CASE REPORT
AN UNUSUAL CASE OF FAMILIAL MEDITERRANEAN FEVER
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SUMMARY
Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent self-limiting attacks of joint, chest and abdominal pain associated with fever. The most serious complication in FMF is the development of amyloidosis, which usually leads to death from renal failure within a year. The use of colchicine has dramatically reduced this complication. We describe a 56-yr-old female patient with FMF in whom the arthropathy became the dominant clinical feature, resulting in the development of an erosive large and small joint arthritis during the course of the disease. The patient was treated with colchicine, but despite this, later developed amyloidosis confirmed on rectal biopsy, and chlorambucil was added to her treatment. For 10 yr, she also suffered intermittent abdominal pain and had terminal ileal changes suggestive of Crohn’s disease. However, she was found to have ischaemic colitis at post mortem secondary to amyloidosis. Ischaemic bowel disease is an extremely unusual event in FMF. Other factors which may have contributed to the terminal ischaemia in this patient include anaemia secondary to blood loss and a drug-induced myelodysplasia, as well as hypotension during the final septicemic illness. Clinicians should consider an ischaemic colitis as a possible differential diagnosis of abdominal pain in patients with FMF even in the absence of other clinical evidence of systemic amyloidosis.

KEY WORDS: Familial Mediterranean fever, Arthropathy, Amyloid.

FAMILIAL Mediterranean fever (FMF) is an inherited disorder characterized by recurrent self-limiting attacks of joint, chest and abdominal pain associated with fever. It occurs predominantly in those of Mediterranean origin [1]. Amyloidosis is a relatively frequent complication of FMF with renal involvement the predominant clinical feature. The use of colchicine has dramatically reduced this complication [2].

The most common articular attack is an acute large joint monoarthritis most often affecting the knee or hip and lasting for several days [3]. Rarely, a more protracted arthritis may occur [4], although residual joint damage is uncommon even in this group. The exception may be the hip joint which appears to be particularly prone to avascular necrosis. Small joint involvement is exceptionally rare [4, 5].

The gastrointestinal tract is almost always involved in FMF amyloidosis, but is rarely clinically significant. Occasional cases of malabsorption secondary to FMF amyloidosis have been described [6].

CASE REPORT
A 56-yr-old Armenian Christian woman resident in the UK since 1960 developed intermittent attacks of acute monoarthritis involving both knees at age 14 yr. During the same year, she experienced monthly episodes of acute abdominal pain, fever and vomiting lasting for a week. At age 20, she underwent an appendicectomy with a histologically normal appendix being removed.

She was first seen in the UK aged 26 with recurrent attacks of knee arthritis. Routine investigations showed an elevated ESR of 70 mm/h, and negative tests for rheumatoid factor (RF) and antinuclear antibody (ANA). A synovectomy was performed on the right knee and non-specific inflammatory changes were seen without amyloidosis. A diagnosis of FMF was made based on ethnic background, recurrent peritonitis, arthritis and family history, as one of her brothers had suffered similar abdominal crises since childhood.

She was first seen at this hospital 4 yr later, aged 30, with a protracted attack of right hip pain and a painful right temporomandibular joint. X-rays demonstrated evidence of avascular necrosis at the right hip. Within 2 yr the left hip became similarly affected and the patient underwent bilateral hip arthroplasties. Both rectal and renal biopsy showed no evidence of amyloidosis. She continued to suffer occasional abdominal crises, although her articular symptoms were the dominant clinical feature. By her mid-thirties, she developed attacks of pain and swelling of both wrists, the right shoulder, left elbow and both knees. This was followed by attacks of synovitis at several PIPs, MCPs and intercarpal joints. She commenced regular colchicine in 1976, aged 35, which reduced the frequency of crises, although it was less effective for the joints.

By age 40, the patient had evidence of marked degenerative disease at most of her large joints, including elbows, shoulders and knees, with joint space narrowing, and sclerosis evident on X-ray. There was erosive change in both wrists and carpi (Fig. 1) without significant deformity and she maintained good function. RF and ANA were repeatedly negative, and synovial fluid analysis showed no evidence of crystal deposition. At age 42, she developed abdominal pain and diarrhoea. Barium follow through

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demonstrated an abnormal terminal ileum with stricture formation suggestive of Crohn’s disease. A rectal biopsy at this stage showed a trace of amyloid.

At age 46, a further rectal biopsy confirmed the presence of amyloidosis and she was commenced on chlorambucil 2 mg daily. For a further 10 yr, her renal function remained within normal limits with no significant proteinuria. During this time, both the arthropathy and bowel symptoms ran a relapsing/remitting course, the latter failing to improve despite a 6 month trial of steroid and sulphasalazine. However, in February 1996, at age 56, she developed a pancytopenia and bone marrow biopsy confirmed myelodysplasia. Two months later, she was admitted with a further flare up of fever, abdominal pain and bloody diarrhoea. She suffered several episodes of presumed septicaemia, although no infective organism was isolated. One such episode precipitated recourse to a laparotomy and small bowel resection, but she died a week later.

