Introduction

Tuberculosis has been associated with a variety of haematological abnormalities. Hypoplasia of the bone marrow (Evans et al, 1952), myelofibrosis (Andre et al, 1961) and polycythaemia (Guild, 1950) have been reported in association with disseminated tuberculosis. In a substantial proportion of the reported cases, the underlying tuberculous process was diagnosed only at autopsy. Leukaemoid reaction closely simulating blastic leukaemia and in some cases impossible to differentiate from true leukaemia have been reported in patients suffering from disseminated tuberculosis. Such a mode of presentation, though distinctly rare, is important to recognise as the treatment of these two diseases is entirely different; anti leukaemic treatment given to a patient with disseminated tuberculosis associated with a leukaemoid blood picture will have disastrous consequences. Such cases are worthy of record from the points of view of therapy as well as diagnosis. Here is reported a case of disseminated tuberculosis presenting with a blood picture closely simulating acute myeloid leukaemia and treated as such. The diagnosis was evident only at autopsy.

Case Report

The patient was a 20 year old aircraftsman with 4 months’ service in the Indian Air Force. He reported to the hospital on 27-9-1973 with complaints of weakness, easy fatiguability and headache of one month duration. The salient clinical features were striking pallor and a non-tender smooth enlargement of the liver. Spleen was not palpable. Lymphadenopathy and bleeding tendencies were absent. Presence or absence of sternal bone tenderness is not documented. Preliminary blood examination showed haemoglobin level of 4 g% and a leucocyte count of 22,500/cmm; 80 to 90% of the leucocytes in the peripheral smear were immature and showed morphological features of myeloblasts; they were peroxicase negative. A few normoblasts were also seen. The bone marrow picture was interpreted as confirming the haematological diagnosis of acute myeloid leukaemia.

He was treated with prednisolone brand of corticosteroid (10 mg/4th hourly), methotrexate (2.5 mg b.d) and ampicillin. After giving a total dose of 40 mg of methotrexate, the peripheral leucocyte count came down to 16,000/cmm. Methotrexate was stopped with effect from 16.10.73. The haemoglobin level was maintained round about 7 to 8 g% by repeated blood transfusions. But the leucocytes and platelets continued to fall steadily. The peripheral leucocyte count reached its lowest level of 2,100/cmm on 28.10.73, a month after admission. The uric acid level in blood showed no raise at any time during life. He became febrile on 27.10.73 and continued to run an irregular pyrexia with temperatures ranging between 100°F and 104°F.

He became toxaeic; abdominal distension and loose stools set in. At this stage the total leucocyte count showed a spontaneous rise to 8,400/cmm. Since 7.11.1973, purpuric spots began to appear in crops all over the body. There was no haematological improvement. He was maintained on corticosteroids and blood transfusions. Meanwhile leucopenia returned in full force (count, 2,200/cmm) and there was severe thrombocytopenia (27,000/cmm). On 15.11.73, “Purinethal” brand of 6-mercaptopurine was substituted for cortisone. Since a single urine culture report showed E. coli, “Furadentin” brand of nitro furanto in was added to the therapeutic regimen. Fundus occuli at this stage showed haemorrhages. It is not stated whether leukaemic deposits or tubercles were seen in addition to the haemorrhage recorded. His general condition began to deteriorate steadily and on 18.11.73 mild icterus was noticed. Though the liver function tests and blood ammonia levels were normal, he was treated as a case of hepatic precoma. He died of sudden cardio-respiratory arrest on 22.11.73 (88 days after the onset of illness).

Salient Autopsy Findings

The body was that of a young male of average build. The conjunctivae were mildly icteric. There were purpuric spots over abdomen, both shoulders and both sides of the neck. Both lungs were oedematous and showed multiple miliary tubercles with surrounding areas of haemorrhages. The para trachea glands were enlarged and showed necrotic tubercles. The peritoneum and the gastro-intestinal mucosae showed petechial haemorrhages.
The liver was enlarged (1650 g), congested and the cut surface showed numerous small whitish tubercles visible to the naked eye. The lymph node at porta hepatitis was enlarged (3 x 1.5 cm) and showed franck caseation.

The spleen weighed 30G g. The appearance of its cut surface was striking. The entire splenic pulp was riddled with numerous whitish soft necrotic tubercles closely set against a congested background. The mesenteric lymph nodes and especially those around the pancreas were enlarged and caseous. The left kidney showed a solitary tubercle. The adrenals were unremarkable. The meninges were free. The sternal and vertebral marrow were hyperemic and did not show the characteristic soft whitish fleshy appearance of acute myeloid leukaemia.

