

# Recalcitrant infective scleritis masquerading an autoimmune necrotising scleritis: a primary presentation of biopsy-proven granulomatosis with polyangiitis

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## SUMMARY

Infectious scleritis is a rare but important cause of scleral inflammation. It is usually associated with an underlying ocular (prior ocular surgery or trauma) or systemic risk factor. A 53-year-old apparently systemically healthy woman presenting with spontaneous-onset pain, redness and watering in the left eye for 10 days was diagnosed with culture-proven *Pseudomonas aeruginosa* anterior scleritis. However, she was non-responsive to organism-sensitive antibiotics and scleral graft was performed twice, which showed graft re-infection. On repeated extensive systemic evaluations, the patient was diagnosed with biopsy-proven granulomatosis with polyangiitis (GPA). The patient was started on mycophenolate mofetil for both induction and maintenance phases and showed dramatic improvement with no recurrence till 1 year follow-up. High index of suspicion for autoimmune disorders, especially GPA, must be maintained for unilateral relentless infective scleritis masquerading as autoimmune necrotising scleritis. Mycophenolate mofetil holds a promising role for inducing as well as maintaining disease remission in ocular GPA.

## BACKGROUND

Infectious scleritis is a rare but important cause of scleral inflammation, and *Pseudomonas aeruginosa* is the most common organism associated with it. The disease carries a grave prognosis, and the majority of cases entail surgical intervention alongside aggressive medical therapy.<sup>1–2</sup> Recurrences may be infrequently noted after cessation of the treatment and thereby necessitate prolonged close observation despite clinical resolution.

While infectious scleritis is usually associated with an underlying ocular (previous ocular surgery or trauma) or systemic (diabetes and liver disease) risk factor, we report a case of spontaneous-onset unilateral relentless bacterial scleritis masquerading as necrotising scleritis, proven to be granulomatosis with polyangiitis (GPA) on inexhaustive systemic evaluation and which responded dramatically to systemic mycophenolate mofetil (MMF).<sup>1–5</sup>

## CASE PRESENTATION

A 53-year-old apparently systemically healthy woman presented with a history of pain, redness and watering in the left eye for 10 days. There was no history of long-standing pain, inflammation

or use of topical steroids or non-steroidal anti-inflammatory drugs. Ocular examination revealed a visual acuity of 6/18, a 6 mm×5 mm oval-shaped multifocal abscess (extending diagonally from 10 o'clock to 2 o'clock) in the superonasal part of anterior sclera abutting the limbus along with its localised thinning and ectasia ([figure 1a](#)), anterior chamber reaction of 2+, normal intraocular pressure and a normal posterior pole in the left eye. The right eye appeared normal.

## INVESTIGATIONS

Microbiological evaluation of scleral scraping specimens revealed that *P. aeruginosa* was sensitive to polymyxin B and resistant to moxifloxacin. B-scan ultrasound was anechoic in the left eye with no peripheral retinal lesions. An urgent referral with an experienced immunologist was promptly sought and systemic evaluation was undertaken to rule out autoimmune necrotising scleritis, which revealed a normal blood profile ([table 1](#)).

