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A boy of early school-age with a painful foot

EDUCATIONAL CASE REPORT

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A previously healthy boy presented to the healthcare services on several occasions with pain in his knee, ankle and foot. Clinical examinations and additional diagnostic testing initially revealed no red flags, but after 5 months, the boy was diagnosed with a serious and unexpected condition.

A previously healthy boy of early school-age was brought by one of his parents to his general practitioner (GP) with pain in his right forefoot, after a trauma to the foot six days earlier. A plain radiograph revealed no sign of skeletal injury, and the pain was treated symptomatically with over-the-counter analgesics.

Six weeks later, the boy was referred urgently from the out-of-hours primary healthcare service to a paediatric outpatient clinic owing to suspected juvenile idiopathic arthritis. The suspicion was based on several weeks of increasing pain, swelling and warmth in the right knee, which had become noticeably worse over the past four days. Clinical examination revealed warmth and erythema over the patella, as well as an extension deficit. Blood tests showed haemoglobin 14.0 g/dL (reference range 11.6–14.0), platelets 245 × 10^9/L (210–590 × 10^9), leukocytes 4.9 × 10^9/L (3.5–14.0 × 10^9) and CRP 1 mg/L (<5). Tests for ANA, ANA Hep2, rheumatoid factor and anti-CCP were negative. The patient was assessed the same day by a rheumatologist, who performed an ultrasound scan of the knee. This showed signs of increased prepatellar vascularisation in the absence of any obvious effusion. Prepatellar bursitis was considered the most likely diagnosis, and symptomatic treatment was initiated with ibuprofen (400 mg orally up to three times a day).

Swelling and pain in the joints are common in children with rheumatic diseases and musculoskeletal disorders. Important differential diagnoses include septic arthritis, osteomyelitis, reactive arthritis, systemic rheumatic diseases, and malignancy. The first step in the workup is to obtain a detailed medical history in order to identify any symptoms that may indicate a serious condition. At this point in time, our patient had relatively innocuous clinical findings. Although prepatellar bursitis is uncommon in his age group, it was considered the most likely diagnosis by both the paediatrician and the rheumatologist.

A further six weeks later, and twelve weeks after symptom onset, the boy attended a scheduled outpatient appointment in the paediatric department. The pain and swelling in his knee had resolved, but he now had pain on the medial side of his right ankle. No swelling, warmth, or restriction of movement were seen in the ankle or any other joint. His gait was normal, with no sign of a limp, and he had no fever or nocturnal pain. Arthritis and other systemic diseases were therefore considered unlikely. No further blood samples were taken, and no diagnostic imaging of the ankle was performed. The ankle pain was attributed to fallen arches and possibly incorrect loading of the joint as a result of the bursitis.

When investigating paediatric joint pain, the medical history offers many useful pointers. It is important to note any red flags, such as fever, intense pain, limping, difficulties with weight-bearing, night pain, and weight loss. Other relevant findings include rash, ocular manifestations, abdominal pain, and symptoms of possible autoimmune disease. Acute bacterial infections will usually affect only one joint, whereas rheumatic and systemic diseases can affect multiple joints. Mechanical causes of joint pain most often cause pain after physical activity, whereas infection and inflammation give rise to persistent pain. If any red flags are present, supplementary diagnostic testing should be performed, including imaging, blood tests, and possibly joint puncture. In our patient, no red flags or alarm symptoms were present at this time, and it was therefore decided to continue observation.

In parallel with the follow-up by the paediatric department, and eleven weeks after symptom onset, the boy attended his GP surgery along with his mother due to swelling and a feeling of heaviness in the right hemiscrotum. The swelling had developed gradually over several days, and the boy noted a

sensation of pressure in the scrotum while running. He had little pain and no urinary symptoms. On examination, the GP found painless swelling of the right hemiscrotum, but no warmth or erythema. The scrotal swelling was not discussed at the paediatric outpatient clinic.

The correct approach to diagnosing paediatric scrotal disorders depends on whether the main symptom is pain as opposed to swelling. A thorough medical history and clinical examination are important for determining the aetiology and in many cases should be supplemented with Doppler ultrasound. Testicular torsion must always be considered in cases of acute testicular pain, as this is an acute surgical condition that requires immediate treatment. Other differential diagnoses of pain include an incarcerated inguinal hernia, torsion of the epididymis, and epididymitis. Unilateral, painless swelling should raise suspicion of a tumour, but other diagnoses to consider are hydroceles, varicoceles and spermatoceles. In most cases, an ultrasound scan will be important for further diagnosis and treatment selection.

