Case report

Should immunosuppressives be stopped in granulomatosis with polyangiitis (Wegener's granulomatosis) patients undergoing dialysis?

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ABSTRACT

Immunosuppressives are frequently stopped in patients with granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) who develop end-stage renal disease. This is done because of the high frequency of infections reported among dialysis patients under immunosuppressives and the former impression that GPA patients no longer experience relapses after the development of end-stage renal disease. We present here a 22-year-old male patient with GPA who had gastrointestinal, genitourinary and respiratory system involvement. The patient died because of a gastrointestinal disease activation that occurred after immunosuppressives were stopped at the initiation of dialysis. The decision to stop immunosuppressives while starting dialysis should be made on an individual basis in patients with GPA, and the risks and benefits should be carefully evaluated.

Introduction

There is a tendency to stop immunosuppressive treatment in ANCA associated vasculitis (AAV) patients after the patient becomes dialysis-dependant, since it is thought that dialysis-dependant AAV patients have lower relapse rates and such patients may have an increased susceptibility to infections under continued immunosuppressive treatment (1). However, caution is required when considering stopping immunosuppressives in such patients. We report here a young man with granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) who had presented with gastrointestinal, genitourinary and pulmonary involvement and had progressed to end-stage renal disease (ESRD). Immunosuppressives were stopped when haemodialysis was started and this resulted in a severe relapse with gastrointestinal and pulmonary involvement, which was fatal.

Case report

In November 2009, a 22-year-old male with known GPA presented with bloody stools, abdominal pain, fever, nausea and vomiting which had started the day before and a bloody sputum which had started 3 weeks ago.

His first admission was in 2004, when he was 17 years old. At that time he had presented with abdominal pain, diarrhoea, haemoptysis, arthralgia, oral ulcers, bloody nasal discharge and a purpuric rash on his extremities. He had cANCA with an anti-PR3 level of >3.5 AU/ml (normal<0.9). Thorax computed tomography (CT) scan had revealed ground glass opacities suggesting alveolar haemorrhage and paranasal CT scan showed mucosal retention cysts. Linear ulcerations were detected on colonoscopic examination; histologic examination revealed a mild degree of active colitis. Visceral angiography showed dilatations and irregularities of hepatic and renal arteries. The patient was diagnosed as GPA. Cyclophosphamide 1g/month, initial 3 methylprednisolone pulses of 1 g, followed by prednisolone 1 mg/kg/day was started. Clinical findings initially improved and anti-PR3 levels decreased under this treatment.

During the next four years, he experienced 3 relapses, once when cyclophosphamide was replaced with azathioprine for maintenance therapy and twice when the patient stopped his immunosuppressives. He was treated with a total of 31 pulses of cyclophosphamide and varying doses of corticosteroids up to 1 mg/kg/day. At the end of 4 years, in October 2008, ESRD developed and haemo-

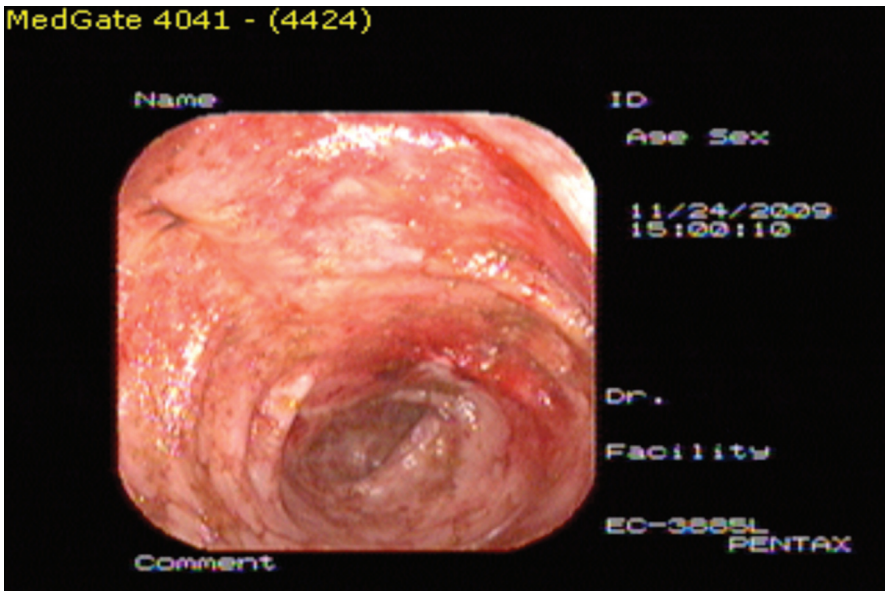

Fig. 1. Colonoscopic examination shows several haemorrhagic areas.

dialysis was started. His corticosteroid and immunosuppressive treatment were stopped by his nephrologist.

