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Histiocytosis X in a patient with leprosy. A case report

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Summary A patient known to have lepromatous leprosy developed multicentric histiocytosis X from which he died. Initial misinterpretation of the histological findings resulted in delay in diagnosis and institution of treatment. The clinical implications are discussed.

Introduction

Foamy histiocytes (Virchow cells) are characteristic of the granulomatous lesions of multibacillary leprosy. Histiocytosis X is another condition in which large numbers of histiocytes are a typical finding on microscopy. The similarity between the histopathological features in the two conditions presents a possible pitfall, and was responsible for delay in diagnosis in the case described.

Case report

A 41-year-old Melanesian male presented to Port Moresby General Hospital in July 1983 with a ten-month history of swelling of the left knee, and swelling of the right elbow for 3 months. Leprosy had been diagnosed in 1969 and his subsequent course had been uncomplicated. At the time of admission he was taking 100 mg per day each of dapsone and clofazimine.

On examination he was febrile and the left knee and right elbow were warm,

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firm, tender and swollen. There was local bony tenderness adjacent to both joints. The range of movement of the elbow was from 20 to 90 degrees, and of the knee from 0 to 90 degrees. The left quadriceps was wasted but there was no effusion in the knee. His leprosy was clinically quiescent, and there was no hepatosplenomegaly. Haemoglobin was 12·3 g/dL, white cell count 6000/cu mm (neutrophils 79%, lymphocytes 10%, eosinophils 10% and monocytes 1%), and the ESR 29 mm/hr. Rheumatoid factor was negative. Radiographically there was patchy rarefaction of the bone ends around both affected joints; a chest radiograph was normal. The principal working diagnosis was of a chronic infective process.

Arthrotomy of the left knee revealed a striking profusion of whitish cheese-like tissue encroaching onto the articular surfaces, and apparently infiltrating the synovial membrane and periosteum. The bone of the distal femur was very friable. Biopsies of the abnormal tissue (Figure 1) contained collections of histiocytic cells and were thought to be consistent with lepromatous leprosy. Biopsies from the femur revealed only necrotic lamellar bone and plentiful leucocytes. Bacterial cultures of both tissues were negative.

Ten days postoperatively thalidomide (100 mg/day) was commenced for a type II leprosy reaction, and rifampicin (600 mg monthly) was added for its mycobactericidal effect, in view of a possible diagnosis—despite the sites—of leprous osteitis.

Both joints remained stiff and painful, and over the next 10 weeks the swelling and tenderness in the left knee progressively increased. A firm, tender left inguinal lymph node appeared and 2 centimetres of hepatomegaly developed. The serum calcium was normal. Aspiration of the knee produced turbid fluid, and a second

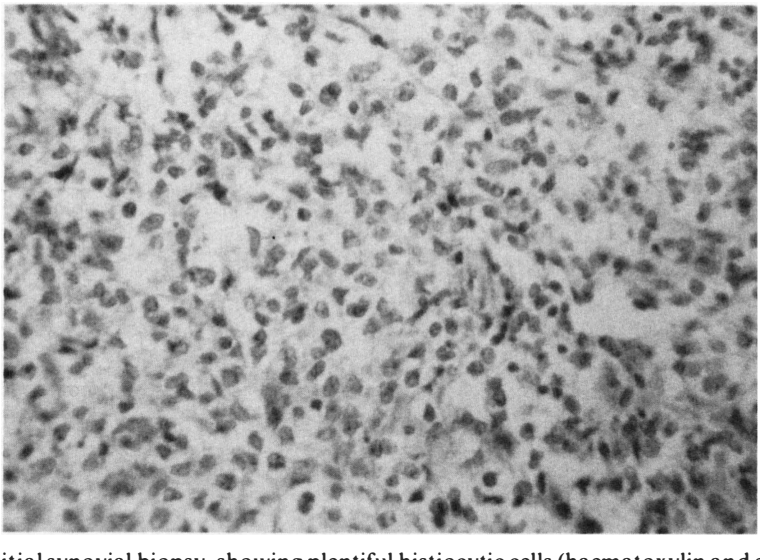

Figure 1. Initial synovial biopsy, showing plentiful histiocytic cells (haematoxylin and eosin, ×40).

arthrotomy three-and-a-half months after admission revealed that the synovium was now almost completely replaced by large amounts of soft yellowish-white material which bled freely when incised. Biopsies were taken from this tissue and from the distal femur, and also from a mass of large friable left inguinal nodes, some apparently replaced by the same abnormal tissue as found in the knee.

