SELF ASSESSMENT ANSWERS

An unusual electrocardiographic abnormality

Q1: What is shown in fig 1 (see p 539), and what is its significance?

Figure 1 shows a prolonged QT interval (corrected QT 520 milliseconds) and macroscopic T wave alternans. T wave alternans is defined as a beat to beat variation in the amplitude or polarity of the T wave. Macroscopic T wave alternans is a predictor of malignant ventricular arrhythmias.[1] Microvolt T wave alternans is a validated predictor of mortality and morbidity in a variety of patient groups.[1] This ECG anomaly is seen with both transient physiological stress (for example, exercise), and with pathological stress such as electrolyte abnormalities and myocardial ischaemia. Indeed, revascularisation in ischaemia has even been shown to reduce the incidence of T wave alternans.[1] It has also been documented in association with the long QT and Brugada syndromes.[2]

T wave alternans on a millivolt scale visible to the naked eye (macroscopic T wave alternans) is predominantly a subject for individual case reports. It is often a precursor to the subsequent development of torsades de pointes (polymorphic ventricular tachycardia). Regardless of amplitude, T wave alternans should be regarded as a warning of malignant arrhythmias.

Q2: What is the arrhythmia in fig 2 (see p 539)?

The upper trace in fig 2 is lead II from a conventional electrocardiographic recording. It shows macroscopic T wave alternans in the first four beats degenerating into torsades de pointes (polymorphic VT). In comparison with fig 1, the QT interval is yet further prolonged. The lower trace shows loss of the arterial pressure waveform.

Q3: What was the procedure used to treat the patient in fig 3 (see p 539)?

Figure 3 shows a ventricular paced rhythm. Torsades de pointes in this patient was treated by ventricular overdrive pacing. The patient was given verapamil to ensure his own rhythm was slower than that delivered by the temporary pacing wire. In addition, the patient received intravenous magnesium sulphate to correct the hypomagnesaemia.

Discussion

T wave alternans is uncommon and often overlooked except when it is of a large (millivolt) amplitude such as in this case. Its mechanism demonstrates modern electrophysiological understanding of the basis of arrhythmia generation.

Many arrhythmias occur as a result of re-entry circuits. A re-entry circuit occurs when a depolarising wave travels in a circle from myocyte to myocyte. Each myocyte becomes refractory for a short time to further depolarisation as the ion channels in the cell membrane are reset. By the time the wave comes full circle, however, the first myocyte is no longer refractory and is able allow the circus movement to continue round the circuit indefinitely.

Such circuits depend on heterogeneity of repolarisation. Normally the myocardium depolarises rapidly and synchronously which is represented on the ECG by the narrow QRS complex. The myocardium is then refractory until ventricular repolarisation is completed. Repolarisation is slower and more heterogeneous than depolarisation and hence the T wave appears as broad deflection on the ECG. The more heterogeneous the repolarisation, the greater the chance that part of the myocardium will no longer be refractory should an ectopic beat occur, and hence allow a re-entry circuit to be established.

Heterogeneity of repolarisation is formally known as transmural dispersion of repolarisation (TDR). Increased TDR occurs with electrolyte abnormalities (for example, hypokalaemia, hypomagnesaemia), with intrinsic abnormalities of the ion channels due to genetic mutations (the congenital long QT syndromes), and as an effect of drug therapy (antiarrhythmics, β-agonists, erythromycin, etc).[3]

Increased TDR manifests on the surface electrocardiogram as alteration in the timing and amplitude of the T wave. This is the mechanism of both T wave alternans and the better known prolonged QT interval. Interestingly, while T wave alternans is always associated with increased TDR, long QT intervals may be found with a normal distribution of repolarisation. A long QT interval may occur when the whole myocardium repolarises late but synchronously (small TDR) or when just part of the myocardium lags behind repolarisation of the rest (large TDR). Drugs such as amiodarone prolong the action potential, and hence the QT interval, yet decrease the TDR.

This patient had two separate factors operating to increase the TDR. Firstly he had a low serum magnesium concentration which like abnormalities in potassium and calcium is known to alter the dynamics of repolarisation of the myocardium. Secondly, he was on nebulised β_2-agonists (salbutamol), and given 1:1000 adrenaline during the cardiac arrest. The dispersion in the rate of repolarisation is therefore increased.

Just as the T waves represent myocardial repolarisation, T wave alternans is the correlate of increased variation in the rate of repolarisation.[4] Sometimes the myocytes repolarise synchronously and sometimes less so; sometimes the wave of repolarisation is in one direction, and sometimes the other. It is an early warning sign of re-entry circuits and ventricular arrhythmias and in particular torsades de pointes. Although T wave alternans is a rare electrocardiographic sign, when present it should be treated with suitable respect.

Final diagnosis

Macroscopic T wave alternans and recurrent torsades de pointes.

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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 presentation may be very variable. It is caused by a Gram positive, PAS positive bacillus called *Tropheryma whippelii* which was identified in 1992.[1]

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 intestine with villous atrophy and malabsorption, resulting in anorexia, weight loss, abdominal pain, anaemia, hypoalbuminaemia and rarely, clotting disorders.

The heart and all its 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, abdominal, retroperitoneal, mediastinal, and peripheral lymphadenopathy which can often be mistaken for lymphoma, sarcoidosis, or other granulomatous disorders. Ten percent of patients have neurological involvement at some stage of their illness. Dementia, ophthalmoplegia, and facial myoclonus are the commonest features.[2]

Q2: What is the pathognomonic central nervous system manifestation?

The answer is facial and ocular myoclonus. This includes oculomasticatory myorhythmia and oculofacial-skeletal myorhythmia.[3] The former is characterised by a slow, smooth convergent-divergent 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 biopsies 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.[4]

Q4: How does one treat this condition?

Current treatment is long term co-trimoxazole (trimethoprim-sulphamethoxazole).[5] 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 while histological remission may take 1–2 years. Relapse rates can be up to 35%.

Final diagnosis

Whipple's disease.

References

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Progressive furrowing of skin with digital clubbing

Q1: What is the diagnosis?

The diagnosis is primary hypertrophic osteoarthropathy or pachydermoperiostitis or Touraine-Solente-Gole syndrome. The presence of characteristic facial features with cutis verticis gyrata and advanced clubbing of the digits in the absence of any systemic features suggest the diagnosis. Radiological evidence of periostitis of the involved bones helps in confirmation of the diagnosis.

Q2: What are the radiological findings shown?

The radiograph of wrist (see p 541) shows periosteal reaction as shaggy new bone formation around the styloid process of radius. Cortical sclerosis and periosteal thickening are seen along lower ends of the shafts of radius, ulna and metacarpals, proximal and middle phalanges of both hands.

Q3: Which other conditions are to be differentiated clinically from this entity?

This condition has to be differentiated from the secondary form of hypertrophic osteoarthropathy, which occurs in relation to bronchopulmonary and rarely other visceral malignancies, suppurative lung diseases, and congenital heart diseases. Here, facial features are minimal or absent and the osteoarthropathy and digital clubbing are painful.[1 2] Associated systemic features are present.

In acromegaly, patients present with similar facial features and cutis verticic gyrata, but in addition, there is prognathism, altered body proportions, change in voice, and visual field defects.[1] Hands and feet are spade shaped but clubbing is absent.

In thyroid acropachy, a rare feature of Graves' disease, facial feature include exophthalmos along with symptoms and signs of hyperthyroidism.[1 2] Pretibial myxoedema is usually associated. Enlargement of distal extremities is confined to hands and feet.

In scleromyxoedema, facial features are identical but widening of distal extremities and digital clubbing are absent.[1]

Discussion

Primary hypertrophic osteoarthropathy is a rare, autosomal dominantly inherited disorder with variable penetrance.[1] It affects males predominantly with a sex ratio of 9:1,[2] and in about one third cases, family history is positive.[2]

Learning points

- Hypertrophic osteoarthropathy secondary to internal malignancy or other systemic illnesses are commoner than primary disease.
- Secondary hypertrophic osteoarthropathy is usually associated with tenderness of the involved joints and tender digital clubbing.
- Radiologically, in primary hypertrophic osteoarthropathy, the periosteal new bone formation is coarser than secondary form and extends distally to involve the epiphysis.

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 hyperactive with increased synthesis of collagen. Molecular studies reveal evidence of upregulated collagen transcription.[2]

The skin becomes thick and coarse with prominence of the usual lines of facial expression. Thickness of the eyelids gives rise to the impression of partial ptosis. Seborrhoea, acne, and folliculitis are common. Overgrowth of scalp tissue in relation to underlying skull bone gives rise to cutis verticis gyrata.

Bilateral, symmetrical, distal long bone involvements are seen, initially involving the distal diaphysis of tibia, fibula, radius, ulna, metatarsals, metacarpals, and phalanges.[2] In advanced disease, proximal long bones and flat bones of the pelvic and shoulder girdles may also be involved.[2] There is periostitis giving rise to radiological features of periarticular, irregular new bone formation and cortical thickening.[3] Compared with the secondary form, this is coarser and extends more distally to involve the epiphyses.[3] Involvement of musculotendinous insertions and interosseous membranes are also seen in the late stage. Calcification of tendo Achillis 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.[1] Advanced clubbing of the digits and palmoplantar hyperhidrosis hampers the daily activities of life.

There may be associated anomalies like hypertrophic gastropathy and peptic ulcer disease,[4] bone marrow failure,[2] gynaecomastia,[2] and acro-osteolysis of fingers and toes.[5] The condition is progressive for 10–15 years and thereafter becomes static.[1] Plastic surgical intervention for the facial features improves a patient's appearance.

Final diagnosis

Primary hypertrophic osteoarthropathy.

References

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Red eyes, reduced vision, and vomiting

Q1: Describe the anterior segment photographs

Both eyes reveal ciliary injection, corneal oedema, and shallow anterior chambers. Both pupils are oval and mid-dilated along with patches of iris atrophy more prominent in the left eye (figs 1 and 2; see p 542).

Q2: What is the diagnosis?

Bilateral simultaneous acute angle closure glaucoma. An acute attack of angle closure glaucoma is normally associated with a very high intraocular pressure along with reduced visual acuity, oedematous cornea, and shallow anterior chamber. The intraocular pressure in this case is low in both eyes because of prolonged attack leading to ciliary body shutdown (shock). The ciliary body shutdown led to reduction in aqueous production and the iris atrophic patches signify prolonged exposure of both eyes to high intraocular pressure.

Q3: How would you manage this patient?

The most important point is to reduce the inflammation so that the antiglaucoma medication can work. The patient was started on prednisolone (0.5%) and pilocarpine (2%) eye drops in both eyes. On further follow up, the corneal oedema resolved and gonioscopy revealed closed anterior chamber angles in both eyes. On her last follow up her visual acuity improved to 6/12 and 6/9 in right and left eye respectively. Later a laser iridotomy was carried out in both the eyes.

Q4: What is the cause?

Bilateral simultaneous angle closure attack has been described in the past to occur with surgical anaesthesia[1] and various drugs including paroxetine,[2] bronchodilators,[3] imipramine,[4] and fluoxetine.[5] Idiopathic bilateral simultaneous attack is a very rare entity. Saunders reported a series of 41 patients who presented with acute angle closure and only one had simultaneous bilateral symptoms of unknown cause.[6] Our patient had no obvious cause and the onset of symptoms of bilateral angle closure attack was spontaneous.

Discussion

An acute attack of angle closure glaucoma is normally associated with a very high intraocular pressure along with reduced visual acuity, oedematous cornea, and shallow anterior chamber. It is an ophthalmic emergency and warrants immediate systemic antiglaucoma medications—for example, acetazolamide or mannitol. Acute angle closure glaucoma can easily masquerade a systemic illness and these patients may present not only with painful eye with reduced vision but also with systemic symptoms and the diagnosis can easily be missed.[7 8] These patients should be referred immediately to the eye department to prevent ocular morbidity from this potentially treatable condition.

Learning points

- Patients with acute angle closure glaucoma may present with systemic symptoms and reduced vision.
- They should be referred urgently to an ophthalmologist to prevent ocular morbidity and blindness.
- An acute attack may spontaneously resolve by causing ciliary body shutdown and iris atrophy and thus bringing intraocular pressure back to normal.

Final diagnosis

Idiopathic bilateral simultaneous acute angle closure glaucoma.

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An odd case of multiple "cannonball metastases"

Q1: What abnormalities are seen on the radiograph?

The chest radiograph (see p 542) shows evidence of a raised left hemidiaphragm 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 knuckle, the other one adjacent to the left heart border.

A subsequent contrast enhanced spiral computed 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.

