Relapsing granulomatosis with polyangiitis provoked by trauma
A case report
Shan Deng, MD, Yida Xing, MD, Hongjiang Wang, MD, Xiaodan Kong, MD*

Abstract

Rationale: The precise cause of granulomatosis with polyangiitis (GPA) remains unclear. Herein we present a case of refractory GPA occurring after trauma.

Patient concerns: A 43-year-old man suffered fractures of the left orbital in an accident, and then received surgical repair. At a postoperative follow-up, he developed maxillary sinusitis. Seven months later, he was hospitalized with symptoms of cough, high-grade fever, and loss of weight.

Diagnosis: He was diagnosed with GPA based on the symptoms of upper and lower respiratory tract involvement, granulomas in a lung biopsy specimen, and presence of PR3-ANCA.

Interventions: Initially the patient responded well to the treatment of glucocorticoids and cyclophosphamide (CYC). Forty days later, he was hospitalized again with symptoms of fever, cephalgia, and recurrent ulcerated subcutaneous nodules, due to the vasculitic manifestations of GPA. This time he was treated with cyclophosphamide and glucocorticoids with no improvement, and then switched to rituximab.

Outcomes: After 4 doses of rituximab, the symptom of cephalgia disappeared and subcutaneous ulcerations and conjunctival congestion diminished.

Lessons: Trauma may act as an inflammatory stimulus to affect the course of disease in GPA. The combination of glucocorticoids and cyclophosphamide is the standard therapy for GPA. Nevertheless, patients who have no response to CYC, especially with predominantly vasculitic manifestations, could resort to rituximab.

Abbreviations: ANCA = antineutrophil cytoplasmic autoantibody, CRP = C-reactive protein, CT = computed tomography, CYC = cyclophosphamide, ESR = erythrocyte sedimentation rate, GPA = granulomatosis with polyangiitis, RTX = rituximad.

Keywords: cyclophosphamide, granulomatosis with polyangiitis, relapse, rituximab, trauma

1. Introduction

Granulomatosis with polyangiitis (GPA) is a form of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies (ANCA) that affects the airways, lungs, kidneys, eyes, skin, and nervous system. The outcome of GPA patients has improved significantly since the introduction of steroids with cyclophosphamide. However, 15–20% of patients are resistant to standard treatment.[1] Rituximab (RTX) is found to be efficient in refractory GPA.

The precise cause of GPA remains unclear. Previous study has reported that ANCA antoantigen is barely detectable at the surface of resting neutrophils, but it becomes highly expressed after inflammatory stimuli.[2] A reasonable hypothesis is that in patients with ANCA, a severe acute injury, which elicits an inflammatory response, may prime neutrophils to interact with circulating ANCA to induce vasculitis. In this regard, trauma seems to be an interesting and possible trigger event. Here, we present our experience with RTX in a case of refractory GPA occurring after trauma.

2. Case presentation

Informed consent for publication of the case details was obtained from the patient. A 43-year-old male worker was admitted to our hospital with left periorbital swelling after his left face was injured by a machine. He had no notable medical history. A computed tomography (CT) revealed fractures of the medial, superior, and inferior walls of the left orbital. Surgical exploration confirmed multiple fractures, and the repair was successful.

