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Polyarteritis nodosa type vasculitis in a patient with familial Mediterranean fever treated with cyclosporin A

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Abstract Patients with amyloidosis secondary to familial Mediterranean fever (FMF) are known to tolerate cyclosporin A poorly. We report a case of severe cyclosporin toxicity in a patient with FMF amyloidosis who underwent kidney transplantation. The clinical syndrome consisted of severe gastrointestinal, neuromuscular, and psychiatric disturbances. Histological examination of the transplanted kidney revealed vasculitis of the polyarteritis nodosa type. We hypothesize that FMF patients are more vulnerable to the acute vascular toxicity of cyclosporin due to defective inhibition of complement activation, leading to a widespread vasculitis of the polyarteritis nodosa type.

Key words Vasculitis, kidney transplantation, cyclosporin
Familial Mediterranean fever, kidney transplantation, vasculitis
Polyarteritis nodosa, kidney transplantation, cyclosporin

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disorder common in Sephardic Jews, Armenians, Turks, and Arabs of the Levant. The disease is characterized by recurrent episodes of sterile peritonitis, pleuritis, or synovitis and results in the development of systemic amyloidosis of the AA type, with early renal involvement [2, 7]. In Mediterranean countries it is not an infrequent indication for renal transplantation, accounting for up to 6% of the renal transplant population in Israel. In this group of patients a high postoperative mortality has been reported when treated with conventional immunosuppressive therapy [13, 23]. Since the introduction of cyclosporin, patients with FMF amyloidosis have also been transplanted with cyclosporin as the main immunosuppressive drug. It appears, however, that patients with FMF amyloidosis tolerate cyclosporin poorly [5, 31, 33]. The mechanisms underlying this cyclosporin intolerance have not yet been elucidated. We report a case of severe cyclosporin intolerance in a patient with FMF amyloidosis who underwent kidney transplantation. The histologic findings in the kidney graft may allow us to speculate on the pathogenesis of cyclosporin intolerance in FMF patients.

Case report

The patient, a Turkish man, was 20 years old at the time FMF was diagnosed in 1981. He presented with seronegative oligoarthritis, recurrent episodes of fever, abdominal pain, and a nephrotic syndrome with normal renal function. A kidney biopsy confirmed the diagnosis of renal amyloidosis, and treatment with colchicine and indomethacine was started. In 1984 the patient was lost to follow-up and discontinued treatment. He presented in 1989 with end-stage renal failure and chronic hemodialysis was started. He underwent a first cadaveric renal transplantation in September 1992. The initial immunosuppressive regimen consisted of cyclosporin A, 10 mg/kg qd in two divided doses, and methylprednisolone, 20 mg qd. The cyclosporin dosage was adapted daily to maintain plasma trough levels between 200 and 300 ng/ml.

The early post-transplant evolution was uneventful with a serum creatinine of 2.1 mg/dl by the 4th day. On the 6th post-transplant day his temperature rose to 38.5 °C and the patient complained of moderate lower abdominal pain. Treatment with colchicine was started, without significant clinical improvement. On the 8th day serum creatinine rose to 3.4 mg/dl, and although the transplant bio-

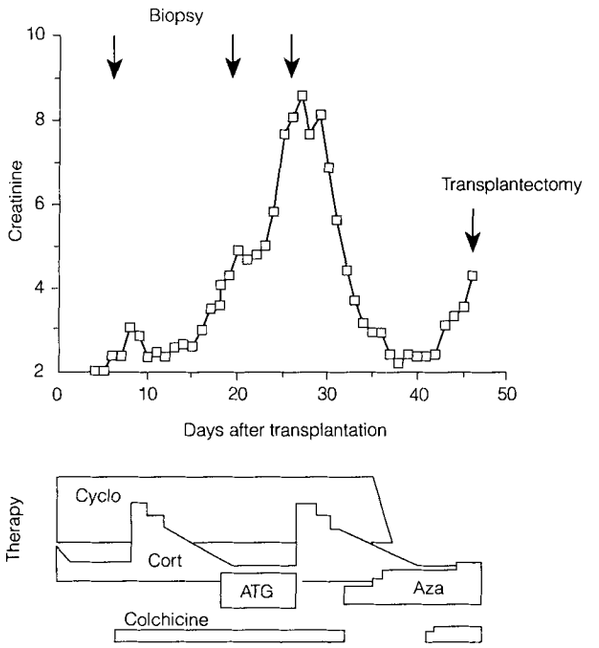

Fig. 1 Evolution of creatinine and therapy (*Cyclo* cyclosporin, *Cort* corticosteroids, *ATG* antithymocyte globulin, *Aza* azathioprine)

psy was not conclusive, an antirejection therapy with high doses of corticosteroids was initiated (Fig. 1).

