Information for patients

Respironics (www.sleepapnea.com)—gives useful information about symptoms of obstructive sleep apnoea

Anesthesia and the apnea patient (www.healthresources.com/sleep/apnea/contrib/anesthes.html)—explains some important considerations for patients with obstructive sleep apnoea having surgical or medical procedures involving anaesthesia

eMedicine (www.emedicine.com/ent/topic370.htm)—an article about snoring, obstructive sleep apnoea, and surgery

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Lesson of the week

Childhood leukaemia masquerading as juvenile idiopathic arthritis

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Children with leukaemia may first present with musculoskeletal symptoms mimicking juvenile idiopathic arthritis and often have normal haematological variables.¹ The correct diagnosis may be delayed because evaluation focuses on the arthritis. Treatment with steroids may be started early, which may delay diagnosis further and reduce the subsequent response to chemotherapy.² We report a case, initially diagnosed as juvenile idiopathic arthritis, in which acute lymphoblastic leukaemia became apparent six months after presentation and only after treatment with both steroids and methotrexate. This case emphasises the importance of early bone marrow examination if there are any atypical features of juvenile idiopathic arthritis and certainly before starting steroids or cytotoxic agents.

Case report

A previously fit 7 year old boy with no relevant family history presented with a one month history of upper

chest and shoulder pain. He had malaise, lethargy, and poor appetite but no history of night sweats. He was pale with low grade pyrexia of 37.8°C. Examination showed reduced range of movements in his shoulder joints, restricted by pain. All other joints were normal. Plain radiographs of the shoulder joints were normal. Erythrocyte sedimentation rate was raised at 90 mm/hour. Full blood count was haemoglobin 11.8 g/dl, platelets $249 \times 10^9/l$, total white cell count $4.7 \times 10^9/l$, and neutrophil count $2.0 \times 10^9/l$. He was diagnosed as having musculoskeletal injury and was given ibuprofen.

Despite this he re-presented a month later after developing pain in his hip, knee, and ankle joints bilaterally associated with further malaise and lethargy. The pain was particularly prominent at night. He was systemically unwell but had no rash, lymphadenopathy, or hepatosplenomegaly. He had tenderness bilaterally over the anterior aspects of the tibia and his right knee was warm, tender, and swollen with an associated effu-

Leukaemia must be excluded in juvenile arthritis before starting steroids or cytotoxic agents

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sion. He was referred to the local paediatric team and provisionally diagnosed as having pauci-articular juvenile idiopathic arthritis. Erythrocyte sedimentation rate remained raised at 90 mm/hour; full blood count was again within normal limits. Autoantibodies and viral studies were negative; immunoglobulin and creatine kinase concentrations were also normal. Radiographs of relevant joints showed no erosive or periosteal changes. He was admitted for bed rest and physiotherapy. His symptoms improved and he was discharged home with naproxen.

After a month he had a further exacerbation of his symptoms and was started on a course of prednisolone, but only after another full blood count within the normal range had been done and after discussion with a local adult rheumatologist (table). He responded well initially but attempts to reduce his dose led to relapse and re-admission with severe pain, treated with oral morphine. He was referred to a paediatric rheumatologist who diagnosed him as having symmetrical polyarticular arthritis because of involvement of shoulders, knees, and ankles. Intra-articular steroid injections were given. He was also given second line treatment with methotrexate because of suboptimal treatment response to steroids, again with some temporary improvement in his symptoms.

One month after being seen by the rheumatologist, he was re-admitted with severe pain and high fever. Full blood count was now haemoglobin 8.1 g/dl, platelets $121 \times 10^9/l$, and neutropenia of $0.8 \times 10^9/l$ with a total white cell count of $2.8 \times 10^9/l$. Methotrexate was stopped. A repeat full blood count a week later confirmed the presence of blast cells on the peripheral film (table). He was referred to a tertiary paediatric oncology centre. Bone marrow examination confirmed the diagnosis of acute lymphoblastic leukaemia and treatment was started according to the national protocol. He relapsed while on treatment, proceeded to bone marrow transplantation but died of complications 10 months later.

Discussion

Acute lymphoblastic leukaemia is the commonest childhood malignancy, with nearly 400 new cases each year in the United Kingdom. Initial presentation may involve the musculoskeletal system in up to two thirds of cases,³ and arthritis may be the only presenting feature of leukaemia.⁴ Consideration of other potential differential diagnoses when a child presents with unusual musculoskeletal symptoms may lead to earlier diagnosis of malignancy. Other reports have found similar diagnostic delay to our case, ranging from three to seven months.¹

Barbosa et al showed that 62% of paediatric patients had musculoskeletal pain, but only 13% had clinical evidence of arthritis, at the onset of leukaemia; 8% of patients had been misdiagnosed with rheumatic fever or juvenile idiopathic arthritis before referral and some of these patients had already received steroids, delaying the start of appropriate treatment.³ However, differentiating rheumatic from malignant causes of musculoskeletal symptoms is difficult because early signs and symptoms are often similar. Comparing the histories of children with leukaemic arthritis and those with juvenile idiopathic arthritis, Ostrov et al showed that nocturnal pain, non-articular bone pain, and lack of joint stiffness were more often found in those with leukaemia.⁵ They also showed that although polyarticular involvement was more common in the juvenile idiopathic arthritis group, the leukaemic group more typically had painful pauci-articular arthritis. Cabral and Tucker also indicate that in those with leukaemia the clinical features are nearly always atypical for childhood rheumatic disease—for example, bone pain or tenderness that is non-articular in nature, especially if unilateral, should be regarded seriously.⁶

