alternate days the neuropathy worsened, the rash returned, and the eosinophil count rose. Azathioprine was added but despite 200 mg daily, giving a neutrophil count of 3.74×10^9/l, the neuropathy, fever, rash and eosinophilia recurred each time the prednisolone dose was reduced below 15 mg/0 mg alternate days. After more than 12 months from initial diagnosis she was referred to our unit for further treatment.

On initial presentation to our unit, she was grossly cushingoid (weight 80 kg) and still complained of numbness in her foot, fatigue, and myalgia. She was started on weekly cyclophosphamide infusions (1 g), the first three infusions with methylprednisolone. Despite weekly cyclophosphamide infusions the neutrophil count remained above 3.5×10^9/l so we were able to increase the cyclophosphamide dose to 1.25 g weekly and then 1.5 g weekly, which brought the pre-treatment neutrophil count down to 1.9×10^9/l. However, all attempts to reduce the prednisolone dose to 5 mg daily precipitated a flare of disease with recurrent rash, fatigue, and neuropathy. After 12 months on pulse cyclophosphamide (total dose 44.75 g) she was still requiring oral prednisolone to control the rash, fatigue, neuropathy, and eosinophilia and her asthma had again deteriorated. The cyclophosphamide was therefore stopped and she was immediately given cyclosporin (Neoral, Sandoz) 150 mg 12 hourly (3.5 mg/kg per day) giving trough blood values of 117 ng/ml. At the time of writing, she has been receiving this treatment for five months, has been asymptomatic from CSS and her asthma since starting the cyclosporin and managed to reduce and stop oral prednisolone without recurrence of symptoms for the first time in 2.5 years. The only side effects experienced are the "burning" sensation in her hands and feet and intermittent mild nausea.

To our knowledge, this is the first report of severe CSS being treated with cyclosporin. Despite 44.75 g cyclophosphamide in 12 months our patient's disease flared each time the oral prednisolone dose was reduced. Clearly, in this patient corticosteroids and pulse cyclophosphamide therapy failed to control the disease although these remain the drugs of choice in severe CSS. Plasma exchange and interferon γ have been used separately in resistant cases of CSS but the role of these treatments are still being evaluated.[2 3] There are a few reports of cyclosporin used in Wegener's granulomatosis with response in doses 5–10 mg/kg per day.[3] Promising results have recently been seen with cyclosporin in the treatment of corticosteroid resistant asthma although larger controlled studies are still awaited.[4] Troublesome residual asthma in CSS may necessitate continuing oral prednisolone even when the vasculitic disease has abated.[5] Cyclosporin therefore, may be a useful treatment in cases of resistant CSS controlling both the vasculitic process and the residual asthma.

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1 Churg J, Strauss L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. Am J Pathol 1951;27:277–301.
2 Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Généreau T, *et al.* Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. Arthritis Rheum 1995;38:1638–45.
3 Gross WL. Systemic necrotizing vasculitis. Baillieres Clin Rheumatol 1997;11:273–81.
4 Spahn JD, Leung DYM, Szefler SJ. New insights into the pathogenesis and management of steroid-resistant asthma. J Asthma 1997;34: 177–94.
5 Lhote F, Guillevin LP. The vasculitides. In: Klippel JH, Dieppe PA, ed. *Rheumatology*. 2nd ed. Vol 2. London: Mosby International, 1998: 24.1–4.

Azoospermia in familial Mediterranean fever patients:the role of colchicine and amyloidosis

Familial Mediterranean fever (FMF) is a hereditary disease characterised by recurrent episodes of fever, peritonitis, pleuritis, arthritis or erysipelas-like skin lesions. The disease affects mainly Jews, Armenians, Arabs, and Turks. Typically, the episodes last two to three days and resolve spontaneously.[1] One of the main complications of FMF is the development of secondary amyloidosis (AA type). The kidneys are the main target organ involved, leading to chronic renal failure.

