14 Hematologic Findings in Mycobacterial Infections Among Immunosuppressed and Immunocompetent Patients

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CONTENTS

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14.1 Introduction

The relationship between hematologic abnormalities and mycobacterial infections dates back to the beginning of the 20th century. Flinn and his colleagues suggested at that time that the change in hematologic parameters is the earliest finding of tuberculosis (TB) (Flinn and Finn 1929). The authors said, 'In connection with the above studies we have formed the impression that an extension of the pathologic process in a tuberculosis lung usually manifests itself first in the blood picture, later by physical signs and x-ray, and often last of all by symptoms.' Before embarking upon a general discussion of hematologic manifestations of mycobacterial infections, I would like to present two cases that were previously discussed at the Medical Staff Conference in the University of San Francisco, California, USA, in 1967. These cases have certain features of the history and clinical findings of TB, in particular, the striking difference in the hematological manifestations between the two cases. A brief summary about the demographics and clinical presentation of *Mycobacterium* TB infection is included thereafter.

Case 1. The first patient is a 50-year-old white man who came in for evaluation of a fever of about 7 months' duration. His symptoms began with multiple episodes of severe pain in the left upper quadrant of the abdomen and nausea. These symptoms were followed in a few days by fever and generalized malaise. According to the patient's description, the febrile episodes would last for approximately 1 week and recurred at approximately 4-week intervals with temperatures in the range of 38.3°C–40.6°C (101°F–105°F). He was noted to have axillary and inguinal adenopathy 2 months later when seen by a physician because of persistent symptoms. Laboratory data included hemoglobin of 12.2 gm/dl, markedly elevated erythrocyte sedimentation rate, increased concentration of serum gammaglobulin, and a positive tuberculin test. Two months later, the patient underwent surgery for the repair of an incarcer-

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ated incisional hernia. An exploratory laparotomy performed at that time revealed no intraabdominal pathology. Two months later, the patient's fever recurred and was associated with night sweats and 13 pounds (6 kg) of weight loss since the onset of his symptoms. At that time no history could be obtained of cough, pleuritic chest pain, hemoptysis, or production of sputum. The family history was negative. The patient had been a heavy smoker for 20 years.

On physical examination, the only abnormalities were slight adenopathy in the inguinal and axillary regions, hepatomegaly, and questionable splenomegaly. Body temperature was 38.3°C (101°F). Hemoglobin content was 8.7 g/dl, WBC of 3400/mm^3, with 30% neutrophils, 65% lymphocytes, 3% monocytes, and 2% basophils. The platelet count was 301,000/mm^3, with reticulocytes forming 2.1% of the total. Additional hematologic data included normal haptoglobulin, leukocyte alkaline phosphatase, coagulation parameters, and serum iron and iron-binding capacity. The bone marrow at that time showed generalized hyperplasia, predominantly of the erythroid series. Skin test was positive with PPD. A chest X-ray showed fibrocalcific densities. There was no active pulmonary disease, but there was evidence of old granulomatous disease. There were granulomas in the right upper lung field and some scattered granulomas in the right mid-lung field. All other work-up for fever of unknown origin was negative. A scalene lymph node biopsy showed multiple confluent and epithelioid caseous granulomas. The patient improved on an anti-TB regimen. Cultures of the scalene lymph node specimen grew acid-fast organisms.

Case 2. The second patient is a 62-year-old man with a chief complaint of tenderness in the left upper quadrant of the abdomen, with weight loss and weakness of 5 months' duration. A mass in the left upper quadrant was noted on routine physical examination. Four months later, the patient first noticed anorexia, weight loss, and weakness. Three months later, he developed anemia and was admitted to the hospital. The patient has had regular chest X-rays taken every 6 months for the past 2 years. These films have shown stable apical infiltrates. He was also known to have a positive PPD skin test. He had been a heavy smoker for the past 45 years; he has had chronic nonproductive cough and a history of acute upper gastrointestinal bleeding, which responded to medical management.

On physical examination, the patient was pale and cachectic. Body temperature was 38°C (101°F). He had several small lymphadenopathies. Lung expansion was decreased bilaterally, and the anteroposterior diameter of the chest was increased. There was dullness and increased fremitus on the right. Peristaltic movement was visible beneath a thin abdominal wall. The spleen, which was large and rock-hard, extended 8 cm below the left costal margin, and there was a tender nodule, 2×3 cm, at the anterior margin. The liver edge was felt 4 cm below the right costal margin. It was not tender and firm. Early clubbing of the fingers and severe muscular wasting of the extremities were noted. Leukocyte numbered 16,000/mm^3, with 60% neutrophils, many immature myeloid cells, 10% basophils, and 10% eosinophils. Hematocrit was 19%, reticulocyte count 2.5% of the total, and platelet count 80,000/mm^3. Normoblasts were present in the peripheral blood. X-ray examination revealed dense bones. Patchy apical infiltrates, which had increased since the previous examination, were noted on chest X-ray. There was a large right pleural effusion. A skin test with PPD was positive. Thoracentesis and pleural biopsy were performed. The latter revealed caseating granulomas. No intrabronchial lesions were seen at bronchoscopy. A bone biopsy was performed since three previous marrow taps had been dry. The bone biopsy revealed sclerotic bone and myelofibrosis. Triple anti-TB therapy was begun. Subsequently, cultures of both sputum and pleural fluid grew acid-fast bacilli.

14.1.1 *Mycobacterium* Tuberculosis

Currently, more than one-third of the world's population is infected with *Mycobacterium* TB: 8 million new cases and approximately 2 million deaths are reported each year (Dye et al. 1999). Although the lung is the primary site of disease in 80%–84% of cases of TB in the USA (Center for Disease Control and Prevention 2000), extrapulmonary TB has become more common with the advent of HIV infection, and the risk of TB increases as the immunosuppression progresses (Moore et al. 1997; Jones et al. 1993; Iseman 2000). The most common extrapulmonary sites of disease are the lymph nodes, pleura, and bones or joints (Center for Disease Control and Prevention 2000).

Lymphatic TB is usually seen in children and young adults; more commonly in women (especially Asian and Indian women). It presents with unilateral, painless, cervical adenopathy, which is connected to the skin by sinus tracts late in the course of disease. Excisional biopsy with culture yields the diagnosis of TB lymphadenitis. PPD is usually positive. It may respond slowly to medication and rarely may require excision (Mandel et al. 2000).

Clinical presentations of TB have changed dramatically since the introduction of anti-TB agents. In the pre-antibiotic era, late generalized TB was often the primary disease, occurring mainly in young adults and frequently associated with pulmonary symptoms. In the antibiotic era, TB commonly occurs together with and is frequently obscured by other diseases. It often afflicts the elderly and is much less frequently accompanied by pulmonary symptoms (Slavin et al. 1980). Disseminated TB involving the lung, liver, spleen, bone marrow, and lymph nodes can occur occasionally in an immunocompetent host and is usually associated with hematologic abnormalities and poor outcome (Charfi et al. 1998). Splenomegaly associated with fever is another clinical sign of disseminated TB (O'Reilly 1998). The histologic appearance in this rare form of disseminated hematogenous TB (nonreactive TB) shows nonspecific necrosis containing disintegrating polymorphonuclear leukocytes and enormous numbers of tubercle bacilli (O'Brien 1954). In a typical case, granulomas and epithelioid cells are lacking, although intermediate cases have areas more typical for TB. The gross pathologic findings are minute soft abscesses up to 1 cm, which always involve the liver and spleen, usually the marrow, commonly the lungs and kidneys, but almost never the meninges. The clinical picture may be overwhelming sepsis, with splenomegaly and often an inconspicuous diffuse mottling on the chest X-ray. Major hematologic abnormalities are common. Whether the lesions are typical or not, it is necessary to have bacteriologic confirmation of TB. Near these lesions, the bone marrow cellularity is often raised or lowered, reticular fibers are often increased, and sometimes reticulin fibrosis is marked (Tulliez 1976).