One year later he started having bloody sputum and bloody stools. He was hospitalised in our unit in November 2009. His physical examination showed abdominal tenderness on palpation. His ESR was 30 mm/hr, CRP 77.8 mg/dl (normal<5), haemoglobin level 11.9 g/dl, and anti-PR3 level 214.7 EU/ml (normal<20). His rectal bleeding continued and the haemoglobin level fell to 6.7 g/dl within 2 days. Colonoscopic examination showed several haemorrhagic areas throughout the colon, especially in the transverse colon (Fig. 1) although ileocecal valve and ileal mucosa were normal. The histological examination of colon biopsy specimens showed moderately active colitis, chronic inflammation with predominant eosinophils, occlusion of the arteries and veins, focal cryptitis, and a mild to moderate crypt distortion. Immunohistochemical analysis for cytomegalovirus antigen and acid-fast staining in colon biopsy specimens were negative.

He was treated with pulse methylprednisolone and cyclophosphamide. The gastrointestinal bleeding stopped briefly, but started again 7 days later. His haemoglobin level dropped to 3.1 g/dl. Rituximab could not be given due to financial reasons. Surgical intervention was not possible because of haemodynamic instability. Despite high dose corticosteroids, several transfusions and intensive supportive therapy, the patient died with abundant bleeding.

Discussion

We present here a patient with GPA with gastrointestinal involvement, a rare manifestation which proved fatal in this patient when immunosuppressive treatment was stopped while under haemodialysis.

Renal involvement is a common complication of GPA which can result in ESRD in 30% of the patients. Rihova *et al*. retrospectively analysed 61 patients with ANCA associated renal vasculitis and found a high rate of ESRD requiring dialysis. Relapses occurred in 44.7%; nineteen of the patients (31%) died and 22 (32.8 %) were dialysis-dependent. Relapses mostly occurred in patients who were no longer on immunosuppressive treatment (2).

There is little data about the safety of immunosuppressive therapy in AAV patients who receive dialysis. Moreover, some authors think that immunosuppressives are no longer necessary after ESRD (1, 3, 4).

Lionaki *et al*. compared the relapse rates in 93 AAV patients with ESRD who were on chronic dialysis, to their pre-ESRD periods and to 359 AAV patients with preserved renal function. They observed that patients on chronic dialysis had a lower relapse rate than the other groups. Infections were more frequent in ESRD patients whose immunosuppressives were continued, and these infections could be fatal. Thus, they concluded that immunosuppressives should be given to patients on dialysis only if they present with active vasculitis (1). Similarly, Weidanz *et al*. observed that AAV patients had lower relapse rates after the initiation of dialysis compared to their pre-dialysis periods (0.05 *versus* 0.13 relapses per patients-years respectively) in 46 patients (3). Infection rates were higher after dialysis. Nine patients died because of an infection and eight of them were on immunosuppressive therapy. Kuross *et al*. described nine GPA patients who underwent dialysis followed by renal transplantation. None of them relapsed. Four of them had received and 5 had not received immunosuppressive therapy during dialysis (4).

In contrast, Haubitz *et al*. did not observe a lower relapse rate in dialysis-dependant GPA patients, compared to what was previously observed in non-dialyzed GPA patients (5). Among the 35 patients they surveyed, 17 (49%) had a total of 29 relapses. The relapse rate was 0.24 per patient-year.

This case teaches us that the decision to stop immunosuppressives while starting dialysis should be carefully made in patients with GPA. Patients with ESRD who are in remission may be treated with less intense or shorter immunosuppressive therapy (6). However, the decision should be made on an individual basis, after evaluating for co-morbidities and additional risk factors for infectious and other complications of immunosuppressives as well as the risk for relapse of vasculitis. This is especially important for patients with anti-PR3 who have a higher relapse rate (7). Finally, gastrointestinal involvement is a rare, but important complication of GPA. Clinicians must be alert for this type of involvement which may be fatal if not treated adequately.

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