A diagnostic conundrum

Q1: What is the diagnosis in this case? The diagnosis is Whipple’s disease. This is a rare multisystem disorder characterised by weight loss, diarrhoea, abdominal pain, arthralgia and lymphadenopathy, though presentations may be very variable. It is caused by a Gram positive, PAS positive bacillus called Tropheryma whippelii which was identified in 1992.

It has been reported in all age groups, though it is commonest in middle aged white males. Whipple’s disease commonly involves the gastrointestinal tract causing a dilated thickened intestinal villous atrophy and malabsorption, resulting in anorexia, weight loss, abdominal pain, anaemia, hypoalbuminaemia and rarely, clotting disorders.

The heart and its all layers can be affected. Polyarthralgia is common though transient and episodic. Generalised hyperpigmentation can be found in up to 50% of patients. One of the striking features is mesenteric, abdomino, retroperitoneal, mediastinal, and peripheral lymphadenopathy which can often be mistaken for lymphoma, sarcoidosis, or other granulomatous disorders. Ten percent of patients will have neurological involvement at some stage of their illness. Dementia, ophthalmoplegia, and facial myoclonus are the commonest features.

Q2: What is the pathognomonic central nervous system manifestation? The answer is facial and ocular myoclonus. This includes oculomasticatory myorhythmia and oculofacial-skeletal myorhythmia. The former is characterised by a slow, smooth convergence-divergence pendular nystagmus associated with synchronous contractions of the jaw and the latter is associated with contractions of other body parts.

These are rare findings present in 20% of patients with central nervous system disease and are as diagnostic as a positive biopsy or a positive polymerase chain reaction assay of the bacterial RNA.

Q3: What is the diagnostic test? The diagnosis of Whipple’s disease requires a high index of clinical suspicion. Routine blood tests are non-specific as are tests of malabsorption. Histopathological examination of biopsy of the organs involved reveal PAS positive macrophages containing clumps of T whippelii. In about 30% of cases this is negative. The current diagnostic test is polymerase chain reaction of bacterial 16S ribosomal RNA from tissue biopsies, cerebrospinal fluid, blood, etc.

Q4: How does one treat this condition? Current treatment is long term co-trimoxazole (trimethoprim-sulphamethoxazole). Initial treatment in those with neurological involvement is an intravenous combination of cephalosporins and aminoglycosides, followed by oral co-trimoxazole. Locomotor and gastrointestinal symptoms may show improvement in days whereas histological remission may take 1–2 years. Relapse rates can be up to 35%.

Final diagnosis Whipple’s disease.
Primary hypertrophic osteoarthropathy starts insidiously in childhood or commonly during puberty and is characterised by remarkable cutaneous features, clubbing, and periostitis. Pathogenesis involves abnormalities in collagen synthesis. Fibroblasts from the affected skin are more profuse with increased synthesis of collagen. Molecular studies reveal evidence of upregulated collagen transcription.

The skin becomes thick and coarse with prominence of the usual lines of facial expression. Thickening of the eyelids gives rise to the appearance of partial ptosis. Seborrhoea, acne, and folliculitis are common. Overgrowth of scalp tissue in relation to underlying skull bone gives rise to cuts verticis gyrata. Bilateral, symmetrical, distal long bone involvements are seen, initially involving the distal diaphysis of tibia, fibula, radius, ulna, metatarsals, metacarpals, and phalanges. In advanced disease, proximal long bones and flat bones of the pelvic and shoulder girdles may also be involved. There is periostitis giving rise to radiological features of periarticular, irregular new bone formation and cortical thickening. Compared with the secondary form, this is coarser and extends more distally to involve the epiphyses. Involvement of musculoskeleton insertions and interfaces are also seen in the late stage. Calcification of tendons Achillises is common. These give rise to painful, restricted movement of distal large joints. Soft tissues over wrists and ankles are thickened and associated carpal and tarsal tunnel syndromes are seen. Advanced clubbing of the digits and palmarhydropsises hampers the daily activities of life.

