

## Scleritis and sclerokeratitis associated with IgA vasculitis: A case series

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## ABSTRACT

**Purpose:** To describe a case series of scleritis associated with IgA vasculitis (IgAV) at a tertiary referral center.  
**Observations:** Three men with scleritis associated with IgAV were identified: one with anterior scleritis alone, one with anterior scleritis and peripheral ulcerative keratitis (sclerokeratitis), and one with anterior and posterior scleritis. Visual acuity was preserved except from the patient who developed posterior scleritis. Ocular pain was the main symptom at presentation. All patients had a previous history of palpable purpura, but only one was aware of his underlying IgAV. Laboratory results revealed microhematuria and proteinuria with normal urinary  $\beta_2$  microglobulin levels and negative serum ANCA. Skin or kidney biopsy demonstrated leukocytoclastic vasculitis or glomerulonephritis with dominant IgA immune deposits.  
**Conclusions and Importance:** Although uncommon, IgAV should be included in the differential diagnosis of anterior scleritis alone or associated with peripheral ulcerative keratitis or posterior scleritis, even in systemically asymptomatic patients. Urinalysis should not be underestimated in assessment of scleritis to detect early stages of glomerular disease. Scleritis may be the first manifestation whose study may lead to the diagnosis of IgAV. Multidisciplinary approach is necessary to prevent irreversible organ damage such as renal failure.

## 1. Introduction

Scleritis is a sight-threatening ocular condition that can occur as an isolated phenomenon or associated with immune diseases or infections. Systemic autoimmune or vasculitis diseases can be found in 48% of cases.<sup>1</sup> Immune-complex deposition in the vessel walls is suggested to play an important role in the pathogenesis of scleritis.<sup>2,3</sup> Immunoglobulin A vasculitis (IgAV) is an immune complex-mediated disease affecting small vessels (predominantly capillaries, venules, or arterioles) with IgA1-dominant immune deposits presenting with purpura, arthralgias, abdominal pain, and renal disease as the classic tetrad.<sup>4</sup> A classification criteria for IgAV proposed in 2010 by the European League Against Rheumatism/Pediatric Rheumatology International Trials Organisation/Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) considered the presence of purpura or petechiae, mainly in lower limbs, as mandatory criterion together with at least one of the

other four criteria: arthritis/arthralgia, abdominal pain, glomerular involvement (proteinuria and/or hematuria), and IgA deposits in a tissue biopsy (skin or kidney) associated with leukocytoclastic vasculitis or proliferative glomerulonephritis. These criteria provide 100% sensitivity and 87% specificity for classifying patients with IgAV.<sup>5</sup> Purpura is the most common manifestation; skin biopsy shows leukocytoclastic vasculitis, an inflammation of the small blood vessels, most prominently in the postcapillary venules.<sup>6</sup> Gastrointestinal tract and renal involvement represent the main causes of morbidity and mortality; in a large study of 250 adults with IgAV, 11% of patients reached end-stage renal disease, 13% had several renal failure, and 14% had moderate renal failure.<sup>7</sup> Treatment remains controversial because disease course ranges from spontaneous remission to end-stage renal disease and the initial presentation does not correlate with the outcome.<sup>8</sup>

Ocular involvement in patients with IgAV is rare: anterior uveitis and episcleritis are the most common associations reported in literature.<sup>9</sup>

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However, reports of scleritis and IgAV are very scarce.<sup>10–12</sup>

Herein, we report a case series of three patients presenting with anterior scleritis alone or associated with peripheral ulcerative keratitis (PUK) or posterior scleritis, in which urinalysis was essential to reveal the undetected nephropathy. IgAV was finally confirmed by tissue biopsy and a multidisciplinary assessment was implemented to prevent further organ damage.

