CASE REPORT

Granulomatosis with polyangiitis: seeing the diagnosis

Max J Blumberg,¹ Cynthia I Tung,² Lindsay A May,¹ Sangita P Patel^{1,3}¹Department of Ophthalmology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, New York, USA²Department of Head and Neck Surgery, Section of Ophthalmology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA³Research and Ophthalmology Services, VA Western New York Healthcare System Buffalo VA Medical Center, Buffalo, New York, USACorrespondence to
Dr Sangita P Patel,
spatel@buffalo.edu

Accepted 22 April 2017

SUMMARY

A 41-year-old woman presented to her primary doctor with nausea, back pain and lower extremity oedema. Initial labs showed elevated serum creatinine and white blood cell count (WBC), which her doctor attributed to ibuprofen use and a recent upper respiratory infection. Five days later, she presented to the eye clinic with eye pain, redness and blurred vision. She was diagnosed with iritis, conjunctivitis and keratitis. The inflammatory eye disease with decreased renal function prompted the ophthalmologist to initiate systemic autoimmune and infectious disease work-up. Before laboratory testing was complete, she developed severe haemoptysis. Diagnosis of granulomatosis with polyangiitis (GPA) was confirmed using blood testing, radiological imaging and kidney biopsy. She received plasmapheresis, then cyclophosphamide and prednisone with good effect. This case highlights the need to consider GPA in the differential when patients present with inflammatory eye disease with decreased renal function and the need for multispecialty collaboration including ophthalmologists in the diagnosis of GPA.

BACKGROUND

Granulomatosis with polyangiitis (GPA) is a rare, autoimmune-mediated, necrotising, granulomatous, small vessel vasculitis which is life-threatening if not diagnosed and treated promptly. Systemic symptoms often present as a non-specific flu-like illness which makes early diagnosis and treatment difficult. However, over half of patients with GPA develop ophthalmic manifestations during the course of their disease.¹ Inflammatory eye disease in the setting of systemic signs and symptoms should trigger systemic autoimmune and infectious disease work-up. This case highlights the central role of eye-findings in the diagnosis of life-threatening systemic illnesses.

CASE PRESENTATION

A 41-year-old woman with no significant medical or ocular history presented to her primary medical doctor with non-specific systemic symptoms which were initially attributed to common isolated conditions in a primary care setting. She had a 'cold' which she did not feel she had recovered from, with continued nausea, left upper quadrant back pain and bilateral lower extremity oedema. Her primary care physician attributed the lower extremity oedema to decreased renal function (increased creatinine) from recent ibuprofen use and prescribed omeprazole for

the nausea. Five days later, she presented to the eye clinic with new onset bilateral severe eye pain, redness and blurred vision. She was diagnosed with bilateral iritis, conjunctivitis and keratitis. The presence of ocular inflammatory disease in the setting of decreased kidney function prompted the eye doctors to order tests for systemic autoimmune and infectious disease. Six days later, before the patient had completed the ordered tests, she presented to a local emergency room with severe haemoptysis.

INVESTIGATIONS

Four years prior to this incident, the patient's serum creatinine was 0.48 mg/dL and white blood cell count (WBC) was $10 \times 10^9/L$. Blood tests performed by the primary doctor at the onset of symptoms for this presentation showed serum creatinine of 1.77 mg/dL, and WBC was $12.6 \times 10^9/L$. Because of the acute kidney failure with bilateral ocular inflammatory disease, the eye doctors initiated work-up for systemic autoimmune disease and infectious disease. However, before work-up could be completed, she was admitted to the hospital. Laboratory results during hospitalisation, including complete blood count, inflammation markers and urinalysis, are summarised in table 1. The positive cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) in conjunction with the elevated erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and positive antinuclear antibody (ANA) supported the diagnosis of GPA. The patient underwent radiological imaging tests showing lesions in the lungs and kidneys. A CT scan of the chest showed diffuse dense bilateral nodular opacification in the upper lobes and perihilar regions. Kidney biopsy showed diffuse necrotising crescentic glomerulonephritis and the pathology report stated that the findings were most consistent with ANCA-associated pauci-immune glomerulonephritis, including Wegener's granulomatosis (also known as GPA) and microscopic polyangiitis. Evaluated in the context of clinical features and diagnostic studies, the consulting rheumatologists, nephrologists, pathologists and pulmonologists agreed that GPA was the most likely diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for decreased renal function (increased serum creatinine) from the patient's initial presentation is broad and includes prerenal, intrinsic and postrenal conditions. However, renal disease in combination with ocular inflammatory

CrossMark

To cite: Blumberg MJ, Tung CI, May LA, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-218030

