A patient with atherosclerosis and livedo reticularis

J L Rodríguez-García, R Manzano, C Mira

A 73 year old man was admitted with progressive dyspnoea. His past medical history included peripheral artery disease (intermittent claudication of lower extremities) and ischaemic heart disease (angina pectoris). Two months before renovascular hypertension was diagnosed after he presented severe hypertension and mild renal insufficiency (plasma creatinine concentration 150.3 µmol/l). Renal angiography showed a solitary stenosis of his left renal artery. He had undergone a renal angioplasty two weeks before admission. On examination he had signs consistent with cardiac failure with pulmonary oedema; systolic blood pressure was 180 mm Hg and diastolic 100 mm Hg. A reticulated reddish mottling of the skin was seen on his feet (fig 1). His plasma creatinine concentration was 353.6 µmol/l. A skin biopsy specimen revealed needle-shaped crystals in his small arteries (fig 2). The patient’s condition continued to deteriorate; he was treated with vasodilators, diuretics, and pentoxifilline but developed progressive renal insufficiency and refractory heart failure and died 10 days after admission.

Questions
(1) What does fig 1 show?
(2) What kind of crystals are those observed on the skin biopsy sample (fig 2)?
(3) What is the final diagnosis?
Fever, rash, swollen joints, and sore throat in a young man

C S Arun, M A M Abbas, E B Henderson, A N Gorsuch

An 18 year old man developed a sore throat followed within two days by pain and swelling of both wrists, knees, and ankles, the metacarpophalangeal joints of both hands, and the metatarsophalangeal joints of both feet. This was associated with erythematous rash over his hands, arms, chest, and thighs down to both knees (see figs 1 and 2). His past medical history was otherwise unremarkable.

On examination he was febrile with a temperature of 38.6°C orally. He had an erythematous rash over the dorsal aspects of both hands, both arms, both thighs down to the knees, and chest. There were small effusions in both knees. Both wrists, both ankles, the metacarpophalangeal joints of both hands, and the metatarsophalangeal joints of both feet were tender and slightly swollen. Examination of the rest of his peripheral joints and of his axial skeleton was normal. Abdominal examination showed moderate splenomegaly, but nothing else. Other systemic examinations were unremarkable.

Investigations on admission included:
- Haemoglobin = 119 g/l
- White cell count = 23.0 × 10⁹/l (neutrophils 21.6 × 10⁹/l)
- Platelets = 338 × 10⁹/l
- Erythrocyte sedimentation rate = 92 mm in one hour
- C reactive protein = 234 mg/l (normal 0–10 mg/l)
- Serum total bilirubin = 16 µmol/l
- Serum alanine transaminase = 166 IU/l
- Serum alkaline phosphatase = 465 IU/l
- Serum albumin = 33 g/l
- Antistreptolysin-O titres = normal
- Serum ferritin = 22 515 µg/l (normal 40–350)
- Blood cultures and viral titres = negative
- Latex and antinuclear antibodies = negative
- White cell scan = normal
- Bone scan = normal

Ultrasound scan of the abdomen confirmed a modest degree of splenomegaly and nothing else.

Question
(1) What is the most probable diagnosis?
A rare cause of respiratory failure

S P L Meghjee, S E Enright, H O’Beirne, S Williams

A 68 year old man with a 60 year pack history (20 cigarettes per day for 60 years) of smoking was admitted via casualty with acute confusion, lethargy, and dyspnoea over three days. He denied any cough or haemoptysis, but was unable to give a clear history. Information from his wife indicated increasing exertional dyspnoea over two years with recent swelling of the ankles. She described increased spinal curvature over the past year with weakness of his arms and legs. On clinical examination he had marked kyphosis and was apyrexial. Pulse was 100 beats/min with a blood pressure of 140/70 mm Hg. Heart sounds were normal. His respiratory rate was 14 beats/min with poor chest expansion and decreased breath sounds bilaterally. He was confused and slightly drowsy with a Glasgow coma scale of 14/15. Cranial nerves were intact. Upper limb examination was normal with no evidence of muscle wasting or fasciculation. Lower limb examination showed right foot drop. Full blood count and electrolytes were normal. Arterial blood gases on admission on 24% oxygen showed pH 7.40, arterial carbon dioxide tension 9.8 kPa, arterial oxygen tension 8.1 kPa, bicarbonate 44 mmol/l, and a base excess of +15. The chest radiograph is shown in fig 1.