## 2. Methods

The electronic health records were reviewed of patients with scleritis associated with IgAV seen at our tertiary referral center from 2015 to 2020. Collected data included age, gender, ophthalmologic examination, and ancillary tests. A comprehensive medical and ophthalmic history was elicited in each patient. Ophthalmologic examination included best-corrected visual acuity (BCVA, Snellen), intraocular pressure (IOP), slit-lamp anterior segment assessment, and dilated fundus examination. Anterior segment photographs and anterior and posterior segment swept-source optical coherence tomography (SS-OCT, Triton, Topcon) images of the altered sclera were analyzed at presentation and follow up. Anterior chamber activity was graded using SUN (Standardization of Uveitis Nomenclature) scale.<sup>13</sup> Extensive workup was undertaken in all patients with complete blood counts, serum chemistry analysis, serum antineutrophil cytoplasmic antibodies (ANCA), urinalysis, and  $\beta_2$  microglobulin in urine. Additional testing was carried out when positive signs or symptoms were found in the review of systems to rule out infectious or autoimmune diseases. IgAV was confirmed based on clinical and histological findings. A multidisciplinary approach with autoimmune disease and nephrology departments was required to assess systemic manifestations.

## 3. Findings

Three patients with anterior scleritis associated with IgAV were identified: one presenting with anterior scleritis alone, one combined with PUK (sclerokeratitis) and one combined with posterior scleritis. Median age was 45 years-old (range: 42–55) and all were male.

All patients had a past history of palpable purpura affecting the lower extremities. Final diagnosis of leukocytoclastic vasculitis was confirmed after skin biopsy in two cases. However, IgA deposits in direct immunofluorescence were demonstrated only in one case (Case 1). IgAV was the underlying disease in the three cases, as confirmed by kidney (two cases) or skin biopsy (one case).

At the time of the scleral inflammation, one patient was already on treatment with systemic immunosuppressive therapy (azathioprine, dapsone and prednisone) to control extra-renal IgAV manifestations (leukocytoclastic vasculitis and arthritis).

Interestingly, all cases developed systemic manifestations before ocular manifestations occurred: IgA nephritis, 30 years prior, and palpable purpura, three years prior (Case 1); leukocytoclastic vasculitis, two years prior (Case 2); leukocytoclastic vasculitis, arthritis, and abdominal pain, two years prior (Case 3).

All patients presented with ocular pain as the major symptom. Slit-lamp examination showed mild anterior chamber cells (SUN scale) only in the patient with sclerokeratitis (Case 2). BCVA was preserved, except from the patient who developed posterior scleritis (Case 3). Scleral thickness measured by SS-OCT was increased in the affected areas.

Regarding clinical course, all cases showed flares of alternating anterior scleritis despite oral nonsteroidal anti-inflammatory drugs (NSAIDs). Urinary  $\beta_2$  microglobulin levels and serum ANCA were normal in all cases.

Baseline ocular and renal characteristics are outlined in the Table. Individual cases are briefly described below:

### 3.1. Case 1

A 42-year-old man presented with ocular pain in his right eye (OD) at our emergency department. He was a former heavy smoker. Past medical history through shared electronic health record revealed a kidney biopsy during his childhood consistent with IgAV. In addition, he suffered from palpable purpuric lesions on his right lower extremity three years prior. Slit lamp examination showed diffuse anterior scleritis OD in the temporal inferior quadrant (Fig. 1A). BCVA and IOP were preserved. No anterior chamber cells were detected and funduscopy was normal. He was diagnosed with diffuse anterior scleritis OD and he was subsequently started on oral ibuprofen 600mg tid improving at one week (Fig. 1B) and resolving at one month (Fig. 1C). Further investigations revealed serum creatinine of 1,3 mg/dL (range: 0,3–1,3), microhematuria, and proteinuria (666 mg/d; range: <150). Accordingly, he was referred to nephrology department. A new kidney biopsy confirmed the suspected diagnosis (Fig. 1D and E) and he was started on an oral angiotensin receptor blocker (ARB) for nephroprotection. Anterior segment SS-OCT revealed scleral and episcleral thickening (Fig. 1F). During follow up, recurrent episodes (twice yearly) of alternating anterior scleritis were noted with good response to oral ibuprofen. He continued follow up with nephrology department.