Colchicine has been the preferred treatment for FMF since 1972.[2] It is effective in suppressing the episodes in more than 90% of the patients and prevents both the development of amyloidosis and the additional deterioration of renal functions in those with early amyloidosis.[3] Colchicine exerts its main effect at the cellular level by its interaction with tubulin at the microtubules, inhibiting motility and exostosis of intracellular granules.[4] Furthermore, it has also a powerful antimitotic effect by causing metaphase arrest and is capable of arresting meiosis.[5] Therefore, in cases of infertility in patients treated with colchicine, it has been speculated that this medication cause azoospermia.[6]

In this report we describe three patients with FMF and infertility who had been taking colchicine for about one to three years before the documentation of azoospermia. All the patients had FMF for at least four years.

Two of the patients (A and B) had nephrotic syndrome at the time of diagnosis and amyloid was demonstrated by kidney and rectal biopsies. The third patient (C) had no clinical signs of amyloidosis. None of the patients experienced any scrotal attack or epididimoorchitis. All of the patients had normal serum profile of sex hormones and a normal kariotype. However, in patient A, testicular biopsy disclosed marked atrophy with Sertrolli cells only. The blood vessels were thickened and their staining by Congo red revealed abundant amyloid (fig 1). In patient B, the biopsy revealed maturation arrest of the spermatocytes with amyloidosis of the walls of the blood vessels (fig 2). In the third patient testicular biopsy showed a pure maturation arrest. Congo red staining failed to show amyloidosis.

Since the introduction of long term preventive colchicine therapy for patients with FMF, concerns have been raised about the development of adverse effects of the drug, including infertility. Initial findings suggested that male fertility was not affected by colchicine.[7] A study by Bremner and Paulsen failed to show any evidence for side effects in six healthy male volunteers with normal liver and kidney function, who received commonly used doses of colchicine during four to six months.[8] However, later observations disclosed that, as many as 20% of male FMF patients receiving long term colchicine therapy may develop fertility problems associated with either azoospermia or impairment of sperm penetration.[9] In a recent study, Sarica et al evaluated 62 male patients with Behcet's

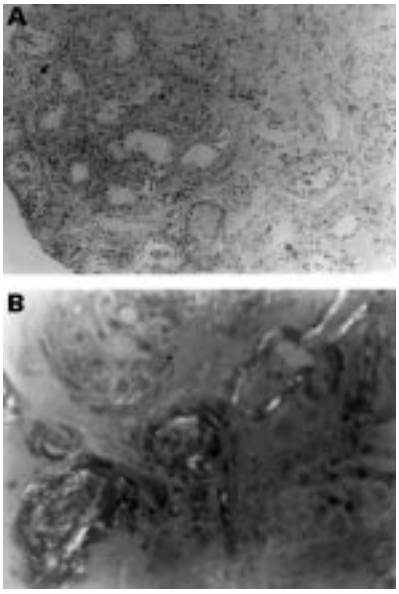

Figure 1 (A) Testicular biopsy specimen obtained from patient A, showing atrophy and fibrosis of the tubules without Leydig cell hyperplasia. Note the thickening of the walls of the tubules and the blood vessels (arrow). (B) Illustrating birefringence of amyloid deposits in tubular and blood vessels walls after Congo red staining.

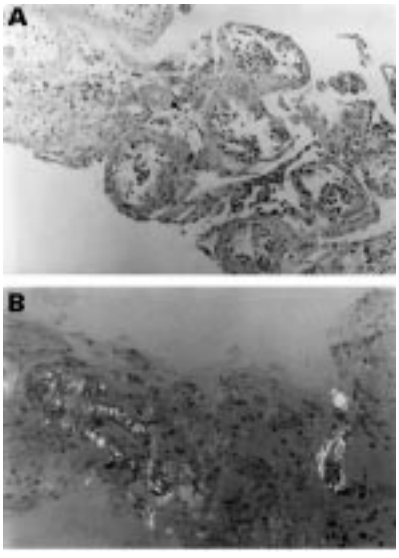

Figure 2 (A) Testicular biopsy specimen obtained from patient C, disclosed maturation arrest and thickening of the walls of the blood vessels (arrow). (B) Illustrating birefringence of amyloid deposits in tubules and blood vessels after Congo red staining.

syndrome who were taking colchicine.[10] They claimed that oligospermia (<20 × 10^6/ ml) was present in 23 patients (37.1%) and azoospermia in two patients. Our experience in treating more than 150 (male) FMF patients, is much more favourable. We have found only two patients with oligospermia and none of whom had amyloidosis.