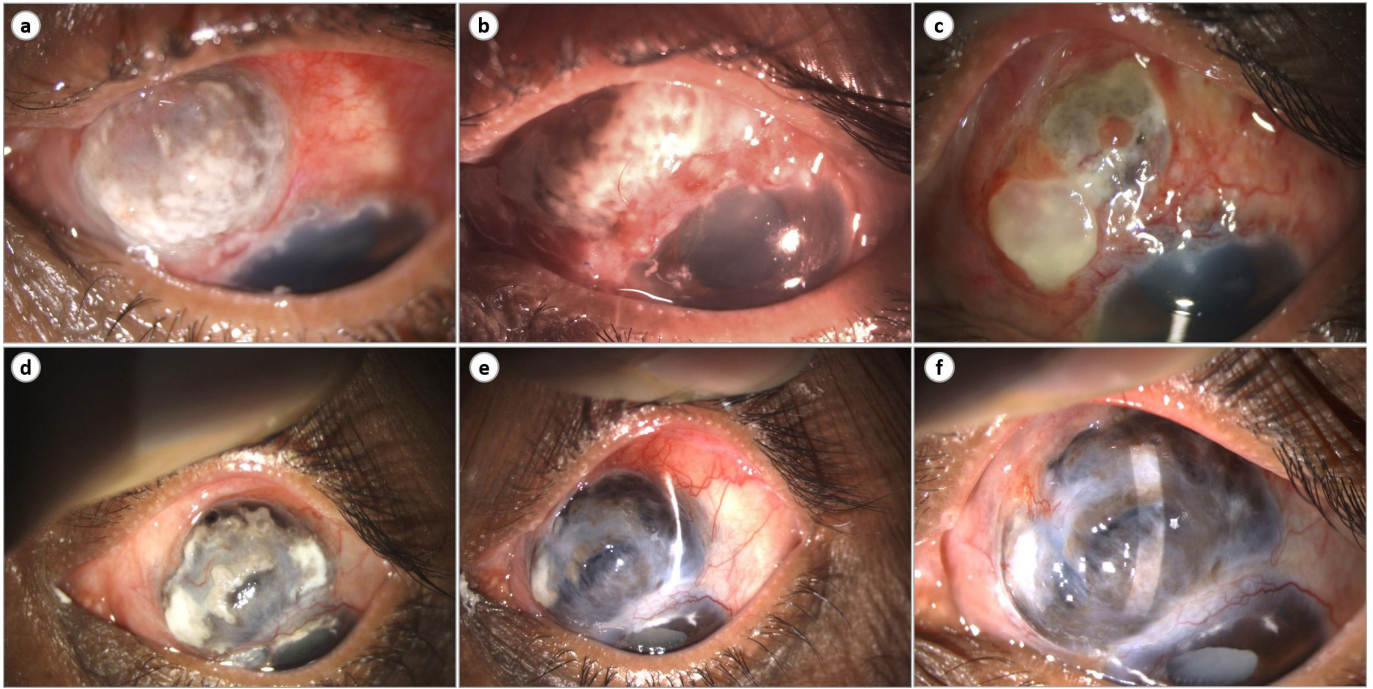
## TREATMENT

Based on the above findings, both topical (10 000 IU every 2 hours) and intravenous polymyxin B (10 000 IU/kg, two times per day) and concentrated cefazolin 5% (two hourly) and homatropine 2% (four times per day) were started. Even though we suspected autoimmune scleritis, we did not start systemic steroids at this time due to a negative systemic profile and a positive microbiological profile, based on the advice of the immunologist. In lieu of worsening ocular condition ([figure 1b](#)), absence of co-existent organisms on repeat scraping and confocal microscopy and normal systemic profile, written informed consent was obtained and a scleral patch graft with a cadaveric donor was performed 4 days after commencing treatment. After an initial period of clinical improvement for 4 weeks, graft infection by the same organism and partial graft melt with surrounding scleral melt were noted ([figure 1c](#)). Again, the patient did not report any systemic complaints and had a normal systemic profile. A repeat patch graft was performed under the cover of systemic and topical polymyxin B and 3 weeks later recurrent graft infection was noted ([figure 1d](#)). However, a repeat systemic profile this time revealed a raised erythrocyte sedimentation rate (ESR) and C reactive protein (CRP). On collaboration with our immunology team,



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**Figure 1** Clinical photographs showing multifocal scleral abscess at presentation (A); status quo after 4 days of treatment (B); recurrent infection after first (C) and second (D) scleral grafts; resolution of scleral infection and inflammation after 8 weeks (E) and 1 year of starting mycophenolate mofetil (F).

contrast-enhanced CT imaging of the orbit, paranasal sinuses, head, chest and abdomen was undertaken and a wedge-shaped hypodense lesion in the lower pole of right kidney was detected (figure 2a). On performing a renal biopsy, this lesion demonstrated necrotising granulomatous inflammation involving tubulointerstitium and the surrounding capsule with focal vasculitis in the capsular region (figure 2b–d), negative staining for acid fast bacilli and later, a negative fungal and mycobacterial culture.

#### OUTCOME AND FOLLOW-UP

A diagnosis of GPA was confirmed and the patient was prescribed intravenous methylprednisolone (1g  $\times$  3 days), polymyxin B (10 000 IU/kg two times per day  $\times$  3 days), oral MMF (1.5 g two times per day) along with vitamin C (400 mg four times per day), doxycycline (100 mg two times per day) along with topical polymyxin B (10 000 IU/kg two times per day) two hourly, moxifloxacin hydrochloride 0.5% (four times per day), prednisolone phosphate 1% (hourly) and homatropine 2% (four times per day) in the induction phase. The patient was shifted to oral steroids (prednisolone phosphate 60 mg one time per day) after 3 days (remaining drugs were continued unchanged) and resolution of scleral inflammation and epithelialisation of the scleral surface were observed at 8 weeks follow-up (figure 1e). During the maintenance phase, oral and topical steroids were tapered, and the patient was continued on MMF (1g two times per day). No recurrence was noted till 1-year follow-up (figure 1f). Patient's systemic profile including ESR and CRP also remained within normal limits.