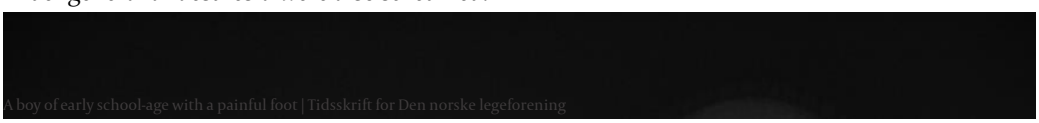
The gradual onset of symptoms and absence of pain meant that testicular torsion was considered unlikely. The patient received a fast-track referral from his GP for an ultrasound scan, which was performed a week later. This revealed normal-sized testicles with preserved blood flow, but a markedly enlarged, hyperemic caput epididymis, as well as 180-degree rotation of the distal spermatic cord. The GP contacted the on-call surgeon, and an additional ultrasound scan and clinical assessment were arranged with the surgeon for two weeks' time.

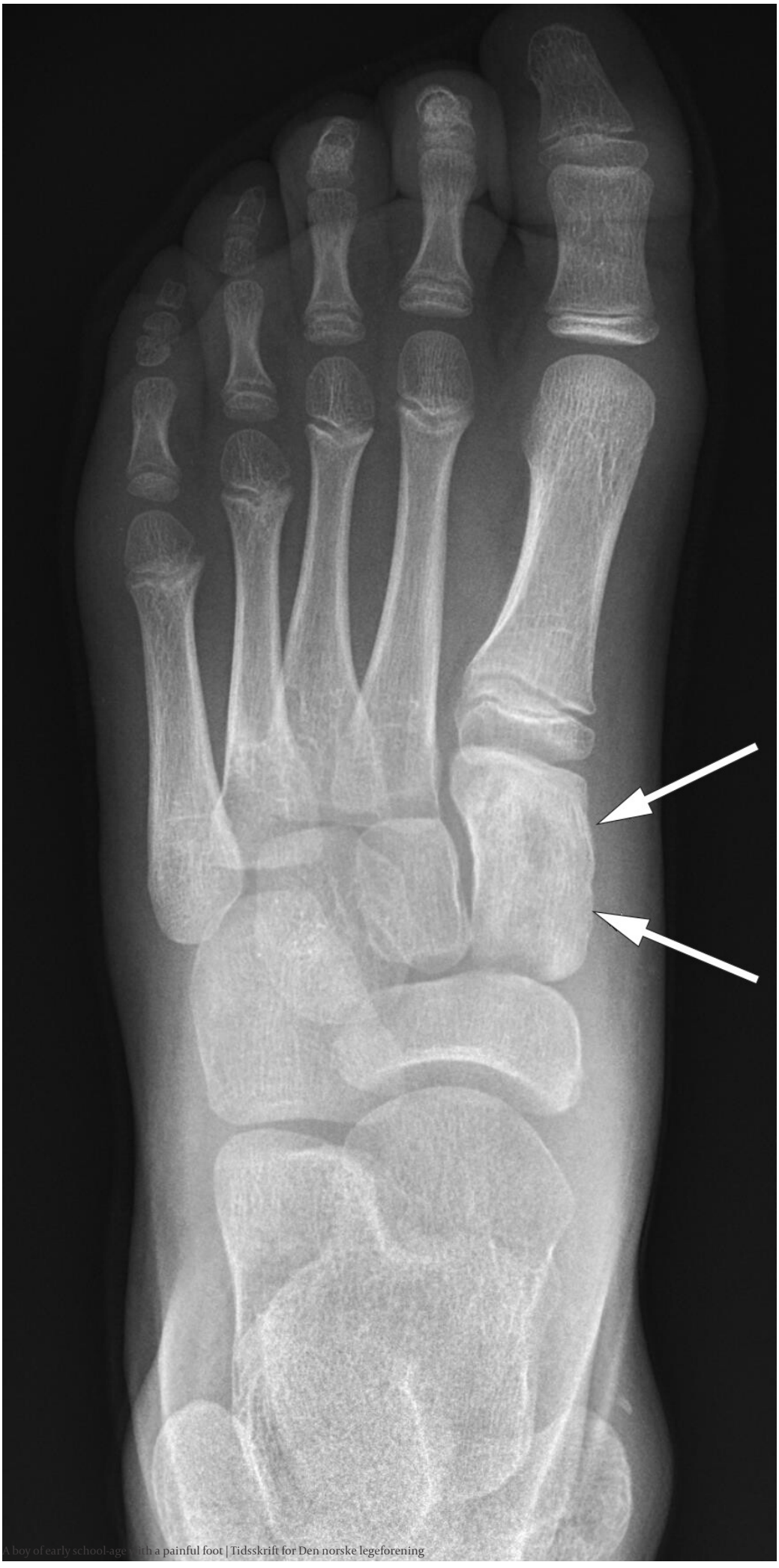
The second ultrasound showed similar findings, and at the surgical outpatient clinic, the gradually increasing but painless right-sided hemiscrotal swelling was confirmed. Fifteen weeks had now passed since the boy first reported pain in his foot, and about four weeks since the onset of the scrotal symptoms. After consultation with a paediatric surgeon at the university hospital, it was decided that the swelling was most likely due to torsion-detorsion, and surgical exploration and orchiopexy were scheduled for the next day. During the operation, no signs of torsion were found, but the radiological findings of normal-sized testicles and a greatly enlarged right caput epididymis were confirmed. The orchiopexy was performed as planned.