In the following sections, common types of mycobacterial infections that are associated with various hematologic findings are discussed.

14.2 Hematologic Findings in Tuberculosis

While most patients with TB do not manifest major hematologic abnormalities, some patients with late generalized or chronic hematogenous TB and most with nonreactive TB have serious hematologic abnormalities, including leukopenia, thrombocytopenia, anemia, leukemoid reactions, myelofibrosis, and polycythemia (Cameron 1974). Leukemoid reactions may suggest acute leukemia, although most patients in whom hematogenous TB coexists with the clinical picture of leukemia have both diseases. Slavin and his colleagues reviewed the medical records of a community-based university teaching hospital over a 10-year period (1978 to 1987) to determine the clinical and laboratory characteristics, diagnostic methods, and prognostic variables in adults treated for miliary TB in the rifampicin era. They identified a total of 109 patients including 12 who did not have miliary nodules on the chest X-ray (all of whom were shown to have hematogenous dissemination). Hematologic abnormalities were common: leukopenia (less than $4\times10(9)/l$) was present in 16 of 107 patients (15%), thrombocytopenia (less than $150\times10(9)/L$) in 24 of 104 (23%), and lymphopenia (less than $1.5\times10(9)/L$) in 82 of 94 (87%). Pancytopenia was found in 6 patients, 3 of whom recovered. Disseminated intravascular coagulation occurred in 4 patients, all of whom died (Slavin et al. 1980).

In a recent study, investigators from India compared peripheral blood and bone marrow findings in patients with disseminated/miliary TB (DTB/MTB) as well as pulmonary TB (PTB) (Singh et al. 2001). They also assessed the effect of anti-TB therapy on the occurrence of hematologic abnormalities. Thirty-two patients with DTB/MTB and 23 patients with PTB were prospectively studied. All patients received standard anti-TB treatment. They were subjected to a hemogram including a peripheral blood examination, which was repeated on completion of the anti-TB therapy. Bone marrow aspiration and biopsy were also done in all patients before starting the treatment. Normocytic normochromic anemia was the most common abnormality observed in all groups and subgroups (DTB/MTB 84%, PTB 86%). Other hematological abnormalities of the white blood cells include leukopenia (DTB/MTB 25%, PTB 0%; $p<0.02$), neutropenia (DTB/MTB 22%, PTB 0%; $p<0.04$), lymphocytopenia, monocytopenia, leukocytosis, neutrophilia, lymphocytosis, and monocytosis. Pancytopenia was observed only in patients with DTB/MTB ($p<0.05$). Thrombocytopenia was more common in patients with DTB/MTB ($p<0.007$), whereas thrombocytosis was more common in patients with PTB ($p<0.04$). The DTB/MTB patients with granulomas in the bone marrow showed certain significant differences compared with those without granulomas. These patients showed severe anemia, peripheral monocytopenia, and bone marrow histiomonocytosis. The hemogram reverted to normal with anti-TB therapy in these patients. Therefore, it is important to include TB in the differential diagnosis in patients with unexplained hematologic abnormalities.

The most frequent hematologic abnormalities associated with TB are cytopenias. In the following section, these hematologic findings are discussed.

14.2.1 Anemia

Severe anemia was quite rare in a large series of patients with pulmonary TB, occurring in less than 20%. It is, however, quite common and occurs in 60%–80% of patients with disseminated TB. Therefore, severe anemia is the rule in advanced TB (Mandell 2000). Normocytic, normochromic anemia (hemoglobin<10 gm/dl) and unexplained fever should raise the suspicion of disseminated TB.

14.2.2 White Blood Cell Abnormalities

Leukopenia, leukocytosis, and lymphocytosis are relatively uncommon in TB. The white blood cell count is usually normal but may be between 10,000 and 15,000 cells/mm^3 in miliary TB (Mandell 2000). Monocytosis is seen in less than 10% of patients. The presence or absence of monocytosis used to be considered a prognostic marker for the clinical course and outcome of patients with tuberculosis (Medical Staff Conference 1967). A rising lymphocyte count and falling monocyte count could be signs of a poor prognosis, and a rising monocyte count a sign of a good prognosis. However, this concept has never been proved. Eosinophilia occurs in about 15% of patients and is more common in pulmonary TB than in extrapulmonary TB.

Leukemoid reactions are extremely rare, occurring in less than 3% of patients with disseminated TB. The peripheral blood findings and the clinical features may be exactly the same as those of chronic myelogenous leukemia or, rarely, acute myeloblastic leukemia. Tuberculous leukemoid reactions and leukemia may be differentiated by cytogenetic studies, which in the case of leukemia will reveal an abnormal karyotype pattern. In patients in whom TB is associated with the hematologic picture of acute leukemia, it is likely that both diseases are present and that TB is complicating acute leukemia. The documented instances of TB producing the entire disease picture of acute leukemia are extremely rare.

14.2.3 Thrombocytopenia

Thrombocytopenia is very rare in pulmonary TB. However, it is a relatively common feature of disseminated or miliary TB. Thrombocytopenia can even be the presenting feature of the latter form (Perez et al. 1998; Ghobrial and Albornoz 2001). When thrombocytopenia occurs in TB, it does so most commonly via nonimmunologic mechanisms, typically manifesting in the context of pancytopenia that develops secondary to granulomatous infiltration of the bone marrow. However, thrombocytopenia and possibly other hematologic complications associated with TB can be immune-mediated. In a recent case report, a 49-year-old man who presented with immune thrombocytopenic purpura (ITP) and disseminated TB was described. In that particular case, the hematological and infectious abnormalities, which did not respond to high-dose intravenous corticosteroids and immunoglobulin, resolved after anti-TB treatment (Ghobrial and Albornoz 2001). An immune basis for TB-induced ITP was also supported by the presence of either platelet antigen-specific antibodies or platelet surface membrane IgG in two studies (Jurak et al. 1983; Boots et al. 1992). In the previous report, thrombocytopenia associated with TB developing concurrently in a mother and son was described. Antiplatelet antibodies were demonstrated in the serum of both mother and son (Jurak et al. 1983). Thrombocytopenia and hyponatremia associated with miliary TB have also been described (Cockcroft et al. 1976).

There are other case reports in which patients with disseminated TB presented with clinical and laboratory features of ITP (Talbot et al. 1998; Hernandez-Maraver et al. 1996; al-Majed et al. 1995; Yasuda et al. 1994; Pavithran and Vijayalakeshmi 1993; Singh et al. 1986; Chia and Machin 1979; Levy and Cooper 1964). The majority of reported patients with TB and ITP were women of Middle Eastern and Asian descent. Although TB-related ITP was distributed across all age groups, it occurred most commonly between the 3rd and 8th decades of life. Pulmonary TB represented the most common clinical presentation, having occurred in 33% of patients, followed by disseminated TB and lymphadenitis at 19% each. Some 81% and 35% of patients presented with a platelet count less than 20×10^9/l and 5×10^9/l, respectively. The highest platelet counts at presentation were seen in 3 of the 4 patients with TB lymphadenitis.

14.2.4 Pancytopenia

TB may be associated with pancytopenia and aplastic anemia. Disseminated TB should be considered when pancytopenia is associated with fever and weight loss

or as a cause of other obscure hematologic disorders. Medd and Hayhoe described a disease called TB miliary necrosis with pancytopenia (Medd and Hayhoe 1955). This disorder had rather distinctive pathologic features with widespread miliary necrosis and very little tissue reaction. Clinical symptoms include a high, spiking fever which is called the 'typhoidal variant' of TB. Leukopenia and splenomegaly are present. This is a rare disease, but it is important to be aware of its existence and to differentiate it from aplastic anemia of other causes. The clue to the diagnosis is splenomegaly, which is not consistent with typical aplastic anemia.