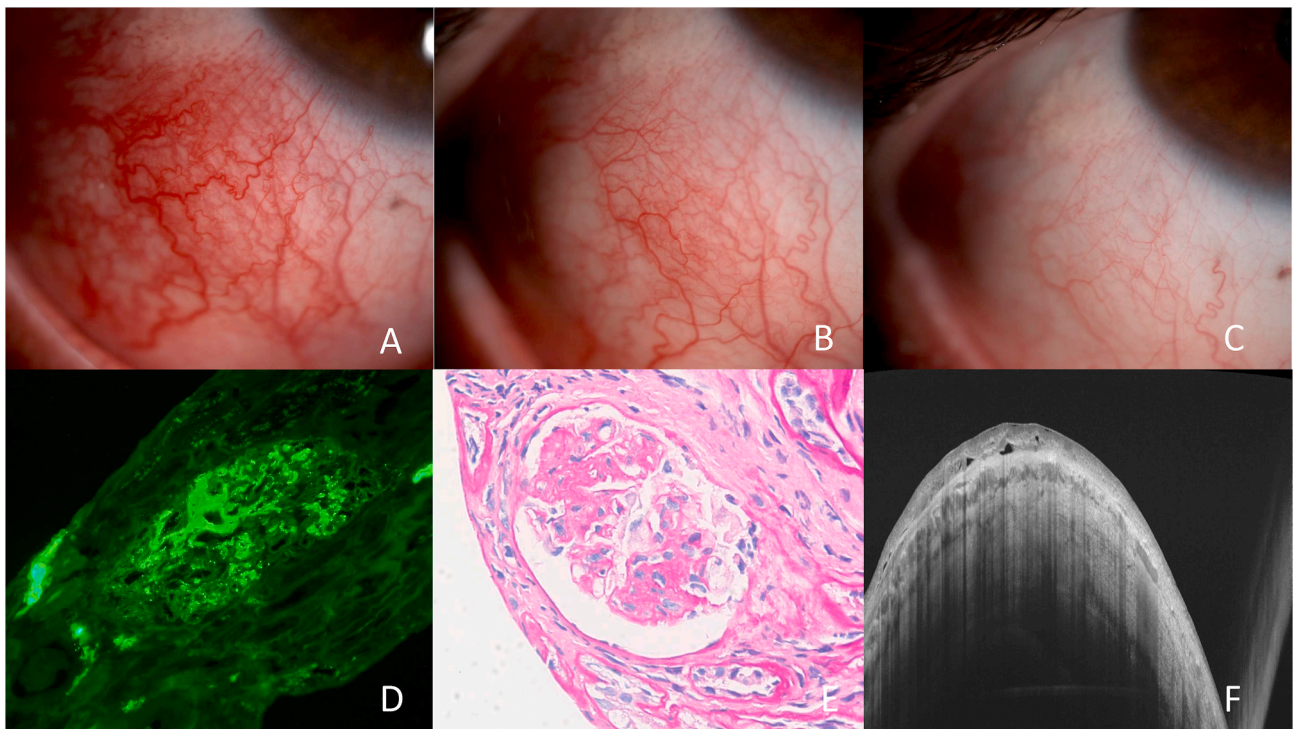
### 3.2. Case 2

A 55-year-old man presented with painful red OS lasting for five days. He was a current smoker. BCVA was 1.0 and IOP was normal in both eyes. His past medical history revealed an isolated episode of leukocytoclastic vasculitis two years prior.