Table 1 Summary of inpatient laboratory testing

	Result	Reference range
White blood cell	13.0 ↑	4.0–10.5 billion cells/L
Haemoglobin	10.1 ↓	12.0–16.0 g/dL
Haematocrit	29.2 ↓	37.0–47.0%
Platelet	194	150–450 billion/L
BUN	48 ↑	5–25 mg/dL
Creatinine	5.75 ↑	0.40–1.40 mg/dL
ESR	129 ↑	0–20 mm/hour
CRP	174.8 ↑	0.20–10.0 mg/L
ANA	1:640 (positive)	<1:40
c-ANCA	≥1:512 (positive)	<1:20
<i>Urinalysis</i>		
Haemoglobin	3+	
Casts	0–2	Hyaline casts/lpf
Total urine protein	152.4	mg/dL

ANA, antineutrophil antibody; BUN, blood urea nitrogen; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate.

disease narrows the differential: tubulointerstitial nephritis and uveitis syndrome, systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, rheumatoid arthritis, GPA, Behçet's disease, syphilis, tuberculosis, toxoplasmosis, brucellosis, histoplasmosis, leptospirosis, Lyme disease and rickettsial infection.^{2–5} Many of the infectious aetiologies can be eliminated with careful patient history. Laboratory testing, as obtained for this patient, narrows the differential further. While the positive ESR, CRP and ANA suggest underlying inflammatory disease, a positive c-ANCA test result has high specificity for GPA (73.9%), followed by microscopic polyangiitis (9.6%).⁶ The specificity for GPA may be as high as 90% when vasculitis is in the differential.⁷ The sensitivity of c-ANCA is also high in active GPA (69–78%).⁸

TREATMENT

Treatment for ocular disease (iritis, conjunctivitis and keratitis) was initiated with prednisolone acetate 1% eye drops 4×/day and cyclogyl 1% eye drops 2×/day for both eyes. After follow-up in the eye clinic showing ocular improvement, cyclogyl drops were reduced to once daily and prednisolone taper was started with complete taper over 1–2 weeks without disease recurrence. Following GPA diagnosis, the patient received plasmapheresis, followed by prednisone and cyclophosphamide for long-term management. The patient has since been on azathioprine with disease remission.

OUTCOME AND FOLLOW-UP

Treatment was well tolerated with good effect. The patient was tapered off eye drops without recurrence of ocular disease. Six months following treatment initiation, her serum creatinine decreased to 1.06 mg/dL and her WBC was 5.6×10^9 /L. Her disease remains in remission for over 1 year since treatment initiation.

DISCUSSION

GPA is an autoimmune-mediated, necrotising, granulomatous vasculitis. The condition is rare but life-threatening if not treated promptly. It most commonly affects the kidneys, lungs and sinuses. Common presenting signs and symptoms include pulmonary infiltrates, sinusitis, arthralgia, fever, otitis, haemoptysis and ocular inflammation.⁹ However, as in the

initial presentation in this case, symptoms and findings are non-specific and easily attributed to other causes. A series of 10 cases reported delay in diagnosis from 2 to 36 months.¹⁰

While ocular inflammation is not the most common presenting symptom in GPA, up to 58% of patients with GPA have ophthalmological manifestations. GPA can affect any part of the eye, with the most common ophthalmological

Patient's perspective

In reading this case—and in experiencing it as the patient—two central points stand out. First is the importance of the ophthalmologist in recognising and treating granulomatosis with polyangiitis (GPA) when there are eye symptoms. In my particular case, the ophthalmologist was the first physician to consider a systemic issue and was the first to recommend further blood work beyond the complete metabolic panel and complete blood count. Further, the ophthalmologist was the only physician who made the connection between ocular and renal disease prior to my admission to the hospital. Despite finding an elevated creatinine, my primary care's office did not suggest any need for follow-up or further testing. In contrast, a few days after my visit to her office, the ophthalmologist called me at home to discuss the possibility of tubulointerstitial nephritis and uveitis syndrome and to suggest follow-up. While the disease ended up being something else, it was this phone call that alerted me to the possibility of a systemic disease.

Second is the importance of multispecialty collaboration. This case alludes to the need for including the ophthalmologist in ongoing GPA care, but it also points out that there may be a gap in collaborative care overall. GPA is a multisystem disease that requires ongoing care from a variety of specialists. As the patient, I am grateful to all of these talented physicians for their knowledge and their expertise in keeping me healthy. However, there is little coordination of care, at least from my perspective, other than the exchange of notes from each visit, and the onus of keeping providers aware of changes in treatment has thus far fallen on me. A key feature of this case, in my opinion, is that it demonstrates the need for more extensive collaboration and communication between all specialties involved in GPA care.

