Cholesterol crystal embolization (CCE) is a disorder of people with widespread atherosclerosis, most of whom are elderly. It often follows a precipitating event, such as angiography, and presents most commonly with renal failure and cutaneous involvement of the feet. The diagnosis is established histologically by demonstrating occlusion of arterioles by cholesterol crystals. At present there is no specific treatment though avoidance of any further precipitating factors is crucial. The role of anticoagulants is uncertain and requires further research. The condition is fatal in some cases, particularly when renal vessels are involved. Less than half of cases demonstrated at post mortem examination had the diagnosis made antemortem, possibly due to a low level of awareness of CCE. Clinicians who make the diagnosis can avoid subjecting their patients to further unnecessary and fruitless investigations and interventions. We present two cases which illustrate the spectrum of the condition, and a review of the literature.

Case Report 1

A 82 year old woman with one year history of intermittent claudication and two month history of rest pain of the right foot was referred for an evaluation. She was an ex-smoker with a 30 pack-year smoking history and was known to have had hypertension and atrial fibrillation for several years. Her drug therapy included digoxin 125 mcg daily, frusemide 40 mg daily with amiloride 5 mg and aspirin 150 mg daily.

Physical examination showed cyanotic discolouration of both legs and early gangrenous changes involving the right great toe. The blood pressure was 180/70 mmHg and pedal pulses were palpable. Doppler ultrasound examination of her lower limb arteries showed biphasic signals and the arterial brachio-pedal index was 0.83 on the right and 0.91 on the left. Ultrasound scanning of the abdomen was normal. An electrocardiogram showed atrial fibrillation, no acute ischaemic changes and an average ventricular rate of 80 per minute. Her blood urea, creatinine and electrolyte concentrations were normal, as was her haemoglobin, total white cell count and differential white cell count. Urine testing showed a trace of protein and no blood; urine microscopy was normal.

A clinical diagnosis of small vessel obstruction was made and it was thought likely that she was suffering micro-embolization from central large arteries rather than thromboembolism from the left atrium. An echocardiograph showed good left ventricular function and no evidence of mural thrombus or left atrial thrombus. She was anticoagulated with heparin but continued to have rest pain. A decision was made to perform axillo-bifemoral bypass grafting with femoral ligation, to prevent further embolization, after angiography had shown a ragged aorto-iliac system with no evidence of obstructive lesions distally. Despite this her right toe became frankly gangrenous and required...
amputation. Histological examination demonstrated cholesterol crystal clefts. (Figure 1). This enabled a diagnosis of CCE to be made. She was treated with analgesics for the discomfort in her foot and anticoagulation was withdrawn. She gradually improved, her renal function did not deteriorate, and she was alive and mobile six months after the operation. Although it is possible for angiography to cause cholesterol crystal deposits in the periphery, we think this is unlikely in this case because the condition did not worsen abruptly after the procedure, and the histological features suggested a more prolonged process as there was evidence if fibrosis around the cholesterol clefts.

This patient illustrates clearly the detection and management of CCE. Because the cholesterol crystals causing the embolisation were probably arising low in the aorto-iliac system there was no involvement of kidneys or other intra-abdominal organs, hence the relatively good prognosis.

Case Report 2

A 66 year old man with known stable angina, hypertension and hypercholesterolaemia was admitted for a routine repair of an abdominal aortic aneurysm. He was an ex-smoker with a 40 pack-year smoking history. His medication consisted of amlodipine 10 mg daily, aspirin 75 mg daily and isosorbide mononitrate 20 mg twice daily. A 7 cm infra-renal abdominal aortic aneurysm had been discovered when he underwent an abdominal ultrasound scan for prostatic symptoms. Twenty four hours post-operatively he developed abdominal distension and hypotension. He was taken back to the operating theatre where a long segment of gangrenous large bowel was resected. He remained hypotensive and died from a myocardial infarction about 24 hours after his bowel resection. Histology of the bowel confirmed cholesterol embolisation (figure 2).

This case illustrates a strong association between surgical disruption of an atheromatous aorta and embolisation of cholesterol crystals. The patient had extensive involvement of critical intra-abdominal organs and therefore fell into a very poor prognostic group.

Review and discussion

Epidemiology

Until recently most of the information on CCE was gathered retrospectively in post-mortem series and case reports. Although Pannum first described CCE, it was Florey who rekindled medical interest in the subject by publication of an autopsy series in 1945. The frequency of CCE in autopsy series has ranged from 0.8% to 18%, indicating that it is a relatively common problem in patients dying in hospital. Recently, a retrospective Dutch study reported an average annual incidence of six cases per million population and another study has shown that CCE was responsible for 5 to 10% of cases of acute renal failure admitted to an American tertiary referral centre. The mean age is around 70 years and the condition is about three times more common in men. The discrepancy between ante-mortem and post-mortem findings suggests that at present the true incidence of CCE is probably underestimated.

Pathology

The pathological hallmark of CCE is demonstration of cholesterol crystals obstructing small arterioles in a histological specimen, usually of skin, muscle or kidney, obtained at postmortem or by biopsy. Cholesterol dissolves during tissue fixation and leaves clefts which are visible under the microscope. Any organ can be involved but most commonly embolisation occurs to the kidney, spleen, pancreas, gastrointestinal tract and skin.

Two types of embolisation occur. The first is composed of cholesterol or its esters and derived from a ruptured plaque. Such emboli tend to be diffuse and bilateral, lodge in arteries and arterioles of 50-200 microns in diameter which are too small for surgical intervention. This is true CCE. These emboli sometimes remain clinically unrecognised.
if the occluded vessel is small and the collateral circulation prevents infarction, but they may be noticed at autopsy. The other type, usually called atheroemboli, consists of thrombi that have been detached from the ulcerated surface of an atheromatous plaque or from a mural thrombus in an aneurysm. Such emboli are larger, occlude larger arteries and histological examination may reveal an atheromatous component, often including cholesterol crystals.

**Risk Factors**

A number of factors have been shown to be associated with increased risk of CCE, particularly, age over 60 years, male sex, hypertension, hypercholesterolaemia, smoking and diabetes mellitus. All these factors predispose to the development of atherosclerosis which is ultimately the main risk factor for the development of this condition. Presence of these factors strengthens the clinical suspicion in the appropriate setting. The more the number of factors, the higher the likelihood of the diagnosis being confirmed. It is not unusual for a patient to have established cerebrovascular, cardiovascular and peripheral vascular disease at the time of presenting with CCE. Indeed, such macrovascular disease represents the main underlying pathology predisposing to CCE and atheroembolism.

**Precipitating Factors**

Though CCE can occur spontaneously, a precipitating event is seen in the majority of patients. Examples include vascular surgery, angiography, angioplasty and cardiopulmonary resuscitation. Such factors are thought to cause CCE by mechanically disrupting an atheromatous plaque.

Although CCE probably occurs within hours of such procedures in most cases, it is important to realise that there may be a delay in clinical presentation of a few days. This can lead to a delay in diagnosis and a search is sometimes made for an alternative diagnosis with inappropriate investigations and subsequent inappropriate therapy. Some very late presentations, of several months, have been described, though in such cases it is not possible to be certain of the causal relationship.

**Clinical Features**

The clinical features seen in patients with CCE are not specific to CCE, and their discriminating power is low. Renal failure is the most common presenting feature and has been described in between 50 and 85% of cases. It can be acute, occurring over a few days, or slowly progressive over weeks to months after a precipitating event in a patient at risk. Renal involvement can be accompanied by accelerated hypertension. Leg pain due to concurrent lower extremity embolization is quite common. With renal involvement, there is usually haematuria and proteinuria detected on urine testing and the patient may require renal support. Cutaneous involvement is the next most common manifestation, described in between 35 and 65% of patients. Livedo reticularis is the most frequent finding. It is usually bilateral involving the feet and legs but can occasionally be seen on the trunk and upper limbs.

Other features include gangrene of the toes, purple toes, ulcers and nodules. The purple toe syndrome, initially described as a side-effect of warfarin therapy, can be due to CCE. Other causes of a bluish discolouration of the feet, such as hypoxaemia, acrocyanosis and venous insufficiency can usually, but not invariably, be differentiated by taking into account the clinical context and arterial blood gas tensions. Palpable pedal pulses in the presence of gangrene should raise the possibility of CCE but this finding has been described in only about 60% of cases and, like other features of CCE, can be caused by other conditions such as diabetic small vessel disease or vasculitis. Gastrointestinal involvement can manifest with abdominal pain, bleeding, pancreatitis and bowel infarction and is usually seen in patients with renal involvement. Non-specific manifestations have included fever, myalgia, weight loss and altered mental status, and CCE can mimic endocarditis, vasculitis or malignant disorders.

**Investigations**

Other than histology there are no specific investigations. Anaemia, mild leucocytosis and an elevated erythrocyte sedimentation rate (ESR) are commonly found and are indicative of the systemic nature of the problem. Eosinophilia and eosinophiluria have been reported in varying frequency (30-100%). Eosinophilia can be a transient phenomenon.

Of course, these investigations have low discriminating power for CCE. Hypocomplementaemia can occur. The serum amylase and creatine kinase may be elevated and represent pancreatic and skeletal or cardiac muscle damage respectively. Abnormalities of renal function, with a raised urea or creatinine, are seen when there is renal involvement. Such patients usually have haematuria and proteinuria.
Diagnosis

A diagnosis of CCE can be suspected in a patient with multiple risk factors and a clear precipitating event. If cholesterol crystals are seen on fundoscopic examination then the diagnosis is almost certain. This finding can only be present if the CCE is arising proximal to the origin of the carotid arteries or in the carotid arteries themselves. The diagnosis mainly rests on demonstrating the presence of cholesterol crystals obstructing an arteriole in a histological specimen. In the absence of histological proof the clinician can try to demonstrate the presence of ulcerated atheroma in the thoracic aorta by transoesophageal echocardiography (TEE). TEE has been used to support the diagnosis, assess the risk of further embolization and formulate therapy, though this is only likely to be helpful in a small proportion of patients. An ante-mortem diagnosis is made in only about 40% of cases at best.

Patient Management

At present there is no satisfactory specific treatment available once CCE has occurred. It is important to provide supportive therapy including transfusion, dialysis, treatment of sepsis and adequate nutrition. High levels of systemic blood pressure require cautious control. The place of anticoagulation is uncertain. Some studies have suggested benefit but others have concluded that there is no benefit or that anticoagulation can be harmful. Further invasive investigations and surgical procedures should be avoided if at all possible. An adequate explanation of the problem should be provided for the patient and the relatives.

Prognosis

The prognosis is very poor. About 50% of patients die within a few months of the diagnosis and most of the remaining patients succumb within a year or two. There are only a few documented examples of long term survival and the majority of these have been in patients with peripheral CCE. Most of the deaths are due to coronary artery disease, progressive renal failure and cerebrovascular disease, or a combination of these. About 10% of the patients die of multiple arterial emboli.

References