By this point, testicular torsion and other acute surgical conditions had been ruled out, but there was still no clear explanation for the scrotal swelling. Malignancy was considered less likely on the basis of the ultrasound results. A follow-up appointment at the urological outpatient clinic was scheduled for two months post-surgery.

Just under two weeks after the orchiopexy, and 17 weeks after symptom onset, the boy sustained an elbow trauma. A plain radiograph showed the anterior fat pad sign, suggesting a possible fracture. The injury was treated conservatively with a sling at the orthopaedic outpatient clinic. While at the clinic, the boy again reported pain in his right foot, and he was referred for assessment by a paediatrician the next day. The paediatrician noted pain upon weight-bearing, but no obvious swelling or warmth. Rheumatic disease was still considered unlikely, and the boy was advised to continue with his existing symptomatic treatment. No further diagnostic testing was performed.

A little over a month later, and now 22 weeks after symptom onset, the boy presented at the out-of-hours primary healthcare service with his mother with a 3-day history of worsening pain in his foot upon weight-bearing and nocturnal pain. He was referred for urgent assessment at the paediatric outpatient clinic. Examination revealed erythema and tenderness to palpation over the medial tarsal bones. The boy also had noticeable swelling under both eyes. Blood tests revealed haemoglobin 13.7 g/dL, platelets 350 × 10^9/L, leukocytes 7.0 × 10^9/L, CRP 10 mg/L and a sedimentation rate of 9 mm/h (<5). Urine dipstick analysis was negative. A plain radiograph of the ankle was considered normal, and the patient was initially sent home. However, when an experienced radiologist scrutinised the images later that evening, s/he noticed that one of the cuneiform bones had an uneven structure, with a small area in the centre that appeared slightly more lucent than the surrounding areas (Figure 1). The patient was therefore admitted for further testing the next day. An MRI scan showed widespread bone marrow oedema in the bones of the foot as well as two suspected abscesses in the cuneiform bones (Figures 2 and 3). Infectious osteomyelitis with abscess formation was considered the most likely diagnosis. Empirical antibiotic therapy was initiated with intravenous clindamycin (10 mg/kg four times daily). An urgent needle biopsy of bone tissue and abscess drainage under general anaesthesia were also scheduled.