Learning points

- ▶ Early diagnosis of granulomatosis with polyangiitis (GPA) is difficult, but critical because of its life-threatening fulminant nature when untreated.
- ▶ Bilateral ocular inflammation, along with systemic symptoms, is a red flag for initiation of systemic autoimmune and infectious disease work-up.
- ▶ Consider GPA in the differential when a patient presents with eye disease in the setting of decreased renal function, pulmonary abnormalities or chronic upper respiratory symptoms.
- ▶ Because eye disease is common in GPA, multispecialty collaboration in the care of GPA should include ophthalmologists.

presentations being orbital, scleral/episcleral and corneal inflammatory disease. Other ocular manifestations include uveitis, dacryoadenitis, conjunctivitis, retinal vasculitis and optic neuropathy. In severe cases, particularly with delayed diagnosis or inadequate treatment, there may be vision loss or blindness.^{1 11}

Without systemic treatment, ocular disease may be recurrent whenever ocular treatment is tapered. However, ocular involvement on its own is uncommon in GPA, so treatment of ocular symptoms is usually in the context of systemic treatment. Initial systemic treatment typically includes a combination of a corticosteroid such as prednisone and an immunomodulating agent such as cyclophosphamide. Corticosteroids alone may worsen morbidity. Once the disease is in remission, treatment is typically transitioned to azathioprine or methotrexate for maintenance therapy.^{11 12} Today, GPA is a very treatable, although incurable, disease. Untreated disease carries 82% mortality, but that improves with treatment to 12% at 5 years.⁹

Ocular inflammation, along with systemic symptoms as in this case, is a red flag for initiation of systemic investigation for underlying disease. Although ocular inflammation is very common, the differential for iritis is narrower. Iritis is often idiopathic or due to HLA-B27-associated arthropathies (human leukocyte antigen-B27). However, in the setting of renal dysfunction and ocular inflammation, the differential is narrowed further and should include GPA and other systemic autoimmune/inflammatory and atypical infectious conditions. Multispecialty collaboration including ophthalmologists is critical in the diagnosis of GPA and other life-threatening systemic illnesses.

Acknowledgements Facilities and resources were provided by VAWNYHS.

Contributors SPP, CIT and LAM contributed to the conception, data collection and data interpretation of this case report. SPP, CIT and MJB drafted the manuscript. SPP and MJB were involved in critical revision of the manuscript. All authors approved of the final version for publication.

Funding This work was funded in part by an unrestricted grant to the Department of Ophthalmology, SUNY-University at Buffalo, from Research to Prevent Blindness, New York, NY.

Disclaimer The opinions expressed herein do not necessarily represent those of the Veterans Administration or the US government.

Competing interests SPP is a consultant to Novartis for expertise unrelated to the topic of this manuscript.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Sadiq SA, Jennings CR, Jones NS, *et al.* Wegener's granulomatosis: The ocular manifestations revisited. *Orbit* 2000;19:253–61.
- 2 Mackensen F, Billing H. Tubulointerstitial nephritis and uveitis syndrome. *Curr Opin Ophthalmol* 2009;20:525–31.
- 3 Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. *Surv Ophthalmol* 2001;46:195–208.
- 4 Rathinam SR. Ocular manifestations of leptospirosis. *J Postgrad Med* 2005;51:189–94.
- 5 Raja H, Starr MR, Bakri SJ. Ocular manifestations of tick-borne diseases. *Surv Ophthalmol* 2016;61:726–44.
- 6 Solans-Laqué R, Fraile G, Rodríguez-Carballeira M, *et al.* Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides: Impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity. *Medicine* 2017;96:e6083.
- 7 Rao JK, Allen NB, Feussner JR, *et al.* A prospective study of antineutrophil cytoplasmic antibody (c-ANCA) and clinical criteria in diagnosing Wegener's granulomatosis. *Lancet* 1995;346:926–31.
- 8 Finkelman JD, Lee AS, Hummel AM, *et al.* ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. *Am J Med* 2007;120:643.e9–643.e14.
- 9 Fauci AS, Haynes BF, Katz P, *et al.* Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983;98:76–85.
- 10 Jiang B, Zhao YY, Wei SH. Granulomatosis with polyangiitis: the relationship between ocular and nasal disease. *Ocul Immunol Inflamm* 2013;21:115–8.
- 11 Tarabishy AB, Schulte M, Papaliodis GN, *et al.* Wegener's granulomatosis: clinical manifestations, differential diagnosis, and management of ocular and systemic disease. *Surv Ophthalmol* 2010;55:429–44.
- 12 Kubaisi B, Abu Samra K, Foster CS. Granulomatosis with polyangiitis (Wegener's disease): An updated review of ocular disease manifestations. *Intractable Rare Dis Res* 2016;5:61–9.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow