrin deposition in small vessels, as in microangiopathic hemolytic anemias; infections and toxins, such as falciparum malaria or certain snake venoms; and severe hypophosphatemia. See Table 2 for the causes of hemolysis broken down by the site of abnormality.

Clinical Aspects

Chronic Congenital Hemolytic Anemias

Even though there are numerous congenital hemolytic disorders, their clinical features are very similar. Chronic congenital hemolytic anemias are usually characterized by anemia, jaundice, periodic crises, splenomegaly, and black pigment gallstones.[2] Other than during a crisis, symptoms are usually mild to moderate because of compensation by several organ systems, including the bone marrow. Chronic symptoms may become severe at times of crisis. Aplastic crisis can be induced by infection with human parvovirus type B19 (fifth disease).[3] The presence of the parvovirus-specific IgM antibody in serum is a marker of recent infection. A single infection results in lifelong immunity (IgG). The virus infects and inhibits proliferation of erythroid progenitors, only in the bone marrow (very low reticulocyte count).

The clinical picture can also worsen with increased RBC destruction (splenic crisis) or folate deficiency (megaloblastic crisis). Leg ulcers can be seen with chronic hemolytic disorders, especially with hereditary spherocytosis and sickle cell anemia. When hemolysis is severe during growth and development, as in thalassemia major, marked expansion of the bone marrow may lead to skeletal changes such as tower-shaped skull, thickening of the frontal and parietal bones, dental abnormalities, and other bony distortions.[4]

Acquired Hemolytic Anemias

If hemolytic anemia develops acutely, as in hemolytic transfusion reaction or G6PD deficiency, the symptoms may suggest an acute febrile illness with skeletal pains, headache, malaise, fever, and chills.[5] Symptoms of shock, renal failure, jaundice, and anemia may be evident in severe cases. Usually, however, the symptoms are more gradual and mimic a congenital hemolytic disease. In other patients, symptoms may be more related to the underlying disease, such as lupus, lymphoma, and mycoplasma infection.

Laboratory Observation

Laboratory abnormalities seen with hemolysis can be traced to increased RBC destruction, increased erythropoiesis by the bone marrow, and disease-specific findings. When RBCs are destroyed at an accelerated rate, bile pigments and carbon monoxide are excreted more than usual. The unconjugated bilirubin is elevated, accounting for more than 80% of the total bilirubin, and is not excreted in the urine. Total bilirubin usually does not exceed 4 to 5 units with hemolysis.[6] Unlike in liver disease, in patients with hemolysis pruritus is usually absent. Fecal urobilinogen excretion increases as an indicator of increased bilirubin metabolism in the liver. When plasma hemoglobin levels exceed haptoglobin binding capacity, the plasma turns pink and is filtered into the urine. The urine becomes red and urine iron levels increase. Other than hemolysis, only in hemochromatosis and nephrotic syndrome can one detect increased urinary iron levels.[7,8]

In hemolytic anemias the reticulocyte count is elevated; this is an indicator of accelerated erythropoiesis. Low reticulocyte count is encountered during aplastic crisis despite hemolysis. The mean corpuscular volume (MCV) may be normal or increased, depending on how many large, immature erythrocytes have prematurely left the bone marrow in response to the anemia. The serum lactate dehydrogenase (LDH) level is increased. Of the LDH isozymes, LDH-2 predominates; in megaloblastic conditions LDH-1 is elevated. LDH values lack specificity in hemolysis because many other conditions can result in high levels.

The serum haptoglobin is commonly diminished. Free hemoglobin in the bloodstream binds to haptoglobin. Haptoglobin/hemoglobin complex is then removed by the liver. Haptoglobin is an acute-phase reactant and levels increase in response to inflammation, infection, and malignancy.
Haptoglobin levels decrease in association with not only intravascular hemolysis but also with extravascular hemolysis (sickle cell anemia, RBC membrane, and enzyme disorders), and intramedullary hemolysis (megaloblastic anemia). One needs to be aware of nonhemolytic conditions that can result in low haptoglobin levels (liver disease, hereditary haptoglobin deficiency after red cell transfusions), and normalized haptoglobin levels despite hemolysis (acute phase surges) during work-up of such patients. Glycosylated hemoglobin levels are also reduced in response to hemolysis, and usually reflect hemolysis over the past 4 to 8 weeks. Glycosylated hemoglobin levels are not reliable in patients with diabetes mellitus because of high glucose levels and in patients with anemia due to bleeding because of hemoglobin loss.