Histopathology of the specimens from the knee showed infiltration of the bone (Figure 2), synovium and subcutaneous connective tissue by masses of ill-defined cells with pale eosinophilic cytoplasm and irregular nuclei with a distinct nuclear membrane and a nucleolus. Some mitoses were present, and no acid-fast bacilli were seen. The lymph-nodes (Figure 3) showed replacement by a mixture of plasma cells and the abnormal cells seen distally. Four pathologists, 1 in Port Moresby, 2 in Brisbane, and 1 in Oxford, independently agreed on a diagnosis of histiocytosis, probably histiocytosis X.

Postoperatively the patient developed a deep wound infection with *Streptococcus pyogenes*, with associated hepatomegaly, jaundice and hypoalbuminaemia. His condition settled on intravenous penicillin therapy. Four months after admission his haemoglobin had fallen to 6·4 g/dL, with a white cell count of 3900/cu mm (neutrophils 67%, lymphocytes 13%, eosinophils 19%, monocytes 1%). Bone marrow examination showed generalized hyperplasia with erythroblastic predominance, but no evidence of malignancy.

Over the next 2 weeks the left knee began to enlarge further rapidly, with the development of satellite nodules in the proximal thigh. A smooth, circumscribed ballottable mass was palpable in the right paraumbilical region, separate from the liver, and not moving with respiration. Intravenous pyelography gave no further

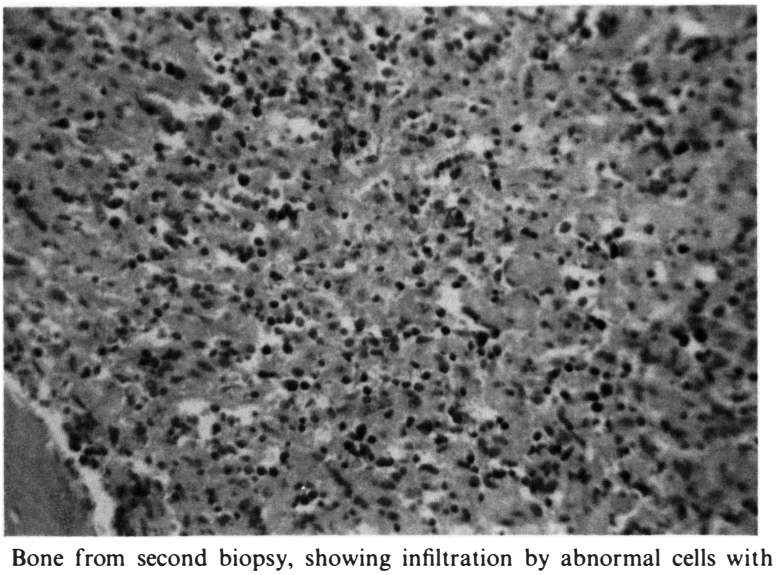

Figure 2. Bone from second biopsy, showing infiltration by abnormal cells with eosinophilic cytoplasm and irregular nuclei (haematoxylin and eosin, × 20).