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 lung 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 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 commonly these 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 and 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 pointing to their source. Rheumatoid nodules are usually small and rarely cavitate. Larger lesions are seen in Wegener's granulomatosis, but those 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 had a total abdominal hysterectomy and bilateral salpingo-oophorectomy for uterine fibroids aged 49 years.

She also had had a right thoracotomy with a wedge resection for a 2 cm diameter encapsulated tumour at the age of 69 years. Histopathological examination revealed spindle shaped smooth muscle cells, fibroblastic elements, and glandular structures lined by low columnar epithelium. Review of slides from the uterine lesions removed at hysterectomy showed similar histology.

Q4: What is the most likely diagnosis?

Spindle cell proliferation consistent with pulmonary leiomyomata secondary to a benign metastasising uterine leiomyoma.

With only around 40 cases reported until 1996,[1] metastasising uterine leiomyomata are fairly rare anatomical and clinical entities. This condition is rather peculiar because of two contradictory findings: the tumour's benign histology and its metastasising capabilities. It is characterised by the early development of a uterine leiomyoma with the appearance of solitary or multiple pulmonary metastases in the premenopausal period.[2] Most patients reported a hysterectomy three to 20 years before diagnosis.[3] Although, like our patient, most of the cases were asymptomatic, presenting symptoms such as dyspnoea, dry cough, or chest pain have been reported.[4] With its incredibly slow tumour growth rate and stabilisation in the menopausal period prognosis is good, although complications caused by metastatic pericardial involvement are possible.[1]

Q5: How would you treat this condition?

Uterine leiomyomas are known to be oestrogen sensitive. In fact, both oestrogen and progesterone receptors have been identified in lung lesions and have led to treatment based on hormonal manipulation with either surgical or medical oophorectomy.[4]

Secretion of the gonadotrophins, luteinising hormone and follicle stimulating hormone, is normally pulsatile, with major pulses released every 1–2 hours depending on the phase of the menstrual cycle. Long acting gonadothrophin releasing hormone analogue (GnRHa), produces down-regulation of the GnRH receptors and subsequent very low androgen or oestrogen levels. Evidence based data shows that GnRHa causes fibroids to shrink but cannot be used long term because of unacceptable symptoms and bone loss.[5] Short term use over six months, however, has been shown to be the treatment of choice in pulmonary metastases to achieve remission and effective prevention of recurrences.[6]

Final diagnosis

Spindle cell proliferation consistent with pulmonary leiomyomata secondary to a benign metastasising uterine leiomyoma.

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A rare cause 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 543) demonstrated considerable reduction in the volume of her right lung with hyperlucency, a paucity of vascular markings on that side, and mediastinal shift to the right, suggesting a possible diagnosis of Swyer-James-MacLeod syndrome (a rare disease with unilateral hyperlucent lung due to bronchiolitis obliterans and pulmonary artery hypoplasia, which generally develops after lower respiratory tract infection during early childhood).

Q2: Describe the findings on bronchoscopy

Bronchoscopy (see p 543) revealed a pigmented tumour causing almost complete obstruction of the right main stem bronchus at the level of the carina.

Q3: What is the most likely diagnosis?

The most likely diagnosis is a benign pigmented lung tumour, or a melanocytic carcinoid tumour. The age of the patient, her general wellbeing and health apart from wheeze

on exertion, and never having smoked, make 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 wheeze on exertion, 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 glycogen granules. An extensive immunohistochemical 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 normalised, with an FEV_1 of 2.39 l/min (95% of predicted value), and FVC of 2.68 l/min (91% 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.[1] 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.[2] The presence of immense quantities of intracytoplasmic glycogen 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.[3] There is a slight female predominance among the patients, ranging from 8 to 67 years of age (median 57).[3]

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 histiogenic relation with other non-melanocytic lesions known to express HMB-45, including lymphangioleiomyomatosis and angiomyolipoma, which are leiomyocytic or perivascular myofibroblastic proliferation.[4] 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 metastatic 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, chromogranin, and usually S-100 protein.[5] Therefore, BCCT of the lung can be distinguished from pulmonary clear cell carcinoma on the basis of electron microscopy and immunohistochemistry. 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.[6] 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.[7] This fatal case indicates that benign behaviour of this tumour is not invariable.

Final diagnosis

Benign clear cell tumour ("sugar tumour").

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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 intrahepatic cholestasis with high bilirubin and acute hepatocellular 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.