Blood smear is the single most valuable test in defining the underlying disorder causing hemolysis. Spherocytes are the hallmark of hereditary spherocytosis, sickle cells of sickle cell anemia, target cells of thalassemia, schistocytes of RBC fragmentation, erythroagglutocytosis of red cell surface damage by complement-fixing antibodies and infections, auto agglutination of cold agglutinin disease, and elliptocytes of hereditary elliptocytosis. Morphologic findings of hemolysis can be confirmed on a blood smear; this may be very helpful in demonstrating polychromatophilia and nucleated red cells, confirming the early departure of red cells from the bone marrow. Abnormalities in red cell shape, such as fragments, sickle cells, spherocytes, or bite cells, provide clues regarding etiology that may be diagnostic or at least highly suggestive of the cause. Other suggestive findings include red cell agglutination, indicating IgM-mediated disease; organisms such as *Plasmodium falciparum* or *Babesia*; and erythroagglutocytosis, seen especially with red cell damage from immune mechanisms but also with certain infections or toxins. The bone marrow usually shows erythroid hyperplasia.

Tests useful in suspected intravascular hemolysis include evaluation of the plasma and urine for hemoglobin and an iron stain of the urine sediment to detect hemosiderin. For immune-related hemolytic anemia, the Coombs test to demonstrate IgG and complement on the red cell or in the serum, and the cold agglutinin test looking for IgM are indicated. A positive Coombs test (direct antiglobulin test [DAT]) indicates that RBCs are coated with IgG or complement, hence an immune etiology for hemolysis. Very rarely a DAT will be negative in immune hemolytic anemia if the amount of globulin on the RBC surface is very low.

With suspected hemoglobinopathies, a hemoglobin electrophoresis is appropriate. An osmotic fragility test may help when hereditary spherocytosis is suspected. Special stains on blood smear to identify Heinz body formation (precipitation of hemoglobin to form inclusions) can help identify patients with G6PD deficiency, unstable hemoglobin disease, and thalassemia. Other laboratory evaluations depend on the likely abnormality and may include searching for rare enzyme defects.

The following is a brief review of some of the major categories of hemolytic disorders.

**RBC Membrane Disorders**

**Hereditary Spherocytosis**
Hereditary spherocytosis is a quantitative defect in the RBC membrane resulting in an aberrant vertical interaction between the skeleton and lipid bilayer. The abnormal red cell membrane is partially digested by the macrophages giving rise to spherocytes, hemolysis, and splenomegaly. Patients have lifelong hemolysis. Diagnosis is established by peripheral smear findings and an osmotic fragility test. Patients with symptomatic disease can be treated with splenectomy.

**Hereditary Elliptocytosis**
Hereditary elliptocytosis is caused by horizontal defects in the RBC membrane. It is usually a milder disease than hereditary spherocytosis.

**Acanthocytosis**
Acanthocytosis is usually seen with chronic liver disease, and is the result of cholesterol accumulation in the red cell membrane.

**RBC Metabolic Disorders**

**Pyruvate Kinase Deficiency**
Pyruvate kinase deficiency is a rare hemolytic disorder caused by abnormalities in the glycolytic pathway. Patients usually have chronic hemolysis without acute events.

**G6PD Deficiency**
G6PD deficiency is a more common disorder mostly affecting males (only rarely females). Hemolysis and anemia occur only under various stress conditions such as infection, metabolic problems, drugs, and favism. Acute intravascular hemolysis, Heinz body development, and bite cells are the
characteristics of the disease.

