Disseminated Tuberculosis, Bone Marrow Necrosis and Lymphoma
A Case Report

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SUMMARY

Tuberculosis often complicates lymphoma, and bone marrow necrosis has been described in disseminated tuberculosis. However, the association of lymphoma, disseminated tuberculosis and bone marrow necrosis is rare. We report a patient with this triple association. After a 3-week influenza-like illness the patient was admitted to hospital semicomatose with pancytopenia and hyponatraemia. During routine examination a bone marrow trephine biopsy revealed diffuse lymphomatous infiltration with scattered necrotic foci. On Ziehl-Neelsen staining these foci exhibited numerous acid-fast bacilli. The patient subsequently died and at autopsy was found to have widely disseminated non-reactive tuberculosis.


Recently Kiraly and Wheby described 13 patients with bone marrow necrosis and reviewed the literature on this subject. They concluded that during life the associated disorders include mainly sickle cell disease and neoplastic disorders. Infection has been associated with bone marrow necrosis but this has been documented only in autopsy cases. Non-reactive tuberculosis is defined as a fatal form of the disease in which many organs contain small foci of necrosis surrounded by normal parenchymal cells with absent cellular response. These lesions usually contain large numbers of tubercle bacilli. Patients with lymphoproliferative malignancies are immunologically compromised and the activity of a tuberculous infection in these patients depends to a large extent on the immunological competence of the host. Adrenocortical therapy will increase the immunosuppression and a more severe and perhaps disseminated form of tuberculosis may occur. Pancytopenia is associated with bone marrow necrosis, disseminated non-reactive tuberculosis and miliary tuberculosis, the severity of involvement of red cells, leucocytes and platelets varying from case to case.

CASE REPORT

In September 1976 a 44-year-old White man presented with a 3-week history of headache, fever, malaise and anorexia, for which he had received penicillin followed by co-trimoxazole.

He was toxic, agitated and mildly confused with a temperature of 40°C. There was bilateral conjunctivitis and a generalized macular rash, more accentuated over the neck and trunk. A soft non-tender liver was just palpable but there was no splenomegaly or lymphadenopathy. Further physical examination was uneventful.

A full blood count showed haemoglobin 11.6 g/100 ml, white cell count 1 700/μl with 25% neutrophils and 75% lymphocytes, and platelets 97 000/μl. The reticulocyte count was 0.5% and the ESR was 72 mm in the first hour (Westergren).

Blood cultures, cerebrospinal fluid and urine cultures, agglutination tests and viral studies were all negative. Screening for collagen disease and malarial parasites was negative. The chest radiograph was normal but there was a slightly elevated serum bilirubin (26 mmol/l) with twice normal values for SGPT, SGOT and alkaline phosphatase. Serum sodium was 113 mmol/l, chloride 87 mmol/l and potassium 3.2 mmol/l. Blood urea was 1.7 mmol/l. Serum osmolality was 250 mmol/kg. Bone marrow aspirate, obtained with difficulty, showed particles packed with cells. The trials showed many broken cells with scattered normal haematopoietic elements and a few plasmacytoid lymphocytes. Bilateral trephine biopsy re-

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revealed diffuse infiltration of small lymphoid cells, some with plasmacytoid features and positive periodic acid-Schiff staining (Fig. 1). There were small foci of normal haematopoietic tissue and also scattered foci of necrosis throughout the specimens (Fig. 2). These necrotic foci on Ziehl-Neelsen staining were seen to be filled with acid-fast bacilli.

In view of the leucopenia and swinging temperature, the patient was started on cephalothin, gentamicin and metronidazole (Fig. 3). The pyrexia continued, the rash became more pronounced and serum bilirubin rose to 69 mmol/l during the first week. Liver enzyme levels rose concomitantly. Prednisone 60 mg/d was begun, whereupon the jaundice and the rash rapidly disappeared and the enzyme levels returned to normal. The swinging pyrexia was unaffected. Repeated administration of small volumes of hypertonic saline corrected the sodium and chloride depletion.

On the fourteenth hospital day the patient suddenly became shocked and died within 12 hours despite initial success in resuscitation.