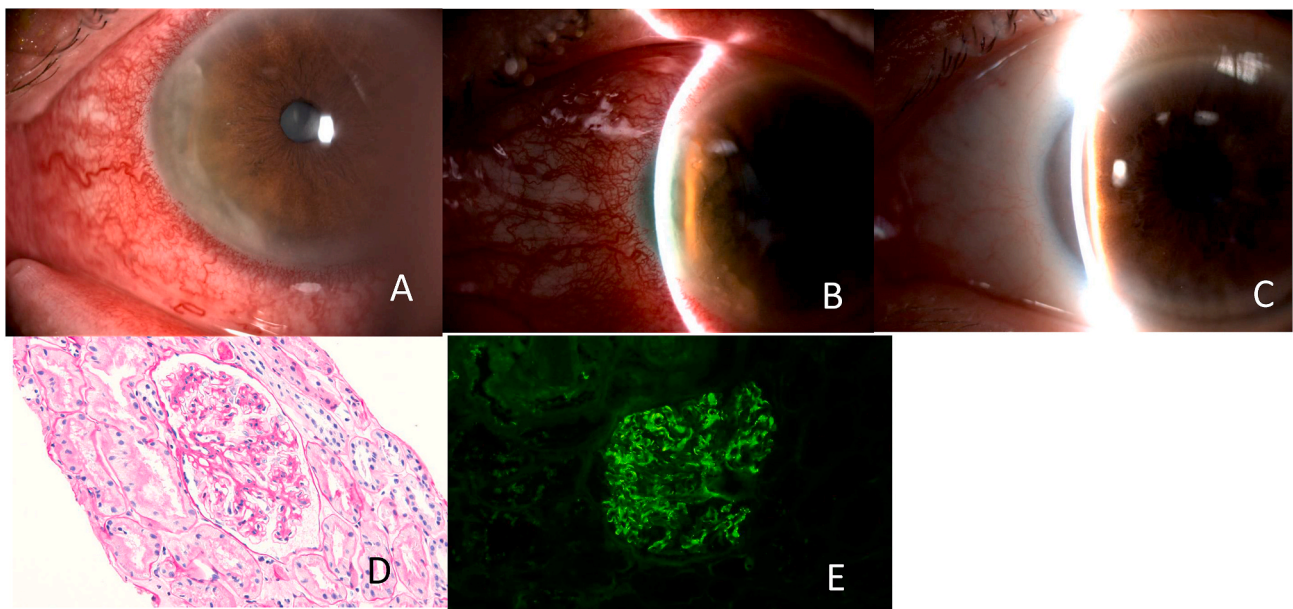
Ophthalmologic examination revealed an inflamed diffuse anterior sclera associated with PUK in OS (Fig. 2A and B). Anterior chamber cell grading was 0.5+ with no other remarkable findings. Funduscopy was normal. He was diagnosed with sclerokeratitis (scleritis and PUK) being started on topical dexamethasone every other hour combined with fluoroquinolone drop qid and ibuprofen 600 mg tid. At one week follow up he showed a good clinical response (Fig. 2C). Complete blood count, liver and renal function, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were normal; rheumatoid factor (RF) and antineutrophil cytoplasmic antibodies (ANCA) were negative. Antinuclear antibody (ANA) was 1:640, serum IgA was increased to 5 mg/dL (range: 0,66–3,65). Syphilis and tuberculosis were excluded. Urinalysis showed marked proteinuria (2140 mg/d; range <150) along with microhematuria. IgAV with kidney involvement was suspected and eventually confirmed by kidney biopsy (Fig. 2D and E). Lastly, he was diagnosed with scleritis in the fellow eye, requiring a new onset of oral NSAIDs. He continued follow up with autoimmune disease and nephrology departments.

### 3.3. Case 3

A 45-year-old man, current smoker, with prior history of IgAV, was referred to our clinic for recurrent episodes of redness and ocular pain in both eyes. At this time, he was treated with azathioprine 50mg/day, prednisone 10mg/day and dapsone 100mg/day for his IgAV systemic involvement (leukocytoclastic vasculitis and arthritis). Laboratory tests showed a glomerular filtration rate (GFR) > 60 mL/min (normal range >90mL/min), and a non nephrotic proteinuria and microhematuria (Table). On examination, BCVA was preserved and IOP was within normal range. Slit-lamp examination showed bilateral diffuse anterior scleritis (Fig. 3A). Anterior chamber was quiet. Funduscopy did not show posterior involvement. He was diagnosed with bilateral diffuse anterior scleritis and was started on ibuprofen 600mg tid. However, subtenon injection of triamcinolone acetonide was required to control scleral swelling (Fig. 3B). During follow up, he suffered from relapsing episodes of anterior scleritis once to twice yearly. Recently, he presented with bilateral anterior scleritis associated with posterior scleritis in OS.



