

Idiopathic giant oesophageal ulcer and leucopenia after renal transplantation

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ABSTRACT

A 45-year-old male recipient of a renal allograft was admitted because of a giant oesophageal ulcer coinciding with leucopenia. An extensive workup revealed no explanation for the ulcer and leucopenia. Our final diagnosis by exclusion was an idiopathic giant oesophageal ulcer and late-onset neutropenia as consequences of rituximab induction therapy given during the transplant procedure. The patient fully recovered after treatment with prednisone. However, after four months, the ulcer and leucopenia recurred and again successfully responded to treatment with prednisone.

KEYWORDS

Idiopathic giant oesophageal ulcer, kidney transplantation, late-onset neutropenia, rituximab

INTRODUCTION

Ulceration and inflammation of the oesophagus are frequently seen in immunocompromised patients, such as transplant recipients, and have a comprehensive differential diagnosis.¹ Gastro-oesophageal reflux, infections, neoplasms, systemic disease, and the use of certain drugs should be considered (*table 1*). An idiopathic giant oesophageal ulcer can be diagnosed when no cause is established despite elaborate investigations.

Idiopathic giant oesophageal ulcers were initially reported in patients with acquired immunodeficiency syndrome (AIDS),² but were later also observed in other immunocompromised patients such as recipients of a solid organ transplant.^{3,5} It has been described in an immunocompetent patient only once.⁶ The pathogenesis of these ulcers, which are typically seen in the distal half of

What was known on this topic?

- Idiopathic giant oesophageal ulcers were initially reported in patients with AIDS and later on also in other immunocompromised patients.
- An idiopathic giant oesophageal ulcer is a diagnosis by exclusion.
- Patients with an idiopathic giant oesophageal ulcer can recover soon after starting steroids.
- Late-onset neutropenia might develop after administration of rituximab.

What does this case report add?

- The concurrence of leucopenia and idiopathic giant oesophageal ulcer points to the use of rituximab as a common pathogenetic mechanism.
- An idiopathic oesophageal ulcer has never been reported before as an adverse event of rituximab.

the oesophagus in the proximity of the gastro-oesophageal junction,⁷ is not well understood.

In our patient, two episodes with an idiopathic giant oesophageal ulcer occurred and these both coincided with leucopenia. To our knowledge, this concurrence has never been reported before, and we will discuss how this finding provides a novel insight into the development of the ulcer. Furthermore, we will argue the choice for treatment with steroids.

CASE

A 45-year-old man with end-stage renal disease due to IgA nephropathy underwent a pre-emptive transplantation with a kidney from a living related donor in November 2008.

Table 1. Causes of oesophageal ulceration

Gastro-oesophageal reflux disease

Infectious

- Virus: cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV)
- Bacterial: mycobacterium
- Fungi: candida, histoplasma
- Protozoa: leishmania

Neoplasms

- Carcinoma
- Lymphoma
- Kaposi sarcoma

Systemic disease

- Systemic lupus erythematosus
- Sarcoidosis

Medication

- Antibiotics: doxycycline, tetracycline, clindamycin
- Nonsteroidal anti-inflammatory drugs
- Bisphosphonates
- Remaining: potassium chloride, quinidine, mycophenolate mofetil

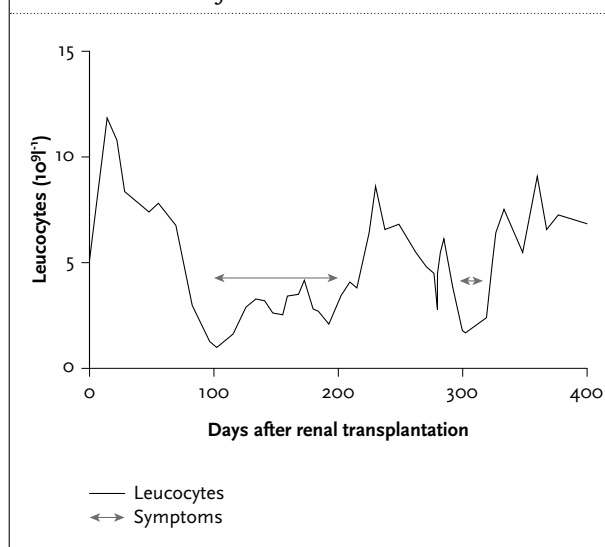
The immunosuppressive regimen consisted of tacrolimus, prednisone and mycophenolate mofetil (MMF). Furthermore, 700 mg of rituximab was administered as induction therapy during transplant surgery in the framework of a clinical trial (clinicaltrials.gov; NCT00565331). Since the donor was seropositive for cytomegalovirus (CMV) while the recipient was seronegative prior to transplantation, prophylactic therapy with valganciclovir was started postoperatively. The direct post-transplantation course was uncomplicated. In April 2009, the patient was admitted because of retrosternal discomfort for three weeks. The pain worsened during food intake. He reported weight loss of six kilograms, fatigue, but no night sweats or fever. Physical examination was unremarkable except for a decreased skin turgor. At admission, the leucocytes were $2.8 \times 10^9/l$ with 84% neutrophils, 9% lymphocytes, 3% monocytes and 4% (meta)myelocytes. Later on, the leucocytes decreased to $1.9 \times 10^9/l$ with 70% neutrophils and 22% lymphocytes. Discontinuation of MMF and co-trimoxazole (prophylaxis for *Pneumocystis jirovecii*) did not have any beneficial effect. The other laboratory results were unremarkable. Upper gastrointestinal endoscopy revealed a cratered oesophageal ulcer covering 33% of the circumference (size 20 by 12 mm). Biopsy samples showed ulceration without any indication of the cause, the cultures were negative. Serological tests for human immunodeficiency virus, CMV, herpes simplex virus, histoplasma, and antinuclear antibodies were also negative. CMV polymerase chain reaction in blood and tissue was negative. PET-CT scan showed increased uptake of (18)F-2-fluoro-2-deoxy-D-glucose in the distal part of the oesophagus without signs of lymphadenopathy. Bone marrow biopsy revealed hypocellular bone marrow with reactive changes without

signs of lymphoproliferative disease. Cytogenetic examination of the bone marrow was unremarkable. Endoscopic ultrasonography revealed thickening of all layers of the oesophageal wall (8.1 mm). Eventually, by exclusion, an idiopathic giant oesophageal ulcer was diagnosed. The patient was treated with prednisone 40 mg/day and the symptoms rapidly decreased and resolved within 72 hours. Repeated upper endoscopy after a few weeks showed a healing ulcer. The leucocytes also improved after increasing the dose of prednisone. Subsequently, the daily prednisone dose was tapered by 10 mg per month. The dose of tacrolimus was continued unchanged. Four months later, the patient was re-admitted because of *Pneumocystis jirovecii* pneumonia and he was successfully treated with co-trimoxazole. After discharge, leucopenia and later on also new oesophageal ulcerations recurred. Elaborate investigations to settle the aetiology of the leucopenia and ulcer were again unsuccessful. After increasing the prednisone dose, the leucopenia and ulceration improved.

DISCUSSION

Idiopathic giant oesophageal ulcers are rarely seen and their pathogenesis is not well understood. In our patient, leucopenia was present during both episodes of ulceration and the degree of leucopenia was related to the severity of the ulceration (figure 1). Therefore, the leucopenia might bear a relationship with the pathogenesis of the idiopathic giant oesophageal ulcer.

Figure 1. Time course of white-cell counts in peripheral blood and symptoms. The period with symptoms of retrosternal discomfort is marked with arrows



Initially, we were not able to clarify the cause of leucopenia despite elaborate investigations and discontinuation of potentially myelotoxic drugs, except tacrolimus. However, our patient had also received rituximab at the time of transplantation, and it is known that leucopenia can occur more than three weeks after the administration of rituximab.⁸⁻¹¹ Typically, it is characterised by profound neutropenia. As in our patient, lymphopenia and hypogammaglobulinemia were also observed.¹¹

The aetiology of this so-called late-onset neutropenia is poorly understood and different hypotheses have been postulated. One of these hypotheses is that late-onset neutropenia after rituximab treatment is the consequence of an immune-mediated imbalance between various lymphocyte subpopulations.¹⁰ Interestingly, an inverted CD4/CD8 ratio has been described in patients with late-onset neutropenia.¹²

Recently, treatment with rituximab has been associated with ulcerative lesions in the large bowel.¹³ Histopathology showed infiltration with CD8 positive T lymphocytes. Identical histopathological findings were reported in AIDS-related idiopathic giant oesophageal ulcers.¹⁴ Notably, in our patient a moderate infiltration of CD8 positive lymphocytes (*figure 2*) was present in the oesophageal biopsy specimen, which is usually not the case.¹⁴ Thus, it appears that an imbalance between various lymphocyte subpopulations can be involved in the rituximab-induced neutropenia as well as in the pathogenesis of giant oesophageal ulcer.

In our patient, the relapse of oesophageal ulcer was accompanied by a recurrence of the leucopenia, which supports a common pathogenetic basis. Recurrent episodes of neutropenia after rituximab, even without repeated administration of rituximab, have also been reported by others.⁹

Although oesophageal ulcers can regress after reduction of the tacrolimus dose,³ we did not change the dose of tacrolimus in our patient. In line with literature data, we treated our patient successfully with corticosteroids.² In AIDS patients, endoscopically documented ulcer healing was observed in 85% of patients treated with steroids.¹⁵ The mechanisms for steroid efficacy are unknown. In AIDS patients the relapse rate after discontinuing steroids is high (40%), but retreatment is usually successful.⁴ In case of refractory ulcers, thalidomide has also been used successfully.⁶

In conclusion, the perioperative administration of rituximab was the likely cause of the relapsing leucopenia and the coinciding idiopathic giant oesophageal ulcer in our patient.

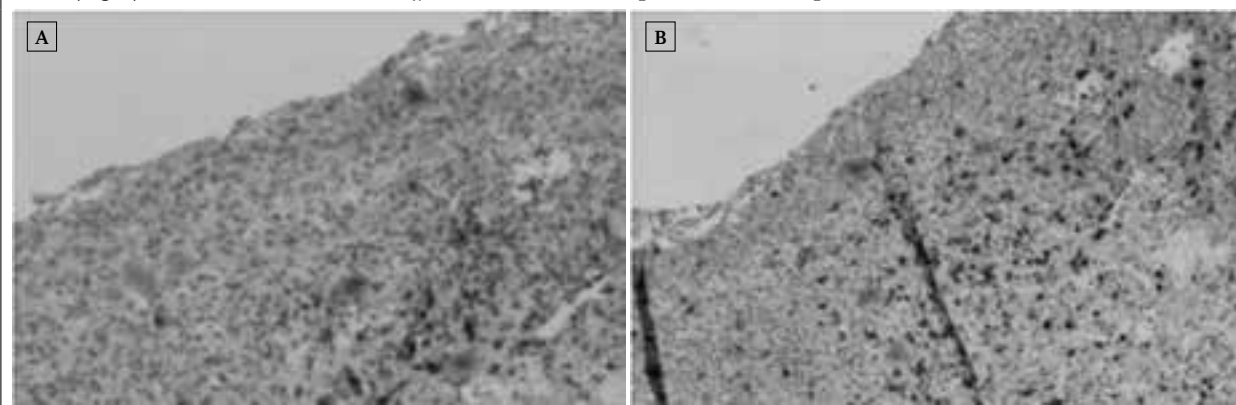
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Figure 2. Immunohistochemical characterisation of the inflammatory giant oesophageal infiltrate by CD 4 (left) and CD 8 (right). The estimated ratio CD4/CD8 is 1.0 in this representative sample



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