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Hematological manifestations of Tuberculosis – a review

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ABSTRACT

Background

Tuberculosis is a major public health problem in India. There is a paucity of literature in the hematological changes associated with tuberculosis, though tuberculosis is a common condition.

Objective: To evaluate the hematological parameters in tuberculosis and find its assertiveness as a diagnostic, prognostic and predictive tool for physicians.

Conclusion

Variety of hematological abnormalities has been demonstrated in patients with tuberculosis in the present review. Many of them are consistent with reported literature and reinforce the fact that they can be valuable tools in monitoring tuberculosis such as anemia and increased ESR. Other findings such as thrombocytosis and pancytopenia suggest the need for further studies in this field.

Keywords: Bone marrow, Hematology, Tuberculosis

INTRODUCTION

Tuberculosis is a major public health problem in India. There are varied clinical manifestations of this epidemic problem. The most common form is pulmonary tuberculosis. Others are cutaneous tuberculosis, abdominal tuberculosis, bone tuberculosis, tubercular meningitis and disseminated tuberculosis. There are lots of nonspecific and specific diagnostic tests available. The chest radiography and montoux being the nonspecific tests. The microbiological investigations are time consuming but considered gold standard. The blood based intereferon gamma release assay and the other nucleic acid based tests such as TB-GOLD are expensive for a developing nation like India. There is a paucity of literature on the hematological changes associated with tuberculosis, though tuberculosis is a common condition and a complete blood picture (CBC) is the most easily available test. This review aims at highlighting few key points which will help in haematological assessment of tuberculosis.

EPIDEMIOLOGY

One third of the world's population is infected and approximately 3 million people die annually from pulmonary tuberculosis, overtaking the number of deaths due to acquired immune deficiency syndrome (AIDS), malaria, diarrhea, leprosy, and other tropical diseases combined.

In India, there are about 100,000 new cases and 6,000 deaths reported every year. Around 10% of tuberculosis cases are in the under 20s, with the most affected age group being the 20–49-year-old, accounting for 70% of all those affected. It affects three times as many men as women [1].

Clinical features

Tuberculosis (TB) is a contagious infection that can present with a variable clinical picture, hence, making the diagnosis difficult. Tuberculosis can affect any organ. Lung is usual site involved. The extra pulmonary sites involved are lymph nodes, pleura, genitourinary tract, bones, joints, meninges, peritoneum. Today as a result of hematogenous dissemination in HIV infection, extra pulmonary is seen more commonly than in the past [2].

Hematopoietic system is another organ seriously affected by tuberculosis. It exerts a dazzling variety of hematological effects involving both cell lines and plasma components. The hematological changes sometimes act as useful factors providing a clue to diagnosis, assessing the prognosis, indicating the complication of underlying infection as well as therapy and response to therapy. The ease of availability of blood investigations, simplicity and relative safety of procedures, the relative low cost factors in these investigations prompted us to review the blood and bone marrow changes, which may help in diagnosis and follow up of patients with tuberculosis.

Reversible peripheral blood abnormalities are commonly associated with pulmonary tuberculosis. Insight into the relationship between hematological abnormalities and mycobacterial infection has come from an understanding of the immunology of mycobacterial infection. The atypical and varied spectrum of clinical presentation of tuberculosis poses a diagnostic and therapeutic challenge to the physicians. Little is known about the prevalence of these hematological abnormalities and the effect of antituberculosis treatment on the various hematological parameters in the Indian subcontinent. This review analyses the hematological parameters in patients with tuberculosis to evaluate their diagnostic and prognostic significance.

Pathogenesis

Tuberculosis (TB) is a highly prevalent chronic infectious disease caused by Mycobacterium tuberculosis, an aerobic intracellular binding bacterium (bacillus); because of this characteristic it prefers tissues which are always in contact with high oxygen levels, as in the lung. After inhaling the bacillus, transmitted by tiny droplets of saliva, the infected individual may develop the disease depending on his immunological state. After taking up residence in the lung, M. tuberculosis can disseminate to any part of the organism. Hence pulmonary and extrapulmonary manifestation of tuberculosis has reached epidemic levels [3].