**Autopsy**

At postmortem examination the pericardium contained 50 ml of clear yellow fluid. The mediastinal lymph nodes were minimally enlarged and both lungs were oedematous. A small retroperitoneal haemorrhage of approximately 100 ml blood was present. The spleen (370 g), liver (2140 g) and adrenals were enlarged and studded with small pale foci 1-2 mm in diameter. The kidneys were oedematous, pale and enlarged, the left kidney weighing 210 g and the right 230 g. The rest of the organs were unremarkable and no primary focus of tuberculosis could be found.

On microscopical examination all the involved organs, i.e. liver, spleen, adrenals, bone marrow and lymph nodes, showed many foci of necrosis surrounded by normal parenchymal cells (Fig. 4). There were no inflammatory or foreign cells around these foci.

![Fig. 2. Bone marrow section showing necrotic focus surrounded by lymphomatous infiltrate (H and E × 40).](image)

![Fig. 3. Diagram illustrating clinical course and therapy.](image)

![Fig. 4. Section of liver showing necrotic focus surrounded by normal parenchymal cells with no inflammatory reaction (H and E × 40).](image)
bone marrow. The bone marrow exhibited a similar picture to that found in the trephine biopsy specimen, i.e. diffuse lymphomatous infiltration with areas of necrosis. The histology was that of an atypical small lymphocytic lymphoma with plasmacytoid features.

DISCUSSION

On presentation the patient clearly demonstrated the features of bone marrow failure, i.e. thrombocytopenia and leucopenia with a superimposed infective process. The hyponaatraemia may have been attributable to severe sweating without parenteral sodium chloride before admission. At first drug-induced marrow hypoplasia was diagnosed. However, after bone marrow examination a diagnosis of lymphoproliferative malignancy was made. The necrotic foci were at first attributed to the malignancy and it was only after Ziehl-Neelsen staining of the trephine biopsy specimen that the true nature of the complicating tuberculous infection became apparent. It has been our experience that lymphoma can present in the bone marrow without accompanying lymphadenopathy.

Histologically, the lymphoma was of the atypical small lymphocytic type with plasmacytoid differentiation. These tumours often do not secrete monoclonal immunoglobulins although the tumour tissue itself may show detectable IgM increases. In lymphoproliferative malignancies there are varying degrees of defective cell-mediated and humoral immunity.

Individuals with a deficit which involves mainly cell-mediated mechanisms are extremely susceptible to tuberculosis. After a primary infection the tubercle bacilli sequestered in a granulomatous focus can exist in a state of microbial persistence for the individual's lifetime. Any factor which disturbs host immunity, such as decreased immunological competence associated with a malignancy, may cause endogenous reinfection. The exact mechanism by which this occurs is not certain but it has been postulated that in some way large doses of bacteria gain entrance to the bloodstream, producing purely necrotic lesions containing large numbers of bacilli. The purely necrotic lesions with no cellular response are the direct result of the immunological unresponsiveness of the host. This type of non-reactive disseminated tuberculosis is always found in the liver and spleen and almost always in the bone marrow. Our patient primarily developed a lymphoma, which decreased his immunological competence and led to the reactivation of an old tuberculous focus. The cortisone therapy, by decreasing his cell-mediated immunity, may have facilitated the spread of the tuberculosis.

Kaplan et al. maintain that death can be ascribed to tuberculosis if there is multiple organ involvement by tubercle bacilli and if the neoplastic process does not involve vital organs. This is in accord with the postmortem findings in our patient. In Kaplan et al.'s series of 201 patients, 34 had disseminated disease which was unsuspected during the patient's lifetime and was only diagnosed post mortem.

In a study of tuberculosis in patients with malignant disease, Feld et al. found that 50% of cases were caused by atypical mycobacterial infections, an incidence 3 times higher than that found in the general population of Texas. In their series of 59 patients there were 7 with lymphoma, of whom 6 were infected with atypical mycobacteria. However, all patients with miliary tuberculosis were infected with Mycobacterium tuberculosis. Most of the patients in the series of Feld et al. had solid tumours, whereas those in other studies showed a preponderance of haematological malignancies. They attributed this to the fact that the latter studies were published before the therapeutic regimens for haematological malignancies were improved. Patients now have prolonged remissions and are less susceptible to infection. Other malignant tumours have not benefited from similar therapeutic advances.