Pancytopenia can be due to hemophagocytic syndrome, an unusual hematologic manifestation of TB (Basu et al. 2000). TB-associated hemophagocytic syndrome was also reported in a hemodialysis patient who presented with fever of unknown origin, anorexia, weight loss, hepatomegaly, and pancytopenia (Yang et al. 1996). Bone marrow biopsy revealed marked hemophagocytosis and granuloma formation with positive staining for acid-fast bacilli. The patient expired shortly after making the diagnosis.

Despite its high mortality, disseminated TB in association with pancytopenia may occasionally respond to anti-TB chemotherapy with bacteriologic cure of TB and concomitant resolution of the pancytopenia. Disseminated intravascular coagulopathy can be accompanied by pancytopenia in some of these patients (Rosenberg and Rumans 1978).

14.2.5 Possible Mechanisms of Hematologic Findings in Tuberculosis

There are five possible explanations for hematologic abnormalities seen during the course of TB:

1. The first possibility is that the association of a blood disorder and TB may be purely coincidental.
2. The second possibility is that the blood disorder favors the development of TB, although this is relatively rare. TB is one of the infections commonly found in patients with hematologic disorders, particularly in those whose immunologic defense mechanisms have been further compromised by chemotherapy.
3. The third explanation is that treatment of blood disorders results in increased susceptibility to TB. Patients are treated with corticosteroids and alkylating agents, which may suppress the normal immune responses and impair the host defense. In patients with hematologic disorders, cellular immunity may be suppressed by the disease itself or by treatment with corticosteroids, immunosuppressants, or anticancer agents. Miliary TB developing in such compromised hosts is cryptic, and thus its diagnosis is difficult to make.
Missing the diagnosis of miliary TB is a growing problem and demands special attention. In the years 1964 to 1974, 37 patients with active TB were misdiagnosed in the Chaim Sheba Medical Center. The diagnosis was made only after death. Twenty-one patients were over 60 years old. Eleven had hematological disorders (Rosenthal et al. 1975). Miliary TB is fatal if it cannot be detected in time. Therefore, the possibility of mycobacterial infection should always be kept in mind when treating patients with hematologic disorders. Consequently, early suspicion and diagnosis of systemic TB may be important. Unexplained pyrexia is the most common symptom of systemic TB (Uetake et al. 1990). Because of the poor prognosis of patients with mycobacterial infection and primary hematologic disorders, prophylactic anti-TB medication may be considered when treating patients with hematologic disorders in areas endemic for TB (Morii and Narita 1998).
4. The fourth possibility is that TB is associated with the blood disease. The most common hematologic abnormality that is associated with TB is cytopenia. There are three possible ways in which TB could cause a reduction in circulating blood cells:
   a. As with any chronic infection, there may be a suppression of normal hematopoiesis. Chronic infections are the major causes of anemia of chronic disease. In association with the latter there is usually low serum iron and iron-binding capacity. The plasma iron turnover rate is rapid, but there is poor utilization of iron for erythropoiesis. It is likely that suppression of erythropoiesis in TB is partly due to increased cytokine release (TNF-α, tumor necrosis factor-alpha) that is the major mechanism in anemia of chronic disease (Dallalio et al. 1999).
   b. TB can produce hypersplenism, and this might be a second cause of cytopenia. It essentially involves increased sequestration because of the large spleen.
   c. There is actual replacement of the marrow with tubercles and the associated fibrotic reaction.

Occasionally, TB may produce changes in the blood that are difficult to distinguish from the underlying hematologic disease. In several large series of patients with TB, approximately 8%–10%

were found to have associated primary blood disorders (Oswald 1963; Glasser et al. 1970). Corr and his colleagues, in reviewing 364 patients with all types of TB, found that 17% had anemia, 3% had leukocytosis, and 1% had leukopenia. They found only one patient with immature granulocytes in the blood, a patient with metastatic carcinoma. They also described 6 patients who had primary hematologic disorders with superimposed TB (Corr et al. 1964).

In the old days, patients who had leukemic blasts in the blood and bone marrow were given anti-TB drugs, and all of them died during the initial acute illness without improvement of the hematologic picture. But since autopsy failed to reveal widespread leukemic infiltrates, leukemia was not believed to be present, and the blasts in the blood were considered to be a response to TB. However, subsequent epidemiologic studies failed to prove this concept. Some of these findings are undoubtedly secondary to the TB. In some cases, however, there is an underlying hematologic disease such as leukemia and aplastic anemia. Glasser et al. in their review suggest that anemia, leukopenia, monocytosis, and granulocytic leukocytosis certainly represent hematologic responses to TB, for they disappear following successful treatment with anti-TB drugs. But the 'leukemic' blood picture or pancytopenia does not resolve, and these patients almost invariably die after very brief illnesses (Glasser et al. 1970). Based on these observations, patients with TB who have blast cells in the peripheral blood and bone marrow also have leukemia and, therefore, merit consideration of anti-leukemic therapy in addition to treatment of TB. Similarly, there is no strong evidence that TB causes a reversible pancytopenia. Such patients, even with anti-TB therapy, invariably die in a relatively short time.

However, several case reports suggest that treatment of TB rarely restores the blood picture to normal. This is important in the prognosis of these diseases. For example, the diagnosis of refractory anemia with excess blasts, a subtype of myelodysplastic syndrome, was made based upon morphological and cytogenetic criteria (del 20q) in a patient with TB lymphadenitis. Hematological parameters remained stable without any specific treatment for several months, cell counts even normalized under anti-TB therapy (Ugo et al. 1996). In another case report, large granular lymphocytosis associated with pulmonary TB was described. Anti-TB therapy was started, and soon after the clinical symptoms and pancytopenia improved, and 1 year later, the hematological abnormalities had disappeared (Otsuji et al. 1990).

TB may occur in the setting of all myeloproliferative disorders. More than 100 patients with pulmonary TB and polycythemia vera have been reported. The association was sufficiently frequent that in the old days, the physicians considered that the lipids of the tubercle bacilli might have erythropoietic activity. Of all the myeloproliferative syndromes, it is myelofibrosis and myeloid metaplasia that have the most intriguing association with TB. There are a number of reasonably documented cases in which the myeloid metaplasia followed the onset of TB. The second case presented at the beginning of this chapter is an example of this. However, the mechanism of this association between the two diseases remained speculative.

Karel Pelger described an abnormality of granulocyte nuclear segmentation in the context of advanced TB. It is now recognized that the Pelger-Huet nuclear anomaly (PHNA) can be either hereditary or acquired with systemic diseases, commonly hematologic dysplasias. A male patient presenting with cachexia, high fever, severe hypoproliferative anemia, and acquired PHNA was described. At autopsy, an overwhelming TB was discovered in the absence of any other underlying disease (Shenkenberg et al. 1982).

Based on the above observations, the following guidelines in the approach to the association of TB and hematological disorders can be used. First, that the possibility of TB exists in any case of myelofibrosis and myeloid metaplasia, aplastic anemia, or atypical or poorly characterized blood disorder. In such a setting, one must make a rigorous search for acid-fast organisms by cultures of gastric aspirates, sputum, BAL, bone marrow, blood, and urine. In addition, the physicians may be forced to consider biopsy of an enlarged lymph node or, failing this, a 'blind' biopsy of the scalenus anticus node. This last procedure yielded the diagnosis in the first case presented at the beginning of this chapter. Molecular diagnostic methods such as polymerase chain reaction analysis should be utilized to diagnose TB in clinically suspicious cases when the standard methods fail to identify TB.

