Chapter 2
Anemia

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Anemia is not a disease by itself but a condition that is a consequence of acquired or genetic abnormalities. Functionally, anemia is defined as an insufficient red cell mass to deliver adequate amount of oxygen to organs and peripheral tissues, and, for practical reasons, an Hb concentration less than 14.0 g/dL for men and 12.0 g/dL for women. At present, Hb concentration, as well as other red cell parameters, is determined by electronic cell counters able to deliver the results in few minutes. In most patients, blood determination of Hb levels is useful for assessing anemia, but there are some limitations that must be recognized:

1. Hb changes may reflect altered plasma volume, not a change in red cell mass. In pregnancy, for example, the increased plasma volume decreases the Hb concentration and, in fact, total red cell mass is increased but to a lesser degree than plasma volume. Likewise, very often the critically ill patient is hyper-hydrated to avoid dangerous hypotension or shock;

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this common therapeutic approach determines an increase of plasma volume and reduces Hb concentration and the degree of anemia may appear severe. Conversely, burn patients, through the injured skin, lose plasma and not red cells; therefore, Hb concentration appears normal or even high while the red cell mass could be decreased.

2. Several abnormal Hb have altered ability to bind and to release the oxygen and this is associated with different Hb concentrations. The carriers of Hb with high affinity for oxygen show levels of Hb higher than normal, while the carriers of Hb with decreased oxygen affinity (and better oxygen delivering to tissues) have lower than normal Hb levels.
3. There are several pathological conditions that determine a compensatory increase of red cell mass, the most common are the emphysema (and similar pulmonary diseases) or the right-to-left cardiac shunt (often unknown). These patients have abnormally elevated Hb levels; therefore, a normal Hb level may represent an "anemia" since tissue oxygenation is impaired. Conversely, the patients with hypothyroidism (decreased oxygen needs) may have low Hb level with adequate oxygen delivery to tissues.
4. Acute blood loss is another example of the problem of evaluating anemia by the Hb concentration. In fact, immediately after blood loss, the Hb is normal because the compensatory response to acute hemorrhage is the vasoconstriction. Therefore, the decrease of the Hb concentration begins after 4–6 h. The recognition of this situation is generally easy for the patients recovered in intensive care units since they are monitored in a continuous fashion.

Once the diagnosis of anemia is defined, the cause of this condition must be identified. The classification of the anemia is not simple, but a useful approach could be to ask several questions stepwise (Fig. 2.1).

