Unusual cause of fever, jaundice, and hepatomegaly in a middle-aged man

Q1: In this patient’s clinical context, how do you interpret the laboratory tests on admission (table 1; see p 566)? This patient had a subacute febrile illness with constitutional symptoms and progressive jaundice. Initial laboratory tests showed severe anaemia with an increased reticulocyte count (corrected for the degree of anaemia) and red cell distribution width, predominately direct hyperbilirubinaemia, modest elevations in transaminases and alkaline phosphatase, hypoalbuminaemia, and mild renal impairment. The abdominal computed tomogram finding of asplenia was later confirmed to be due to splenectomy done during trauma surgery many years earlier. This imaging study also excluded biliary obstruction, pyaemic liver abscess, and metastatic liver disease, but did not exclude biliary obstruction. This was consistent with haemolysis. The tests done between days 2–4 revealed decreased haemoglobin levels, increasing macroglobulinaemia, and low haptoglobin levels. This imaging study also excluded biliary obstruction, pyaemic liver abscess, and metastatic liver disease, but did not exclude biliary obstruction. This was consistent with haemolysis. The tests done between days 2–4 revealed decreased haemoglobin levels, increasing macroglobulinaemia, and low haptoglobin levels. This was consistent with haemolysis. The negative blood cultures and absence of radiographic evidence of biliary obstruction made cholangitis less likely as a cause for his fever. Infectious conditions that can produce haemolytic anaemia are listed in box 1.

Q2: What does the blood smear show? What is the differential diagnosis? The peripheral blood smear shows an erythrocyte infected with Babesia microti (fig 1, arrow; see p 566) piroplasms, so called because they are pear-shaped. The organisms within the red cell appear as darkly staining ring forms that are about 2 μm in size and contain pale blue cytoplasm (fig 1, inset; see p 566). These intraerythrocytic ring forms closely resemble Plasmodium falciparum. Three distinguishing features differentiate the two: babesiae form tetrads (“Maltese cross”), do not have haemoglobin pigments within the affected red blood cells, and have extracellular merozoites. Geographic factors and travel history would also be relevant diagnostic pointers in deciding between the two organisms.

Babesiosis was first described in 1957 and is distributed worldwide, but most clinical cases have been described in the temperate regions of the United States and Europe. In North America, it is endemic in the islands off the coast of Massachusetts, including Nantucket and Martha’s Vineyard and in eastern Long Island in New York. The predominant organism is Babesia microti, a natural parasite of rodents, which is transmitted by the bite of the tick Ixodes scapularis. Based on serosurveys, the estimated seroprevalence has been varyingly reported to be between 8% and 16%, but true prevalence is difficult to estimate since most human infections are subclinical. In asplenic and immunocompromised individuals, the disease is often more severe. More recently, in the western United States, a yet unnamed piroplasm (designated WA1) has been described as a putative agent for human babesiosis, mostly in asplenic individuals. The overall mortality rate for clinical cases of B microti is about 5% in the United States.

In contrast, symptomatic babesiosis is much less prevalent in Europe, with fewer than 30 cases reported so far, mostly from the British Isles and France. Most such cases (83%) are due to Babesia divergens, a bovine pathogen. B divergens tends to produce a more severe illness with a shorter incubation period (1–3 weeks after the tick bite), tends to occur mostly in splenectomised individuals, and has a much higher mortality rate, about 42%. While seeing the piroplasms in stained preparations of thin blood smears remains the gold standard for diagnosis, immunofluorescence antibody test and polymerase chain reaction are also being used, mostly as epidemiological or research tools. Transfusion associated babesiosis has been described, as also has been coinfection with other tick-borne pathogens such as Borrelia burgdorferi (Lyme disease), ehrlichiae, and Bartonella bacilliformis (Oroya fever). Also, babesiosis tends to run a severe course in patients with AIDS.