5. Finally, anti-TB drugs can cause hematologic abnormalities. These drugs may all individually or collectively produce pancytopenia or decrease individual blood elements. Anti-TB medications can cause hematologic side-effects, and the inci-

dence of hematologic abnormality appears to be associated with the degree of immunosuppression (Kavesh et al. 1989). Leukopenia is the most common side-effect of anti-TB drugs.

Anti-TB drugs may cause idiosyncratic reactions, malabsorption, interference with iron metabolism, and hemolysis in patients with red blood cell enzyme deficiencies. Idiosyncratic reactions manifested by depression of any or all of the three cellular blood elements may be caused by any of the anti-TB drugs. Para-aminosalicylic acid (PAS) and streptomycin are the drugs most often responsible (Whitfield 1970). In patients who have red blood cells deficient in enzymes such as glucose 6-phosphate dehydrogenase, oxidizing agents such as PAS may cause hemolytic anemia (Whitfield 1970). Evidence of small-bowel intestinal malabsorption was found in 36% of 14 patients studied who were taking PAS for TB (Akhtar et al. 1968). In another study of 68 patients taking PAS, approximately 90% had subnormal blood folic acid levels, in contrast to 35% of a control group of similar patients (Roberts et al. 1966).

Both serum and stainable bone marrow iron levels are commonly elevated in patients taking isoniazid (INH) for 6 months. Sideroblastic anemia has also been reported in patients receiving INH therapy. This is likely to be related to interference with pyridoxine metabolism by INH (Whitfield 1970). Hematologic abnormalities developed in 4 of 814 patients (0.5%) with pulmonary TB who were treated for 9 months with INH and rifampicin, daily for 1 month and twice weekly for the other 8 months, between January 1976 and June 1981. Given the infrequency of hematologic side-effects, only clinical surveillance for toxicity was recommended (Dutt et al. 1983) for patients receiving anti-TB medication. Perhaps a complete blood count should be added to the liver function studies that are evaluated during the course of TB therapy.

14.2.6 Prognostic Significance of Hematologic Abnormalities

Some of the hematologic manifestations of TB are predictive for the prognosis. In a recent study, the extent and severity of hematological abnormalities in 380 patients with pulmonary TB were evaluated. Full blood count, bone marrow aspiration smears, and bone marrow biopsy were performed. There was a close correlation between the hematologic abnormalities and the severity of clinical findings of pulmonary TB. This survey revealed that hematologic abnormalities are relatively common in severe pulmonary TB. Body weight loss, white blood cell count, hemoglobin level, and erythrocyte sedimentation rate appeared to be useful indices for the severity of TB. The return of these indices to a normal level may indicate disease control correlating with sputum conversion to acid-fast bacilli negative status (Bozoky et al. 1997). In a retrospective cohort study, 26 patients (24%) died of miliary TB a median of 6 days after starting treatment. Survivors were followed up for a median of 51 weeks. Stepwise logistic regression identified age greater than 60 years, lymphopenia, thrombocytopenia, hypoalbuminemia, elevated transaminase levels, and treatment delay as independent predictors of mortality (Maartens et al. 1990).

14.2.7 Tuberculosis-Induced Lymphopenia and Immunosuppression

TB is clearly responsible in some patients for CD4 cell lymphocytopenia that reverses with treatment (Onwubalili et al. 1987; Turett and Telzak 1994). Many HIV-negative patients with active TB have CD4 cell counts much lower than 500 cells/l, which return toward normal with treatment of TB. Recent clinical data on 85 HIV-negative patients with TB indicated that there is a close relationship between the CD4+ T-cell count and the severity of TB. The disease severity was associated with greater depression of the total lymphocyte and CD4 cell counts. CD4 cell counts returned to normal levels in most patients after 1 month of therapy (Jones et al. 1997).

In TB, *Mycobacterium* tuberculosis (MTB)-stimulated T-cell responses are depressed transiently, whereas antibody levels are increased. Lymphoproliferative responses of peripheral blood mononuclear cells (PBMCs) from Pakistani TB patients to both mycobacterial and candidal antigens were suppressed by approximately 50% compared with healthy purified protein derivative (PPD)-positive household contacts. Production of interferon-gamma (IFN-γ) in response to PPD also was depressed by 78%. Stimulation with PPD and the 30 kDa alpha antigen of MTB (30 kDa antigen) induced greater secretion of transforming growth factor-beta (TGF-β), but not of interleukin 10 (IL-10) or TNF-α, by PBMCs from TB patients compared with healthy contacts. The degree of suppression correlated with the duration of treatment:

patients treated for less than 1 month had significantly lower T-cell blastogenesis and IFN-γ production and higher levels of TGF-β than did patients treated for longer than 1 month. Neutralizing antibody to TGF-β normalized the lymphocyte proliferation in response to PPD, partially restored blastogenesis to candidal antigen, and significantly increased PPD-stimulated production of IFN-γ in TB patients but not in contacts. Neutralizing antibody to IL-10 augmented, but did not normalize, T-cell responses to both PPD and *Candida* in TB patients and candidal antigen in contacts. TGF-β, produced in response to MTB antigens, may therefore play a prominent role in down-regulating potentially protective host effector mechanisms and can be an important mediator of immunosuppression in TB (Hirsch et al. 1996).

14.3 Hematologic Abnormalities Associated with Mycobacterial Infections in Immunocompromised Hosts

14.3.1 Hematologic Complications of HIV Infection and AIDS

The hematologic manifestations of HIV infection and AIDS are common and may cause symptoms that are life-threatening and impair the quality of life of these patients. These manifestations include morphologic abnormalities of peripheral blood and bone marrow changes (Aboulafia and Mitsuyasu 1991). Cytopenias are the most common hematologic findings in HIV patients. Anemia and neutropenia are generally caused by inadequate production because of suppression of the bone marrow by the HIV infection through abnormal cytokine expression and alteration of the bone marrow microenvironment. Thrombocytopenia is caused by immune-mediated destruction of the platelets in addition to inadequate platelet production. The incidence and severity of cytopenia are generally correlated to the stage of the HIV infection. Other causes of cytopenia in these patients include adverse effects of drug therapy, the secondary effects of opportunistic infections, especially mycobacterial infections, malignancies or other preexisting or coexisting medical problems that may be prevalent in the HIV-infected population. Diagnosis of the mechanism and cause of the cytopenia may allow for specific management (Coyle 1997).

In evaluating HIV-infected patients with abnormal blood counts, one must consider the hematologic effects of various infectious pathogens or malignancies. Infectious agents such as *Mycobacterium avium* complex (MAC) or TB may cause direct bone marrow suppression or reticuloendothelial system dysfunction, resulting in depressed blood cell counts (Castella et al. 1985; O'Hara 1989).

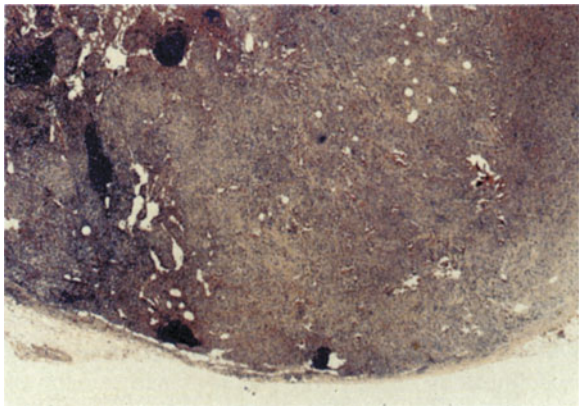
14.3.2 *Mycobacterium avium* Complex in HIV-Infected Patients

Disseminated MAC infections are common in patients with HIV/AIDS, occurring in up to 50% of patients (Ellner et al. 1991; Nightingale et al. 1992). In contrast to the immunocompetent host, in which MAC disease is usually limited to the lungs, bacteremia is by far the most common syndrome in patients with AIDS. Frequently, there is widespread dissemination, often to the liver, bone marrow, lymph nodes (Fig. 14.1), and spleen. In one study, lymphadenopathy, hepatosplenomegaly, and severe anemia (<8.5 g/dl) were seen in 37%, 24%, and 85% of patients evaluated, respectively (Benson and Ellner 1993).