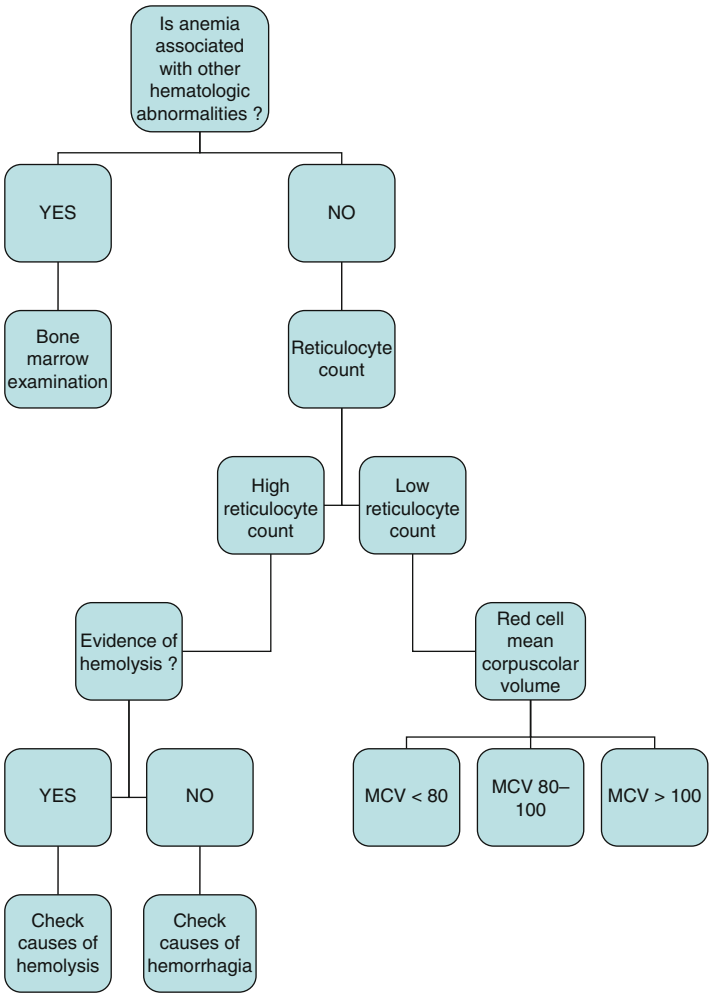

Fig. 2.1 Diagnostic algorythm for anemia

The first question is whether anemia is associated with other hematological abnormalities such as low platelet levels and/or low leukocyte counts and/or presence of abnormal leukocytes (blasts) on blood smear. If this is the case, the presence of bone marrow failure (aplastic anemia) or of malignant hematological disorders such as acute leukemias or myelodysplastic syndromes is likely. In these cases, the bone marrow biopsy and the appropriate cytometric studies of marrow and peripheral blood are mandatory.

The second question is whether anemia determined is associated with an appropriate reticulocyte response. The reticulocyte count is important to evaluate the new red cell production and is very helpful in determining the marrow response to anemia. Very often the reticulocyte count is lacking for the evaluation of the anemic conditions, while this test has a crucial role in the diagnostic process. Until a few years ago, the red blood cells were stained with brilliant cresyl blue, which allows the visualization of ribosomes and reticulin network, thereafter the blood smear was examined by microscope with manual count of stained cells. This method was time-consuming and often the responses were delayed, thus reducing the clinical impact of the test. Lately, automated reticulocyte analyzers are available; these counters have a higher degree of precision than can be achieved manually and, in addition, the responses are immediate. These automated reticulocyte counters may show errors in few rare conditions as the case of presence of Heinz or Howell-Jolly bodies inside red cells. Much more important than the percentage of reticulocytes is their absolute count, which can be easily determined starting from the red cell count: absolute reticulocytes count = % of reticulocytes × red cells count/L^3. The value over 100×10^9/L is indicative of a bone marrow responding normally to hemolysis or blood loss. If the anemia is associated with a poor reticulocyte count (less than 25×10^9/L), an impaired red cell production is likely.

2.1 Anemias with High Reticulocyte Count

In the case of high reticulocyte count, the subsequent question is: Is there evidence of hemolysis or not? The laboratory tests used to identify a hemolytic process are available easily in any hospital: *Serum unconjugated bilirubin*, *serum lactic dehydrogenase* (*LDH*), and *serum aptoglobin*. These tests are related to the red cell increased destruction rate and, in most patients, are indicative of a hemolytic process, but in critically ill patients may be misleading. An increased level of total and unconjugated bilirubin is a common finding in intensive care units for several reasons: prolonged fasting or artificial nutrition, hypotension or shock with reduced liver blood flow, heart failure or tamponade with secondary liver venous stasis, hepatosplenic blood flow modification by endotoxemia or peritonitis, portal thrombosis, preexisting chronic liver diseases, and other less common causes. LDH is an enzyme not specific to the red cells, and it can be found in any organ and tissue; therefore, any cytolitic process is able to increase LDH serum levels. In critically ill patients, high of very high level of serum LDH can be found very easily due to crush syndrome with muscle necrosis, lung inflammatory processes, chronic and acute viral liver diseases or acute cholestasis, fatty liver, sepsis, myocardial ischemia, bone fractures, and others. In addition, high LDH levels without evidence of disease can be found in about 3 % of normal people. The LDH isoenzymes could be useful for determining the involved tissue, but this test is not available in most hospitals and it is used for research purposes only. In conclusion, LDH is not trustworthy in the context of the critically ill patient. The haptoglobin is a protein synthesized by the liver, and it is able to bind to Hb when this molecule is released in the plasma (like occurs in hemolysis). The complex haptoglobin-Hb is removed by the hepatocytes. Despite the presence of haptoglobin in serum only, this protein decreases or becomes undetectable in