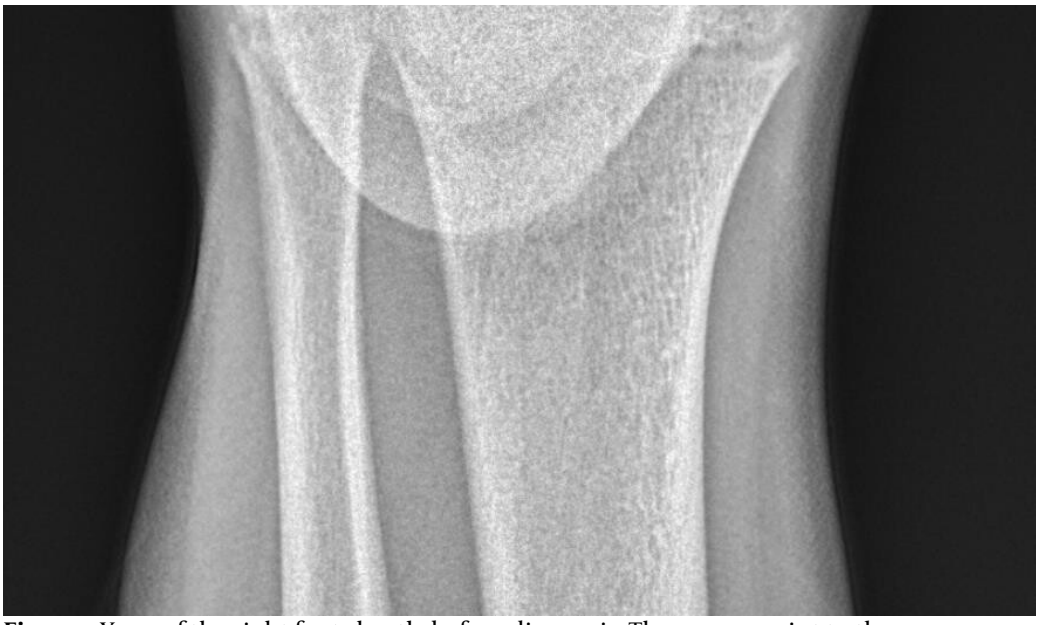


Figure 1 X-ray of the right foot shortly before diagnosis. The arrows point to the uneven structure of one of the cuneiform bones.