Our patient was 44 years old, and Medd and Hayhoe found a predominance of disseminated tuberculosis in middle-aged patients. Feld et al. ascribe this to the increased frequency of both malignancy and tuberculosis in older patients.

Bone marrow necrosis, disseminated non-reactive tuberculosis and lymphomatous infiltration of the bone marrow can all present with varying grades of pancytopenia involving red cells, leucocytes and platelets to varying degrees. All three processes were present in our patient but he exhibited mainly leucopenia and thrombocytopenia. In the series of Kiraly and Whewley there were only 2 cases of lymphoma exhibiting bone marrow necrosis. Brown, in his study of 70 cases of bone marrow necrosis, found only 1 in which had been demonstrated ante mortem in a patient with sickle-cell crisis. Infarction has been described in marrow packed with leukaemic cells, with the outlines of necrotic cells persisting as 'ghost' cells. The infarcts may have been due to leukaemic cells occluding the lumina of periosteal blood vessels, or the tumours may have outgrown their blood supply. Necrosis occurs far more commonly in acute lymphoblastic leukaemia than in acute myeloblastic leukaemia. After attacks of bone pain and marrow infarction there are often periods of pancytopenia which may be due to infarctions of large portions of marrow, leaving little viable marrow capable of releasing cells into the peripheral blood. Bone marrow necrosis during life has been demonstrated mainly in association with neoplasia and sickle cell disorders. As far as can be ascertained, it has been documented only twice in association with lymphoma. Our patient had lymphomatous infiltrates and necrotic foci of non-reactive tuberculosis in his bone marrow. The possibility of an underlying tuberculous infection should always be considered in patients with malignancy presenting with unusual signs and symptoms. It is our practice to treat all patients with a history of tuberculosis or radiological evidence of past tuberculous infection with INH; in this way the mortality may be reduced.

We should like to thank Dr U. Bierbaum for Fig. 3.

REFERENCES

Medical Management of the Trapped Patient

A. G. MAC MAHON

SUMMARY

This article deals with some of the unique problems encountered when people, injured in road traffic or industrial accidents, are trapped as a result of the accident. Mining accidents are specifically excluded because I have no personal experience of them and also because they occur in circumscribed conditions which the average practitioner does not encounter. Dealing with trapped and seriously injured patients is a very harrowing experience for all concerned, and it is as well to examine factors which contribute to this as it is the doctor who can introduce a measure of calm into these situations.


MOTOR ACCIDENTS

People vary of course, but the overriding concern of the trapped victim of an accident is almost always to be released from his confined position and the sensation of pain is largely suppressed. This is of course accentuated when patients are intoxicated, which is frequently the case in traffic accidents. Being trapped leads to shouting and screaming, verging on a hysterical reaction on the part of the victim which conveys itself to the onlookers. These people then become emotionally involved and, to vent their feelings, they resort to all manner of irrational actions and speech. They continually press for greater speed in the rescue of the patient and, unless there is firm control, start to take over this function themselves with dangerous consequences for the patient. Inevitably, out of morbid fascination they crush around the vehicle in which the victim is trapped, making rescue even more difficult.

Faced then with the double pressure, from an irrational patient and from an emotive public, the rescuer’s natural reaction is to proceed with excessive haste and to try and extricate the patient, without first making a cool assessment of the situation. This reaction is often second nature to the rescuers, who are usually firemen trained to deal rapidly and efficiently with a fire. I have no doubt that this branch of the emergency services is the most suited to these rescue tasks, but a new assessment of priorities is required in training for this aspect of their work. In this instance speed is not the criterion by which success is measured, although equipment available should be such as to ensure rapid extrication when required.

This then is the rather confusing situation which usually confronts a doctor on arrival at an accident scene: a disturbed patient, a restless public and rescue services anxious to release the patient as quickly as possible.

Medical aid measures to be carried out have been described in a previous article and will not be repeated here. Only those aspects peculiar to the trapped patient will be discussed.

ASSESSMENT OF THE SITUATION

The conditions prevailing at the scene of the accident must be assessed so that one does not enter an unsafe