**PATHOLOGY**

At the laparotomy, 30 cm of terminal ileum, the ileocaecal valve and 5 cm of ascending colon were resected. The terminal ileum was thickened and narrowed with numerous aphthoid ulcers between 3 and 20 mm in diameter distributed along the length and in the resected colon (Fig. 2). Histology showed punched-out ulcers down to the muscularis propria with surrounding normal mucosa and normal bowel wall. There were no granulomas, no transmural inflammation, or aggregated lymphoid collections suggestive of Crohn’s disease. The submucosal blood vessels stained extensively for amyloid (Congo red positive with green birefringence). No amyloid deposition was seen outside the blood vessels. In the absence of positive features of Crohn’s disease, the pattern of ileocolonic ulceration was felt to be ischaemic secondary to the amyloid vasculopathy. Post-mortem examination revealed peritonitis with numerous post-operative adhesions. The surgical anastomosis was intact. The mesenteric blood vessels were patent. The distal half of the small intestine and colon contained blood. There was extensive aphthous ulceration of the neo-terminal ileum and residual right colon similar to that in the surgical resection. Histology was also identical with discrete ulceration and prominent amyloid in submucosal blood vessels. In addition, there was extensive amyloid involving the liver, spleen, lung, kidney and heart. Death was attributed to gastrointestinal haemorrhage secondary to the amyloid-induced ischaemic enterocolitis and accompanying myelodysplastic pancytopenia.

Review of the joint pathology in the light of the recurrent problems since 1972 showed evidence of inflammatory joint disease involving the hips and knees with secondary changes of osteoarthritis. There was no evidence of synovial amyloid. Autopsy sec-
tions from a knee joint showed an inactive end-stage arthritic picture with islands of dead cartilage on the surface and some calcium pyrophosphate crystals. Amyloid was not identified.

**DISCUSSION**

FMF is characterized by brief, but severe, self-limiting attacks of peritonitis, synovitis and pleurisy [1]. The typical articular attack in FMF is an acute monoarthritis of the lower limb lasting for several days with no long-term sequelae [3]. More protracted articular attacks may also occur and may persist for months. In these prolonged attacks, the hips and knees are most commonly affected, although complete resolution tends to occur. The exception is, however, the hip joint when long-term sequelae ranging from limitation of motion to complete ankylosis of the joint can occur [4]. Involvement of the small joints of the hands and feet is exceptionally rare [4, 5].

Radiological changes in patients with the chronic arthropathy consist of osteopenia, joint space narrowing, osteophytosis and sclerosis [7]. Single lytic intra-articular changes in MTPs and IP joints have also been described [4]. Our patient developed the typical large joint involvement at the onset of the disease, complicated by avascular necrosis of both hips. The arthropathy appeared to progress with sequential involvement of multiple small joints, thus producing a symmetrical erosive arthropathy, not, to our knowledge, previously associated with FMF. It could be argued that our patient developed co-existent seronegative rheumatoid arthritis (RA), although the clinical course seems to suggest a single disease process and the synovial histopathology was not suggestive of RA. Furthermore, typical RA has not been described in association with FMF, whereas it has occurred in association with ankylosing spondylitis [8, 9]. Interestingly, an erosive arthritis mimicking RA has been documented in patients with amyloidosis secondary to multiple myeloma [10] and 'primary' amyloidosis [11]. In the current case, the arthropathy appeared many years prior to the development of amyloidosis, as demonstrated on rectal biopsy, and at no stage during the disease course was there evidence of amyloid in synovium.

Subclinical gastrointestinal involvement in amyloidosis is common, occurring in up to 98% of patients [12]. It is more difficult to assess the incidence of clinical symptoms, which are said to occur in <20% of cases. The clinical manifestations are varied, including motility disorders, bleeding, malabsorption, obstruction, protein-losing enteropathy and perforation. The deposition of amyloid in the gastrointestinal tract depends on the type of amyloid. Primary amyloidosis is distributed in the muscularis and ‘outer’ layers of blood vessels, whereas secondary amyloidosis (which includes FMF) shows deposits in the mucosa and ‘inner’ layers of blood vessels [12].

**Fig. 2.** A section through the large bowel showing a punched-out ulcer. The adjacent mucosa is normal. Note the absence of transmural lymphoid aggregates and granulomas (H + E).
Our patient had ischaemic colitis developing insidiously over a period of at least 10 yr. Chronic ischaemia results in fibrosis and stricturing of the bowel wall, with the compromised circulation producing mucosal ulceration. The clinical, radiological and histopathological appearances may mimic Crohn’s disease, as they did here, with amyloidosis being a recognized cause of such intestinal ischaemia. Some cases of amyloid angiopathy have partial or complete occlusion of the affected vessels, but occlusion is not essential for the production of ischaemia. It can be produced by episodes of hypotension or an anaemia reducing the available oxygen in areas already suffering chronic hypoxia because of narrowed non-compliant blood vessels. This is known as the non-occlusive mesenteric ischaemia syndrome [13]. Our patient was anaemic because of blood loss and myelodysplasia, as well as intermittently hypotensive during the final septicemic illness which may have contributed to the acute ischaemia. A similar case has been described of a patient with FMF developing a colonic stricture as a result of chronic ischaemic colitis secondary to amyloid infiltration of the colonic blood vessels [14]. However, this patient was also on long-term haemodialysis for FMF nephropathy.

The use of chlorambucil in our patient would appear to have been beneficial as the patient did not develop clinical evidence of FMF nephropathy. Furthermore, 13 yr elapsed between the initial demonstration of amyloid on rectal biopsy and the patient’s terminal illness. However, such treatment has other risks, exemplified by the development of a secondary myelodysplasia.

In summary, we report a patient with FMF amyloidosis treated with colchicine and chlorambucil. This treatment was partially successful by reducing renal damage. The alteration of the natural history of the disease resulted in the rheumatological and gastrointestinal manifestations being the dominant clinical features, the latter contributing to the ultimate cause of death.

REFERENCES