Case Report

Successful treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis presenting with gastrointestinal bleeding: a case report and literature review

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Abstract: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is often associated with multi-systemic involvement and bleeding from multiple organs, with alveolar and cerebral hemorrhage being the most frequent complications. Although the gastrointestinal tract is less commonly involved, the prognosis is poor in patients presenting with involvement of this site, and the treatment options are relatively limited. A previously healthy 42-year-old woman was diagnosed with ANCA-associated vasculitis with gastrointestinal involvement. Secondary to an inadequate response to the conventional therapy, she underwent colonoscopic examination to determine the bleeding site. Colonoscopic examination revealed active bleeding from an ileal ulcer, necessitating surgical resection of the ulcerated bowel to control the bleeding. At the 6-month follow-up, her perinuclear ANCA (pANCA) and serum creatinine levels were observed to be within the reference range. Timely diagnosis and prompt administration of immunosuppressants, combined with surgical intervention, are important to improve the prognosis. In addition, the use of emerging novel agents/therapies could potentially improve patient outcomes.

Keywords: Anti-neutrophil cytoplasmic antibody, primary small-vessel vasculitis, GI hemorrhage, immunosuppressive therapy

Introduction

Primary small-vessel vasculitis comprises a group of systemic autoimmune diseases characterized by inflammation of the walls of small vessels and cellulosic necrosis as typical histopathological features. The largest subgroup within this category is collectively referred to as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis, and necrotizing crescentic nephritis. The incidence of AAV has been estimated at 23.1 per million person-years [1], with an increasing trend observed over successive years. Elderly patients are more susceptible to the disorder, whose pathogenesis has been attributed to several environmental factors, including infection and exposure to ultraviolet light and silica [2]. Despite advances in the treatment of AAV, the associated mortality rates remain high [3], particularly in patients with gastrointestinal (GI) involvement. GI involvement is an infrequent but challenging complication of AAV [4]. Patients can benefit from timely diagnosis and specific treatment [5]. In this report, the case of a woman diagnosed with AAV showing GI involvement who did not significantly improve after conventional therapy is presented. This report aims to demonstrate the efficacy and safety of immunosuppressive therapy combined with surgical intervention for the management of patients diagnosed with AAV presenting with GI bleeding.

Case presentation

A previously healthy 42-year-old woman was admitted to our hospital on October 28, 2016, with symptoms of fatigue and anorexia over a month and edema over 7 days prior to presen-
tation. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Jilin University. Written informed consent was obtained from participant.

Her laboratory test results showed the following: white blood cell count, $4.57 \times 10^9$/L; neutrophil, 86.0%; hemoglobin concentration, 10.3 g/dL; hematocrit level, 31.5%; and platelet count, $404 \times 10^9$/L. Her blood biochemistry tests showed the following results: total protein, 68.2 g/L; albumin, 34.1 g/L; blood urea nitrogen, 12.1 mmol/L; and creatinine, 296.0 μmol/L. Urinalysis revealed proteinuria (3+), occult blood (3+), and urinary protein 5.7 g/24 hours. Anti-neutrophil antibody testing (confirmatory and screening) revealed an anti-myeloperoxidase (MPO) antibody level of 30.12 IU/mL and a perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) titer of 1:32.

Histopathological examination of a renal biopsy specimen was performed. Light microscopy revealed 12 glomeruli obtained from within the kidney tissue, including 8 cellular and 1 fibrocellular crescents. The biopsy specimen stained negative in the periodic acid silver methenamine-Masson staining. The tubulointerstitium showed mild acute and chronic lesions, as well as small foci of renal tubular atrophy, and basement membrane thickening. In addition, mild diffuse widening of the tubulointerstitium was observed with edema and fibrosis; neutrophilic, lymphocytic, plasma cell, and eosinophilic infiltrations with small focal aggregates; and segmental and transparent degeneration of small arteries. Immunofluorescence microscopy revealed 4 glomeruli on fluorescent staining of the frozen section, focally distributed farred fluorescence, and mass deposition in the mesangial area; other results were negative.

To summarize, the key findings observed were crescentic glomerulonephritis with loop necrosis and AAV (Figure 1). Her clinical diagnosis was AAV and rapidly progressive glomerulonephritis, and her histopathological diagnosis

Figure 1. Renal biopsy of the patient. A. Periodic acid-Schiff staining; B. Masson staining; C. Periodic acid-silver methenamine staining; D. Immunofluorescence staining. Original magnification: × 400.
was crescent nephritis with loop necrosis (AAV-induced kidney damage). Methylprednisolone (500 mg/day) was administered as pulse therapy for 3 days, followed by oral prednisone (60 mg/day) in addition to concomitant administration of intravenous cyclophosphamide (0.8 g).

On November 12, she was observed to have 3 episodes of hematochezia with an estimated total blood loss of 300 mL. Her hemoglobin level decreased to 73 g/L. Anti-neutrophil antibody screening was repeated and showed a p-ANCA titer of 1:320. No significant improvement was observed with conventional therapy, which included fasting, inhibition of gastric acid secretion, hemostasis, and administration of fluids. The immunosuppressant administered was switched to methylprednisolone (60 mg/day). Colonoscopic examination revealed active GI bleeding from ileal ulcers associated with dark-red blood scab formation and signs of chronic colitis (Figure 2). She was transferred to the department of general surgery and underwent resection of the ulcerated bowel segments combined with terminal ileostomy at the proximal end of the resection. Post surgery, she was transferred back to our department. No recurrence of GI bleeding was observed, and her symptoms of fatigue and anorexia showed improvement. She was administered intravenous methylprednisolone at a dose of 60 mg/day for 1 week, followed by oral prednisone (50 mg/day). On November 30, the screening and confirmatory tests for anti-neutrophil antibody were repeated and her MPO antibody level was 8.25 IU/mL and the p-ANCA titer was < 1:10. Her blood urea nitrogen level was 17.1 mmol/L and serum creatinine level was 122.7 µmol/L. The patient attained a stable condition and was discharged from the hospital. During her 6-month follow-up, she showed normal p-ANCA titers, decreased serum creatinine level to 102 µmol/L, and a urinary protein level of 1.5 g/24 h. Her current treatment regimen comprises prednisone at a dose of 20 mg/day with intravenous cyclophosphamide (0.8 mg) administered once a month.

Discussion

Diagnosis of AAV may be challenging owing to the occurrence of non-specific symptoms, which are often indistinguishable from those of infection and thromboembolic disease. In addition to the kidneys, the lungs, ears, nose, throat, and skin are commonly involved [6, 7]. However, GI tract involvement is relatively uncommon [8]. Nonetheless, GI tract involvement is associated with a significant risk of GI bleeding. A study performed by Pagnoux et al. [9] that included 62 patients with systemic vasculitides and GI involvement showed that approximately 16% of these patients demonstrated hematochezia or melena. A study by Cabral et al. [10] that included 231 patients showed that severe GI bleeding or ischemic abdominal pain was observed in < 5% of patients with both MPA and GPA, although these
Treatment of AAV combined GI bleeding

Table 1. New treatment strategies and biological agents of AAV

<table>
<thead>
<tr>
<th>Biological agents</th>
<th>BLys</th>
<th>C5a</th>
<th>B cell</th>
<th>NSPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emerging treatment</td>
<td>Belimumab</td>
<td>CCX168</td>
<td>Fostamatinib</td>
<td>Anakinra</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Monoclonal antibody inhibits BLys</td>
<td>C5a inhibitor</td>
<td>Syk inhibitor</td>
<td>IL1-β inhibitor</td>
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BLys, B lymphocyte stimulating protein. NSPs, neutrophil serine proteases. Syk, spleen tyrosine kinase. IL1-β, interleukin 1-β.

conditions could be associated with significant morbidity and mortality. It has been observed that histopathological changes could show a significant association with the prognosis of the disease [11]. Renal recovery is more likely in patients presenting with mild renal fibrosis, and these patients show a better overall prognosis.

This patient presented with indications of disease activity such as glomerular crescent formation and rapidly progressive kidney damage; therefore, a regimen of glucocorticoids with additional cyclophosphamide was used, which helped achieve complete remission of AAV. However, GI bleeding occurred during the treatment, and repeat testing showed a significant increase in the pANCA titer (1:320) as compared with that observed at the time of admission. This useful biomarker reflects vasculitic activity and disease severity. Therefore, glucocorticoids and other immunosuppressants are needed to control the primary disease. However, in this patient, the occurrence of GI bleeding limited the efficacy of glucocorticoids, and the institution of adjuvant therapy was particularly important in this situation. Thus, glucocorticoid pulse therapy was not chosen and the patient was switched to intravenous methylprednisolone (60 mg/day) administration. As the patient did not show an adequate response to conventional treatment, the surgical approach was chosen.

Similar cases have been reported earlier in the literature. Cao et al. [12] reported the case of a patient with AAV concomitant with multiorgan bleeding (pulmonary hemorrhage and GI bleeding) that was successfully treated with plasma exchange, methylprednisolone pulse therapy, and an increase in cyclophosphamide dose. Li et al. [13] reported the case of a patient who showed significant improvement in GI bleeding after mesenteric artery embolization, plasma exchange, and gamma globulin indicating the efficacy of immune regulation therapy in controlling the primary disease.

A significant observation in this patient (compared with previous case reports) was that the patient’s medical condition precluded plasma exchange therapy or mesenteric artery embolization. Thus, glucocorticoids were used in addition to surgical treatment comprising resection of the ulcerated bowel with a terminal ileum colostomy at the proximal end of the resection. This approach could be considered an effective life-saving strategy in several patients. In recent years, several developments in treatment approaches to AAV, particularly the introduction of targeted biological therapy directed toward lymphocytes, cytokines, and the complement system, have confirmed the role of these factors in the pathogenesis of AAV [14]. A few new treatment strategies have been demonstrated in clinical trials or have been applied to clinical therapy (Table 1).

In the absence of specific biological markers to predict the risk of GI bleeding in patients with vasculitis, careful observation of these patients is essential. Passage of black tarry stools (melena) and/or elevated ANCA levels are findings that warrant close attention in such patients. Minimal/mild GI bleeding can be managed by strengthening immune regulation and auxiliary treatments. However, excessive/severe bleeding necessitates surgical intervention. Therefore, a proactive approach can improve the prognosis, and the use of emerging novel agents/therapies can potentially improve patient outcomes.

Disclosure of conflict of interest

None.

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References