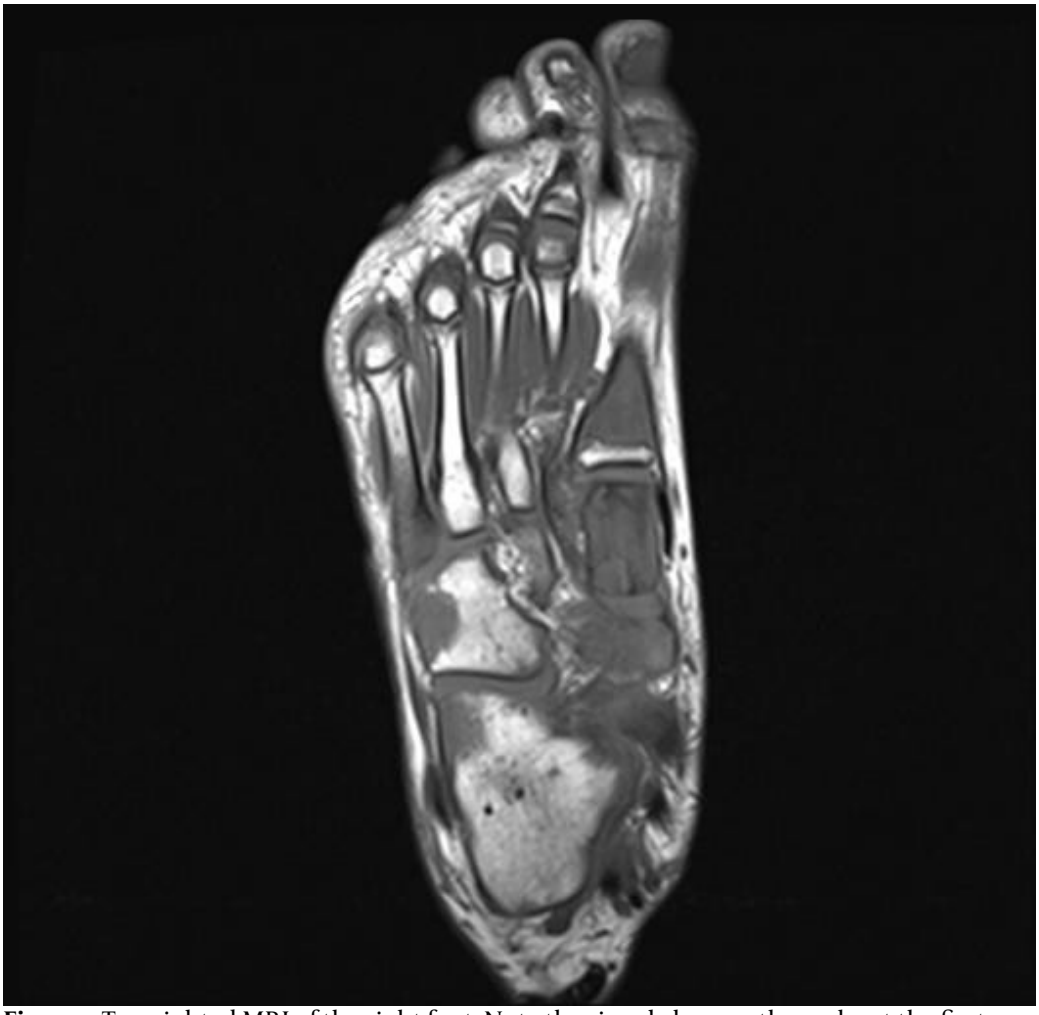


Figure 2 T1-weighted MRI of the right foot. Note the signal changes throughout the first metatarsal and proximal fifth metatarsal as well as patchy signal changes in the tarsal bones.