At a postoperative follow-up, the patient showed no signs of the left periorbital swelling. Nevertheless, he reported recurrent conjunctival congestion and new symptoms of nasal obstruction...
and purulent/bloody discharge. Seven months later, he was hospitalized with symptoms of cough, fever, and loss of weight. He had high-grade fever without chills. No source of infection was identified after thorough evaluation including blood culture, bone marrow aspiration, echocardiogram, and abdominal film. A further computed tomography of the chest showed multiple pulmonary nodules in the bilateral lung fields and patchy shadows in the middle lobe of right lung (Fig. 1). He was treated with moxifloxacin for 7 days without resolution of fever. ANCA was positive, proteinase 3 (PR3)-ANCA 381.20 RU/ml, erythrocyte sedimentation rate (ESR) 106.00 mm/h, and C-reactive protein (CRP) 259.14 mg/L. Further tests showed normal renal function and urine dipstick. Lung biopsy specimen demonstrated vasculitis and granulomatous inflammation. Based on clinical symptoms of upper and lower respiratory tract involvement, granulomatous inflammation found in lung biopsy and presence of PR3-ANCA, granulomatosis with polyangiitis (GPA) was recognized. Activity was assessed by the Birmingham Vasculitis Activity Score for GPA (BVAS/GPA = 5 point). The patient was treated with glucocorticoid pulse (methylprednisolone 1.0 g × 3 days i.v.) followed by intravenous methylprednisolone (80 mg/day) and pulses of cyclophosphamide (CYC) in dose 1.5 mg/kg infusion. The patient reported prompt improvement of his symptoms. But on the third day after methylprednisolone was tapered, he got fever again and developed right wrist drop and numbness in the right hand. We administered the second glucocorticoid pulse and infusions of cyclophosphamide 1.5 mg/kg once a week. The patient responded well to treatment, wrist flexion improved, and numbness of the right hand was reduced. His respiratory status showed a brisk recovery. A chest CT scan confirmed the improvement (Fig. 2), and CRP and PR3-ANCA levels also declined (CRP 58 mg/L, anti-PR3 79 RU/ml). Then, steroid was slowly tapered, and cyclophosphamide was administered every two weeks.

Forty days later, the patient was hospitalized again due to fever, conjunctival congestion, cephalgia, and recurrent ulcerated

Figure 1. Chest CT at presentation showed multiple pulmonary nodules in the bilateral lung fields (A) and patchy shadows in the middle lobe of right lung (B). CT = computed tomography.

Figure 2. CT of the chest after treatment with glucocorticoids and cyclophosphamide showed regression of changes and no new infiltrates in the lung. CT = computed tomography.
subcutaneous nodules. In laboratory tests, elevated inflammatory markers (CRP 76 mg/l, ESR 84 mm/h) and increased level of PR3-ANCA antibodies (anti-PR3 86 RU/ml) were observed. An infectious work-up was negative. The patient was treated with intravenous methylprednisolone (1 mg/kg/day) and intravenous cyclophosphamide weekly again. Unfortunately, the patient did not respond to the above treatment this time. Due to resistance to CYC, RTX (4 doses of 375 mg/m² at weekly intervals) was administrated. The symptoms of cephalalgia disappeared and subcutaneous ulcerations and conjunctival congestion diminished. During the follow-up visits for 6 months, even though ANCA remained positive at low titer and there was another minor relapse, the patient responded well to increased doses of oral prednisone and CYC. The follow-up would be continued.

3. Discussion

The present case is the first report to show trauma as a possible initiating event for GPA. In this case, the patient had no symptoms of nasal blockade and discharge at the first presentation. The orbital fractures and surgical repair appear to provoke inflammation of the nearby maxillary sinus and conjunctiva and subsequent development of GPA. To the best of our knowledge, trauma has been shown to precipitate inflammatory disease previously, such as maxillary sinusitis occurring after facial trauma and necrotizing sweet syndrome of the upper extremity induced by hand surgery. O’Donoghue found that the latent period between surgery and the appearance of inflammation was about 9 months. As previously mentioned, an inflammatory process could prime neutrophils to interact with ANCA to induce vasculitis. This suggests that trauma may act as an inflammatory stimulus to affect the course of disease in GPA. GPA is a granulomatous small and medium vessels vasculitis. Since the introduction of glucocorticoids and cyclophosphamide as the standard remission induction therapy for generalized GPA, survival of patients has improved considerably. But GPA has a high relapse rate, and some patients do not respond to the above treatment. Rituximab has been demonstrated to be effective in the relapsing disease.

The initial symptoms of our patient include the involvement of the upper and lower airway and mononeuropathy, which respond to the treatment of cyclophosphamide and glucocorticoids. While the disease relapsed a month later, the symptoms switched to conjunctival congestion, cephalalgia, and subcutaneous ulcerations, which were mainly due to the vascular manifestations. He was treated with cyclophosphamide and glucocorticoids with no improvement, and then switched to RTX. The rapid and dramatic response to RTX we observed appears to support the premise that this therapy works best for vasculitis. Previous studies have found that the granulomatous form of GPA appeared to be more likely resistant to RTX than vasculitic manifestations. Aires et al reported failure of RTX treatment in patients with predominantly granulomatous manifestations of GPA. Another retrospective study also showed that complete remission was more common in patients with vasculitic manifestations, not granulomatous manifestations. A probable explanation is that GPA granulomas is a consequence of an antigen-specific T cell immune response. However, some studies included patients with predominantly granulomatous disease reported success of using RTX.

More studies are needed to determine whether there is different efficacy of RTX in the two manifestations of GPA.

To our knowledge, this is the first case where trauma as an inflammatory stimulus may change the course of disease in GPA. The combination of glucocorticoids and cyclophosphamide remains the standard therapy for GPA. Nevertheless, patients who have no response to CYC, especially with predominantly vasculitic manifestations, could resort to the option of treatment with RTX.

Acknowledgment

We thank the patient for his kind cooperation. Informed patient consent was obtained for publication of this case report.

Author contributions

Conceptualization: Shan Deng, Xiaodan Kong.
Data curation: Yida Xing.
Formal analysis: Hongjiang Wang.
Investigation: Shan Deng, Hongjiang Wang.
Methodology: Yida Xing.
Supervision: Xiaodan Kong.
Writing – original draft: Shan Deng.
Writing – review & editing: Shan Deng, Xiaodan Kong.

References

[1] Holle JU, Gross WL, Latza U, et al. Improved outcome in 445 patients with Wegener’s granulomatosis in a German vasculitis center over four decades. Arthritis Rheum 2011;63:237–66.
[2] Schreiber A, Xiao H, Jennette JC, et al. C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. J Am Soc Nephrol 2009;20:289–98.
[3] Stone JH, Hoffman GS, Merkel PA, et al. A disease-specific activity index for Wegener’s granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum 2001;44:912–20.
[4] Simunits R, Kubilus R, Ryskiene S, et al. Odontogenic maxillary sinusitis obscured by midfacial trauma. Stomatologija 2015;17:29–32.
[5] Lipof JS, Beck LA, Reddy SC, et al. Necrotising sweet syndrome of the upper extremity after elective hand surgery. J Hand Surg Am 2018;43:389.e1–e6.
[6] O’Donoghue E, Lightman S, Tuft S, et al. Surgically induced necrotising sclerokeratitis (SNS)—precipitating factors and response to treatment. Br J Ophthalmol 1992;76:17–21.
[7] Jennette JC. Nomenclature and classification of vasculitis: lessons learned from granulomatosis with polyangiitis (Wegener’s granulomatosis). Clin Exp Immunol 2011;164:7–10.
[8] Suhler EB, Lim LL, Beardsley RM, et al. Rituximab therapy for refractory orbital inflammation: results of a phase 1/2, dose-ranging, randomized clinical trial. JAMA Ophthalmol 2014;132:572–8.
[9] Aries PM, Hellmich B, Voswinkel J, et al. Lack of efficacy of rituximab in Wegener’s granulomatosis with refractory granulomatous manifestations. Ann Rheum Dis 2006;65:853–8.
[10] Holle JU, Dubrau C, Herlyn K, et al. Rituximab for refractory granulomatous polyangiitis (Wegener’s granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations. Ann Rheum Dis 2012;71:327–33.
[11] Lamprecht P, Gross WL. Current knowledge on cellular interactions in the WG granuloma. Clin Exp Rheumatol 2007;25:S49–51.
[12] Joshi L, Lightman SL, Salama AD, et al. Rituximab in refractory Wegener’s granulomatosis: PR3 titers may predict relapse, but repeat treatment can be effective. Ophthalmonology 2011;118:2498–503.
[13] Costa C, Santiago T, Espiro Santo J, et al. Pachymeningitis and cerebral granuloma in granulomatosis with polyangiitis: is rituximab a promising treatment option? Acta Reumatol Port 2017;42:82–7.