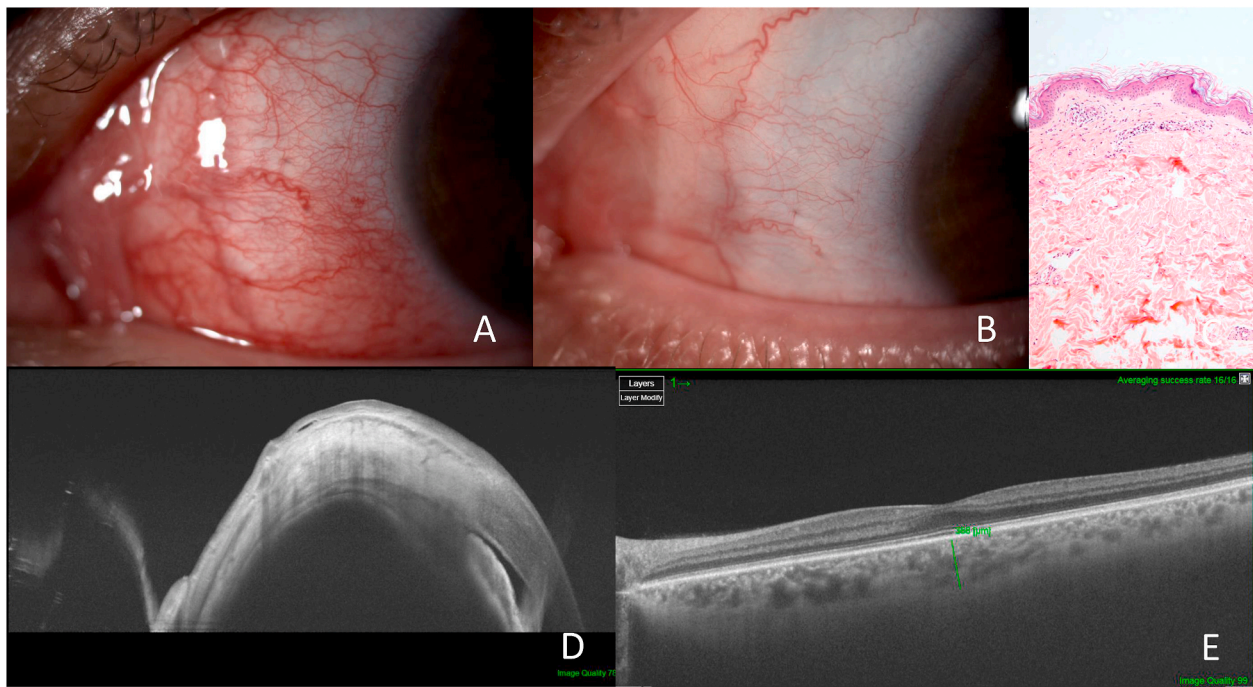
**Fig. 1.** Ophthalmologic examination and kidney biopsy of anterior scleritis associated with IgA vasculitis. Right eye. Slit lamp photograph with x16 magnification showing diffuse non-necrotizing temporal inferior scleral inflammation, at presentation (A) and follow up: one week (B) and one month (C) after adequate treatment. D: Pathology of kidney biopsy: Immunofluorescence (x200) showed strong granular mesangial staining for IgA (+++). E: Pathology of kidney biopsy (400xPAS staining): Light microscopy of a glomerulus showing increased mesangial matrix with mild mesangial hypercellularity. F: anterior segment SS-OCT showing scleral and episcleral thickening.



**Fig. 2.** Ophthalmologic examination and kidney biopsy of anterior scleritis and peripheral ulcerative keratitis (sclerokeratitis) associated with IgA vasculitis. Left eye slit-lamp photographs showing diffuse non-necrotizing scleritis with peripheral ulcerative keratitis (A) and subsequent corneal thinning (B). Intense treatment with topical dexamethasone drops was started with scleral normalization and restored cornea (C) at follow up. (D) Pathology of kidney biopsy (200xPAS staining): Light microscopy of a glomerulus showing mild increased mesangial matrix with mesangial hypercellularity. (E) Pathology of kidney biopsy: Immunofluorescence (x200) showed mesangial staining for IgA (++)

BCVA was 1.0 and 0.8 in OD and OS, respectively. SS-OCT showed increased anterior scleral thickness (Fig. 3D) and choroidal thickness (Fig. 3E) and B-scan ultrasonography revealed the scleral and choroidal thickening and the presence of fluid in the subtenon space. No macular

fold, subretinal fluid or disk edema were detected. Skin biopsy showed vasculitis (Fig. 3C) and deposits of IgA. As agreed by a multidisciplinary committee, he was started on low-dose boluses of oral methylprednisolone (400mg/day for three days) followed by oral prednisone 30 mg/