Tsai et al analysed results from patients initially diagnosed as having juvenile idiopathic arthritis in whom the diagnosis of acute lymphoblastic leukaemia was eventually made. They showed a lower white count and relative lymphocytosis on initial blood count compared with those who had a final diagnosis of juvenile idiopathic arthritis.⁷ Ostrov et al also showed that whereas neutrophilia was uniformly present in juvenile idiopathic arthritis, in acute lymphoblastic leukaemia a lymphocytosis predominated.⁵ From initial presentation until the week before the diagnosis of acute lymphoblastic leukaemia finally being made in our patient, the total white count ($3.9\text{--}5.2 \times 10^9/l$) and neutrophil count ($1.5\text{--}2.5 \times 10^9/l$) were always at the lower end of the reference range, with a relative lymphocytosis, correlating with these reports. Frank leucopenia and neutropenia did not appear until the week in which blasts became apparent on the peripheral blood film (table). Cabral et al compared similar groups and suggested that those with a normal or low platelet count at presentation were also more likely to have malignancy.⁸ Low or low normal counts suggest possible marrow infiltration and warrant further investigation, since an inflammatory process would be expected to result in raised counts. Serum lactate dehydrogenase is known to be a useful marker of cell turnover and is often raised in malignancy. Wallendal et al showed that although normal lactate dehydrogenase concentrations do not exclude malignancy, the presence of arthritis with raised lactate dehydroge-

Sequential full blood counts and inflammatory markers from presentation until final diagnosis of leukaemia made at six months

Investigation	Time (months)					
	Presentation	1	2	4	6	6
Haemoglobin (g/dl)	11.8	10.4	10.1	12.4	8.1	7.9
White cells ($10^9/l$)	4.7	4.3	3.9	5.2	2.8	3.9*
Neutrophils ($10^9/l$)	2.0	2.1	1.5	2.5	0.8	1.4
Platelets ($10^9/l$)	249	438	319	393	121	219
Erythrocyte sedimentation rate (mm/hour)	90	90	42	20	—	—
C reactive protein (mg/l)	16	84	17	16	41	—
Treatment	Ibuprofen	Naproxen	Prednisolone	Methotrexate	Methotrexate discontinued	Diagnosis of acute lymphoblastic leukaemia

*Blasts seen on peripheral blood film.

Atypical features of juvenile idiopathic arthritis**Clinical**

- Predominantly nocturnal pain, may cause waking*
- Degree of pain or systemic upset disproportionate to severity of arthritis*
- Bony, non-articular pain or tenderness*
- Pain requiring opiate analgesia*
- Sequential improvement on initiation of steroid or cytotoxic treatment then subsequent rapid deterioration*
- Asymmetrical pauciarticular pattern in presence of other atypical features

Laboratory

Severe anaemia
Low normal white cell and neutrophil count with relative lymphocytosis*
Thrombocytopenia
Increased serum lactate dehydrogenase concentrations
Acute phase response disproportionate to severity of arthritis

*Features present in our case.

nase and otherwise normal laboratory results is a cause for concern.⁹ Cabral et al, however, found that lactate dehydrogenase concentrations were raised in only 24% of patients who were subsequently diagnosed with acute lymphoblastic leukaemia,⁶ and Ostrov et al found no significant difference.⁵ Lactate dehydrogenase concentrations may not, therefore, be a reliable marker to distinguish juvenile idiopathic arthritis from acute lymphoblastic leukaemia.

Treatment with steroids is known to cause a left shift in the bone marrow and may cause difficulty in interpretation of aspirates. Révész et al showed that pre-treatment with steroids or other cytotoxic agents, such as methotrexate, may allow the malignant cells to develop resistance to these chemotherapeutic agents.² Definitive treatment is more likely to be unsuccessful, with relapse of disease more common in these patients. Our experience is that about 15% of patients newly diagnosed with juvenile idiopathic arthritis receive either oral or intravenous steroid treatment of which

only one quarter currently receive a bone marrow examination before starting treatment.

We therefore recommend that malignancy and, in particular, leukaemia must be considered in the initial differential diagnosis when a child presents with unexplained musculoskeletal symptoms. This caveat assumes even greater importance when the clinical or laboratory findings are atypical for juvenile idiopathic arthritis (box). Initially, however, the full blood count may well be normal or show only subtle changes and other markers such as erythrocyte sedimentation rate or lactate dehydrogenase are not reliable tests to differentiate malignancy from other diagnoses such as arthritis. Therefore we strongly advise that a paediatric rheumatologist should be involved early in the assessment of children with arthritis and a bone marrow examination should be done in atypical cases, certainly before commencing steroids or other cytotoxic agents.

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