Immunopathology of tuberculosis

Initially, combat against M. tuberculosis is mediated by inflammatory cytokines such as IL-1, IL-2, and mainly TNF-α; these are essential for controlling acute infection by both local inflammatory process and macrophage (microbicide mechanisms) activation. TNF-α, produced by alveolar macrophages, increases nitric oxide (NO) expression and inducible nitric oxide synthase enzyme (iNOS), favoring granuloma maintenance and integrity [4, 5].

IL-2 and IFN-γ secretion which characterizes Th1 profile is seen during initial infection stages and Th2 profile, characterized by IL-4, IL-5, IL-6, and IL-10 secretion, is apparent in later stages of the disease. Bacillus survival inside macrophages causes the immune response of immunocompetent individuals to constantly activate T lymphocytes which will produce large quantities of INF-γ and TNF-α leading to the accumulation of macrophages and lymphocytes, which possibly form the granuloma and latent foci. In immunosupression states, these foci may be reactivated and the infection progress. Cytokines are responsible for clinical and laboratory alterations which occur during the inflammatory process, such as fever, leukocytosis, thrombocytosis, and acute phase hepatic responses and hence called acute-phase proteins. These include α1glycoprotein acid, mucoprotein, α1-globulin, α2-globulin, and the γ-globulins. Mucoprotein is a glycoprotein rich in

acid polysaccharides, the main component being α1-glycoprotein acid, the inflammatory activity marker responsible for performing immunomodulatory activities. The globulins (α, β and γ) influence ESR, a non-specific test for inflammatory and infectious processes used to evaluate activity level and disease extent, response to treatment, and the prognosis of subacute and chronic diseases such as tuberculosis [4, 5].

Microbiological diagnosis

Routine diagnosis of pulmonary and extra-pulmonary tuberculosis is by bacilloscopy (BAAR); it is an easy, quick and safe method to justify starting treatment. The identification of the acid fast bacilli by Ziehl-Nielson Stain in pulmonary samples is the most commonly approached method. However, a more specific and sensitive method is mycobacteria isolation in culture medium, which has the disadvantage of slow bacteria growth resulting in longer diagnosis time [2].

Hematological manifestations of tuberculosis

Tuberculosis can present with variable hematologic abnormalities including anemia, leucopenia, leucocytosis (leukemoid reaction), thrombocytopenia, thrombocytosis and monocytosis, and rarely pancytopenia. Certain factors are thought to contribute to the variable peripheral blood picture such as disease severity, other underlying pathologies leading to immunocompromised state, immunosuppressive therapies, and delay in initiation of appropriate treatment.

Almost all patients of tuberculosis present with anemia. A blunted erytropoietic response of the bone marrow, release of TNF-α and other cytokines by tuberculosis activated monocytes suppressing the erythropoietic production, block in the reticuloendotheial transfer of iron in to the nucleus of developing red cell are also postulated as cause for anemia. Also majority of the patients belong to the lower socioeconomic strata, so concurrent presence of nutritional anemia cannot be ruled out. But serum iron profile of the patient becomes mandatory before giving iron medications as it can do more harm than good. Literature reveals decreased serum iron, total iron binding capacity, trasnferrin saturation and increase in serum ferritin in patients with tuberculosis. These abnormalities result from redistribution of iron as an acute phase reaction. Elevated serum ferritin is because of its behaviour as an acute phase reactant. Though the total iron stores are normal, iron is unavailable for normal hematopoiesis and excess non-hemic-iron is visible in the bone marrow. Another contributing factor is macrophage activating syndrome (MAS), which is a nonspecific clinical syndrome comprising of pancytopenia, hypertriglyceridemia, and hyperferritinemia [6, 7].

The most common type of anemia is the normocytic normochromic type. However, other types of anemias that is microcytic and macrocytic anemias are also noted.