Usually, FMF associated amyloidosis of the AA type involves the kidneys, liver, spleen, heart, and intestines. Involvement of the testes has been seldom reported. In an animal model, testicular amyloidosis was induced in hamsters by infecting the animals with *Leishmania donovani*.[11] Testicular biopsies disclosed total azoospermia in the final week of the pathological process. This study and other sporadic cases[12] show that amyloidosis by itself can cause oligo or azoospermia.

In FMF patients, it is tempting to ascribe the complication of azoospermia to colchicine therapy. However, testicular biopsies in two of our cases demonstrated amyloidosis of the testes. Furthermore, one of the patients had taken little colchicine before the diagnosis of infertility. Therefore, it is conceivable that the pathological process of amyloidosis may also be responsible for azoospermia in these patients.

The relatively high frequency of oligospermia and azoospermia in patients with Behcet's disease[10] compared with patients with FMF or gout is puzzling. The common presence of epididymitis or vasculitis, or both, of the testes in Behcet's disease may have an important role in predisposing the patients to this complication while they are taking colchicine. In FMF, recurrent orchitis or epididimitis are relatively rare. However, amyloidosis of the testicular blood vessels in these patients may have a role parallel to the vasculitis in Behcet's disease in predisposing to azoospermia while on colchicine therapy.

Based upon these findings we propose that the possibility of testicular amyloidosis should be included in the differential diagnosis of oligo or azoospermia in FMF patients.

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1 Eliakim M, Levy M, Ehrenfeld M. *Recurrent polyserositis (familial Mediterranean Fever.* Amsterdam: Elsevier/North Holland Biomedical Press, 1981.
2 Goldfinger S E. Colchicine for familial Mediterranean fever. [Letter]. N Engl J Med 1972;287: 1302.
3 Ben-Chetrit E, Levy M. Colchicine treatment in familial Mediterranean fever (FMF): reappraisal after 15 years. Semin Arthritis Rheum 1991;20:241–6.
4 Liang J C. Response of murine spermatocytes to the metaphase arresting effect of several mitotic arrestors. Experientia 1985;41:1586–8.
5 Handel M A. Effects of colchicine on spermatogenesis in the mouse. J Embriol Exp Morphol 1979;51:73–5.
6 Merlin H E. Azoospermia caused by colchicine. A case report. Fertil Steril 1972; 23:180–1.
7 Levy M, Yaffe C. Testicular function in patients with familial Mediterranean fever on long term colchicine treatment. Fertil Steril 1978;29: 667–8.
8 Bremner W J, Paulson C A. Colchicine and testicular function in men. N Engl J Med 1976;294:1384–5.
9 Ehrenfeld M, Levy M, Margalioth E J. The effect of long term colchicine therapy on male fertility in patients with familial Mediterranean fever. Andrologia 1986;18:420–6.
10 Sarica K, Suzer O, Gurler A, Bataci S, Ozdiler E, Dincel C. Urological involvement of behcet patients and the effect of colchicine on fertility. Eur Urol 1995;27:39–42.
11 Gonzalez J L, Gallego E, Castano M, Rueda A. Testicular amyloidosis in hamsters experimentally infected with Leishmania Donovani. Br J Exp Pathol 1983;64:518–23.
12 Handelsman D J, Yue D K,Turtle J R. Hypogonadism and massive testicular infiltration due to amyloidosis. J Urol 1983;129:610–11.