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Failure to thrive in a 3 month old boy

Q1: What are the radiological findings and findings on peripheral smear and bone marrow? The radiograph (fig 2; see p 567) shows symmetric stippled calcific deposits in both adrenals. On an abdominal ultrasound (fig 3; see p 567) this appears like radio-opaque periosteal ossicles. The peripheral smear shows lymphocytes containing small vacuoles (fig 1; see p 567). Bone marrow aspiration shows lymphocytes and many macrophages with vacuolated cytoplasm and a foamy appearance (fig 4; see p 567), similar to that seen on a peripheral smear.
Q2: What is the diagnosis? What are the possible differential diagnoses?

The diagnosis is Wolman’s disease, a characteristic feature of which is diffuse calcification of symmetrically enlarged adrenal glands. From the clinical presentation in the above case, a differential diagnosis would include any of the common storage disorders like Gaucher’s and Niemann-Pick disease, congenital leukaemias, osteopetrosis, and histiocytosis. Foamy cells as in fig 4 (see p 367) are seen in Gaucher’s and Niemann-Pick disease. Calcification of adrenals is not seen in these two conditions. Idiopathic adrenal calcification, adrenal haemorrhage, tumours, or granulomas are other causes of adrenal calcification, however these are usually unilateral.

Q3: What is the prognosis and treatment of this condition?
The prognosis is usually bad and patients do not survive beyond one year, most succumbing to gastrointestinal and haematological complications. The treatment is bone marrow transplantation; however, other experimental treatments of treatment like low-fat diet and a diet free of hydrophobic esters, in which cholesterol and essential fatty acids are bound to protein, have been tried with varying results.

Discussion

Wolman’s disease is an autosomal recessive lipid storage disorder secondary to a deficiency of lysosomal acid lipase hydrolysis resulting in accumulation of cholesterol esters in all organs especially the liver, bone marrow, and spleen.1 ‘The first report described the disease in three siblings who were Persian Jews.’ The original belief that the disease was confined to one ethnic group has been negated as the disease has been reported subsequently in a wide variety of races and ethnic groups. The genetic defect is on the long arm of chromosome 10 (10q23.2–10q23.3).1 Cholesterol ester hydrolyses cellular cholesterol esters and triglycerides after uptake of low density lipoprotein. Acid lipase deficiency results in intralysosomal storage and abnormal regulation of cellular cholesterol.2 Near total deficiency of acid lipase is found in tissues, leucocytes, and cultured fibroblasts from these patients.

In infants usually present with failure to thrive, developmental delay, diarrhoea, and hepatosplenomegaly. Adrenal failure is relatively rare.3 The neurological manifestations include mental retardation, spasticity and dementia, which though at first mild, have been known to progress rapidly.4 The extent of the neurological disease is not very clear as these infants usually succumb to gastrointestinal and haematological complications and die early. The vomiting and diarrhoea results from severe damage to the microvilli and the accumulation of foam cells in the intestinal mucosa.5 A thickened bowel wall may also be seen on ultrasonography.6

Anaemia usually occurs by the sixth week and becomes progressively severe, though thrombocytopenia is relatively rare.7 This is because of replacement of marrow by foamy macrophages. There may be a papulo-eruption rash on the face. There are a few patients with persistent jaundice as the presenting complaint. In the liver, this disorder is associated with increased fibrosis and ultimately cirrhosis. Liver function tests are normal unless hepatic fibrosis is extensive and the serum triglycerides and cholesterol are usually always normal in these patients.8 The enlarged liver has a distinct orange appearance on postmortem examination.

Cholesterol ester storage disorder is a milder allelic form of this disease.9 The residual enzymes are greater and onset is delayed until early adulthood. They usually present with hepatosplenomegaly and premature atherosclerosis. Adrenal calcification is a characteristic feature of this disease that have been thought to be detected and prenatal diagnosis, based on acid lipase activity in chorionic villi and in cultured amniotic cells using cholesterol oleate as a substrate, is possible.

Final diagnosis

Wolman’s disease.

References


Refusal to walk in an afebrile well toddler

Q1: What is the likely diagnosis and what do the magnetic resonance imaging studies (figs 2 and 3; see p 570) show?