case of both intravascular and extravascular hemolysis. Serum haptoglobin determination is useful in the diagnostic path of the majority of patients, but in the intensive care units the interpretation of its levels is complicated and its diagnostic power is significantly reduced. In fact, haptoglobin is an acute-phase protein, therefore, its synthesis increases in response to inflammation, infections, or malignant diseases. Taking into account these characteristics, in critically ill patients, the increased synthesis of this protein due to sepsis, infections, inflammatory states of various etiologies, may overcome the decrease induced by hemolytic process. Conversely, abnormal low levels of haptoglobin can be found in the absence of hemolysis in the case of malnutrition or of the other clinical situations characterized by abnormal protein loss like occurs after extensive burns or for nephritic syndrome; by preexisting chronic liver disease; or by the impossibility of a normal aliment absorption like occurs in large intestine resections for vascular disease or for accident perforation, events not uncommon in the intensive care units. In conclusion, the usual laboratory tests used to identify a hemolytic process are have a limited diagnostic value in the intensive care setting and, often, additional tests and a careful follow-up of the patient are needed for a correct diagnosis. Even the diagnosis of posthemorrhagic anemia may be difficult in these patients. In fact, after an acute blood loss, the plasma volume and red cell mass are reduced in proportional amount; consequently, the Hb concentration does not change. Therefore, the amount of blood loss can be underestimated by the degree of anemia, especially early. In the days following the blood loss, the reticulocyte count is normal and increases only after 6–10 days; in this "window," even the iron stores are unmodified, and mean corpuscular volume is still normal. An external hemorrhage sufficient to determine anemia is usually evident, but internal bleeding may be less apparent. If the hemorrhage occurs in retroperitoneal space, into a body cavity or in a cyst, the decrease of Hb level may be a diagnostic problem. In

addition, the breakdown and the absorption of red cell in the tissues are able to increase indirect bilirubinemia, and this picture, along with high reticulocyte count, can be confused with a hemolytic anemia. Therefore, a careful follow-up of the patient and appropriate tests are mandatory for a correct diagnosis.

If repeated tests confirm high reticulocyte counts (in the absence of blood loss) and a possible hemolytic process is suspected, the main causes of hemolysis should be carefully checked. Since in the adult patients the most common acquired hemolytic disorders are the immune-mediated processes, the direct anti-globulin test (Coomb's test) should be determined. Thereafter, the diagnostic process can be separated for the patients with positive and negative direct anti-globulin test.

2.1.1 Patients Positive for Direct Anti-globulin Test

These cases have presumably an immune-hemolytic anemia and can undergo immediate glucocorticoids therapy, which remains the treatment of choice of this immune disorder. Intravenously administered doses of 1.0 mg/kg b.w. of methyl-prednisolone daily are efficacious in most cases. The response may not be evident for several days and an increase of Hb level can be noticeable only after 7 days of treatment. A further delay in the response is expected in critically ill patients since many acute factors may interfere in the red cell production like prolonged fasting or artificial nutrition, hypotension, reduced liver blood flow, acute renal failure with reduced erythropoietin production, endotoxemia or other acute stress situations. In the rare cases of lack of response or in the case of worsening of the hemolytic process, high-dose i.v. immunoglobulin administration (1 g/kg b.w.) can be useful in decreasing the clearance of the red cells by the monocyte macrophage system. This therapy can be repeated after 1 or 2 weeks if required.