Microscopic Findings

Microscopic examination confirmed the naked eye impression of disseminated miliary tuberculosis. Mediastinal lymph nodes, mesenteric lymph nodes, left kidney, liver, spleen, lungs, and bone marrow showed numerous discrete necrotic granular eosinophilic staining foci. The appearance in the liver, spleen and bone marrow was striking.

The liver (Fig. 1) showed numerous necrotic miliary granular foci in the portal tracts. These foci showed poor mesenchymal cellular response around them. They showed nuclear debris scattered as basophilic staining precipitates against a background of eosinophilic staining granular mass. The necrotic foci varied in size. Some were big enough to encroach upon and destroy the hepatic and plates. There were no leukaemic infiltrates in the liver.

The spleen showed a picture similar to that seen in the liver. The whole of the splenic pulp was riddled with necrotic granular foci (Fig. 2). The primary lymphoid follicles were atrophic. Reticulum cells proliferation and plasmacytoid transformation of the lymphocytes in the surviving Malphigian Corpuscles were seen. The splenic sinuses were dilated and there was no evidence of leukaemia in the spleen.

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The bone marrow (9th dorsal vertebral body) showed a well preserved cancellous boney trabaculae in the meshes of which were seen hypoplastic marrow elements and fat. Scattered against such a background were seen discrete eosinophilic necrotic granular foci dusted with basophilic nuclear debris (Fig. 3). There was no evidence of leukaemia.

The left kidney showed a solitary miliary tubercle. Both kidneys showed no evidence of leukaemic infiltration. Lungs showed focal oedema, generalised congestion and scattered
miliary tubercles. The myocardium showed no evidence of leukemic infiltration. The lymph nodes from the mediastinum and the mesentery showed widespread foci of necrosis and haemorrhages and the necrotic areas were similar to those seen in other viscera. The brain showed only oedema and there was no evidence of leukemic infiltration or meningitis. Ziehl-Neilsen's stain showed numerous acid fast organisms in all the involved organs.

Discussion

Coley and Ewing (1911) were the first to show in their autopsy studies the association between leukaemoid reaction and disseminated tuberculosis. Mills and Townsend (1937) diagnosed this condition ante mortem. Twomey and Byrd (1965) give a full review of 38 cases of tuberculosis with leukaemoid reaction reported in the literature (1911-1965) and added 3 cases of their own. They have included only those cases which fulfilled two conditions: (1) Tubercle bacilli had to be demonstrated in the lesions. (2) There should be excessive leucocytosis or abnormal shift towards immaturity in the peripheral blood or in the bone marrow. “A diagnosis of leukaemia was considered to be excluded if a lasting haematological recovery occurred or if visceral infiltrations with leucocytes could not be demonstrated at autopsy” (Twomey and Byrd, 1965).

Clinical Aspects

The clinical features of disseminated tuberculosis with leukaemoid reaction vary widely in the reported cases; the patients were usually middle aged. The ages range from 22 to 76 years. 47% of cases present with ill defined malaise and weakness as in the case under report. Only 10% of cases show respiratory symptoms even though the lungs may be the seat of miliary tuberculosis. In the patient under report, gastrointestinal symptoms of distension and diarrhoea manifested towards the later stages of the disease when the toxæmia was advanced. A mild icterus was noticed towards the end. Hepatosplenomegaly is a frequently observed clinical feature. 88% of cases reviewed by Twomey and Byrd (1965) showed either hepatomegaly or splenomegaly or r both. In this patient a smooth nontender enlargement of the liver was a prominent clinical feature. Spleen was not felt. Lymph node enlargement is seen only in 16% of cases showing myelogenous type of leukaemoid reaction. Those with lymphoid type of reaction show frequent lymph node enlargement (Gardner and Mettier, 1949). In none of the reported cases was sternal tenderness elicited. It is unfortunate that in the case under report there is no reference to the presence or absence of sternal tenderness during life. Absence of sternal tenderness may alert the clinician to the possibility that the leukaemic picture may be secondary to an infection.

Haematological Aspects

Haematological picture accompanying disseminated tuberculosis may show diverse features. Haematological complications may fall under three broad groups, viz., (a) Leukaemoid reaction (b) Myelosclerosis with leucoerythroblastic reaction (c) Pancytopenia with normal marrow cellularity or hypoplastic marrow without fibrosis. These groups are net sharply differentiated from each other and intermediate forms may occur. The severity of anaemia may vary widely. But most of the reported cases show anaemia except in the case reported by Guild (1960) where polycythemia was a feature. In the case under report, the haemoglobin at the time of admission was low (4.0 gm %). It is this combination of severe anaemia and leukaemia-like peripheral picture that makes this condition so easily confused with acute leukaemia.