Colony stimulating factor-1 in synovial fluids from osteoarthritic and injured knees

Subchondral bone density as a possible pathogenetic factor contributing to articular cartilage degeneration in osteoarthritis (OA) has been receiving increasing attention.[1] The Kellgren-Lawrence system for grading joint OA emphasised subchondral bone sclerosis and osteophyte formation more than joint space narrowing, a view, however, that has recently been questioned.[2] The importance of subchondral bone density in contributing to cartilage degeneration has been emphasised for years in the work of Radin and colleagues.[3] Observations that dense subchondral bone may indeed precede cartilage degeneration and thereby be an initiating factor, or that bone density may be involved in the progression of OA, have been advanced by studies on animal models.[4 5] However, little is known about the basis for subchondral bone density in OA, or its consequences.

Colony stimulating factor-1 (CSF-1) is the primary regulator of mononuclear phagocyte production and has important effects on bone.[6 7] Among other cell types, CSF-1 is secreted by osteoblasts, and is required for the differentiation of osteoclast progenitors to osteoclasts.[6] Our interest in CSF-1 in relation to bone density in OA arose from studies on a mouse model of osteopetrosis (*op*/*op*)[8] where an inactivating mutation in the gene encoding CSF-1 impairs osteoclast development; the bone formed cannot be resorbed. We considered that increased bone density in the joint in OA is most probably caused by low CSF-1 concentrations in the subchondral bone; however, it is also possible that low concentrations of synovial fluid CSF-1 could contribute to the increased bone density. We used a radioimmunoassay to measure CSF-1 concentrations in synovial fluid and plasma from subjects with severe knee OA, and compared the results with similar studies on a "control" group with acute traumatic or athletic injury to the knee.

Table 1 summarises aspects of the clinical condition of patients in group A with the diagnosis of OA of the knee,[9] and those patients in group B who sustained injuries of the knee and underwent arthroscopy. Circulating CSF-1 was measured in plasma and synovial fluid by a modified[10] radioimmunoassay (RIA) that specifically detects biologically active CSF-1 in the range of 0.02–3.60 ng/tube. Synovial fluid samples were incubated with one tenth volume of bovine testicular hyaluronidase (Sigma) (1500 units per ml in RIA buffer) for 10 minutes at 37°C before RIA. Normal rabbit serum (20 µl) was added to 20–100 µl samples of the hyaluronidase treated synovial fluid to control for protein concentration in the RIA before assay. Differences between the groups with regard to standardised CSF-1 concentrations in blood and synovial fluid, as

Table 1 Characteristics of patients in this study

	Patient	*Age*	*Sex*	*Diagnosis*
Group A				
Severe OA				
	1	73	F	Bilateral knee OA, THR 7/94; TKR
	2	80	F	Bilateral knee OA
	3	63	M	Bilateral knee OA
	4	71	F	Bilateral TKR
	5	86	F	Bilateral TKR
	6	75	F	Bilateral left TKR 1/91; TKR
	7	82	F	Bilateral left TKR 1/91; TKR
	8	69	M	Bilateral left TKR 1/91; TKR
	9	82	F	Bilateral TKR
Group B				
Traumatic knee injury				
	1	46	M	Patella subluxation
	2	18	M	Menisceal tear
	3	30	M	Osteochondral defect
	4	45	F	Patello-femoral irregularity
	5	43	M	Menisceal tear
	6	16	M	Avulsion fracture tibial plateau
	7	35	F	Menisceal tear
	8	25	F	Menisceal tear

OA = osteoarthritis; THR = total hip replacement; TKR = total knee replacement during course of this study.

Table 2 Descriptive statistics for patients studied

	Severe OA		*Traumatic injury*		
Characteristic	*No*	*Mean (SD)*	*No*	*Mean (SD)*	*p Value**
Age (y)	9	76.1 (7.8)	8	32.5 (11.8)	<0.001
Plasma CSF-1 (ng/ml)	8	3.12 (1.30)	8	2.96 (0.68)	>0.20
Synovial fluid CSF-1 (ng/ml)	9	3.03 (0.91)	7	2.60 (1.39)	>0.20

*p Value based on standardised scores.