2.1.2 Patients Negative for Direct Anti-globulin Test

In these cases, the clinical history (when available) is helpful to exclude the exposure to chemical or physical agents; thereafter, some infections (malaria, leishmaniasis, trypanosomiasis, bartonellosis) should be taken into consideration in white people back from recent adventure travels in the third world or in people shortly after arriving from Africa or from other underdeveloped countries. In critically ill patients, the septicemia of Clostridium perfrigens should be taken into consideration, in fact it may occur after traumatic wound infections, necrotizing enterocolitis, genitourinary or gastrointestinal surgery, and other acute severe conditions. In this case, a severe, often-fatal, hemolytic anemia occurs with a massive hemolysis, and hemoglobin concentration may fall to a very low level in a matter of hours. The diagnosis is suspected when high fever, jaundice, and anemia occur together in a patient of the intensive care unit. The clostridial infection responds well to antibiotics therapy but the treatment must be started as quickly as possible, even before the blood culture results are available.

After the exclusion of these infective causes with appropriate tests, the other causes of nonimmune hemolytic anemia should be considered. For the diagnosis of the most common diseases, a few laboratory investigations are needed:

1. Hb electrophoresis
2. Osmotic fragility test
3. Red cell enzyme determination
4. Blood smear examination

The Hb electrophoresis may indicate the presence of genetic diseases like sickle cell anemia, or thalassemia or of the rare conditions associated with abnormal Hb (Hb C, SC, D, SD, and

E). The osmotic fragility test is able to discover the spherocytic anemia and related disorders, and, finally, the enzyme determination is useful to detect the glucose-6-phosphate deficiency (G6PD), known as favism, or pyruvate kinase deficiency. All these conditions are inherited diseases; some of these are common in Italy like thalassemias or favism, while others are very rare in Europe, like sickle cell anemia or the unstable Hb diseases. All these diseases worsen the degree of anemia in patients in critical medical conditions and should be recognized to avoid unnecessary support treatments or delay in discharging the patient fearing covert bleeding.

The blood smear examination by microscope is a disregarded tool, which, on the contrary, is able to give important information on the etiology of many hematological disorders even in the setting of the intensive care units. In the case of patients with overt hemolysis and negative for the direct anti-globulin test, the blood smear is very important for the diagnosis of the so-called *fragmentation hemolysis*, a relatively common condition in the critically ill patient.

When the red blood cells are subjected to physical trauma, as occurs in the alterations of heart or for the appearance of microvascular thrombi in small vessels, they may undergo fragmentation, thereby resulting in hemolytic anemia. In these cases, the blood smear shows characteristic fragmented red blood cells named schistocytes; these cells have a crescent shape or take the form of triangles or helmets or other bizarre forms. The identification of the presence of schistocytes is very important since usually there are not other diagnostic tools to recognize the clinical condition characterized by the fragmentation hemolysis. The main causes of red cell fragmentation are indicated in Table 2.1. As shown, only a fraction of the pathological conditions indicated in the table are associated with acute diseases that can be found in the intensive care units; in the following paragraphs only these conditions will be discussed, since the others are outside the scope of this book.

Table 2.1 Clinical condition associated with fragmentation hemolysis

Heart and great vessels abnormalities
Synthetic valvular prostheses (especially aortic)
Unoperated valve diseases (especially aortic stenosis)
Teflon patch repair of atrio-ventricular defects
Ruptured chordae tendineae
Valve porcine xenografts or homografts or xenobioprostheses
Coarctation of aorta
Small vessel diseases (*microangiopathic hemolytic anemias*)
Thrombotic thrombocytopenic purpura (Moshkowitz's disease)
Hemolytic uremic syndrome
Disseminated malignant disease
Transplant-associated microangiopathy
Malignant hypertension
Disseminated intravascular coagulation
Giant hemangiomas and liver hemoangioendothelioma
March hemoglobinuria
Pregnancy-associated thrombotic microangiopathy
HELLP syndrome
Pregnancy-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome
Autoimmune diseases
Lupus erythematosus
Wegener granulomatosis