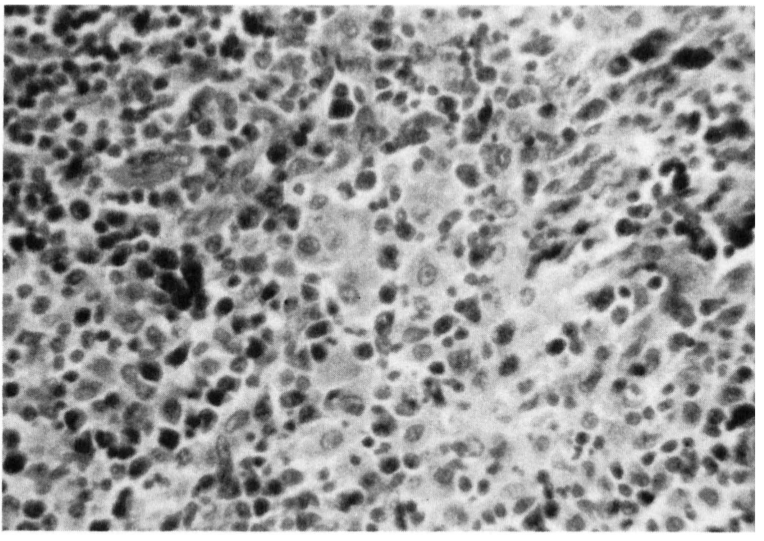

Figure 3. Lymph node containing plasma cells and infiltration of abnormal cells as in Figure 2 (haematoxylin and eosin, ×40).

helpful information. Chemotherapy was commenced with intermittent intravenous vinblastine, with continuous allopurinol cover and prednisolone 40 mg daily. Within 2 weeks there was an obvious reduction in the size of both the knee and the abdominal mass, but the arthrotomy wound then broke down completely and bled freely, necessitating transfusion, and despite further doses of vinblastine the patient's general condition deteriorated and he died 7 months after admission. Permission for autopsy was withheld.

Discussion

When a resident of a tropical country presents with subacute symptoms referable to multiple bones or joints a chronic infective process such as tuberculosis is among the leading differential diagnoses. In the case described, after exclusion of the commoner infective causes, we were left with a histological picture apparently consistent with leprous osteitis, albeit in an unusual site. It was only when the patient's condition continued to deteriorate despite mycobactericidal chemotherapy that the findings were reviewed and further investigations were undertaken leading to the definitive diagnosis.

Many patients with leprosy ultimately develop secondary bony changes, but true invasion of the skeleton by *Mycobacterium leprae* is responsible for less than 10% of such cases, occurring in 2–3% of all leprosy patients. The great majority of radiologically apparent bone abnormalities in leprosy are due to 'aseptic necrosis' in anaesthetic limbs, with or without superadded pyogenic infection introduced

through ulcers or burns. One study[1] postulates that episodes of leprous osteitis or the development of leprous osteomata may be provoked by lepra reactions causing activation of macrophages already containing leprosy bacilli. In their experience it is usually the small bones of the hands and feet which are affected, and they describe almost complete replacement of the bone marrow by large histiocytes, some with 'pink granular cytoplasm', together with some lymphocytes and plasma cells.

Exactly the same cells are present in the lesions of the histiocytosis X complex (eosinophilic granuloma, Hand–Schuller–Christian disease, and Letterer-Siwe disease), where again the histiocytes have been described as containing 'abundant eosinophilic cytoplasm'.[2] Indeed, one study[3] contends that this disease probably represents a reaction of macrophages to an as-yet unidentified infective or toxic agent.

Another study[4] points out that histoid leprosy, a rare form of lepromatous leprosy occurring in long-standing patients treated with sulphones, closely resembles fibrous histiocytoma, both grossly and microscopically. It has been suggested that the lesions occur as a result of the emergence of sulphone-resistant bacilli, which can be demonstrated intracellularly with special stains.

Histiocytosis X is a rare condition, usually affecting the flat bones of children[2] with an estimated annual incidence in the United Kingdom of 0·5 per million.[5] In Papua New Guinea, with a population of 3 million, a total of 4 cases were reported to the Tumour Registry over the 5 years to 1983 (unpublished data). The natural history of the disease is unpredictable, though the course is commonly self-limiting. Affected joints are permanently damaged. Recent reviews[2,3,6] have pointed out that study of the clinical syndromes characterized by the development of eosinophilic granulomatous lesions is made very difficult by their relative rarity, by multiple systems of classification based on questionable criteria, and by the inability to predict the outcome from the histopathological findings. The patient reported here was certainly older than the average, and his disease followed an uncharacteristically aggressive course, despite treatment with vinblastine which is generally held to be the most effective single agent for the management of such cases.

The estimated prevalence for leprosy in Papua New Guinea is 280 per 100,000 (Department of Health, unpublished data). Although 'common things occur commonly' is an axiom which should guide much clinical practice in a small developing country where diagnostic and treatment facilities of all kinds are in short supply, this is not always the case.

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