MAC infection is one of the most common complications seen during the course of HIV infection and is associated with significant suppression of blood counts (Castella et al. 1985). Bone marrow aspiration and biopsy may be useful in making a specific diagnosis of several complications of AIDS that result in cytopenia. In histologic sections of bone marrow, the diagnosis of MAC infection is suggested by the finding of granulomas and aggregates of foamy histiocytes (Figs. 14.1b and 14.2a,b) in which the organisms can be seen by acid-fast staining (Fig. 14.2c). Granuloma formation is frequently lacking or scarce (Fig. 14.2b), so the pathologist should be alerted that disseminated MAC is suspected to ensure that acid-fast staining is performed (French et al. 1997).

14.3.3 Anemia Associated with MAC in HIV-Infected Patients

Severe anemia (hematocrit <26%) has been reported to be present in 76% of patients with disseminated MAC disease (Horsburgh et al. 1994). The presence of anemia has been correlated with the presence of disseminated MAC disease in HIV-infected patients who have absolute CD4+ lymphocyte counts below 100/ml (Havlick et al. 1992). The survival of patients with MAC disease was negatively correlated to the



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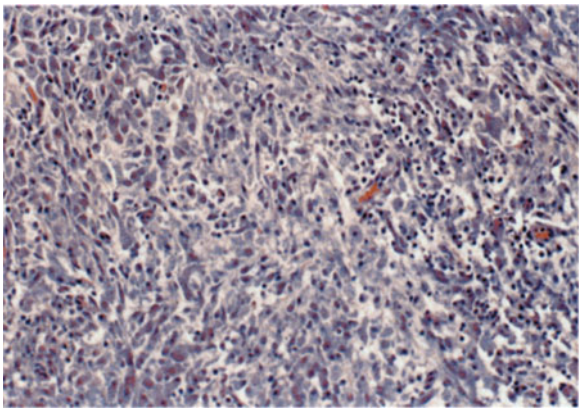

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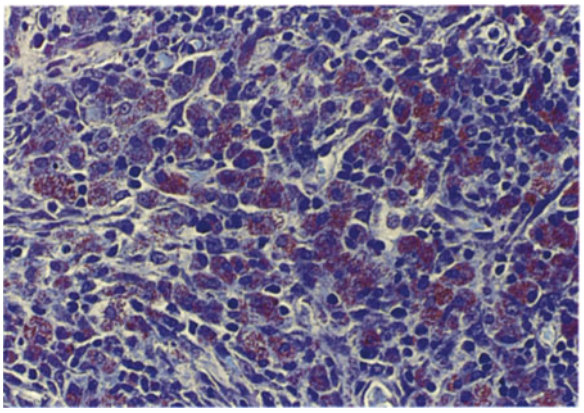

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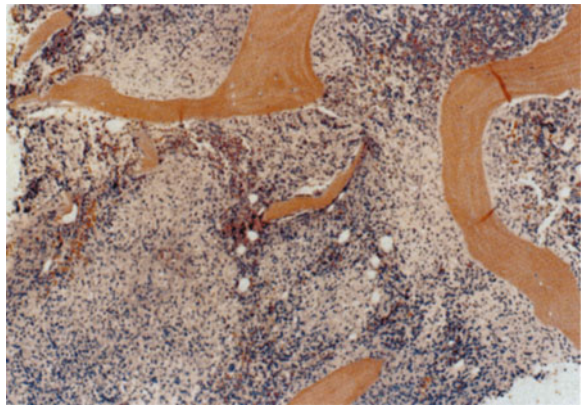

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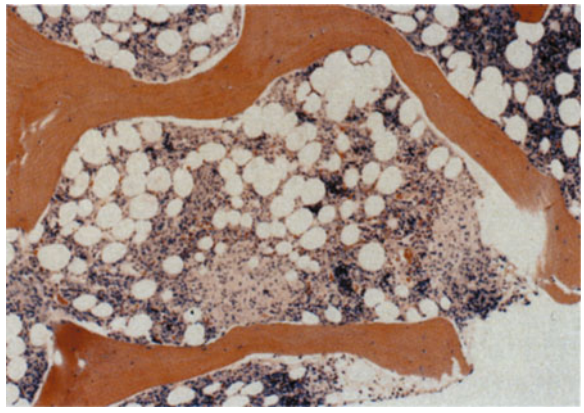

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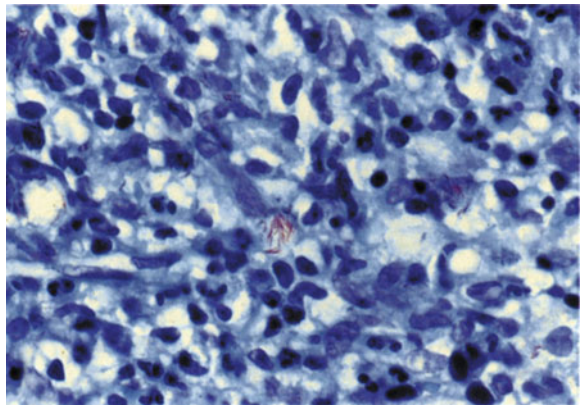

c

Fig. 14.1a–c. Lymph node histology in an HIV-infected patient with co-existing MAC infection. **a** Poorly formed granulomas (–100). **b** Poorly formed granulomas composed of numerous foamy histiocytes (–400). **c** AFB stain shows numerous intracellular acid-fast mycobacteria (*M. avium intracellulare*) (–1000). Courtesy of Metin Ozdemirli, MD, PhD, Assistant Professor in Hematopathology, Georgetown University, Washington, DC, USA

Fig. 14.2a–c. Bone marrow histology in an HIV-infected patient with co-existing MAC infection. **a** Numerous, well formed granulomas (–100). **b** A few paratrabecular poorly formed granulomas (–100). **c** AFB stains show scattered acid-fast mycobacteria (*M. avium intracellulare*) (–1000). Courtesy of Metin Ozdemirli, MD, PhD, Assistant Professor in Hematopathology, Georgetown University, Washington, DC, USA

presence of anemia (Horsburgh et al. 1994). The presence of anemia, fever, and weight loss in patients with advanced immunodeficiency should prompt an evaluation for MAC disease (Coyle 1997).

The anemia in MAC disease is thought to be due to high levels of inflammatory cytokines as well as a direct disturbance of the bone marrow microenvironment by mycobacteria (Coyle 1997). Serum TNF levels were demonstrated to be markedly elevated in children with anemia and MAC diseases. In a recent study, the hematologic manifestations of MAC in 37 HIV-infected infants and children were reviewed. Anemia was the predominant feature in all patients, with severe anemia (hemoglobin <6 g/dl) occurring in 7 of 34 (21%) patients. This was followed by leukopenia (79%), monocytosis (82%), thrombocytopenia (59%), leukoerythroblastic changes (68%), and neutropenia (41%). Serum TNF-a was markedly elevated in all patients with MAC, and there appeared to be an association between elevated TNF-α and anemia in these patients (Ellaurie and Rubinstein 1995).