**Wilson’s Disease**

Wilson’s disease is characterized by neurologic symptoms, hemolysis, hepatomegaly, low ceruloplasmin levels and copper overload. Hemolysis occurs as a result of inhibition of glycolysis.

**Congenital Hemoglobinopathies**

**Sickle Cell Anemia**

Sickle cell anemia, the most common hemoglobinopathy, occurs with the inheritance of a beta gene from each parent. This gene, which encodes the beta-globin subunit of hemoglobin, is most prevalent in the populations of tropical Africa, but also occurs in people from Mediterranean countries, Saudi Arabia, and portions of India. In the United States, the gene is present in about 8% of blacks and, accordingly, sickle cell anemia (the homozygous state) occurs in about 1 of 625 black infants.

Because of a single substitution of an amino acid in this gene abnormality, the hemoglobin produced differs from hemoglobin A in having a valine, rather than glutamic acid, in the sixth position from the N terminal of the beta chain. This results in beta-globin tetramers that tend to aggregate. The disease is not evident during intrauterine life because beta chain synthesis begins after birth. When deoxygenated, this abnormal hemoglobin aggregates into large fibers that make the red cell rigid and give it the classic sickle cell shape. In addition, damage to the erythrocyte membrane occurs, producing dehydrated, shrunken cells that may permanently sickle. These factors lead to chronic hemolysis.

Sickle cell trait is caused by having one mutated gene and one normal gene. In patients with sickle cell trait, hemoglobin electrophoresis usually reveals about 60% hemoglobin S and 30% hemoglobin A. In the homozygous state, about 90% is hemoglobin S.

When the deoxygenated, abnormal cells adhere to the vascular endothelium, they can obstruct the circulation, leading to ischemia or necrosis of areas that these vessels supply. Such vascular occlusion accounts for most of the clinical features of this disease. One manifestation is painful crises, which commonly last 4 to 5 days and may involve any tissue but especially the skeleton, abdomen, and chest. Involvement of vessels to the bones causes progressive discomfort, especially in the humerus, tibia, and femur, but also the ribs, causing thoracic pain. Sometimes vascular occlusion causes marrow necrosis and the release of fat particles (emboli) that travel to the lung or other areas. Abdominal crises probably arise from infarcts to the mesentery and abdominal organs, including the spleen.

Some acute events can cause sudden worsening of anemia. In aplastic crises fever occurs and red cell production markedly diminishes, resulting in a rapid decrease in circulating erythrocytes as the chronic hemolysis continues. The most common cause is infection with parvovirus B19, which directly damages the erythroid precursors. Patients typically recover in 5 to 10 days. A megaloblastic crisis can also develop, in which folate deficiency from inadequate nutrition or concurrent alcoholism decreases erythropoiesis. Bone marrow infarction, chronic renal failure, and iron deficiency can also contribute to the degree of anemia.

Early in life, the dorsa of the hands and feet can swell (dactylitis), often accompanied by fever and leukocytosis; the mechanism is probably avascular necrosis of the bones. Children may also experience episodes of acute splenic sequestration in which red cells abruptly accumulate in the spleen, causing pain, splenic enlargement, and increased anemia. As patients age, the spleen becomes shrunken, scarred, and nonfunctional because of repeated infarcts, and sequestration no longer occurs.

Another sudden event is the acute chest syndrome, characterized by fever, shortness of breath, chest pain, leukocytosis, and pulmonary infiltrates. Acute chest syndrome is often self-limited, but on occasion can lead to severe pulmonary failure and death. Several entities can cause this condition, including infections, pulmonary vascular occlusion, and fat emboli. In some cases the chest pain arises from rib infarcts.

Central nervous system crises can manifest as stroke, bleeding, or seizures, especially in children, and they tend to recur. The predominant cause is occlusion of the major cerebral vessels, but sometimes they arise from subarachnoid or intracerebral hemorrhage. Priapism can develop in both pre- and postpubertal males. Episodes are usually short-lived but often recurrent, and occur from stagnation of blood in the corpora cavernosa. Repeated episodes may lead to fibrosis and impotence.