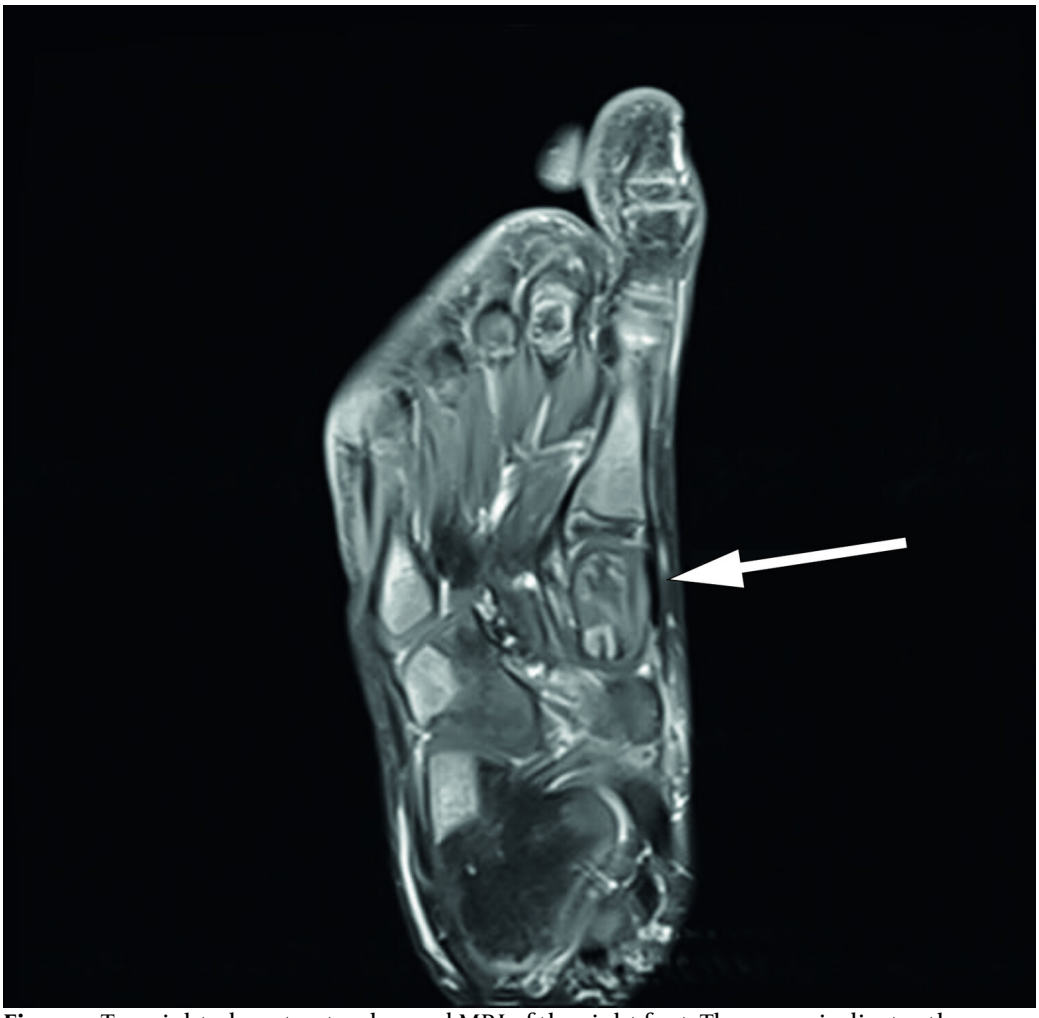


Figure 3 T1-weighted contrast-enhanced MRI of the right foot. The arrow indicates the medial cuneiform bone with signal changes suggestive of an abscess and a fluid-filled structure in the medial plantar area.

Osteomyelitis is an infection localised to the bone, usually caused by the haematogenous spread of bacteria. In cases of suspected osteomyelitis, every effort should be made to obtain a biopsy as quickly as possible. MRI or scintigraphy are indicated if radiography shows soft tissue changes and a periosteal reaction. However, plain radiography can also appear normal in the early stages of osteomyelitis, and it may therefore be appropriate to initiate empirical antibiotic therapy before MRI or scintigraphy results are available. The plain radiograph obtained during our patient's first appointment, more than five months earlier, had been normal.

No pus or signs of bacterial infection were observed perioperatively. Chronic recurrent multifocal osteomyelitis was therefore considered a more likely diagnosis. The patient remained in hospital and antibiotic treatment was continued pending the biopsy and culture results. Analgesia in the form of naproxen (250 mg twice daily) and paracetamol (500 mg up to four times daily as required) was also initiated, as recommended for the treatment of chronic recurrent multifocal osteomyelitis.

Six days after surgery, the biopsy results from the suspected abscess revealed massive infiltration of B lymphoblasts. The boy was transferred to the university hospital the same day to undergo testing for lymphoma and leukaemia. On examination, his general condition was found to be good. He had swelling under both eyes with small, hard, palpable infiltrates bilaterally and a small cutaneous lesion ventrally on the left side of the thorax. Palpation revealed both testicles to be pathologically enlarged, to 6 cm and 3 cm on the right and left sides, respectively. There was no hepatosplenomegaly or generalised lymphadenopathy. Flow cytometric analysis of the bone marrow showed 35 % immature B lymphoblasts from the right iliac crest and 14 % from the left iliac crest. The boy was diagnosed with pre-B acute lymphoblastic leukaemia (ALL).

Induction therapy for pre-B acute lymphoblastic leukaemia was started in accordance with the ALLTogether protocol, a large multinational research and treatment study for children and young adults aged 1–45 years with acute lymphoblastic leukaemia (clinicaltrials.gov: NCT04307576). The study is based in part on the earlier Nordic NOPHO ALL-2008 protocol (1). The boy showed a good clinical response to the induction therapy. After a few days, the pain in his foot had significantly decreased, the cutaneous infiltrates underneath his eyes had disappeared, and his testicles had decreased in size.

Upon evaluation of minimal residual disease in the bone marrow on day 29 after the start of induction therapy, the boy was found to be in complete remission with no evidence of disease. He continues to receive treatment in line with the standard risk arm of the ALLTogether study protocol and has been informed that his prognosis is good.

Discussion

Early in the disease course, the patient showed relatively minor symptoms in the form of knee pain that rapidly resolved, and pain in the right foot that was initially attributed to a trauma. Haematological status and a plain radiograph of the foot were both normal, and the boy was therefore treated symptomatically without any underlying condition being diagnosed. Four months after symptom onset, the boy began to have difficulty bearing weight on his foot. This is a red flag, but unfortunately no additional diagnostic testing was performed. After a further month of increasing pain upon walking and eventually also nocturnal pain, another radiograph was obtained. This triggered the testing that led ultimately to the correct diagnosis. This case report is thus an example of a workup involving professionals from many different disciplines in both the primary and specialist healthcare services, but where a lack of communication and oversight may have resulted in a delayed diagnosis.