At the same time, the patient complained of colicky abdominal pain with watery diarrhea. Clinical examination revealed increased abdominal sounds, without peritoneal irritation. A standing abdominal X-ray revealed air-fluid levels without significant dilatation in the small and large bowel. The pain persisted during the following 2 weeks. On day 18 a second acute rejection was diagnosed, based on histological findings in a transplant biopsy, and treatment was started with antithymocyte globulin (Fresenius). Renal function deteriorated further and a repeat renal biopsy was performed on day 25 that showed persistent signs of rejection. The antithymocyte globulin was stopped and high doses of corticosteroids were given, after which renal function improved.

Meanwhile, the abdominal pain continued. Abdominal ultrasound and computed tomography revealed only a slight amount of ascites. A gastroscopy was normal and a colon enema showed no obstruction. From day 26 on there were increasing liver enzyme abnormalities with rising levels of SGPT, LDH, and bilirubin with concomitant signs of discrete hemolysis. The patient became increasingly agitated and displayed unreasonable behavior, increasing muscular weakness, anorexia, and weight loss. Creatine phosphokinase levels rose to 545 U/l on day 34. Hepatitis B surface antigen was negative, antihepatitis B surface antibody was positive, and antihepatitis C antibodies were negative. Antineutrophil cytoplasmic antibodies were also negative.

Electromyography showed myopathic changes without spontaneous activity and a discrete axonal polyneuropathy. Colchicine was discontinued on day 32 without any improvement in the clinical situation. On day 34 the cyclosporin dosage was halved, and on day 36 it was completely stopped. There was a spectacular improvement, with disappearance of the abdominal pain, the anorexia, and the anxiety, and normalization of the enzyme levels during the following days. On day 39 colchicine was reintroduced without recurrence of the

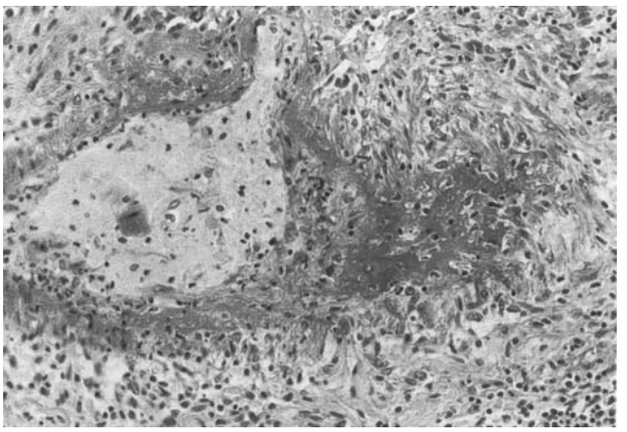

Fig. 2 Large interlobular artery showing fibrinoid necrosis and infiltration with mainly polymorphonuclear leukocytes throughout the vessel wall (H & E, × 155)

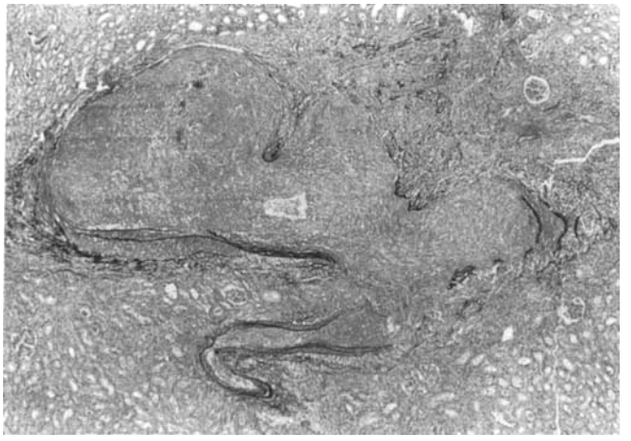

Fig. 3 Arcuate artery showing several disruptions of the elastic laminae (orcein, × 26)

clinical and laboratory abnormalities. From day 43 on renal function again deteriorated. On day 46 a transplantectomy was performed.