With repetitive episodes or chronic ischemia, permanent tissue damage can occur in many other
locations. Avascular necrosis of the femoral head causes persistent pain and abnormal gait, and involvement of the humeral head typically produces protracted shoulder discomfort. Ischemic or necrotic bone predisposes to osteomyelitis, especially from *Salmonella* species. Damage to the kidneys can produce an inability to concentrate the urine normally (hyposthenuria) and impair excretion of hydrogen ion (renal tubular acidosis). Hematuria may occur, sometimes associated with renal papillary necrosis, which also predisposes to urinary infections. Sloughing of the papillae can lead to urinary tract obstruction.

Eye complications include proliferative retinopathy because of chronic ischemia, visual loss, and vitreous hemorrhage. Persistent or recurrent painful ulcers sometimes form over the distal leg, especially above the malleoli, usually in adulthood. These ulcers are more common in males than in females and typically have a deep base with raised margins. Another common finding in older patients is bilirubin gallstones, a complication of chronic hemolysis.

Sickle cell anemia predisposes patients to infections, not only because of the presence of ischemic or necrotic tissues but also because of decreased splenic function, which impairs antibody production and splenic phagocytosis of organisms. The alternate complement pathway may also be faulty. In childhood the most common serious infections are from *Streptococcus pneumoniae*. The anemia is normochromic, normocytic, and associated with a hematocrit typically in the range of 15% to 33%. Mild leukocytosis, with increased neutrophils, and thrombocytosis are common. The reticulocyte count is usually 10% to 20%. The blood film characteristically demonstrates the crescent-shaped sickle cells, target cells, polychromasia, basophilic stippling, macrocytosis (due to large immature red cells), and nucleated red cells. Except in very young children, Howell-Jolly bodies are usually seen, indicating splenic hypofunction from recurrent infarctions and splenic fibrosis. The presence of macroversicles, polychromasia in several erythrocytes, and the nucleated red cells indicate early release of erythrocytes from the bone marrow secondary to a severe anemia.

Vaccinating to prevent infections, optimizing vitamin and iron levels, managing pain during painful crises, and maintaining adequate hydration and oxygen support are the principles of treatment for patients with sickle cell anemia. Exchange transfusion is usually considered in patients with central nervous system crisis, acute chest syndrome, embolism, refractory priapism, ocular events, complicated pregnancy, and pending major medical procedures that may induce a severe crisis. Hydroxyurea treatment can reduce pain crises, chest syndrome, and transfusion needs.

**Hemoglobin C Disease**

Hemoglobin C disease is the result of a mutation in the beta-globin. Hemoglobin C occurs commonly in West Africans and in about 2% to 3% of African-Americans. Patients may be homozygous (CC), heterozygous with normal hemoglobin A (hemoglobin C trait), heterozygous with sickle cells (SC disease), or heterozygous with beta-thalassemia. Red cells containing hemoglobin C are abnormally rigid, and their fragmentation may lead to microspherocytes. Their life span is shortened to about 30 to 35 days.

In patients with hemoglobin C trait, anemia is absent. Blood smears show increased target cells and sometimes hypochromic, microcytic erythrocytes. Hemoglobin electrophoresis typically demonstrates that 30% to 40% of the hemoglobin is type C and 50% to 60% is type A. In homozygous (CC) disease, splenomegaly is usually present. Both aplastic crises and cholelithiasis may occur. Mild to moderate hemolytic anemia is present, with hematocrit being about 20% to 30% and reticulocyte count typically 2% to 6%. The erythrocytes may be microcytic and are usually dense, as detected in an increased mean corpuscular hemoglobin concentration. Target cells are abundant, and numerous small, dense, and irregularly shaped red cells are present. Crystals of oxygenated hemoglobin C are sometimes visible on peripheral smears as brick-shaped objects, usually within an erythrocyte otherwise devoid of hemoglobin. Polychromatophilia and nucleated red cells, consistent with hemolysis, may be apparent. On electrophoresis, hemoglobin C predominates, A is absent, and F is slightly increased.