Acute leukaemia is the most common cancer in children (0–18 years). There were 44 new cases in Norway in 2020, of which 80 % were acute lymphoblastic leukaemia (2). With modern treatment protocols, the prognosis in children is good with five-year survival of up to 94 % (1). The diagnosis is made upon establishing that > 25 % of cells in the bone marrow are immature B or T lymphoblasts (1, 3). The typical symptoms of leukaemia result from involvement of different haematological cell lines: increased bleeding tendency or cutaneous haematomas due to thrombocytopenia; pallor and fatigue due to anaemia; and fever and increased vulnerability to infection due to neutropenia (4). Extramedullary involvement can give rise to palpable leukaemic infiltrates in organs including the skin, testicles, and lymph nodes. Musculoskeletal symptoms are common in leukaemia and occur in up to one third of patients, most often in cases of B-cell acute lymphoblastic leukaemia (5, 6). These symptoms can be challenging to diagnose, as they often occur in isolation (7). A retrospective analysis of 783 children with acute lymphoblastic leukaemia found that those presenting with musculoskeletal symptoms were more likely to have normal leukocyte, platelet, and haemoglobin levels, and less likely to have hepatomegaly or splenomegaly (5). As a result, their symptoms are often viewed as being of orthopaedic or rheumatological origin (8). Delayed diagnosis does not seem to affect the prognosis, however, possibly because these individuals tend to have less aggressive forms of the disease (5, 7).

Our case report is an example of a leukaemia that manifested with sparse musculoskeletal symptoms, and where further diagnostic testing revealed few additional signs and symptoms. Nevertheless, studies have shown that certain signs and symptoms are positive predictors for a diagnosis of acute lymphoblastic leukaemia in children with bone pain. A retrospective multicentre study of 277 children who received a diagnosis of either acute lymphoblastic leukaemia or juvenile rheumatoid arthritis found that nocturnal pain, a low leukocyte count ($<4 \times 10^9$/L), low-to-normal platelet levels ($150–250 \times 10^9$/L), and low haemoglobin levels (<11 g/dL) were positive predictors of acute lymphoblastic leukaemia

(9), with the combination of low leukocyte count, low-to-normal platelets and nocturnal pain having a sensitivity of 100 % and a specificity of 85 % for this diagnosis. Antinuclear antibodies (ANA), rash and objective signs of arthritis are not useful in differentiating between leukaemia and juvenile arthritis (9).

Ultrasound and MRI scans are currently considered the best imaging modalities for evaluating suspected juvenile arthritis (10). Plain radiography is less precise but can be useful when evaluating differential diagnoses. It can also help identify leukaemia in patients presenting with bone pain, even when the findings are subtle (11). The presence of lucent metaphyseal bands, osteolysis, a periosteal reaction or osteosclerosis had a sensitivity of 90.0 % and specificity of 99.8 % for a leukaemia diagnosis (11). Our patient's first radiograph was normal, as was his haematological status. When his symptoms worsened and he began to experience weight-bearing pain four months later, unfortunately no further diagnostic imaging was performed. In retrospect, another X-ray or MRI scan could have been considered as soon as this red flag was identified.

The presence of leukaemic infiltrates in the testicles and under the eyes could also have allowed the diagnosis to be made earlier. The boy reported a painless scrotal swelling just over two months before he was diagnosed. Although this is in principle a red flag, it was probably assigned less importance because two ultrasound scans had shown normal-sized testicles and an enlarged epididymis; findings that were confirmed during surgery. Scrotal swelling is a rare early symptom of leukaemia, with one study reporting its presence in only 1.9 % of boys under 15 years of age (12). Cutaneous leukaemic infiltrates are also an infrequent early manifestation of acute leukaemia and are most often associated with acute myeloid leukaemia (AML) (13). In our patient, the cutaneous infiltrates were noticed only a few days before the diagnosis was made.

Although acute paediatric leukaemia often presents with atypical symptoms, the disorder is usually characterised by a constellation of multiple signs and symptoms or abnormal blood cell counts. Musculoskeletal symptoms, however, tend to occur in isolation. Leukaemia should therefore be considered as a differential diagnosis in patients with musculoskeletal symptoms, especially if any red flags are present. It is also important to examine the testicles when clinically indicated in boys. Testicular swelling should always be considered pathological, and the cause investigated. There should be a low threshold for additional diagnostic testing, including blood tests, radiography and ultrasound, in cases of unexplained skeletal pain and scrotal swelling. In most cases the results will raise suspicion of leukaemia as the underlying diagnosis.

The patient's guardians have consented to the publication of this article.

The article has been peer-reviewed.

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