MAC infection may disrupt erythropoiesis in HIV patients by direct invasion of the bone marrow. Patients with disseminated MAC appear to have greater impairment of erythropoiesis than those without MAC. This impairment appears to be mediated by selective suppression of hematopoietic progenitors (Gascon et al. 1993) and production of inhibitory TNF-α (Ellaurie and Rubinstein 1995). To elucidate the mechanisms of anemia and other cytopenias in HIV patients, various cytokine and cytokine receptor concentrations were measured by ELISA in bone marrow aspirate supernatants from 19 HIV patients undergoing diagnostic evaluation and 14 healthy paid volunteer controls. IL-1β and IFN-γ were rarely detectable. All cytokines/receptors detectable in marrow supernatant, except RANTES, showed mean concentrations 1.6- to 6.2-fold higher in patients with HIV compared with healthy controls. Elevated TNF-α and MIP-1β was associated with marrow involvement by lymphoma, Hodgkin disease, or mycobacterial infection. Concentrations of all cytokines/receptors measured correlated with the severity of the anemia. CD8+ lymphocytes were inversely correlated with concentrations of all cytokines measured other than MIP-1a (Dallalio et al. 1999).

14.3.4 Other Cytopenias Associated with MAC in HIV-Infected Patients

Bone marrow infiltration with MAC may cause thrombocytopenia or increase the severity of existing HIV-associated thrombocytopenia. However, thrombocytopenia due to bone marrow infiltration is not nearly as common as anemia of MAC infection (Coyle 1997). The absence or presence of megakaryocytes on bone marrow examination is often useful in distinguishing thrombocytopenia caused by decreased production due to marrow infiltration of mycobacteria from thrombocytopenia caused by increased destruction during the course of HIV infection or due to drug side-effect (Coyle 1997). Bone marrow infiltration with disseminated MAC infection may cause neutropenia by suppression of bone marrow progenitors (Coyle 1997).

14.3.5 MAC Infections in Other Immunocompromised Hosts

Infection with atypical mycobacteria occurs mainly in patients with a compromised cellular immune system, in particular in those with a defective T-cell or monocyte function. The specific immune response of an adolescent HIV-negative patient with disseminated *M. avium* infection and fatal varicella zoster virus infection was studied in a patient who presented with dysplastic hematopoesis of all cell lineages and anemia plus leukopenia. No hematologic malignancy was found. Peripheral lymphopenia and monocytopenia as well as a lack of natural killer (NK)-cells and B-cells were noted. Lymphocytes consisted of T-cells (95%), which contained up to 40% of TCR γδ+CD4-CD8- T-cells, few monocytes and B-cells. Approximately 50% of CD3+ T-cells showed a CD57+ NK-like phenotype. Functional analysis of mononuclear cells revealed a good antigen-specific T-cell function if the antigen-presenting cells were supplemented from a HLA-matched donor. Moreover, a strong *M. avium* specific cytotoxicity mediated by TCR αβ+ T-cells could be found in vitro and even ex vivo. In contrast, NK-killing was absent. No evidence for a defect in IL-12 or IFN-g production and signaling was found (Wendland et al. 2000).

In a patient with pulmonary MAC disease associated with idiopathic CD4+T lymphocytopenia, hematologic studies showed a low CD4+ cell count in the absence of any identifiable immunodeficiency, including HIV infection. With the combination of chemotherapy and surgery, he had a good clinical outcome (Ishida et al. 1998). Disseminated atypical MAC infection in a patient receiving interferon treatment for hairy-cell leukemia was also described (Maurice et al. 1988).

14.3.6 Hemophagocytic Syndrome Associated with MAC

This rare manifestation of MAC was recently described. A 37-year-old man with insulin-dependent diabetes mellitus complicated by end-stage renal disease who had received a second cadaveric kidney transplant 4 years earlier presented with symptomatic splenomegaly, progressive anemia, prolonged fever, dysphagia, and weight loss. The first kidney transplant, as well as a pancreatic transplant, had been lost because of acute rejection 7 and 3 years previously, respectively. Owing to chronic rejection of his kidney transplant, he required intensive immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil, and prednisone. Abdominal CT performed on admission revealed splenomegaly with a subcapsular hematoma. Analysis of a bone marrow aspirate revealed numerous large histiocytes with striated cytoplasm (onion-skin appearance), resembling Gaucherie's cells. Acid-fast staining of a bone marrow biopsy specimen showed that the histiocytic inclusions were actually innumerable acid-fast bacilli. PCR analysis of the bone marrow identified the microorganism as MAC. Despite appropriate antibiotic therapy with azithromycin and ethambutol, respiratory, renal, and liver failure developed, and the patient ultimately died of profound lactic acidosis and septic shock due to disseminated MAC infection (Argiris et al. 1999).

14.3.7 Miliary/Disseminated Tuberculosis in AIDS

HIV-infected patients are predisposed not only to reactivation of remote TB but also to rapid progression of recently acquired infection (Daley et al. 1992; Di Perri et al. 1989). It is also probable that AIDS increases the susceptibility to acquisition of new infection, and the diagnosis of TB among hospitalized adults aged 15–44 years is also very commonly associated with concurrent HIV infection (40% of patients) (Rosenblum et al. 1994). With advanced HIV infection, TB often has an atypical presentation, with extrapulmonary disease a prominent feature. The most common forms of extrapulmonary TB are lymphadenitis and disseminated disease (Fig. 14.3). In patients with advanced HIV, TB may present as progressive primary infection or disseminated disease. In AIDS patients, 10% with TB and 38% with extrapulmonary TB have miliary disease (Shafer et al. 1991).

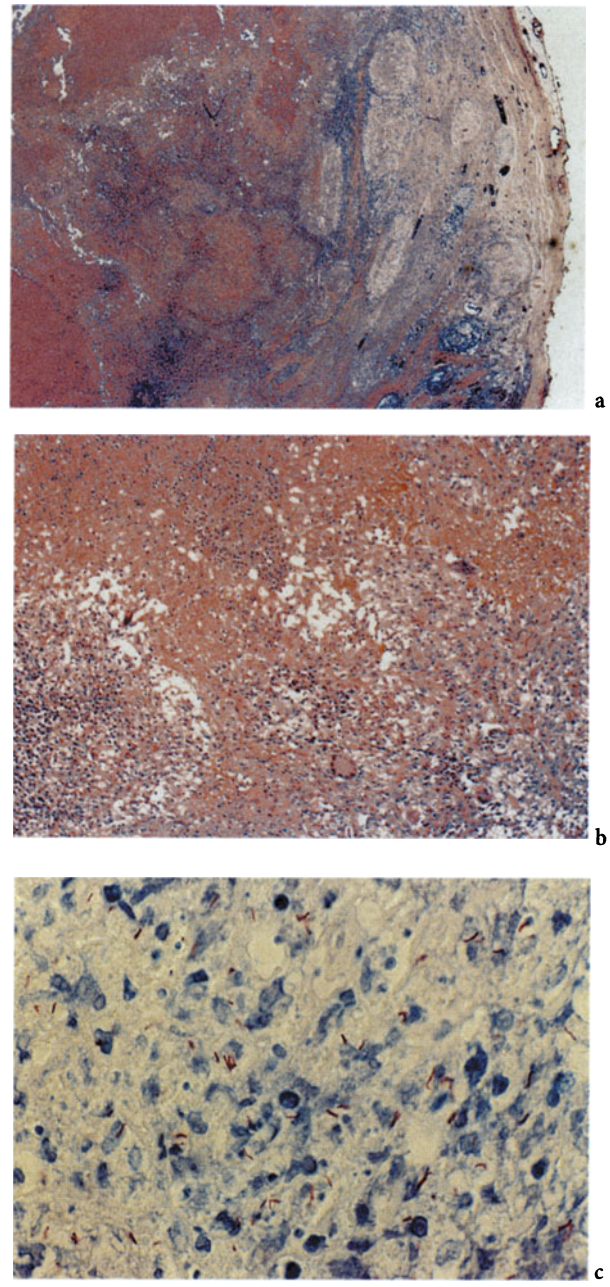

Fig. 14.3a–c. Lymph node histology in an HIV-infected patient with co-existing tuberculosis. **a** Granulomas with central necrosis (–25). **b** Granulomas with central necrosis and occasional Langerhans giant cells (–100). **c** AFB stain shows acid-fast mycobacteria (*M. tuberculosis*) (–1000). Courtesy of Metin Ozdemirli, MD, PhD, Assistant Professor in Hematopathology, Georgetown University, Washington, DC, USA.