With hemoglobin C/beta-thalassemia, mild to moderate hemolytic anemia is typical. The blood smear shows microcytosis, hypochromia, target cells, and the small, irregular erythrocytes described above. Hemoglobin C crystals may be visible as well. Electrophoresis typically demonstrates 65% to 80% hemoglobin C, 20% to 30% hemoglobin A, and 2% to 5% hemoglobin F.

**Hemoglobin SC Disease**

Although the red cells in hemoglobin SC disease sickle, causing vascular occlusion, this disorder is milder than sickle cell disease, and life expectancy is nearly normal. It occurs in about 1 in 800 black infants in the United States. Acute painful episodes (crises) are less frequent and typically shorter than in sickle cell disease. Aseptic necrosis of the humeral and femoral heads, however, may occur. The spleen is usually enlarged and, although susceptible to infarcts, does not become obliterated as
in sickle cell disease. Patients with SC disease may suddenly develop the acute splenic sequestration syndrome, especially when at high altitudes: red cells rapidly accumulate in the spleen, causing abdominal pain, progressive splenic enlargement with tenderness, and abrupt decreases in hematocrit, sometimes producing shock.

Patients have a mildly enhanced susceptibility to infections, primarily with *Streptococcus pneumoniae* and *Hemophilus influenzae*. Spontaneous abortions are increased, but the leg ulcerations and neurological complications seen in sickle cell disease are uncommon. Proliferative retinopathy, however, is more frequent in sickle cell disease than in sickle cell anemia. The hematocrit typically exceeds 27%, and the red cells are usually normocytic, but denser than normal, with an increased mean corpuscular hemoglobin concentration characteristic of erythrocytes containing hemoglobin C. Target cells are numerous. "Billiard ball" cells, in which a round mass of hemoglobin appears in the erythrocyte with a clear space separating the mass from the red cell membrane, are a characteristic finding. The erythrocytes are often dense and disfigured, sometimes with branching projections, and they may contain clusters of hemoglobin C crystals of various sizes and shapes, which create straight edges and blunt angles. Sickle cells, boat-shaped cells, and nucleated red cells are other findings. Polychromasia may be present, and in those with functional asplenia, Howell-Jolly bodies are visible. Hemoglobin electrophoresis reveals about equal amounts of hemoglobin C and hemoglobin S.

**Hemoglobin E Disease**

Hemoglobin E disease is the second most prevalent hemoglobinopathy, and it is mostly seen in Southeast Asia. Patients are usually asymptomatic with mild anemia, markedly low mean corpuscular volume levels and high numbers of target cells.

**Thalassemias**

Mutations or deletions in one globin gene lead to quantitative deficiency of that chain causing an imbalance between alpha and beta chains. In alpha-thalassemia, one through four of the four alpha genes are deleted, the number of genes deleted directly correlates with the severity of the disease. When all four alpha genes are deleted neonatal death occurs (hydrops fetalis). In beta-thalassemia, on the other hand, there is no intrauterine disease because beta chain synthesis begins with birth. Beta-thalassemia patients can have thalassemia trait, intermedia, or major types depending on the level of hemoglobin A synthesis. Further details of laboratory and clinical aspects of thalassemias are beyond the scope of this review.

**Red Cell Fragmentation Syndromes**

Shear forces within the cardiovascular system can slice off portions of the circulating red cells.[15] The erythrocytes then seal their membranes to form fragmented cells (schistocytes). Injured red cells may appear as triangles, helmet cells, microspherocytes, crescents, or other irregularly shaped erythrocytes that phagocytes remove prematurely from the circulation. The amount of red cell destruction may be sufficient to cause intravascular hemolysis, with hemoglobinemia, hemoglobinuria, and the presence of hemosiderin in the urine. The erythrocyte damage can occur in the heart and great vessels or in the microcirculation.