#### DISCUSSION

GPA, previously known as Wegener's granulomatosis, is a rare systemic disorder associated with necrotising granulomatous inflammation of small-sized and medium-sized blood vessels.<sup>3–6</sup> It majorly affects the upper and the lower airways and kidneys, which are also the most common reasons for seeking medical

care. Inflammatory eye disease, as a result of focal vasculitis, thrombosis or ischemia, is reported to occur in 30%–60% patients over the entire course of GPA and ophthalmic disease may be its primary manifestation in 8%–20% cases.<sup>3–6</sup> While scleritis in GPA is usually non-infectious (nodular, diffuse or necrotising) and severe in nature, to the best of our knowledge, recalcitrant infective scleritis as its primary presentation is being reported for the first time.

The sequence of events in our case (culture-proven infective scleritis with normal systemic profile, scleral graft, graft infection with normal systemic profile, repeat scleral graft, graft infection with elevated CRP and ESR, radiologic evaluation, renal biopsy-proven GPA, controlled on immunosuppressants) suggests that our case was primarily an autoimmune necrotising scleritis with secondary bacterial infection. At the onset, the diagnosis, although highly suspected, was missed due to a normal blood profile and positive microbiological growth. This was also the reason for the delay in starting on systemic steroids in our case. Diagnosis of GPA was particularly challenging in our case due to the absence of characteristic non-ocular complaints (upper/lower respiratory tract, kidney) and normal serum levels of antineutrophil cytoplasmic antibodies (ANCA). However, due to no-response to organism-sensitive antibiotics, a high index of suspicion was maintained for autoimmune scleritis and repeated systemic evaluations were undertaken for the patient. As soon as an elevated ESR and CRP were detected, a radiologic imaging was undertaken which further facilitated renal biopsy thereby establishing the correct diagnosis of GPA. It is evident from the present chronology that repeated haematological work-ups play a crucial role in unmasking a serious life-threatening autoimmune disorder in patients presenting with spontaneous onset recalcitrant infective scleritis. Additionally, elevated ANCA levels may not be detected in all cases of GPA and eyes with high index of clinical suspicion mandate radiological imaging for localising systemic lesions to further guide a tissue biopsy for diagnosis of GPA.

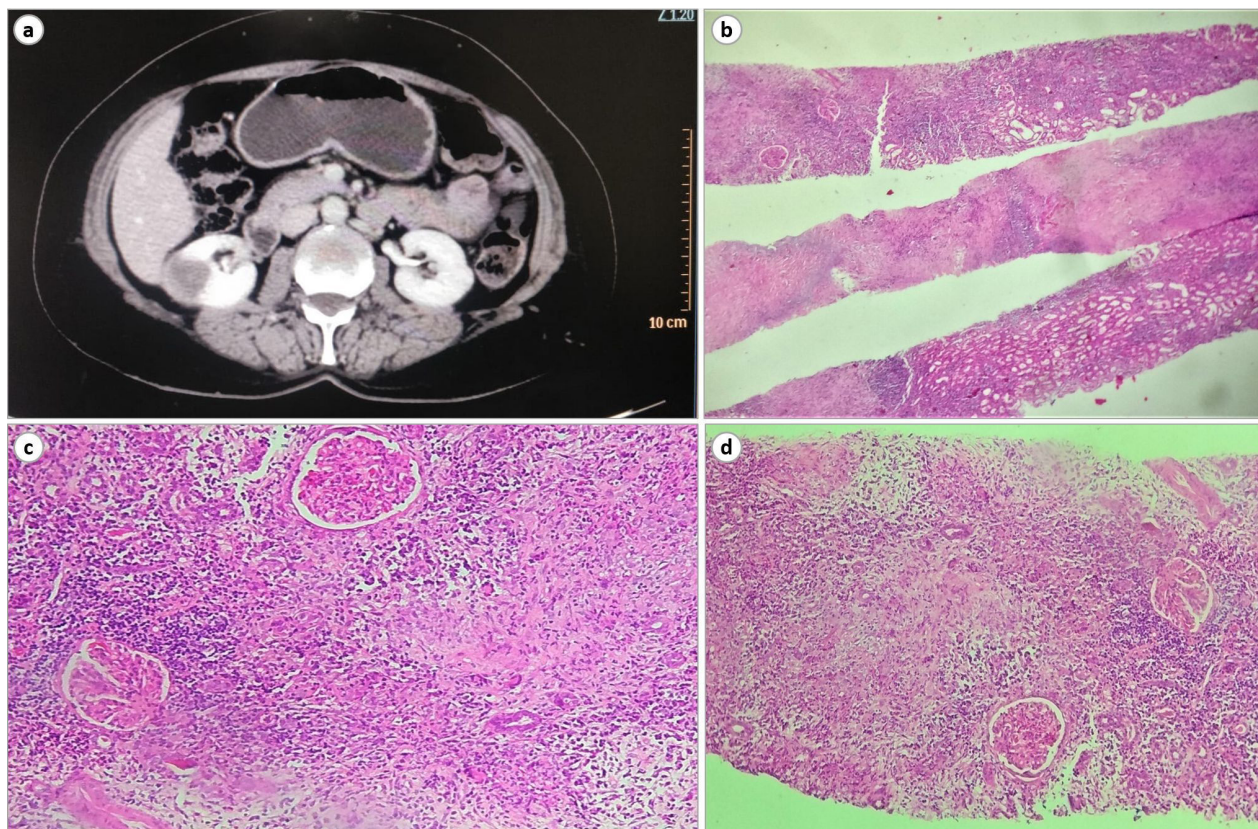
**Table 1** Systemic profile of the patient