The total leucocyte count may vary from 368,000 to as low as 600 cells per cmm. In the 4 cases reported by Medd and Hayhoe (1955), the presenting haematological feature was that of a pancytopenia. In the majority of reported cases the leucocytic response is of the myelogenous type. A small proportion of cases may respond with a lymphocytosis of a degree sufficient to be confused with lymphatic leukaemia (Gardner and Mettier, 1949). Gibson (1946) reported monocytic leukaemoid reaction associated with tuberculosis and mediastinal teratoma.

The status of marrow response varied from hypercellularity to frank hypoplasia in the reported cases. The hypercellular state of the marrow may be a temporary phase and with efflux of time may pass into a state of hypoplasia (Crail et al, 1948). The hypercellular marrow showing predominantly blast cells is difficult to distinguish from true leukaemia as it happened in this case. In this situation special staining techniques like alkaline phosphatase scores may not be helpful. Presence of Auer bodies is believed to be characteristic of leukaemic blast cells. This assumption is open to doubt in view of their presence in cases of disseminated tuberculosis with leukaemoid reaction as reported by Twomey and Byrd (1965). The diagnostic value of Auer body is now questioned (Leavell and Twomey, 1964). In cases of doubt histological examination of marrow tissue for tubercles is mandatory. A reliable method is given by...
The nature of leucocytic response in cases of well established tuberculosis of diverse organs was investigated by Muller (1943). She found leukaemoid reaction extremely rare in blood and marrow. The cause of this abnormal haematological response to disseminated tuberculosis is obscure. An abnormal immunologic mechanism may play a part.

**Pathology**

The pathology of this condition shows a more or less uniform picture. The lesions are extensive and widely scattered in individual organs. The striking feature of these lesions is that they are granular eosinophilic masses in which are seen basophilic nuclear debris. Lack of mesenchymal cellular response around these lesions is a note-worthy feature, seen in this case as well as in those reported in the literature. Unless a Ziehl-Neilsen stain for acid fast bacilli is done, the tuberculous nature of these lesions may escape detection. Such foci have been described as "aregenerative tubercles" or acute military necroses" in the literature (Gougerot, et al, 1953).

Occurrence of such bland lesions in patients rendered sensitive to the protein moiety of the tubercle bacilli were reported by Rich (1946) and Ball et al (1951). The pathogenesis of these lesions is obscure. Mammalian (human or bovine type) type of tubercle bacilli have been cultured from these lesions, (Rich, 1946). Necrosis can occur at any time in the life history of a tubercle. This is a function of the number of bacilli in the tissue and the state of tissue hypersensitivity. Even in a highly sensitised tissue, more than one or two bacilli are required to induce necrosis of the tissue. Where the number of bacilli is high, the necrosis is wide spread and the lesions abound in bacilli. In cellular tubercles, bacilli are scanty. As the fresh necrotic lesions age, the number of bacilli become less. Temporary depression of resistance accounts for the large number of tubercle bacilli seen in these lesions. Such a phenomenon is known to follow a massive bacterial inoculum in to the blood stream (Rich, 1946). In the case under report it is reasonable to postulate that one of the many caseous enlarged lymphnodes in the mediastinum and in the porta hepatis might have burst into a vein and initiated a tuberculous septicemia. Some believe that in addition to hypersensitivity mechanism direct toxic effect due to the bacilli themselves plays a part (Ball et al, 1953).

The lack of cellular response around the necrotic foci is attributed to a state of immunologic exhaustion following overwhelming infection (Arends, 1955). The cellular response in the lesions may improve with specific treatment and some may assume the appearance of a sarcoïd (Medd and Hayhoe, 1955).

**Pathogenesis of Leukaemoid Reaction**

The association of leukaemoid reaction with tuberculosis raises important questions. Is there a true leukaemoid reaction associated with tuberculosis? Can this be an association of two independent conditions, namely, true leukaemia and tuberculosis?

Some believe that what is seen is an association of true leukaemia and tuberculosis and the patient dies before visceral infiltration takes place (Milder et al, 1961). It is well known that infections modify the course of leukaemia and may even induce remission (Diamond and Tubly, 1951; Ulrich, 1940). The onset of tuberculous infection might induce a spontaneous remission and hence the lack of tissue evidence of leukaemia at autopsy.