Six weeks before this admission he had been seen in a respiratory clinic for investigation of his dyspnoea but no mention of muscular weakness was made. His past medical history included a neck injury after a road traffic accident 14 years previously with no associated neurological deficit. Chest examination at that time revealed kyphosis with markedly decreased chest expansion with reduced air entry.

Cardiovascular examination was normal. Detailed neurological examination was not recorded. Full lung function tests showed peak flow 320 l/m (predicted 505 l/m). Forced expiratory volume in one second was 2.2 l/sec (predicted 2.65 l/sec). Forced vital capacity was 2.4 litres (predicted 3.65 litres), and transfer factor of carbon monoxide per unit of volume was 19.4 ml/min/mm Hg (predicted 17.6). Cervical radiography is shown in fig 2. Arrangements were made to review him after further investigation.

Questions
(1) How would you interpret the arterial blood gases and the lung function tests?
(2) What is the differential diagnosis?
(3) What do the chest and cervical radiographs show?
(4) What further investigations might be helpful?
(5) What would be your initial management of this patient?
(6) What is the long term respiratory management of this condition?
Refractory seizure with hypokalaemia

D Vanpee, A Dive, M Ossemann, J B Gillet

A 67 year old woman was admitted to hospital because of intractable seizures. She was brought to our emergency department by her husband; he was frequently hospitalised in our institution. She had no previous history of epilepsy, alcoholism, or other neurological problems. She took benzodiazepines regularly for anxiety and sleep disorders. Examination showed a typical convulsive generalised tonic-clonic seizure, followed by myoclonic jerk of the right arm.

Her temperature was 36°C, the pulse was irregular at 140 beats/min, and blood pressure was 130/70 mm Hg. The biochemical tests showed potassium at 2.4 mmol/l, phosphate 0.35 mmol/l, calcium 2.5 mmol/l, sodium 139 mmol/l, creatinine 60 mmol/l, aspartate transaminase 47 UI/l, and alanine aminotransferase 25 UI/l.

Electrocardiography showed atrial fibrillation. An electroencephalogram disclosed left anterior epileptiform activities. Computed tomography of the brain demonstrated cortical atrophy only. Despite intravenous diazepam and valproic acid, she required intubation and assisted ventilation for status epilepticus.

Questions
(1) What is the missing biochemical request?
(2) What is the most probable diagnosis?
(3) What further investigation would you perform?

A complication after internal fixation of fracture

W J Sotheran, P M Perry

A 66 year old man was referred to the vascular surgery department from the orthopaedic unit. The patient had developed an abnormal, bleeding swelling over the lateral aspect of the left leg. Twelve days earlier he had had an open reduction and internal fixation of a comminuted fracture of hisibia and fibula. The injury was sustained seven months earlier. Previous surgery to the injury had resulted in non-union of fracture. At operation, a thigh tourniquet was employed. Corticocancellous bone grafts were taken from the posterior iliac crests. A rigid eight hole plate was applied across the fracture site. An interfragmentary screw was used. The wound was bleeding in the recovery room but no further surgical intervention was required.

Diagnostic imaging was requested. The radiological findings are shown in fig 1.

Questions
(1) What is the investigation and what does it show?
(2) What clinical symptoms may be associated with this type of lesion?
(3) How should this lesion be managed and what are the complications?
SELF ASSESSMENT ANSWERS

A patient with atherosclerosis and livedo reticularis

Q1: What does the fig 1 show (see p 206)?
Livedo reticularis. This is due to random spasm of cutaneous arterioles with secondary dilatation of capillaries and venules. Livedo reticularis is a common cutaneous manifestation of several conditions such as antiphospholipid syndrome, polyarteritis nodosa, Sneddon’s syndrome, dermatomyositis, cryoglobulinaemia, hepatitis C virus infection, amantadine intake, chronic pancreatitis, primary hyperoxaluria, and cholesterol emboli syndrome.

Q2: What kind of crystals are those observed on skin biopsy sample (fig 2, see p 206)?
The skin biopsy specimen shows cholesterol crystals filling the small deep arterial lumen of small arteries.

Q3: What is the final diagnosis?
Cholesterol emboli syndrome.

Discussion
Cholesterol emboli syndrome is a condition that may be increasingly iatrogenic in origin. Diagnosis is difficult and requires a high index of suspicion, an appropriate clinical picture, and usually, confirmation by biopsy. Although cholesterol emboli occur spontaneously, most patients have undergone an invasive procedure such as diagnostic angiography, percutaneous transluminal coronary angioplasty or cardiovascular surgery, which have the potential for arterial trauma and consequent cholesterol embolisation. The temporal relation of the procedure to the clinical presentation is highly variable, the interval ranging from one day to four months. Anticoagulants and fibrinolytics are also triggering factors for cholesterol embolisation.1, 2

The parts of the body most often affected are the kidneys, skin, muscles, and abdominal viscera. Thus, the presence of acute hypertension, renal insufficiency, livedo reticularis, and/or gangrenous skin changes are characteristic manifestations of the multiple cholesterol emboli syndrome.3, 4 Ophthalmoscopy may demonstrate bilateral retinal cholesterol emboli.5 Laboratory findings that suggest atheroemboli include eosinophilia, a raised erythrocyte sedimentation rate, leucocytosis, and anaemia. Transoesophageal echography may demonstrate ulcerated atheromatous plaques of the thoracic aorta responsible for cholesterol emboli.6

Although the apparent increasing numbers of cholesterol emboli may be a reflection of the increased use of arterial invasive procedures, they are being performed on an older, more severely ill population, with other risks factors for the development of embolic phenomena—for example, age, smoking history, diabetes mellitus, hypertension, and peripheral vascular disease. Thus, there is now growing emphasis on the concept of the triggering factors with the multiplication of endovascular radiological investigations, the more widespread availability of cardiac surgery, and the use of anticoagulants and fibrinolytics.1

Prognosis is related to the extent of systemic involvement but renal disease is particularly threatening and gangrene and infection can be lethal. Patients usually die of multisystem failure. A multiple therapeutic regimen has been generally unsuccessful in altering the course of the disease process. However, supportive treatment can reduce mortality. Treatment includes management of heart failure with vasodilators, loop diuretics, ultrafiltration or haemodialysis; enteral or parenteral nutritional support to avoid cachexia; haemodialysis for severe metabolic disorders, and corticosteroids when there is laboratory evidence of inflammation.1 Isolated reports have recommended the use of pentoxifylline,7 simvastatin,8 and prostacyclin analogues.9 However, the most significant impact on the disease can be made by its prevention.

Final diagnosis
Cholesterol emboli syndrome.

Learning points
- Common clinical presentation of cholesterol emboli syndrome includes renal failure and livedo reticularis in atherosclerotic patients over 60 years of age with a recent history of vascular catheterisation.
- Cholesterol emboli syndrome is often unrecognised or misdiagnosed and a better evaluation of risks factors (smoking history, diabetes mellitus, arterial hypertension, peripheral vascular disease) in patients undergoing invasive vascular procedures could prevent this severe complication.
- Supportive treatment can improve prognosis but the most significant impact on the disease can be made by its prevention.

8 Carr ME Jr, Sanders K, Todd WM. Pain relief and clinical improvement temporally related to the use of pentoxifylline.
Fever, rash, swollen joints, and sore throat in a young man

Q1: What is the most probable diagnosis?
The most probable diagnosis in this patient is adult onset Still’s disease. This patient had fever for more than a week, rash, arthralgia, and leucocytosis fulfilling the four major criteria for the diagnosis of adult Still’s disease. He also had minor criteria (lymphadenopathy, sore throat, liver dysfunction, and negative rheumatoid factor, and antinuclear antibodies), thus confirming the diagnosis. The investigations excluded infections, malignancies, and rheumatic diseases. The markedly raised serum ferritin concentration strengthens the diagnosis of adult onset Still’s disease.

Discussion
Adult Still’s disease is one of the febrile disor-
ders of unknown aetiology characterised by
typical spiking fever, evanescent rash, and
involvement of various organs. The
diagnosis especially in the early stages of
the disease is difficult because of the lack
of specific clinical, laboratory, and histological
features. Most patients will not present all the
characteristic features such as high fever, joint
symptoms, rash, and leucocytosis. The delay in
the diagnosis may result in prolonged and
unnecessary investigations or in unwarranted
treatment. Though various diagnostic and
classification criteria have been proposed,
Yamaguchi criteria have the highest sensitivity
(96.2%) and specificity (92.1%). The
preliminary criteria for the classification of
adult onset Still’s disease involve four major
and four minor criteria (box 1).

Box 1: Criteria for adult onset Still’s
disease
Major criteria
(1) Fever of 39°C or higher, lasting one
week or longer.
(2) Arthralgia lasting two weeks or longer.
(3) Macular or maculopapular
non-pruritic salmon pink eruption
usually appearing during fever.
(4) Leucocytosis (10 × 10^9/l or greater)
including 80% or more of
granulocytosis.

Minor criteria
(1) Sore throat.
(2) Lymphadenopathy and/or
spleenomegaly.
(3) Liver dysfunction.
(4) Negative rheumatoid factor and
antinuclear antibodies.

Q1: What is the most probable diagnosis?
The most probable diagnosis in this patient is adult onset Still’s disease. This patient had fever for more than a week, rash, arthralgia, and leucocytosis fulfilling the four major criteria for the diagnosis of adult Still’s disease. He also had minor criteria (lymphadenopathy, sore throat, liver dysfunction, and negative rheumatoid factor, and antinuclear antibodies), thus confirming the diagnosis. The investigations excluded infections, malignancies, and rheumatic diseases. The markedly raised serum ferritin concentration strengthens the diagnosis of adult onset Still’s disease.

Final diagnosis
Adult onset Still’s disease.

Box 2: Causes of markedly raised serum ferritin
- Malignancies, such as acute and chronic leukaemias, malignant lymphoma, melanoma, germ cell tumour, and neuroblastoma.
- Acute liver necrosis.
- Haemochromatosis.

The diagnosis of adult onset Still’s disease requires five or more criteria including two or more major criteria and needs exclusion of infections, malignancies, and rheumatic diseases. Increased concentrations of ferritin have not been included in the criteria list, but are recognised as an important discriminator. It has been suggested in many reports that increased serum ferritin of greater than 4000 µg/l is a useful test to aid in the diagnosis of adult onset Still’s disease. Besides being an important tool it also helps to monitor disease activity and guide decisions about treatment. Other causes with high serum ferritin are listed in box 2, but the values of serum ferritin in these conditions rarely exceed 5000 µg/l.

A rare cause of respiratory failure

Q1: How would you interpret the arterial blood gases and the lung function tests?
Arterial blood gases show compensated type 2 respiratory failure. Lung function tests show predominantly restrictive lung disease with greater than predicted transfer factor. These two tests indicate that the main problem is that of chest wall or neuromuscular weakness rather than alveolar level problem.

Q2: What is the differential diagnosis?
The differential diagnosis is:
- Neuromuscular pathology, for example, motor neurone disease, Eaton-Lambert syndrome, myasthenia gravis.
- Diaphragmatic paralysis.
- Kyphoscoliosis.
Q3: What do the chest and cervical radiographs show? (see p 208)
The chest radiograph is normal with no evidence of diaphragmatic paralysis. Cervical radiography shows no evidence of kyphoscoliosis.

Q4: What further investigations might be helpful?
Nerve conduction studies and Tensilon test (edrophonium chloride).

Q5: What would be your initial management of this patient?
Controlled oxygen therapy and non-invasive positive pressure ventilation or full ventilation. Despite treatment with controlled oxygen therapy, intravenous doxapram, steroids, nebulisers and antibiotics, the patient continued to deteriorate, and required endotracheal intubation and invasive ventilation. Non-invasive ventilation was not tried, as it is not currently available in our hospital.

Once he was stable a tracheostomy was performed to aid “weaning”. The Tensilon test was normal but electromyography showed scattered denervation and clear neurogenic changes indicating lower motor neurone weakness in some muscles sampled. There was no evidence of an underlying myopathy but changes indicating lower motor neurone weakness with partial denervation in some muscles were present. This was consistent with the diagnosis of motor neurone disease (amyotrophic lateral sclerosis). It proved extremely difficult to wean him off the ventilator. As the motor neurone disease was previously undiagnosed, the question of life support had not been discussed, and yet he had been precipitated into complete dependency on a ventilator. As he had normal cognitive function and was able to communicate, his diagnosis and prognosis were discussed with him and his family in a frank and compassionate manner. The patient and his family were given ample time to consider their options. They decided that they would like him to be considered for home non-invasive positive pressure ventilation. Unfortunately, while still being ventilated, he developed a pneumothorax (treated with intercostal chest drain) followed by an overwhelming nosocomial pneumonia and died. The rapidity of the clinical progression suggested fairly aggressive disease.

Q6: What is the long term respiratory management of this condition?
Specific respiratory treatment involves protection against aspiration and non-invasive ventilation. Aspiration can be prevented by mechanical means, for example, raising the head, regular swallowing assessment, use of anticholinergic drugs to reduce oral secretions, chest physiotherapy, early insertion of a gastrostomy tube, and in some specific cases, a tracheostomy. As the expertise of portable non-invasive home ventilation increases (either applied through use of a nose or facemask or via tracheostomy), it should be offered to selected patients (see discussion), as this has been shown to prolong survival.2

Discussion
Motor neurone disease (amyotrophic lateral sclerosis) is a progressive disease of adults resulting from variable degeneration of the upper motor and lower motor neurones. Worldwide annual incidence rates for classical amyotrophic lateral sclerosis ranges from 0.4 and 1.8/100 000 population.3 A point prevalence study of patients in the counties of South Glamorgan, Mid Glamorgan, and Gwent gave a point prevalence of 2.73/100 000 population. In the same study, 94% of the patients were living at home, of whom 65% had some degree of mobility impairment and 20% were wheelchair bound. Swallowing speed was reduced in 67% of patients and 8% had a percutaneous endoscopy gastrostomy feeding tube. Only one patient (2%) was receiving home non-invasive ventilation.4 In patients with amyotrophic lateral sclerosis, significant bulbar and respiratory weakness occurs in about 50%, and in few cases respiratory failure requiring mechanical ventilation is the presenting complaint.4 Respiratory compromise is due to impairment of any or all of the three muscle groups, which are essential for normal ventilation: the muscles of inspiration, muscles of expiration, and the muscles that control the upper airway.5,6 The manifestations of amyotrophic lateral sclerosis on respiratory muscles can be additive and progress in a vicious cycle to respiratory failure. Aspiration and loss of cough causes atelectasis and decreased compliance, decreased inspiratory muscle strength causing further atelectasis, and infection or aspiration pneumonia, increasing respiratory demand. Hypoxaemia and acidosis also impair respiratory muscle function by direct effect on the diaphragm.6

The usual relentless course of amyotrophic lateral sclerosis leads to death in 50% of patients within three years from the onset, invariably from respiratory failure. The three major predictors of survival in classical amyotrophic lateral sclerosis are age of onset, clinical variant of disease (predominantly bulbar involvement), and pulmonary function.7

As portable non-invasive positive pressure ventilation becomes more readily available it should be considered for selected patients, as this has been shown to prolong survival. These forms of non-invasive positive pressure ventilation have the added advantage of stabilising the oropharyngeal airway and prevent upper airway obstruction during sleep. Sherman et al have shown that in patients with amyotrophic lateral sclerosis and respiratory failure, the institution of non-invasive mechanical ventilation significantly prolonged survival in the treatment group (80.4 days v 19.25, p<0.01).1 Long term assisted ventilation in a disease that ultimately produces paralysis in the majority of patients causes significant ethical, legal, and psychological concerns. It is imperative that discussion with patients and family members about the pros and cons of ventilatory care be frank and take place early in the course of the disease, so as to help the patient make an informed decision. This will enable patients to make advance directives (living will) or have an
appropriate legal surrogate in cases when the patient's condition deteriorates.