2.2 Heart and Great Vessels Abnormalities

Many patients, after open-heart surgery, are recovered in the intensive care units; therefore, in the management of these patients, medical staff should be able to recognize the laboratory signs of fragmentation hemolysis. In fact, some patients, soon after surgery, develop anemia of different severity. The incidence of hemolysis is reported to be variable ranging from 5 to 25 %. This great variability depends on the method used for detecting hemolysis, lower if only haptoglobin level is determined, higher if more sophisticated methods, like red cell

survival, are available. Several mechanisms are involved in the hemolysis, but all are referable to high turbulence. When the lumen of the aortic prosthesis is small relatively to the stroke volume, a shearing stress higher than 3,000 dyn/cm^2 can easily be generated and this determines mechanical hemolysis. The presence of a severe fragmentation hemolysis with anemia requiring transfusions immediately after open-heart surgery often indicates malfunction of valvular prosthesis. Since this condition does not improve spontaneously, a prompt surgery and valve replacement is indicated. Awaiting the surgery, the patients must be kept at bed rest since hemolysis becomes worse after even slight physical activity.

2.3 Thrombotic Thrombocytopenic Purpura (TTP)

This disease is characterized by disseminated microvascular thrombi in small vessels and by a syndrome including hemolytic anemia, severe thrombocytopenia, neurological symptoms, renal dysfunction, and fever. At the time of presentation, the clinical conditions of the affected patients can be critical; therefore, they are often recovered in intensive care units. Excluding the very rare inherited forms (Upshaw-Shulman syndrome) that appear during childhood, TTP has a peak of incidence between 30 and 40 years. Like most autoimmune diseases, TTP is more common in women than in men (ratio of 2:1). The pathogenesis of the TTP has been clarified in the past years. The von Willebrand Factor (vWF) is a multimeric protein synthesized and stored as ultra-large multimers in endothelial cells, and released at constant rate in circulation. The ultra-large multimers of vWF are immediately cleaved by a metalloprotease present on surface of the endothelial cells and in plasma. This enzyme, known as ADAMTS13, is able to cut the ultra-large

vWF in small multimers necessary for normal platelet adhesion. If the ADAMTS13 does not work for either inherited disease or for antibodies, the ultra-large vWF multimers bind to platelets, promoting platelet agglutination and aggregation, and, at the end, coagulation activation and disseminated microthrombi formation. These microthrombi may be found throughout the body, but they are seen most commonly in brain (especially cortical grey matter), kidney, pancreas, spleen, heart, and cortical glands. The hemolytic anemia is related to the red cell damage for the interaction with fibrin networks and microthrombi in the small vessels, this interaction produces the schistocytes evident on blood smear. Schistocytes have a short life span since the spleen rapidly removes them.

At the presentation of TTP, the neurologic symptoms are the most common, while, despite severe thrombocytopenia, the hemorrhagic problems are not remarkable. The neurologic symptoms include headache, cranial nerve palsies, paresis, dysphasia, aphasia, and confusion; these symptoms are transient but recurrent and, if the disease is not recognized, may progress shortly to stupor, seizures, and coma. Fever and the symptoms of a rapid-onset anemia are present in 50 % of the cases. Less common symptoms are abdominal pain (due to pancreatitis), acute respiratory distress symptoms, cardiac conduction abnormalities, and infarcts.

In addition to anemia and thrombocytopenia, the main laboratory findings are those of a hemolytic process, that is, elevated unconjugated bilirubin, undetectable haptoglobin, and very high level of LDH, usually more than 1,000 U/L. The LDH increase may be the expression of not only red cells' destruction but even of disseminated tissue damage.

The diagnosis of TTP is clinically easy since the presentation, at the same time, of neurologic symptoms associated with hemolytic anemia and thrombocytopenia is uncommon in other diseases. However, the presence of some comorbidities like preexisting neurologic problems or liver cirrhosis or other

diseases able to lower platelet levels, may confound the clinical picture. In these cases, there are no diagnostic tools to confirm the diagnosis of TTP outside blood smear examination for detecting schistocytes. At present, commercial kits to determine ADAMTS13 activity as well as the presence of anti-ADAMTS13 antibodies are available, but these tests are troublesome and cannot be used in an emergency since responses are delayed for weeks. Conversely, we need to confirm the clinical suspect of TTP as soon as possible, since the treatment should start immediately to avoid fatal neurologic complications. Therefore, the detection of schistocytes at the microscopic examination of blood smear remains the stronghold of the diagnosis.

