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Missed Diagnosis

Arthritic presentation of childhood leukaemia

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Summary: Three cases of childhood acute lymphatic leukaemia masquerading as juvenile chronic arthritis are presented. All had symptoms and signs for at least 4 months before leukaemia was diagnosed and in two the full blood count was normal at presentation. The importance of a high index of suspicion is emphasized, particularly if the white cell count is low.

Introduction

Leukaemia is the commonest childhood cancer.[1,2] Up to a third of cases of childhood leukaemia present with bone or back pain[1,3,4] or with joint swelling; radiographic bone abnormalities occur at presentation in more than half.[1,3] Nevertheless insufficient attention can be given to the possibility that juvenile arthritis may be the presenting feature of leukaemia. We report three cases, each initially labelled as juvenile chronic arthritis, in which leukaemia became apparent with time.

Case reports

Case 1

A three and a half year old girl developed a limp in her left lower limb; movements of the left hip and knee were painful but radiographs of these joints and of the chest were normal. Her full blood count showed haemoglobin 11.3 g/dl, white cell count 4.5×10^9/l (52% polymorphonuclear cells and 41% lymphocytes) and platelet count 608×10^9/l. The erythrocyte sedimentation rate was 42 mm in the first hour. Intradermal tuberculin testing was negative at a concentration of 1 in 1000.

Two months after her first symptoms she was admitted with neck and bilateral knee and elbow pain. She was pyrexial. Both hips were held flexed. The haemoglobin concentration was 10.7 g/dl and the white cell count 1.8×10^9/l (53% polymorphonuclear cells, 47% lymphocytes). The Paul-Bunnell test was negative. Rheumatoid and antinuclear factors were absent from the serum. Still's disease (systemic juvenile chronic arthritis) was diagnosed and the patient was given benorylate, with resolution of her fever but with minimal improvement in her joint symptoms. Four months after the first symptoms, bone marrow aspiration was performed because of recurrent joint symptoms, persistent anaemia and leucopaenia; changes diagnostic of acute lymphoblastic leukaemia were seen. The leukaemia remitted with UKALL V continuous treatment but a subsequent relapse was characterized by joint symptoms.

Case 2

A ten year old West African boy developed fever, flitting joint pains, marked anorexia and weight loss. The small joints of both hands were swollen. A differential diagnosis of rheumatic fever or juvenile chronic arthritis led to treatment with penicillin, prednisolone and aspirin. Bone marrow examination, performed 4 months after the first symptoms because of failure to respond to treatment, revealed changes of acute lymphoblastic leukaemia. The patient was transferred to the United Kingdom for further management.

On examination at that time he had hepatosplenomegaly and diffusely-enlarged, mobile, nontender lymph nodes. There was active synovitis at the metacarpophangeal joints of both thumbs and index fingers, at the right elbow and at the left wrist. The haemoglobin concentration was 6.1 g/dl, the white cell count 4.1×10^9/l and the platelet count 124×10^6/l. A peripheral blood film revealed that 13% of the white cells were blast cells. This was confirmed by specific cytological techniques. Radiographs of the hands showed osteoporosis and lytic areas in the digits.

The patient responded slowly to treatment with

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the UKALL X protocol, but 13 months after his first symptoms he had a relapse heralded by fever and recurrence of polyarthritis. He died a month later.

Case 3

A 14 year old boy presented with a 4-month history of swelling of the left knee. He had considerable synovitis at that joint, wasting of the left quadriceps and 2 cm shortening of the left lower limb. The haemoglobin concentration was 13 g/dl, the white cell count 5.3×10^9/l, the platelet count 506×10^9/l and the erythrocyte sedimentation rate 13 mm in the first hour. Rheumatoid and antinuclear factors were absent from the serum. He was negative for HLA B27. Naproxen and intra-articular steroids failed to improve the knee swelling.

Arthroscopy performed 4 months after presentation revealed an inflamed-looking synovium, biopsy of which failed to yield sufficient tissue for histological examination. A seronegative spondarthropathy was diagnosed and treatment with sulphasalazine was instituted, but without improvement in synovitis. At this time the haemoglobin was 11.4 g/dl, the white cell count 3.0×10^9/l and the platelet count 288×10^9/l. A further fall in the haemoglobin concentration and white cell count 6 months after presentation led to a bone marrow examination which confirmed CALLA-positive acute lymphatic leukaemia.

The disease was slow to go into remission on standard treatment with UKALL × A Schedule D, so the patient underwent bone marrow transplantation from his HLA-compatible brother. Unfortunately he developed severe graft-versus-host disease and died of pneumonitis 18 months after his initial presentation. The joint disease had settled rapidly after initiation of anti-leukaemic therapy and did not recur.

Discussion

Juvenile chronic arthritis (JCA) can be a mainly-systemic illness (Still's disease) or predominantly-arthritic (polyarticular or pauci-articular JCA).[5] Our cases span these modes of presentation. Symptoms and signs had been present at least 4 months in each case prior to diagnosis of leukaemia. Other reports have shown similar diagnostic delay, ranging from 3 months[6] to 7 months;[7] early bone marrow examinations may fail to show diagnostic changes of leukaemia.[6–9] This emphasizes the need to avoid the label of 'juvenile chronic arthritis' for bone and joint symptoms before several months have elapsed.[5,8] Prior to that, a wider differential diagnosis should be considered including infection, malignancy and blood disorders.[9]

Systemic JCA (Still's disease) is characterized by a polymorphonuclear leukocytosis.[10] With hindsight the low white cell count in Case 1 should have cast considerable doubt upon the diagnosis of systemic JCA (Still's disease). In Case 2 the presence of lymphadenopathy and hepatosplenomegaly correctly led to bone marrow aspiration after inappropriate 'blind' treatment with prednisolone. In Case 3 there were no pointers to leukaemia until the white cell count fell during sulphasalazine treatment. Although histological examination of synovium from the affected knee joint proved to be unhelpful, evidence of leukaemic infiltration of synovium is seen in some cases; even nodules and a positive rheumatoid latex test have been observed in childhood leukaemia.[9] Possibly leukaemia and JCA coexisted in Case 3 but the time scale of presentation coincides with that of the other two cases.

Case 2 illustrates the importance of early radiographs of clinically-affected areas in children with bone and joint symptoms or signs. Commonly-seen abnormalities in leukaemia include vertebral wedge fractures, osteoporosis, 'raindrop' lytic areas, and horizontal lucent bands in the metaphyses of long bones and in the subchondral zones of the vertebral bodies. Sclerotic lesions and periosteal reaction in the long bones are less common.[1,2,9] These radiographic appearances occur in all types of acute leukaemia.[11]

Leukaemia (and other malignant diseases such as neuroblastoma or histiocytic medullary reticulosis[9]) should always be considered in the child with unexplained pain in the back or at the ends of long bones, or with joint pain out of proportion to the apparent degree of arthritis.[7] Leukaemic bone or back pain is due to proliferation of malignant cells within the marrow cavity.[1] Leukaemia may also present as 'osteomyelitis' or 'septic arthritis'; absence of a leukocytosis, failure to isolate a causative organism and poor response to antibiotic treatment should prompt a search for an underlying leukaemia.[1]

In conclusion, radiographs should be performed and bone marrow aspiration considered in the child with recent-onset arthritis, particularly if lymphadenopathy, hepatosplenomegaly or neutropenia are present; repeated bone marrow aspirations may be needed as diagnostic changes of leukaemia can develop slowly despite generalized marrow involvement.[9]

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