Using home ventilation requires cooperation from patients, carers (who need to be trained), and the multidisciplinary input from doctors and other health care workers. Not only does this involve much time and energy from family and health care workers, but it also has a large cost implication. Due to the progressive nature of this incurable disease, the decision to utilise these modalities must be made with realistic consideration of the patient's quality of life.

Final diagnosis
Respiratory failure secondary to motor neurone disease (amyotrophic lateral sclerosis).

Q3: What further investigation would you perform?
In addition to a complementary history from the husband, a serum theophylline concentration should be obtained. Four days after admission the husband told us by chance that she had taken several tablets. Serum theophylline was not suspected on admission as the history from her husband was not contributory. It was only on the fourth day after admission that he told us she occasionally ingested theophylline tablets.

Theophylline has a narrow therapeutic range. Except for suicide attempts, theophylline intoxication can be attributed predominantly to therapeutic misadventure. Common clinical manifestations of theophylline intoxication include nausea, vomiting, diarrhoea, agitation, tremor, hyperventilation, supraventricular and ventricular arrhythmias, hypotension, and seizures. Severe toxicity may not be preceded by milder symptoms, as in our patient.

In theophylline intoxication, seizures are a life threatening complication. Seizures may be partial or generalised and can be refractory to most conventional therapy. In their study, Olson et al reported that patients suffering from chronic overmedication developed seizures in seven out of 15 cases and serious arrhythmias in four of 15 cases with serum concentrations of 40–70 mg/l.

Hypokalaemia and hypophosphataemia are common metabolic disturbances in theophylline intoxication, but have also been reported in patients with plasma theophylline concentrations within the therapeutic range. Hyperglycaemia and hypomagnesaemia are also common findings.

The combined mortality of theophylline induced seizures reported in the literature is approximately 40%. This high mortality rate may be related mainly to cardiorespiratory arrest and/or hypoxic encephalopathy resulting from protracted seizures, or refractory cardiac arrhythmias. In some cases, the severity of the underlying disease is the major cause for mortality.

Clinicians should consider drug toxicity in all patients with seizures. Theophylline should be suspected in the presence of hypokalaemia and hypophosphataemia particularly when other signs of toxicity (such as atrial fibrillation) are present. This case also underlines the prominent role of a good and comprehensive history.

Final diagnosis
Seizures related to theophylline intoxication.

A complication after internal fixation of fracture

Q1: What is the investigation and what does it show?
Figure 1 (see p 209) shows contrast angiography of the lower leg. The swelling was consistent with a false aneurysm of the anterior tibial after iatrogenic trauma. The lesion was 30 × 30 mm. Duplex Doppler imaging confirmed the origin and extent of the lesion.

Q2: What clinical symptoms may be associated with this type of lesion?
Clinical symptoms are variable and include pain, swelling, recurrent bleeding, compartment syndrome, and claudication. The presentation may be late. The case reported here was diagnosed in the second postoperative week. In other cases, the lesion has presented months or years after surgery.

Q3: How should this lesion be managed and what are the complications?
Repair of traumatic false aneurysms is most commonly by direct ligation or end-to-end anastomosis. In this case urgent surgical exploration was undertaken, the arterial injury was identified, and a primary repair carried out using a 6/0 polypropylene suture. This patient made an uneventful recovery and was discharged home after one week. A complication rate of 6% is described where primary repair is achieved. The most important complications are infection, recurrence of pseudoaneurysm, and limb loss. The commonest causes of false aneurysm are vascular surgical procedures, vascular interventional radiology procedures, and penetrating trauma. Iatrogenic orthopaedic trauma has been implicated in the aetiology of false aneurysms in several reports.

Final diagnosis
False aneurysm of the anterior tibial artery after trauma.