Parameter (units)	At primary presentation	After first scleral graft	After second scleral graft	At 1 year	Range
FBS (mg/dL)	93	92	94	89	70–100
Urea (mg%)	12	10	11	12	10–50
Creatinine (mg%)	0.6	0.5	0.6	0.7	0.5–1.8
Calcium (mg%)	9.6	9.7	9.5	10.0	9–11.5
Phosphate (mg%)	3.9	3.7	3.9	3.8	2.5–4.5
Uric acid (mg%)	5.4	5.4	5.4	5.5	2.5–6
Sodium (mEq/L)	141	135	138	140	130–149
Potassium (mEq/L)	4.1	4.06	4.12	4.11	3.5–5
Chloride (mEq/L)	102	104	104	103	101–109
Bilirubin (total) (mg%)	0.4	0.39	0.50	0.4	0.1–1
UB (mg%)	0.34	0.35	0.33	0.38	0.2–0.8
CB (mg%)	0.05	0.04	0.04	0.03	0–0.20
Total protein (mg%)	6.7	6.5	6.6	6.6	6.6–8.7
Globulin (mg%)	2.3	2.4	2.3	2.5	3.8–4
Albumin (mg%)	4.4	4.1	4.3	4.1	4–5.5
AST (IU/L)	15	16	16	17	0–50
ALT (IU/L)	14	10	13	12	0–50
ALP (IU/L)	188	171	169	187	80–240
Haematocrit (%)	34.8	35	35.2	34.5	36–46
Haemoglobin (g/L)	131	133	132	133	120–150
RBC (no. of cells in 10 <sup>12</sup> /L)	4.17	4.16	4.18	4.07	4–11
WBC (no. of cells in 10 <sup>9</sup> /L)	11.600	11.800	11.980	11.760	4.000–11.000
Neutrophils (%)	64	57	63	62	45%–70%
Eosinophils (%)	2	3	2	2	0%–5%
Monocytes (%)	4	4	5	4	2–10
Lymphocytes (%)	34	34	36	35	20–40
Platelet (no. of cells in 10 <sup>6</sup> /L)	323	325	320	330	150–400
ESR (mm/hour)	14	14	35	15	0–15
CRP (mg/dL)	1.4	1.8	6.4	5.4	0–6.00
c-ANCA	Negative	Negative	Negative	Negative	<1/20
p-ANCA	Negative	Negative	Negative	Negative	<1/20
ANA HEp-2	Negative	Negative	Negative	Negative	0-1/40
S ACE (μL)	10	8	12	12	8–50
Anti-CCP antibodies	5	7	6	6	0–20
RF (IU/mL)	1.11	1.34	1.41	1.42	0–20
HBsAg	Negative	Negative	Negative	Negative	–
Anti-HCV antibodies	Negative	Negative	Negative	Negative	–
VDRL assay	Negative	Negative	Negative	Negative	–
PT (s)	11.8	11.6	11.4	11.7	11–14
INR	1.076	1.075	1.065	1.071	<1.1
CXR	NAD	NAD	NAD	NAD	–
Urine analysis	NAD	NAD	NAD	NAD	–
Scleral scraping	<i>Pseudomonas aeruginosa</i>	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	Not performed	–
Blood culture	Sterile	Sterile	Sterile	Not performed	–
Mantoux	5 mm	–	–	–	–
2D Echocardiogram	Normal study	–	–	–	–