The treatment of TTP is based on aggressive plasma exchange. If the treatment starts shortly after the diagnosis, the survival rate is more than 80 %. Before the introduction of this procedure, TTP was fatal in over 80 % of the cases within 3 months and only less than 10 % of the patients survived more than 12 months. Plasma exchange determines a favorable outcome even in the presence of renal failure or advanced neurologic complications. The infusion of large amount of fresh plasma, containing intact ADAMTS13, can be considered only as a temporary therapy in the case of delay of the plasma exchange. In fact, in a controlled prospective therapeutic trial comparing plasma infusion and plasma exchange, the latter demonstrated significantly better outcomes. The extraordinary effect of plasma exchange is due to the removal of anti-ADAMTS13 antibodies and of ultra-large vWF multimers together with the replacement of the fresh enzyme, able to cleave residual abnormal vWF multimers. The response is often dramatic; the neurologic complications disappear within a few hours and main laboratory alterations improve in a short time. The procedure should be performed daily until the platelet count is normal and hemolysis is minimal. Since the disease is due to autoantibodies, traditionally patients receive, in addition to plasma exchange, high-dose corticosteroids. Immunosuppressive

treatment seems more useful to prevent early relapse than to reduce the specific antibodies levels, thus increasing significantly the serum ADAMTS13 activity.

2.4 Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS) is a rare disease characterized by three primary symptoms: hemolytic anemia (with schistocytes), low platelet count, and acute renal failure. HUS is classified into two primary types: (1) HUS due to infections, often associated with diarrhea; and (2) HUS related to complement abnormalities—such HUS is also known as "atypical HUS" and is not diarrhea associated. The HUS associated to infection is common in children aged 1–5 years, at least in Europe and North America. The disease is due to a toxin (Shiga toxin) produced by some bacteria: *Escherichia coli* is the most commonly involved species; *Shigella Dysenteriae* type I and *Citrobacter freundii* have been less frequently observed. The toxin, produced in the gut, is absorbed and, in target organs (e.g., kidney and gut) it binds to glycolipid receptors on the cell surface, then the toxin is endocytosed and transported to the Golgi apparatus and the endoplasmic reticulum, it is later translocated to the cytosol where it inactivates ribosomes and causes cell death. HUS is a pediatric disease and diagnosis is relatively easy in cases of typical presentation with watery diarrhea, followed by bloody diarrhea and abdominal cramps. In the following days, the symptoms are related to severe anemia, hemolysis, and renal failure. The diagnosis of the atypical HUS, or not-infectious HUS, is much more complicated since the diarrhea is absent and a trigger of the disease cannot be found. The atypical HUS is a very rare event (0.2 cases/100,000/year) and more than 70 % of cases are in pediatric age, since the disease is related to inherited abnormalities of some complement factors or of the

cobalamin metabolism. In children, the age of onset, family history, and clinical presentation are useful for a correct differential diagnosis, while in adults, autoimmune diseases, pregnancy, transplantation, and drugs are causes of atypical HUS. In adult patients with thrombocytopenia and hemolysis presenting renal involvement, the presence of atypical HUS should be suspected and the blood smear examination for schistocytes is mandatory. The diagnosis might be performed as soon as possible since a prompt treatment avoids the progression of the renal failure. The treatment is the fresh frozen plasma infusions, and, when disease activity is not controlled, the plasma exchange should be performed. Prophylactic antibiotics should be administered because infections can trigger relapse.

2.5 Disseminated Intravascular Coagulation (DIC)

This disease is a relatively common problem in the intensive care units, and DIC still remains a diagnostic and therapeutic challenge. The clinical features of DIC are bleeding manifestations, often very serious and of abrupt onset, therefore, the anemia is due more easily to hemorrhages than to hemolysis. However, clinicians should be aware of the possibility of the presence of a hemolytic process proportional to the severity of the coagulation abnormalities, this to avoid unnecessary tests and/or treatment delay. The prognosis of DIC depends on its etiology and on the possibility to remove or to treat the trigger of the process; the most common causes of DIC are reported in As shown, some hematological diseases can determine DIC, and, in rare cases the beginning of the disease could be a DIC.