The likely diagnosis is L5–S1 discitis. Magnetic resonance imaging of the spine (fig 2) shows bulging both anteriorly and posteriorly of the L5–S1 disc with erosion of the anterior corners of both the L5 and S1 vertebra. There is evidence of fluid between the anterior aspects of the vertebral bodies. The radiological appearances are more likely to be consistent with a mild discitis. Repeated magnetic resonance imaging of the spine (fig 3) a year later showed resolution of the bone changes and a mild reduction in the disc signal at the L5–S1 level with also some reduction in the degree of bulging.

Q2: What are the alternative differential diagnoses of refusal to walk in a well afebrile toddler?

The diagnosis depends on the onset of walking difficulties. An afebrile well toddler who is slow to achieve the walking milestone might be a bottom shuffler, have benign familial hypermobility joint syndrome, have congenital hip dislocation, cerebral palsy, myopathy, neuropathy, or have inherited mild forms of defects in collagen synthesis such as osteogenesis imperfecta type IA or Ehlers-Danlos syndrome type III. An afebrile well toddler presenting with sudden onset of walking difficulties, as in our case, has to be investigated. Conditions that should be considered are shown in box 1. Acute lymphoblastic leukaemia (ALL) may present with musculoskeletal complaints. Clinical features suggestive of ALL are hepatosplenomegaly, anaemia, and bruising. There may be characteristic bony changes on radiography. In tuberculosis of the spine, the disc is usually reduced in association with vertebral collapse. Areflexia or hyporeflexia and raised cerebrospinal fluid protein are suggestive of peripheral neuropathy. Investigations that should be performed in a toddler with refusal to walk, as in our patient, are full blood count, blood film, C reactive protein, erythrocyte sedimentation rate, blood culture, plain radiograph of the spine, bone scan, and spinal magnetic resonance imaging. Plain anteroposterior and lateral spinal x-ray findings and magnetic resonance imaging appearances are consistent with the diagnosis of discitis.

Discussion

Discitis, an uncommon, usually benign and self limiting disease in children, tends to present with refusal to walk, stand, or sit. Other symptoms are fever, reduced range of motion, exclusion of an abdominal pain, nausea, and irritability. Physical signs are difficult to elicit in the very young. It is an important observation by parents that their patient disliked having his nappy changed when flexion of the disc space is obviously involved. Crawling was not a problem as he was comfortable with lumbar spinal extension. The pathophysiology of discitis is not fully understood. Most authors believe in an infectious etiology where there is haematogenous spread of the infecting organisms to the disc space via vascular channels in the cartilaginous vertebral endplates and in the immature discs. Others feel that discitis is caused by trauma, namely a partial dislocation of the epiphysis secondary to a flexion injury.10 Investigations show raised erythrocyte sedimentation rates and C reactive protein. White blood cell count may be normal. Interestingly, the inflammatory markers of our case started to fall before the start of antibiotics. This may support the theory of a non-infectious aetiology. Studies have shown that only about 28% of blood cultures11 and only 25% of disc space biopsy specimens are culture positive (positive cultures usually yield Staphylococcus aureus). Plain anteroposterior and lateral spinal radiographs should be taken initially in suspected discitis, although radiographic changes may be delayed for 2–8 weeks after the onset of symptoms. Bone scans may be

Box 1: Main causes of sudden refusal to walk in an afebrile well toddler

- Joint: septic arthritis, transient synovitis.
- Bone: osteomyelitis, tuberculosis of the spine, bone tumour.
- Nervous system: Guillain-Barré syndrome, spinal cord tumour.
abnormal one week after symptoms appear, but a normal bone scan does not exclude discitis as illustrated in our case. The sensitivity in diagnosing discitis is greater with computed tomography and magnetic resonance imaging compared with bone scans with magnetic resonance imaging becoming the diagnostic tool of choice. Treatment is controversial. Most authors recommend bed rest with or without external immobilisation and analgesia. While most routinely use antibiotics, others reserve antibiotics for patients with septicemia. Antibiotics should be broad spectrum and penicillinase resistant (preferably a second generation cephalosporin), beginning with parenteral antibiotics when the child is toxic, and once non-toxic, conversion to oral therapy until the three week course is complete. Discitis does not seem to result in any adverse long term sequelae. The prognosis in our case is good as x rays do not show any significant disruption of the disc spaces.

Final diagnosis
Discitis.

References
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