ALP, alkaline phosphatase; ALT, alanine transaminase; ANA HEp-2, antinuclear antibodies against human epithelial cells; ANCA, antineutrophil cytoplasmic antibodies; AST, aspartate transaminase; CB, conjugated bilirubin; CCP, anticyclic citrullinated peptide; CRP, C reactive protein; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INR, international normalised ratio; NAD, no abnormality detected.; PT, prothrombin time; PT, prothrombin time; RBC, red blood cells; RF, rheumatoid factor; UB, unconjugated bilirubin; VDRL, venereal disease research laboratory; WBC, white blood cells.

While necrotising scleritis can be an indicator of both morbidity and mortality in GPA, absence of systemic manifestations does not represent a systemically quiet disease and may be associated with subclinical inflammation (renal mass in our case). We believe that coexistent necrotising scleritis-induced scleral ischaemia prevented the healing of infective scleritis

by limiting the penetration of organism-sensitive antibiotics besides causing poor uptake of scleral graft and culminating in recurrence of graft infection in our case. Appropriate control of ongoing inflammation is, therefore, mandatory before performing a patch graft in eyes with autoimmune scleritis to prevent graft failure and re-infection. Hence, an aggressive



**Figure 2** Wedge-shaped hypodense lesion in the lower pole of right kidney (A); necrotising granulomatous inflammation involving tubulointerstitium and the surrounding capsule with focal vasculitis in the capsular region (B–D).

systemic and topical immunosuppression were advocated in our patient.

MMF is a potent inhibitor of purine synthesis and it suppresses proliferation of T and B lymphocytes by hydrolysing mycophenolic acid. It is an effective and well-tolerated immunosuppressive agent that has found its role in the maintenance phase of several autoimmune disorders including GPA and in decreasing the rejection rates of solid organ transplants including high-risk corneal grafts.<sup>7–9</sup> Due to its low side-effect profile, it holds a promising alternative role to other inducing agents (mycophenolate versus cyclophosphamide (MYCYC) trial) such as methotrexate, azathioprine and cyclophosphamide in GPA.<sup>10</sup> In our case, it was started as an inducing agent at the first diagnosis of GPA after collaboration with our immunology team. Although our patient reported minor side effects such as abdominal pain and diarrhoea in the beginning, the drug appeared to be well tolerated in the long run with no ocular relapses or deranged systemic profile noted at 1-year follow-up. However, larger studies are required to validate these results.

As it is already known that peripheral ulcerative keratitis and anterior uveitis are poor prognostic indicators of ocular GPA and as globe perforation (due to structurally weak sclera) and cataract and glaucoma (due to chronic inflammation or corticosteroid treatment) could ensue with time, our patient was advised polycarbonate protective glasses and was also maintained on life-long ophthalmologic follow-up, in collaboration with an immunologist.

To conclude, the present case is being reported such that the clinicians maintain a high index of suspicion for autoimmune necrotising scleritis, especially secondary due to GPA, in all cases with relentless infective scleritis. Normal ANCA levels may

not refute the diagnosis and repetitive in exhaustive systemic work inclusive of radiologic imaging, and tissue biopsy should be undertaken in eyes with high index of clinical suspicion for establishing correct diagnosis of GPA. MMF appears to be a well-tolerated agent and holds a promising role for inducing as well as maintaining disease remission in ocular GPA.

### Learning points

- ▶ Autoimmune necrotising scleritis can rarely present as relentless infective scleritis leading to poor uptake of scleral patch grafts and repeated graft infections
- ▶ A high index of suspicion needs to be maintained for autoimmune necrotising scleritis, especially associated with granulomatosis with polyangiitis (GPA), in all cases with recalcitrant infective scleritis
- ▶ Normal antineutrophil cytoplasmic antibody levels do not refute diagnosis of GPA, and radiologic imaging and subsequent biopsy must be undertaken for appropriate diagnosis in eyes with high index of clinical suspicion.
- ▶ Mycophenolate mofetil appears to be a well-tolerated agent and holds a promising role for inducing as well as maintaining disease remission in ocular GPA.

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