The most common cardiac etiology is the presence of a prosthetic valve, usually a mechanical device in the aortic position, often associated with regurgitation. Occasionally, the abnormality is severe aortic stenosis of a native valve, coarctation of the aorta, or an intracardiac patch made from artificial material used to correct anomalies such as septal defects. In each of these situations, excessive turbulence damages the erythrocytes. With chronic mild hemolysis anemia is absent or slight, the red cells are normal or show some macrocytosis from the presence of immature cells, polychromatophilia is present, and the reticulocyte count is elevated. With more severe hemolysis, erythrocyte fragments appear on the blood smear, the anemia is moderate to profound, the serum bilirubin and LDH levels rise, haptoglobin decreases, and hemosiderin appears in the urine. With protracted intravascular hemolysis, urinary hemoglobin loss may cause iron deficiency, with hypochromic, microcytic red cells.

When diseases affecting the small vessels produce fragmented red cells, the term used is microangiopathic hemolytic anemia. In these disorders, endothelial damage or fibrin deposition in the small vessels damages the red cells as they traverse the abnormal vasculature. One cause is disseminated cancer usually a mucin-producing neoplasm. Especially common is gastric carcinoma, which accounts for about 50% of cases. Most of the other malignancies producing microangiopathic hemolytic anemia originate from the breast, lung, and pancreas. About one-third of patients have
leukoerythroblastosis on the blood smear, about one-half have laboratory evidence of disseminated intravascular coagulation, and about 60% have tumor cells detectable on bone marrow specimens. Some medications can cause microangiopathic hemolytic anemia, such as mitomycin (Mutamycin) and ticlopidine (Ticlid). The disease usually begins several weeks to months after initiation of the drug, renal failure and thrombocytopenia are common, and laboratory evidence of disseminated intravascular coagulation is absent. A similar syndrome may occur after solid organ or bone marrow transplantation, possibly precipitated by the preceding cytotoxic medications and total-body irradiation used in preparation for the transplant procedure.

Other common causes of microangiopathic hemolytic anemia are thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, malignant hypertension, disseminated intravascular coagulation, and severe hypertension during pregnancy (preeclampsia or eclampsia). Immunologic damage to the vessels that occurs in such disorders as systemic lupus erythematosus, Wegener’s granulomatosis, systemic sclerosis, and microscopic polyangiitis can cause microangiopathic hemolytic anemia. It also may arise from the abnormal vasculature of a giant hemangioma (Kasabach-Merritt syndrome) or a hepatic hemangioendothelioma. Platelets can be markedly diminished as well.

### Immune Hemolysis

#### Warm-Antibody Acquired Autoimmune Hemolytic Anemia

In autoimmune hemolytic anemia (AHA), RBC life span decreases because autoantibodies (usually polyclonal IgG) are optimally active against erythrocytes at body temperature. These warm antibodies account for about 80% to 90% of acquired autoimmune hemolytic anemia, and only about 10% are caused by antibodies maximally active at lower temperatures (cold-reactive autoantibodies).[16] In about one-half of cases, an underlying disorder is present—most commonly a lymphoproliferative disease such as chronic lymphocytic leukemia or lymphoma, but also systemic lupus erythematosus, Wegener’s granulomatosis, systemic sclerosis, and microscopic polyangiitis. Certain drugs can also play a role in the development of these warm antibodies and hemolysis: levodopa (Dopar, Larodopa) and penicillin can cause IgG, and quinidine can cause IgM-type antibodies and AHA.

In warm AHA, IgG coats many red cells with or without complement. Macrophages in the spleen and Kupffer cells in the liver trap these erythrocytes, sometimes ingesting them whole. More commonly, they remove a portion of the membrane, and the surviving red cell re-forms as a spherical cell with a smaller diameter. These spherocytes are seen on peripheral blood smear, which also discloses evidence of polychromatophilia, indicating the release of immature red cells from the bone marrow. Erythrocyte fragments, nucleated red cells, and hemophagocytosis by monocytes may also be visible. In addition to anemia, the automated blood count often reveals an increased mean corpuscular hemoglobin concentration, reflecting the presence of the spherocytes. The reticulocyte count is usually increased, as are the serum indirect bilirubin and LDH levels. Immature white cells occasionally appear on the peripheral smear. In Evans’ syndrome, immune thrombocytopenia is also present.