Among these cases, the promyelocytic leukemia is the most common: a sudden and severe bleeding often of serious magnitude

can be the onset of the disease. To recognize immediately the presence of this leukemia is very important since the treatment must start immediately and, consequently, the prognosis is very good with a predicted long-term survival of more than 90 % even avoiding chemotherapy. In these cases, together with the clinical and laboratory signs of the DIC, abnormal leukocyte count with immature cells are present on peripheral blood, therefore the diagnosis is easy. The age-adjusted incidence rate of acute myeloid leukemia (AML) in adults is about 3.7 per 100,000/year for both sexes, and promyelocytic leukemia represents the 10–5 % of all AML, therefore promyelocytic leukemia has an incidence ranging from 0.4 to 0.2 cases/100,000/year.

Even rarer is the paroxysmal nocturnal hemoglobinuria (PNH) whose incidence is still unknown, but the data collection from different sources has given quotes of about 0.5 cases/100,000/year. Since the disease is underdiagnosed, its incidence may be higher. This disease, due to the mutations of the gene PIG-A placed on X chromosome, shows a complex pathogenesis and it may present mild hemolytic anemia associated with recurrent hemoglobinuria, mainly during the night, or the features of an aplastic anemia, and finally a thrombotic syndrome. In rare cases, the onset of the disease is a severe hemolytic episode; these attacks are associated with general malaise, fever, headache, and abdominal and lumbar pains. Since in PNH the hemolysis is intravascular, a massive hemolytic episode is able to activate coagulation cascade and to initiate the DIC. In these very rare cases, the diagnosis is particularly difficult: only the more or less massive hemoglobinuria may suggest PNH, while the other laboratory features of the disease are not specific. In addition, the diagnosis underlies on the demonstration of the lack of CD59 and CD55 expression on red cells, granulocytes, and platelets on flow cytometry, not available in any hospital.

Sickle cell anemia is an inherited disease due to the substitution of a single mutation (GAG vs. GTB) in the sixth codon of

the β gene; this determines a substitution of valine instead of glutamine in the sixth position of the β chain in the Hb (HbS). This also determines a decrease of the Hb solubility of Hb when deoxygenated with formation of HbS polymers inside red cells and subsequent erythrocyte deformation. These "sickled" erythrocytes have poor deformability and patients develop a diffuse veno-occlusive disease and, consequently, with acute events like painful crisis; stroke; acute chest syndromes; priapism; and chronic organ damage, especially bones and joints, cardiovascular system, kidney, pulmonary system, liver, and eyes. The disease has its highest prevalence in tropical Africa; in several countries about 45 % of the population has sickle trait. In USA, about 8 % of Afro-Americans are carriers of the sickle gene. In Europe, sickle cell anemia is present only in the countries of the Mediterranean basin (Italy, Greek) with a very low incidence. In some cases, even in carriers of the trait only, life-threatening hyper-hemolytic crisis may occur with abrupt anemia; the massive hemolysis (like in PNH) is able to activate the coagulation and a DIC may appear. The hyper-hemolytic crisis may be triggered by infections or by exposition to cold temperature and by strenuous physical exercise. The diagnosis of sickle cell anemia should be suspected in any African or Afro-American patient, and, since there are an increasing number of immigrants in any European country, the doctors, especially those working in intensive care units, must be able to recognize the disease. The diagnosis is straightforward since a simple electrophoresis using cellulose acetate is rapid, inexpensive, and effective to separate the normal Hb from variants and the method is available in any hospital. The presence of other inherited Hb diseases, like β-thalassemia, may complicate the diagnostic path and additional tests are required like isoelectric focusing or HPLC. However, the presence of HbS on electrophoresis must be considered as the hallmark of the disease, also if other Hb electrophoretic abnormalities are found. Therefore, in addition to the therapy of the DIC, in patients with hyper-hemolytic crisis

other therapeutic measures are indicated such as red cell transfusion, hyper-oxygenation, and blood alkalization to avoid further HbS polymerization.

Suggested Reading

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