Major constitutional symptoms and hectic fevers are characteristic. The chest X-ray is abnormal in 80% and may include typical miliary mottling. Only 10% are tuberculin-positive (Salzman et al. 1992). The sputum smear is positive in only 25% (Shafer et al. 1991), but cultures of many materials are positive, including blood in 50%–60%. Biopsies show a typical tuberculous histologic appearance but with more stainable organisms than in non-HIV miliary TB (Fig. 14.3). In contrast, the histologic picture is often nonreactive TB in fatal cases (Salzman et al. 1992).

Miliary TB in HIV-infected persons may also cause acute respiratory distress syndrome or tuberculous papular skin lesions. Smears of respiratory secretions are positive in 80%. Fulminant miliary TB may be associated with severe refractory hypoxemia (adult respiratory distress syndrome) and disseminated intravascular coagulation (DIC). In such cases, adjunctive corticosteroids (60–80 mg of prednisone daily) are indicated.

14.3.8 Diagnostic Yield of Bone Marrow Aspiration/ Biopsy for Mycobacterial Infections in Patients with HIV Infection

Hematology consultants are frequently involved in the care of patients with HIV/AIDS through requests for diagnostic bone marrow (BM) aspiration and biopsy, particularly when opportunistic mycobacteria or histoplasma infections are suspected. MAC and TB infections in particular continue to be important causes of HIV-related deaths (Selik et al. 1995; Sehonanda et al. 1996; Chin et al. 1994). Consequently, a determination of optimal strategies for the diagnosis of these infections continues to be an important clinical issue. While multiple retrospective studies have been reported (Barreto et al. 1993; Northfelt et al. 1991; Ciaudo et al. 1994; Riley et al. 1995; Benito et al. 1997; Kilby et al. 1998), no consensus has emerged with respect to the specific value of BM examinations in the diagnosis of MAC or TB infections in immunocompromised HIV-infected patients.

BM examination can be a useful method of diagnosing opportunistic mycobacterial and fungal infections in patients with fever, anemia, or neutropenia, and underlying HIV infection. Detection of granuloma with or without positive AFB staining is a common and valuable histologic clue to opportunistic infection. The diagnostic yield of BM granuloma formation was evaluated in 6988 BM biopsies taken from 1973 to 1986. Granulomas were identified in 72 specimens. The granulomas were associated with infectious disease (30%), hematologic disorders (25%), sarcoidosis (11%), nonhematologic malignancies (10%), drug reaction (5%), other diseases (6%), and no final diagnosis (6%). Patients with fever of unknown origin were 15 times more likely to have marrow granulomas than patients biopsied for other reasons (Bhargava and Farhi 1988).

In another series of 342 BM examinations from 314 patients with HIV infection, 70 examinations (20%) detected opportunistic mycobacterial or fungal infections. Of the 314 patients, 111 had such infections, and, hence, 63% (70/111) were detected by BM examination. Special stains for microorganisms detected 16 (32%) of 50 MAC, 10 (22%) of 45 TB infections, 8 (73%) of 11 *Histoplasma capsulatum* (HC) infections, and 5 (83%) of 6 *Cryptococcus neoformans* infections. BM cultures detected 36 (72%) of the 50 MAC infections, 13 (29%) of the 45 TB infections, and 63% of the fungal infections. Marrow examination revealed infection in only 1 of the 70 specimens (1%) collected to evaluate thrombocytopenia alone or hematologic malignancy, but in 69 (25%) of 274 with fever, neutropenia, anemia, or miscellaneous other indications for marrow examination. Granulomas were detected in 102 (30%) of the biopsy specimens, including 71 (64%) of those in patients with mycobacterial or fungal infection. The granulomas showed caseous necrosis in 9, all in patients with TB, and the 27 patients with TB-associated granulomas tended to show large, tightly cohesive granulomas. The presence of granulomas correlated with opportunistic infection in 82 (80%) of 102 cases. Without granulomas, special stains were positive in only 8 (3%) of 240 specimens, suggesting that special stains alone may not be a cost-efficient way to diagnose such infections (Nichols et al. 1991).

Although these pathogens are not associated with specific BM findings, disseminated MAC or TB may cause increased reticulum, occasional granulomas, and positive smears for AFB (more abundant in MAC cases and relatively sparse in TB cases), and rarely pseudo-Gaucher cells in the BM (Solis et al. 1986; Argiris et al. 1999). The most common manifestation of fungal and mycobacterial infection is a diffuse marrow infiltrate of loose aggregates and clusters of macrophages (Fig. 14.2b) (Castella et al. 1985; O'Hara 1989). The configuration of acid-fast bacilli in or around the granuloma also differs between these two *Mycobacterium* species. In TB, AFBs resemble a bunch of cigarettes with a single cigarette dropped next to the bunch. In MAC, the AFBs tend to be seen as clumps of bacilli in loose aggregates (Carl J. O'Hara, personal communication). Histiocytic erythrophagocytosis has

Table 14.1. Sensitivity, specificity, and positive and negative predictive values of studies for identification of mycobacterial infection and histoplasma (Akpek et al. 2001)

Study	Sensitivity[a]	Specificity[b]	Predictive value	
			Positive[c]	Negative[d]
BM culture	63% (20/32)	100% (24/24)	100% (20/20)	67% (24/36)
Blood culture	63% (20/32)	100% (24/24)	100% (20/20)	86% (31/36)
(+) AFB in BM	19% (6/32)	100% (24/24)	100% (6/6)	48% (24/50)
(+) Granuloma	34% (11/32)	96% (23/24)	91% (11/12)	52% (23/44)

[a] Sensitivity: The percent (or proportion) of patients ultimately diagnosed with MAC/TB or HC who had positive studies.
[b] Specificity: The percent (or proportion) of patients who had negative studies who ultimately did not have MAC/TB or HC.
[c] Positive predictive value: The percent (or proportion) of patients who had positive studies who were ultimately diagnosed with MAC/TB or HC.
[d] Negative predictive value: The percent (or proportion) of patients who had negative studies who were ultimately not diagnosed with MAC/TB or HC

also been observed and is a nonspecific finding often seen in association with infections, including mycobacterial infections and lymphomas.

Successful detection of organisms in the BM of AIDS patients requires the use of special stains and sensitive culture techniques (O'Hara 1989). The highest yield from special stains is obtained when there is a plentiful infiltrate of macrophages, especially in aggregates or in poorly formed granulomas (Castella et al. 1985). Even in the absence of noticeable granulomas or macrophage infiltration, acid-fast organisms and fungi can be diagnosed when present in high numbers (Cohen et al. 1983).

In order to determine the value of BM culture and BM histology in the diagnosis of opportunistic MAC/TB and HC infections in immunosuppressed patients with HIV, we retrospectively reviewed the records of 56 adult patients with HIV who underwent a single BM aspiration, biopsy, and culture because of unexplained fever and/or other clinical features suggestive of MAC/TB or HC infection (Akpek et al. 2001). Thirty-two patients (57%) were ultimately diagnosed with MAC/TB (n=30) or HC (n=2) infection by positive cultures of BM, blood, sputum, or bronchoalveolar lavage (BAL) fluid or by the histologic detection of organisms in biopsies of BM or other tissues.