The direct antiglobulin test detects the presence of antibodies and complement on erythrocytes by using a reagent that contains antibodies directed against human immunoglobulin and complement components (primarily C3). This test is nearly always positive in warm AHA, but when IgG is present in very small quantities, other diagnostic techniques may be necessary to detect them. Autoantibodies unattached to erythrocytes may be present in the serum and are detectable by incubating the patient’s serum or plasma with normal red cells, to which the antibodies then attach. These erythrocytes are then tested for the presence of autoantibodies with the Coombs reagent. This is the indirect antiglobulin or Coombs test.

Treatment of AHA will depend on the underlying etiology if one can be identified. Patients with warm AHA usually respond to prednisone. In patients who are refractory to prednisone, intravenous immunoglobulin, danazol, plasma exchange, splenectomy, and cyclophosphamide (Cytoxan, Neosar) can be considered as other options. Recently, the CD20 antibody rituximab (Rituxan) has been found to be effective in AHA associated with lymphoproliferative disorders.

#### Cold Agglutinin Disease

Cold agglutinins are IgM antibodies that bind red cells at cold temperatures. They may be polyclonal or monoclonal. Nearly all healthy people have low titers of clinically insignificant polyclonal cold agglutinins. Cold AHA can be idiopathic or secondary (infection, lymphoma).[17] In certain infections, transient, high titers of polyclonal cold agglutinins appear, causing the abrupt onset of anemia.
that is short-lived, but occasionally severe. Cold agglutinin disease is mediated by a complement-fixing monoclonal IgM antibody either in an acute (mycoplasma or Epstein-Barr virus infection) or chronic setting (lymphoproliferative disorders).

Infectious mononucleosis (IgG or IgM) and infections with *Mycoplasma pneumoniae* (IgM) are the two most common causes; the target of the antibodies in the former is typically the i antigen found on the red cell membrane of fetal erythrocytes, while that in the latter is the I antigen found on adult erythrocytes. Hemolysis is usually intravascular and in the liver. Agglutination is seen when blood is cooled. Splenomegaly is rare.

The chronic form of cold agglutinin disease typically occurs in older adults, and many have an underlying B-cell neoplasm, such as Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia, or non-Hodgkin's lymphoma. Exposure to cold may precipitate attacks of acrocyanosis created by agglutination of erythrocytes in cool peripheral areas such as the fingers, toes, nose, and earlobes. It may also cause worsening anemia as the temperature-dependent IgM antibody activates the complement pathway on the red cell membrane, producing intravascular hemolysis, sometimes with sufficient hemoglobinuria to cause acute renal failure. Ordinarily, however, the anemia is mild and stable for the following reasons: (1) the antibody binds to erythrocytes only at temperatures below normal body temperatures; (2) hepatic macrophages do not avidly phagocytize red cells coated with Cd3, the usual complement component on the membrane; and (3) the serum Cd3 inactivator system degrades Cd3 into components even less tempting to the macrophages. Hemolysis in cold AHA is usually refractory to steroids or splenectomy. Plasmapheresis or chemotherapy may be necessary to control the hemolysis in severe cases.

**General Therapeutic Considerations**

Appropriate management of hemolytic anemia depends on the specific diagnosis. Thus, initial efforts should focus on reaching a diagnosis rapidly along with supportive care measures. Supportive care measures should involve measures to avoid shock and fluid/electrolyte imbalance, and measures to ensure adequate renal and cardiovascular function. Risks and benefits of blood transfusion should be carefully determined, since transfused blood may worsen the hemolysis and promote end-organ damage.

Appropriate blood-banking procedures are invaluable in managing patients with hemolytic anemia. Because the spleen is often a major site of RBC destruction, splenectomy may bring relief. This is especially true in patients with RBC membrane disorders, enzyme deficiencies, immunohemolytic anemias, and some unstable hemoglobin disorders. Patients with splenomegaly respond better to splenectomy than those patients without a palpable spleen. Steroids can be very effective in immunohemolytic anemias. In patients with chronic hemolysis, folic acid supplementation can prevent megaloblastic crisis.

**References:**


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