On transplantectomy a kidney of 369 g was resected. The cortex looked somewhat hemorrhagic. On microscopic examination the interstitium of the cortex was diffusely edematous and contained a more or less diffuse mononuclear infiltration with signs of tubulitis, leading to foci of tubular necrosis. Small infarction areas were found in the peripheral cortex. The small vessels showed prominent endothelialitis, extending to the arteries of the size of the larger interlobular vessels. Some of the larger vessels were partially occluded. In a few vessels, fibrinoid material was found in the media. Some arcuate and lobar arteries showed interruption of the internal elastic membrane with proliferation of the intima and pseudoaneurysm formation (Figs. 2, 3). The lesions of the larger vessels could not be distinguished from those of periarteritis nodosa.

Table 1 Similarities and differences between acute rejection and polyarteritis nodosa (PAN)

	Acute rejection	PAN
Interstitium		
Edema	Diffuse	Absent
Infiltrate	Diffuse	Focal
Small vessels		
Endothelialitis	Present	Absent
Fibrinoid necrosis of vessel walls	Present	Absent
Medium-sized and large vessels		
Endothelialitis	Present	Present
Lymphocytic infiltrate	Present	Present
Polymorphonuclear infiltrate	Absent	Present
Fibrinoid necrosis of vessel walls	Absent	Present
Disruption of elastic membrane/aneurysms	Absent	Present

Discussion

Cohen and coworkers [5, 6] were the first to report that seven of their eight patients who received renal transplantation for FMF amyloidosis tolerated cyclosporin poorly. Severe gastrointestinal side effects were noted in all; these effects included diarrhea, nausea, vomiting, and persistent colicky abdominal pain. These signs occurred between the 4th and 9th postoperative days, disappeared upon stopping the cyclosporin, and reappeared in the two patients in whom it was reintroduced. In five of these seven patients, profound muscular weakness was noted that developed after 5–18 days. In one patient elevated creatine phosphokinase levels were noted.

Siegal and coworkers [33, 34] also reported seven patients undergoing renal transplantation for FMF amyloidosis who experienced severe side effects related to the cyclosporin therapy – mainly gastrointestinal, neuromuscular, and psychiatric – occurring in the 3rd week following transplantation. The clinical picture included abdominal pain, anorexia, weight loss, ascites, jaundice, muscle weakness, sudden sharp leg pains, severe depression, hallucinations, convulsions, tremor, and paralysis of the girdle muscles.

The symptoms seen in our patient are very similar to those described by Cohen and Siegal and can be considered as another example of FMF-related cyclosporin intolerance. As far as we know, a clear etiopathological explanation for this syndrome has not yet been found.

Although gastrointestinal complaints with abdominal cramps and swelling have been described in patients under cyclosporin therapy, they usually remain mild and transient. Recently, some cases of myopathy have also been described, both in transplanted and nontransplanted patients treated with cyclosporin therapy [10, 20]. To our knowledge, the full-blown syndrome, as seen in our patient and in the patients described by Cohen and Siegal, has not been reported in non-FMF amyloidosis renal transplant patients. Two Scandinavian groups recently reported the results of renal transplantation in 94 non-FMF amyloidosis patients [11, 12]. Approximately two-thirds of the patients were treated with cyclosporin. No mention of cyclosporin intolerance or of unexplained gastrointestinal, neuromuscular, or psychiatric disturbances was made.

The clinical syndrome in our patient was definitely different from an FMF attack. There was never any sign of peritoneal irritation and therapy with colchicine, 1 mg qd, had no beneficial effect.

An important question, already raised by Cohen et al. [6], is whether colchicine may account for part of the toxicity. The gastrointestinal side effects of colchicine are well known and consist mainly of abdominal cramps and diarrhea. Kuncl et al. [15] described a colchicine myopathy and neuropathy in patients with renal dysfunction who were taking colchicine on a chronic basis. Jonsson et al. [14] reported a case of a colchicine-induced myoneuropathy in a renal transplant patient suffering from amyloidosis of the AL-type. However, it is unlikely that the syndrome described here is caused by colchicine. Firstly, colchicine has been used extensively in patients with FMF amyloidosis after kidney transplantation who receive conventional immunosuppressive therapy, apparently without significant toxicity [17]. Secondly, in the patients described by Cohen and Schmueli [5, 6, 31], the syndrome regressed after cyclosporin administration was stopped, even though colchicine was continued. Finally, in our patient, the electromyographic pattern was different from that described by Kuncl et al. in colchicine myopathy, namely, by presenting no abnormal spontaneous activity.