There are, however, grounds to believe that there is a true leukaemoid reaction in tuberculosis. The evidence in favour is:

1. Reversion of the abnormal blood picture to normal under anti-tuberculous therapy (Mills and Townsend, 1937).
2. The tuberculous lesion antedates the leukaemoid reaction by several years in some cases.
3. Leukaemoid reaction has been elicited by injecting tuberculo-proteins into animals rendered previously sensitive to tuberculin (Stassney and Feldman, 1938). Injecting large doses of tuberculo-protein into sensitised animals produces depression of bone marrow and peripheral pancytopenia. This may explain the association of pancytopenia and miliary tuberculosis in the cases reported by Medd and Hayhoe (1955). Sabin (1932) showed that unsaponified higher alcohol derivatives of the waxes of tubercle bacilli induced striking hyperplasia of fibroblasts in tissue culture. This observation may be of significance in tuberculous myelofibrosis.

Friend and Thackray (1952) reported a few cases of hepatosplenic tuberculosis with unusual haematological manifestation and postulate a hypersplenic mechanism for pancytopenia. It should be noted that neither hypersplenism nor extensive involvement of bone-marrow by tuberculous necrosis can be invoked to explain all the haematological manifestations in the reported cases of disseminated tuberculosis.
tuberculosis may not only share a common casual agent but also an underlying mechanism, which is probably an abnormal immunological reaction.

In disseminated tuberculosis some product of the tubercle bacilli may act as a stimulant to the bone marrow, sensitised to the tuberculoprotein. Presence of large number of bacilli in the lesions, their peculiar necrotic granular nature and lack of mesenchymal cellular response are evidence for the operation of disordered immune mechanism.

In the case under report the tissues including the bone marrow showed no evidence of leukemic infiltrates and the patient was treated with anti-leukaemic drugs (Methotrexate and 6-mecraptopurine) during life.

It is unlikely in this case that exhibition of antileukaemic drugs would have obliterated all evidence of leukaemia. The drugs used might have contributed to some extent to the lack of cellular response around the areas of tuberculous destruction (Aregenerative tubercles). However it is pointed that are generative tubercles were reported in patients who did not receive any such drugs.

Significance of the case under report

Ante mortem diagnosis is rendered easier if it is known that the patient has tuberculosis elsewhere in the body. It is difficult to diagnose this condition if the patient presents, as he did in this case, with severe anaemia, hepatomegaly, leucocytosis and leukaemoid peripheral blood picture. Cases presenting with fever, leucopenia and a palpable spleen may be mistaken for typhoid fever. Some cases of pancytopenia with myelosclerosis reported in the literature may well be cases of missed disseminated tuberculosis. Only 8 out of 47 patients reviewed by Twomey and Byrd (1965) were diagnosed antemortem. Most of these patients were diagnosed as suffering from leukaemia or other myeloproliferative disorder and treated with poor results. A correct diagnosis is vital to the patient. Since effective treatment for tuberculosis is available, “the clinical picture and means of diagnosis should be better known to the general physicians and haematologists into whose hands these cases usually fall” (Medd and Hayhoe, 1955).

Careful clinical examination and search for atypical features are important. Skiagram of chest for miliary shadows may or may not be rewarding. Bone marrow smears should be carefully assessed.

Had the cytotoxic drugs been withheld in this patient, he would have shown with efflux of time evidence of metastatic tuberculosis in clinically sensitive locations like the meninges and that would have given a clue to the diagnosis and with it perhaps a hope of cure.

Bone marrow is frequently involved in children dying of miliary tuberculosis (Emey and Gibbs, 1954); liver biopsy reveals miliary tubercles in such cases (Graddock and Meredith, 1949).

Bone marrow aspiration biopsy, staining the smears of the aspirate for acid fast bacilli, histological examination of the aspirated material (a sadly neglected procedure) liver biopsy, X-ray examination of the lungs for miliary shadows and careful fundoscopic examination for choroidal tubercle should be employed if we are to diagnose disseminated tuberculosis masquerading as a haemoto logical abnormality.

Clinical picture of tuberculosis is fast changing and in Western countries where tuberculosis is effectively controlled in the young it is not uncommon to read reports of cases of tuberculosis in the elderly presenting with unusual features and dying of undiagnosed tuberculous septicemia and leucopenia (Ball et al, 1951). This aspect is of particular importance to our country where tuberculosis is rampant and its protean manifestations can lead astray even the astutest of clinicians.

Summary

1. A young man of 20 years who had disseminated tuberculosis presented with clinical and haematological features of acute myeloid leukaemia.

2. A brief review of the literature pertaining to leukaemoid and other abnormal haematological reaction to disseminated tuberculosis is given.

3. The peculiar pathology and pathogenesis of this condition is discussed. The importance of bone marrow and liver biopsies in the diagnosis of this condition is emphasised.

4. The importance of recognising this association in our country, where tuberculosis still remains a major killer, is stressed.

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REFERENCES