Mild leucocytosis has been uniformly found in patients (8-40%) and there may be “shift to left” with increased premature forms in the peripheral blood. The occurrence of leucocytosis is manifested in neutrophilia, lymphocytosis and occasionally monocytosis. Although, changes have been reported in relative number of lymphocyte and monocyte and polymormponuclear leucocytes, these had not proved useful either as clinical or prognostic value.

The reported prevalence of leucopenia in tuberculosis is 1-4% with Neutropenia being the predominant. The various pathophysiological mechanism implicated in neutropenia are poorly understood. However, it is a consequence of the combined effect of hypersplenism, excessive margination of neutrophil or marrow granulopoietic failure mediated by the T- lymphocyte showing granulopoietic inhibitor activity. Associated malnutrition may also result in neutropenia [7, 8].

A relevant hematological parameter in pulmonary tuberculosis is platelet count. When high, it characterizes an abnormal fibrinolytic system which leads to hypercoagulability. Thrombocytosis is postulated to be due to increased thrombopoietic factors as an inflammatory response in immunocompetent individuals. Interleukin-6 (IL-6) has been known to promote platelet production. Since platelets have been proposed as immune cells in recent years, the distinctive morphologic features of platelets with higher PDW and MPV values in tuberculosis may be a reflection of an activated platelet form as observed for most other cells of the immune system. Thrombocytopenia is also invariably noted, the exact incidence being unknown. Varied mechanisms like drugs, immune mechanisms, bone marrow fibrosis, granulomatous

involvement of bone marrow and hypersplenism have all been put forward as possible causal factors for thrombocytopenia [9].

Pancytopenia developing about two weeks after initial leucocytosis is an uncommon hematological manifestation seen in about 8% cases and may rarely result in bleeding diathesis also. Numerous hypotheses have been put forward to explain the occurrence of pancytopenia in disseminated tuberculosis, such as hypersplenism, histiocytic hyperplasia and phagocytosis, bone marrow infiltration by tubercular granuloma or occasionally maturation arrest. Bone marrow biopsy has been widely used as one of the diagnostic tools when blood counts show a picture of pancytopenia. Histopathological changes in the bone marrow can range from normal marrow to typical granuloma formation, marrow hypoplasia and caseous necrosis of the marrow. Finding of acid fast bacilli in marrow or yield of bacilli on bone marrow culture are interesting but rare findings [10, 11].

Haemophagocytic syndrome is a rare but potentially life threatening condition, characterized by cytopenias and morphological evidence of macrophage phagocytosis of red cells, granulocyte and platelets. The marrow can be hypocellular in about one-third of the patients with hemophagocytosis syndrome. This syndrome has been associated with genetic syndromes as well as immune deficiency, lymphoma, viral infection, fungal, bacterial as well as in parasitic infection. Definitive diagnosis of tuberculosis could be achieved by demonstrating epithelioid cell granuloma, Langhans' giant cells and focal necrosis in bone marrow biopsy specimen only [7].

The ESR is seldom the sole clue to disease in asymptomatic person and is not a useful screening test. When the ESR is increased a careful history and physical examination can disclose the cause. Studies on the value of the ESR as a test of activity in pulmonary tuberculosis have concluded that the ESR is useful practical method of obtaining accurate and dependable information about the actual progress or retrogression of tuberculous lesion, before these can be demonstrated by other clinical and laboratory procedures. Changes in the sedimentation rate exactly parallel alteration in the tuberculous focus. Some studies have documented an elevated ESR level in majority of patients which decreased significantly when sputum becomes negative. Nevertheless, there is a large range of individual values with considerable overlap, making it difficult to see how individual patient values could be of any utility in either diagnosing or excluding tuberculosis. But it still remains an important prognostic tool as an indicator of severity of disease [6, 7].

CONCLUSION

Hence the complete blood picture plays an important role in understanding the severity of the disease, the concurring clinical parameters and in predicting the response to treatment. So physicians should follow up this very basic laboratory test on an interval basis to combat this deadly but treatable disease on an epidemic level. However there is a need for further research in this area to reinforce the use of routinely available complete blood picture in this particular clinical scenario.

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