The diagnostic sensitivity of blood cultures was equivalent to that of BM culture (63%) in the diagnosis of MAC/TB and HC infections, as reported by others (Northfelt et al. 1991; Kilby et al. 1998) and was greater than that of BM histopathology alone (34%) (Table 14.1). Blood cultures were found to be negative in 5 of 20 patients for which BM samples were culture-positive.

Granuloma and/or histologically apparent organisms were seen in BM biopsy specimens in 11 of 32 individuals (34%) ultimately diagnosed with MAC/TB or HC infections. Among these 11 patients, both granuloma and acid-fast staining organisms were found in the BM biopsy specimens of 2 individuals for whom both BM and blood cultures were negative. The diagnosis would have been missed in 6 patients (19%) if the BM had not been examined. The 34% diagnostic sensitivity of BM histopathology observed in our study is similar to the 20%–30% sensitivities reported in other studies (Riley et al. 1995; Kilby et al. 1998; Nichols et al. 1991). One-fourth of BM biopsy specimens showing granuloma were not associated with positive blood or BM cultures, and this finding suggested a 9% false-positive rate for this histopathologic feature by itself. The low diagnostic sensitivity of BM histopathology alone is not surprising. An autopsy study of 44 AIDS patients with MAC bacteremia found no histologic evidence of MAC in 30% (Torriani et al. 1994). Other studies have also indicated that some individuals suffer mycobacterial bacteremia without detectable organ or tissue invasion (Torriani et al. 1996).

A detailed evaluation of clinical and laboratory parameters observed in our study population indicates that the specific clinical features of high peak temperature, longer duration of febrile days, and elevated direct bilirubin at least greater than 1 mg/dl of the upper limit are predictive of MAC/TB or HC infections and are therefore useful in selecting patients most likely to derive diagnostic benefit from BM examination (Akpek et al. 2001).

With recent evidence supporting the value of MAC prophylaxis in immunosuppressed HIV-infected patients (Pierce et al. 1996), it is likely that in the future an increasing proportion of patients may receive antimycobacterial prophylaxis at the time of diagnostic evaluation for infection. This change in practice

could affect the diagnostic yield of both cultures and BM histopathology. Furthermore, with the development of new molecular methods for the detection of mycobacterial DNA or ribosomal RNA in clinical specimens within 24 h, with sensitivities ranging from 40% to 77% and specificities greater than 95% (Havlir and Barnes 1999; Barnes 1997; Condos et al. 1996), it is likely that a reluctance to carry out diagnostic BM examinations will continue, particularly given the additional considerations of cost, patient discomfort, risk of needle-stick exposures for individuals involved in BM sampling, and evidence for responses to empiric anti-MAC therapy in some patients.

While the diagnostic sensitivity of BM cultures may not be greater than that of blood cultures in detecting MAC/TB or HC infections in immunosuppressed HIV+ patients, histopathologic examination of BM specimens often results in the relatively rapid identification of nearly one-third of infected patients who underwent BM examination and can also identify infections in some patients who are culture-negative. Based on the above findings, we should continue to use BM aspiration, biopsy, and culture for the diagnosis of opportunistic MAC/TB or HC infections in immunosuppressed HIV+ patients, particularly when selected clinical features are present.

14.3.9 Other Mycobacterial Infections Associated with Hematologic Disorders

Mycobacterial disease, especially atypical mycobacteria, is relatively often seen in hairy-cell leukemia (HCL). The clinical picture is usually dominated by persistent fever. Sweet's syndrome manifested by fever, skin rash, and HCL has been described (Kramers et al. 1992). Blood cultures grew *M. kansasii*. The patient recovered after treatment with recombinant IFN-α and tuberculostatic drugs. The skin lesions completely regressed within 1 week after the start of r-IFN-α. Leukopenia secondary to *M. leprae* was also described (Brooks et al. 1990).

14.4 Coagulation Abnormalities Associated with Mycobacterial Infections and Clinical Presentations

14.4.1 Disseminated Intravascular Coagulation

DIC is a very rare complication of pulmonary TB. However, there have been numerous case reports published about the association between DIC and TB (Krishnaswamy 1969; Goldfine et al. 1969; Mavligit et al. 1972; Jenss and Ostendorf 1980). Clotting factors might be locally consumed, thus producing the syndrome of 'multifocal vasculopathic coagulation' (Krauss and Walker 1979). A patient with cavitary TB complicated with DIC has been described (Fujita et al. 1997). Rifampin was considered to treat the clinical course of DIC. Another patient developed subclinical DIC due to anti-TB drugs, probably rifampicin. The patient also developed marked leucocytosis, a flu-like illness, intravascular hemolysis, and acute renal failure as part of the drug reaction (Ip et al. 1991).

A review of all 13 patients reported to date shows that the patients are generally black, middle-aged, male, alcoholic, and febrile. The form of TB is generally miliary and is associated with a high mortality. Eight of these patients had associated ARDS. Only one patient had an acute tuberculous peritonitis. In 6 patients the coagulopathy began after the start of therapy; steroids did not appear to affect survival. The exact pathophysiologic mechanisms involved in the development of DIC are unknown (Stein and Libertin 1990).

TB-associated hemophagocytic syndrome (HPS) has recently been recognized as a benign reactive histiocytic proliferation with marrow hemophagocytosis. A patient with TB complicated by severe BM failure and DIC was reported. The immunological disturbances usually occurring in miliary TB may play a role in the pathogenesis of HPS (Eliopoulos et al. 1992).

14.4.2 Deep Vein Thrombosis Associated with Tuberculosis

Deep venous thrombosis (DVT) associated with TB infection has rarely been reported (Gogna et al. 1999). In a pediatric patient who developed DVT of the left leg in association with pulmonary TB, transient protein S deficiency and anticardiolipin

IgG and IgM antibodies were identified (Casanova-Roman et al. 2002). In a retrospective analysis of clinically diagnosed and lower limb DVT proven by contrast venography, DVT complicated admissions in 46 (3.4%) of 1366 adult patients treated in a TB hospital during 1986. Analysis of 7542 admissions during 1978–1986 showed a relative risk of about 5 in patients treated with regimens including rifampicin compared with other regimens. DVT was significantly more common in the winter months and usually occurred within 2 weeks of treatment being started (White 1989). This probable association between rifampicin and DVT does not contraindicate use of this drug, but measures to prevent DVT should be taken for patients receiving rifampicin.

14.4.3 Thrombotic Thrombocytopenic Purpura Associated with Mycobacterial Infections

Thrombotic thrombocytopenic purpura (TTP) during infectious diseases is a known but rare event (Pene et al. 2001). Various therapeutic approaches were used with the patient who developed TTP during the course of primary TB infection: fresh frozen plasma infusions and plasma exchange, specific anti-TB therapy, antiplatelet drugs, and steroids. A complete remission occurred 3 months after the onset of the acute disease (Toscano et al. 1995). One of the hypotheses about the pathogenesis of TTP might be an increased procoagulant activity of IL-1 on endothelial cells. Rifampicin therapy was reported to be associated with the development of TTP in a patient with TB (Fahal et al. 1992). A patient with disseminated MAC infection also developed TTP (Skopinski et al. 2001).

Excessive bleeding with unclear etiology can occur rarely in patients with TB. A fatal case of pulmonary TB masquerading as diffuse alveolar hemorrhage after autologous stem-cell transplant was recently reported (Keung et al. 1999).

14.5 Conclusion

The types and mechanisms of hematologic findings seen during the course of mycobacterial infections were covered in this chapter. Hematologic findings in patients with active mycobacterial infections are usually considered by clinicians a part of the chronic inflammatory condition, and thus they are usually overlooked. However, it is extremely important to recognize the diagnostic and prognostic value of these hematologic findings because of the possible impact on the outcome of these patients. Severe hematologic abnormalities indicate an advanced mycobacterial infection that requires immediate attention regarding diagnosis and treatment, which may alter the course in these deadly diseases.

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