There may be associated anomalies like hypertrophic gastropathy and peptic ulcer disease; bone marrow failure; gynaecomastia; and acro-osteolysis of fingers and toes. The condition is progressive for 10–15 years and thereafter becomes static. Plastic surgical intervention for the facial features improves a patient’s appearance.

**Final diagnosis**

Primary hypertrophic osteoarthropathy.
The radiological appearances as well as clinical features help to narrow the differential diagnosis down. On inspection of the radiograph one should note size, distribution, presence of cavitation, and that of calcification. Malignant tumours that commonly metastasise to the pulmonary are those include breast, thyroid, gastrointestinal tract and renal cell carcinomas, also head and neck tumours and soft tissue sarcomas. Metastases are present in variable numbers and are usually very well defined and peripheral in distribution. Cavitation is occasionally seen with squamous cell carcinomas and calcification is unusual except for chondrosarcoma and osteosarcoma metastasis. The main distinguishing features from benign lesions are the rate of growth and the presence of systemic symptoms. Hamartomas and carcinoid tumours have almost identical appearance on radiography, however most carcinoid tumours are solitary with hamartomas being peripheral and often calcified and carcinoid being perihilar. Other conditions that cause multiple lung lesions are lymphoid malignancies and Kaposi’s sarcoma. Finally infectious diseases including fungus granulomas, abscesses and hydatid disease also connective tissue disorders should be mentioned. Fungus granulomas and hydatid disease may well be asymptomatic, while multiple abscesses will manifest with fever and symptoms proportional to their source. Rheumatoid nodules are usually small and rarely cavitate. Larger lesions are seen in Wegener’s granulomatosis, but these are characteristically cavitating and often associated with haemoptysis and other symptoms of systemic vasculitis.

Q3: What important piece of information from the patient’s past medical history is missing and would highlight a possible diagnosis?

The patient had a total abdominal hysterectomy and bilateral salpingo-oophorectomy at the age of 69 years. She also had a right thoracotomy with lung biopsy and thoracic aortography during early childhood.

Q4: What is the most likely diagnosis? Spindle cell proliferation consistent with pulmonary metastases to achieve remission of a uterine leiomyosarcoma.

A rare case of wheeze in a young adult

Q1: Describe the findings on radiography and computed tomography.

The plain radiograph and computed tomogram of the chest (see p 542) shows evidence of a radiolated left hemithorax and a small left pleural effusion. Two pulmonary nodules, which have no visible calcification or cavitation but well defined margins, are noted overlying the left midzone. One lesion lies adjacent to and above the aortic knob, the other one adjacent to the left heart border. A subsequent contrast enhanced spiral computerised tomogram of her chest showed two small focal nodules in the right lobe, two moderate sized in the left upper lobe, and one large mass measuring approximately 6 × 9 × 11 cm replacing most of the left lower lobe, also a small left pleural effusion; there was no lymphadenopathy.

Q2: What is the differential diagnosis? The differential diagnosis of multiple lung masses is quite complex, with metastatic disease being the most common cause. Other possibilities include an inflammatory process such as fungus, tuberculosis, nocardiosis, or septic emboli. In asymptomatic patients further considerations include the presence of arteriovenous malformations, rheumatoid nodules, or amyloidosis. Less common pulmonary lesions also include fibromas, chondromas, lipomas, hamartomas, and leiomyomas.
on exertion, and never having smoked, made a malignant tumour unlikely.

Q4: How would you manage this patient?
The most appropriate management is surgical excision, in view of the symptoms of progressive exertional dyspnoea and exertional wheeze, and to prevent complete obstruction of the bronchus.

Discussion
In our patient, a surgical opinion was sought, and a right upper lobectomy with sleeve resection of the right main stem bronchus and carina, with carinal reconstruction by tracheobronchial anastomosis was performed. Light microscopy disclosed a tumour composed of polygonal cells with clear and abundant cytoplasm. The cytoplasm contained abundant periodic acid-Schiff positive material which was digested by diastase, indicative of glycolen granules. An extensive immuno-histochemical panel was applied to the tumour, which revealed positivity to HMB-45 (a marker of melanocytic lineage). Histology was consistent with a nodular clear cell tumour, with prominent melanin pigment deposition and a very low mitotic index. Abdominal ultrasonography revealed no evidence of a primary intra-abdominal tumour. On review three months later in the outpatient clinic, the patient was in excellent health, and pulmonary function tests had returned to predicted value, and FVC of 2.68 l/min (95% of predicted value). The patient was now off all inhaled therapy, and her wheeze on exertion had resolved.

Benign clear cell tumour (BCCT) or “sugar tumour” of the lung is an unusual primary tumour originally described in 1963 by Liebow and Castleman. Since this time more than 40 cases of BCCT of the lung have been published worldwide, but there is only one prior report on the occurrence of a BCCT in the conducting airways. The presence of immense quantities of intracytoplasmic glycoprotein is a distinguishing feature, responsible for the name “sugar” tumour. Patients with BCCT of the lung are usually asymptomatic, and tumours are most often peripheral coin lesions discovered incidentally on routine chest radiographs. There is a slight female predominance among the patients, ranging from 2 to 12 years of age (median 7). BCCT has been thought to originate from smooth muscle cells, pericytes or neuroendocrine cells including melanocytes, although the origin of BCCT has not been clearly defined. Recent reappraisal of the entity came from the discovery of HMB-45 positivity in sugar tumour cells, suggesting an histioclonic relationship with other non-melanocytic lesions known to express HMB-45, including lymphangiomyomatosis and angiomyolipoma, which are leiomyocytic or perivascular myofibroblastic proliferation. Recognition of “sugar tumour” of the lung is clinically important, as the histology of this benign tumour closely resembles pulmonary clear cell carcinoma, and also the clear cell pattern of renal cell carcinoma metatstatic to the lung. However, only the BCCT demonstrates abundant intracytoplasmic glycogen, HMB-45 positivity, and negative staining for epithelial markers such as cytokeratin, epithelial membrane antigen, and chromogranin, and usually S-100 protein. Therefore, BCCT of the lung can be distinguished from pulmonary clear cell carcinoma on the basis of electron microscopy and immunochemistry. Renal cell carcinoma should further be excluded by ultrasonography or abdominal computed tomography. Although slow growth is a characteristic feature of BCCT of the lung, a case report described a tumour that doubled its diameter within 21 months. Furthermore, while BCCT of the lung has traditionally been considered benign, a 1988 report described the case of a patient who died from metastatic BCCT of the lung. This fatal case indicates that benign behaviour of this tumour is not invariably.

Final diagnosis
Benign clear cell tumour (“sugar tumour”).

References

Deep jaundice in an adolescent
Q1: What is the main differential diagnosis of this patient’s initial syndrome?
In this young girl a syndrome of fever, lymphadenopathy, and hepatosplenomegaly were accompanied by infrahepatic cholestasis with high bilirubin and acute hepato cellular damage.

The differential diagnosis initially includes any cause of acute hepatitis (box 1) and/or cholestasis (box 2). The patient was not pregnant, she was not alcoholic, took no medication, and had no history of chronic disease.

Q2: What is the laboratory test of choice you would perform on the third hospital day?
The patient presented with cholestatic jaundice but on the third postadmission day her jaundice suddenly became deeper with a greater increase in unconjugated bilirubin. Moreover, an important fall in her haemoglobin level was seen. Therefore, an episode of acute haemolysis complicated the initial clinical presentation in this patient. The direct Coombs test was negative. A spot urinal test was positive for haemoglobin and the haemoglobulin level was low. The laboratory test of choice was to perform the cold agglutinin titre which was raised (1/1024) with an anti-“i” specificity.

The glucose-6-phosphate dehydrogenase level was within normal limits and haemoglobin electrophoresis showed no abnormalities.
Q3: What is the diagnosis and the treatment of this syndrome?

Acute haemolysis due to cold agglutinins together with mononucleosis-like syndrome and icteric hepatitis suggests an acute and severe Epstein-Barr virus infection. The IgM antibodies against Epstein-Barr virus capsid antigen were raised in a titre of 1/320 and the IgG antibodies 1/160. Whole blood examination with polymerase chain reaction for Epstein-Barr virus DNA was positive.

In patients with Epstein-Barr virus hepatitis and/or cholestasis, conservative measures are usually sufficient. In patients in whom haemolysis due to cold agglutinins occur, corticosteroid therapy is controversial but sometimes recommended. Although it is of proven benefit in the case of autoimmune haemolysis due to warm antibodies.

Progress

The patient started folate administration and a short course of corticosteroid treatment. Her condition progressively improved. Packed cell volume, bilirubin, and cold agglutinin titres during follow up are shown in Fig 1. She was discharged on the 20th postadmission day with a packed cell volume of 32%, haemoglobin 106 g/l, reticulocyte count 3.9%, total bilirubin 3.8 mg/dl (65 µmol/l), direct bilirubin 3.04 mg/dl (52 µmol/l), and still moderately raised liver enzymes. Six months later the patient was in good health with complete clinical and biochemical recovery.

Discussion

This young patient presented with a severe Epstein-Barr virus infection complicated by icteric hepatitis and secondary haemolysis due to cold haemagglutinins. Nevertheless, lack of the classical symptoms of infectious mononucleosis and the negative test for heterophil antibodies made the initial diagnosis difficult. The rapid heterophil antibody test has an important role in the diagnosis of Epstein-Barr virus infection. However, false negative tests have been reported in 20% of the cases in children and 15% in adults. At presentation, a moderate hepatocellular injury, with raised liver enzymes, a normal prothrombin time but unusual high conjugated bilirubin level was predominant. Any other causes of acute hepatocellular damage and intrahepatic cholestasis have been excluded. Acute hepatitis at presentation is reported in 20–50% of the cases of Epstein-Barr virus infection, however, mild hyperbilirubinemia is present in only half of these patients. Cases of cholestasis with clinical relevant deep jaundice are rarely reported, with peak serum bilirubin levels ranging from 18 mg/dl (308 µmol/l) to 23 mg/dl (393 µmol/l).

During hospitalisation our patient presented a rapid fall in haemoglobin level (from 116 g/l to 65 g/l) and her jaundice became “deeper”. The initial high bilirubin levels resembling predominantly conjugated bilirubin (68% of the total bilirubin level) became more raised with a switch to predomi-nantly unconjugated bilirubin (62.5% of the total bilirubin level). The finding of high anti-”i” cold agglutinins titre demonstrated that acute haemolysis had complicated the course of the disease. Anti-”i” cold agglutinins may be present in fewer than 2% of patients with Epstein-Barr virus infection but clinically relevant haemolytic anaemia is usually mild and self-limiting.

Severe haemolysis with an important fall in haemoglobin level and deep jaundice, as in our patient, has rarely been described. In a previous study, seven patients with primary Epstein-Barr virus infection had peak bilirubin levels of 10.2–23 mg/dl (174–393 µmol/l). In five of these seven cases, however, there was evidence for both hepatocellular dysfunction and an ongoing haemolytic process either due to anti-”i” cold agglutinins or due to positive antihydroxyethyl antibodies.

Deep jaundice with signs of haemolysis always raises the possibility of Wilson’s disease. In our patient serum ceruloplasmin and copper were normal and no increased urinary copper or the presence of Kayser-Fleischer ring could be documented. Although these findings do not absolutely exclude Wilson’s disease, the fact that the patient is healthy now, more than six months after the episode of jaundice, clearly demonstrates that she can not have any chronic metabolic disease.

In conclusion, classical Epstein-Barr virus infection is usually a benign and self limiting disease. Despite this fact, close follow up of cases in order to prevent and identify possible complications is necessary. The present case should raise clinicians’ indices of suspicion for the described unusual complications of the well known syndrome of infectious mononucleosis. A cholestatic form of Epstein-Barr virus induced hepatitis may be present in several cases, while a deepening jaundice may be the result of haemolysis due to cold haemagglutinins.

Final diagnosis

Epstein-Barr virus infection.

References


Figure 1 Packed cell volume, bilirubin, and cold agglutinin titres during follow up (to convert bilirubin from mg/dl to µmol/l multiply by 17.1).
Red eyes, reduced vision, and vomiting

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