Box 1: Differential diagnosis of acute hepatocellular damage

- Viral hepatitis (hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus, cytomegalovirus).
- Autoimmune hepatitis.
- Drug reaction (isoniazid, antibiotics, methyldopa)
- Ischaemia (hypertension, vascular occlusion).
- Metabolic/inherited disorders (Wilson's disease).
- Pregnancy related disorders (acute fatty liver of pregnancy).

Serological testing excluded acute viral hepatitis A, B, and C, which may be associated with icterus, low grade fever, lymphadenopathy, and hepatosplenomegaly. Autoimmune hepatitis may present with the same signs and symptoms, although acute icteric hepatitis as a presenting symptom is rather unusual. An important step during differential diagnosis is to exclude Wilson's disease, which may be present in young adolescents, but acute hepatitis with cholestasis is also unusual. Moreover clinical and laboratory testing failed to diagnose Wilson's disease in our patient.

Taking into consideration the patient's age and the acute presentation of her disease (fever, lymphadenopathy, and atypical lymphocytes on blood smear), mononucleosis-like syndrome must also be considered in the list of differential diagnoses (box 3). On the other hand, pharyngitis was not present, the heterophil antibody test was negative, and cholestasis with high bilirubin is very unusual in classical infectious mononucleosis.

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 urine test was positive for haemoglobin and the haptoglobin level was low. The laboratory test of choice was to determine 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.

Box 2: Acute hepatocellular damage with prominent cholestasis

- Icteric viral hepatitis (hepatitis A, hepatitis B, Epstein-Barr virus, cytomegalovirus).
- Drug reaction (anabolic steroids, oestrogen).
- Granulomatous diseases (mycobacterial infections, sarcoidosis, brucellosis).
- Infiltrative malignancies (lymphoma).
- Inflammation of intrahepatic bile ducts (acute cholangitis, graft versus host disease, AIDS, cholangiopathy).
- Systemic bacterial infection.
- Alcoholic liver disease.

Box 3: Differential diagnosis of mononucleosis-like syndrome

- Epstein-Barr virus infection.
- Cytomegalovirus infection.
- *Toxoplasma gondii* infection.
- Streptococcal or gonococcal pharyngitis.
- Hepatitis virus A or B infection.
- Acute HIV infection.
- Hodgkin's or non-Hodgkin's lymphoma.

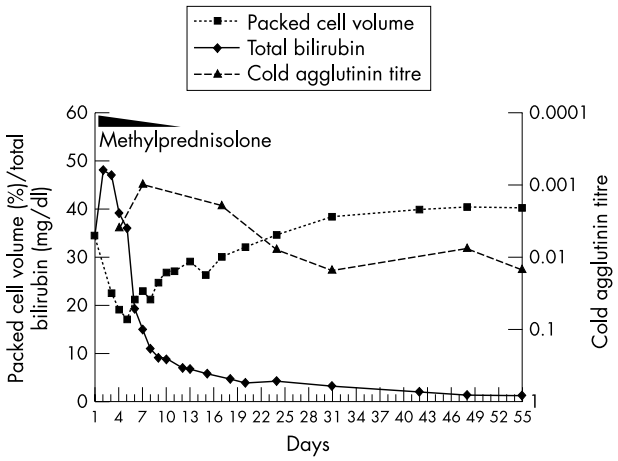

Figure 1 Packed cell volume, bilirubin, and cold agglutinin titres during follow up (to convert bilirubin from mg/dl to µmol/l multiply by 17.1).

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,[1] 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 diagnose of Epstein-Barr virus infection. However, false negative tests have been reported in 20% of the cases in children and 15% in adults.[2]

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,[3] however, mild hyperbilirubinaemia is present in only half of these patients.[4] Cases of cholestasis with clinical relevant deep jaundice are rarely reported,[2 5] with peak serum bilirubin levels ranging from 18 mg/dl (308 µmol/l)[6] to 23 mg/dl (393 µmol/l).[7]

During hospitalisation our patient presented a rapid fall in haemoglobin level (from 116 g/l to 63 g/l) and her jaundice became "deeper". The initial high bilirubin levels resembling predominantly conjugated bilirubin (68% of the total bilirubin level) become more raised with a switch to predominantly 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[8] 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.[3] 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).[7] 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 antierythrocyte 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.

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