The anatomopathological findings of polyarteritis nodosa (PAN) in the excised kidney graft in our case are most interesting. The graft showed severe signs of acute transplant rejection, yet the destruction of the elastic membrane and aneurysm formation of the larger arteries are very uncommon in acute rejection; we therefore assumed that it was due to something other than the acute rejection. The similarities and differences between acute rejection and PAN are summarized in Table 1. Only the kidney was available for histological examination at transplantectomy; no other tissues were available for pathological diagnosis.

The clinical picture of severe gastrointestinal, neuromuscular, and renal disturbances seen in our patient mimics the presentation of systemic vasculitis of the PAN type. We think that the clinical syndrome described in our patient was caused by a PAN type of vasculitis and we suggest that the other reported cases of FMF-related cyclosporin intolerance may have been caused by the same type of vasculitis. PAN is an uncommon vasculitic disorder with predominant involvement of small and medium-sized muscular arteries. The clinical spectrum is highly

variable and comprises mainly gastrointestinal, neurological, and renal manifestations. The neurological abnormalities are typically of the mononeuritis multiplex type, but symmetrical peripheral polyneuropathy has also been described. Fever, weight loss, and other aspecific inflammatory signs are also common [4, 16].

As far as we know, only one case of de novo vasculitis has been reported in a kidney transplant recipient [32]. This patient was transplanted due to end-stage autosomal, dominant, polycystic kidney disease and developed a polyarteritis type of necrotizing vasculitis in the small bowel more than 1 year after transplantation. The immunosuppressive therapy consisted of cyclosporin, azathioprine, and prednisone. The vasculitis regressed after increasing the dosage of prednisone.

It may be of interest that early reports on the use of FK 506, an immunosuppressive drug with a working mechanism similar to that of cyclosporin, mention vasculitis as a frequent side effect in dogs [21, 35]. However, to our knowledge, vasculitis with FK 506 has not been reported in other species or in humans.

Lesions of the small arteries are an important feature of acute cyclosporin toxicity. In acute cyclosporin toxicity an arteriolopathy is seen with necrosis of myocytes in the vessel wall and deposition of immunoglobulins and complement components, resulting in hyalinosis of the media [3, 19].

It is possible that FMF patients are more vulnerable to the acute vascular toxicity of cyclosporin due to defective inhibition of complement activation in the vessel wall. It has recently been shown that there is an absence of an inhibitor of C5a, a major chemotactic anaphylatoxin, in the peritoneal fluid of patients with FMF [1, 18]. Others have supposed an uncontrolled tumor necrosis factor (TNF) release during an attack of FMF [28]. This combination of excessive TNF release and C5a utilization seems to play a critical role in the induction of the FMF attack. The current hypothesis is that in FMF any minor inflammatory stimulus at the serosal surface leads to an uncontrolled inflammatory reaction with complement activation and TNF release, due to the absence of adequate inhibition of complement activation [27].

We suggest that during acute cyclosporin toxicity, complement activation occurs in the vessel walls, and that due to the defective inhibition of complement activation in FMF, this leads to inflammation and necrosis of the wall of these small arteries, mimicking PAN.

PAN has been reported to occur in non transplanted FMF patients [9, 22, 24, 30]. We are aware of 15 such cases in the literature. Since the incidence of PAN in FMF patients is many times higher than in the control population, this association of FMF with PAN does not seem to be coincidental. Moreover, the clinical presentation of PAN in FMF patients is somewhat different from that of classic PAN: in FMF with PAN, the vasculitis occurs at a younger age and is more frequently accompanied by severe myalgia and life-threatening perirenal hematoma. FMF is also associated with other forms of vasculitis, such as Henoch-Schönlein purpura [8, 29] and rapidly progressive glomerulonephritis [25, 26].

PAN and Henoch-Schönlein purpura are diseases probably mediated by immune complex formation and deposition. Perhaps FMF predisposes one to Henoch-Schönlein purpura and other types of vasculitis because of inadequate inhibition of complement activation following those antigenic stimuli, which could be the triggers for the vasculitis.

In conclusion, we suggest that our patient is an example of FMF-related cyclosporin intolerance. We assume that the other reported cases could also have been caused by the type of vasculitis, very similar to PAN, described in our case. PAN has been described in association with FMF. However, our case is, as far as we know, the first case of PAN-like vasculitis described in an FMF patient after renal transplantation. We propose the hypothesis that FMF patients are more vulnerable to various aggressors to the vascular wall due to defective inhibition of complement activation. In cyclosporin-treated FMF patients, it is possible that the vascular toxicity of cyclosporin leads to inflammation and necrosis of the vessel walls, mimicking PAN. We recommend that in FMF amyloidosis patients who undergo kidney transplantation, cyclosporin be used very carefully.

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