**Fig. 3.** Ophthalmologic examination and skin biopsy of anterior and posterior scleritis associated with IgA vasculitis. Left eye slit-lamp photographs showing diffuse anterior scleritis in the nasal quadrant (A) at presentation and after adequate treatment (B). Anterior segment SS-OCT revealed scleral and episcleral thickening (D) with intrascleral edema (white arrow) and choroidal thickening (E) as a result of posterior scleritis. (C) Pathology of skin biopsy showing a mild perivascular inflammatory infiltrate predominantly lymphocytic with interstitial foci of karyorexis, occasional eosinophils and erythrocyte extravasation. These findings are consistent with an evolved vasculitis (200xHE staining).

day, and azathioprine 150mg/day. Despite this therapy, two intravenous infusions of rituximab (1000mg, separated by 2 weeks) were required to control his ocular condition. Thereafter, he showed good clinical response with no new flares up to date. He continued follow up with autoimmune disease and nephrology departments.

#### 4. Discussion

Scleritis is a sight-threatening inflammatory eye disease resulting from an identifiable cause in more than half of patients.<sup>1</sup> Although rheumatoid arthritis is the most frequent associated disease, infectious and other autoimmune diseases should be ruled out for a correct therapeutic approach.<sup>1,14</sup>

Regardless of its origin, scleritis pathogenesis involves local vasculitis as a result of immune-complex deposition, among others.<sup>2</sup> Hence, systemic vasculitis, such as IgAV, can be manifested locally in the ocular tissues as scleral inflammation.<sup>2,3</sup> In this regard, IgA immune-complexes and the role of poorly O-galactosylated IgA1 and O-glycan specific antibodies seems to play a crucial role in the pathogenesis of IgAV.<sup>15</sup> IgA immune-complexes results in mesangial cell activation, and release of pro-inflammatory and pro-fibrotic mediators, and complement activation.<sup>15,16</sup> Mesangial and scleral damage in IgAV are suggested to be the result of a unique pathogenic pathway.<sup>10–12,17</sup> For that reason, IgA vasculitis should be considered in the differential diagnosis of scleritis/sclerokeratitis.<sup>10–12,17</sup>

Moreover, the preferential deposits of immune-complexes in the anterior sclera compared to the posterior, along with the increased levels of complement at this level-especially surrounding the corneal edge - may explain why anterior scleritis is more frequent than posterior scleritis,<sup>3</sup> and why peripheral cornea (sclerokeratitis) can be involved in the same process.

Two of our patients with scleritis were not aware of their underlying systemic disease in spite that they had previously developed systemic manifestations in different locations (leukocytoclastic vasculitis or

nephritis). As a result of that, they were not correctly assessed by a specialist. For that reason, we consider that our contribution as ophthalmologists was essential to reach the final diagnosis.

Tubulo-interstitial nephritis and uveitis (and/or scleritis) (TINU) and ANCA vasculitis are highlighted as differential diagnoses in scleritis patients with proteinuria and/or hematuria; normal levels of urinary  $\beta_2$  microglobulin and negative serum ANCA may help in the differentiation with IgAV;<sup>18</sup> in addition, tissue biopsy demonstrates the presence of IgA deposits in IgAV. As noted, all of our patients were current or former smokers. Hocevar et al. reported active smoking as a severity factor in IgAV, showing worst prognosis and greater needs of intense immunosuppressive therapy.<sup>19</sup> Concurrently, Booman et al. reported delayed response to treatment in smoking patients with scleritis and thus a need for more intensive therapy.<sup>20</sup>

Oral NSAIDs are considered the first-line therapy for non-necrotizing anterior scleritis.<sup>21</sup> In case of therapeutic failure or active nephropathy, oral glucocorticoids are a well-tolerated strategy that should be closely monitored for short-term management due to ocular and systemic side effects. Topical corticosteroid drops for mild cases with intraocular inflammation might be used in association, but avoided as monotherapy. Long-term management in refractory cases of anterior scleritis may include immunosuppressive agents and biologics.<sup>21,22</sup>

In cases of recurrent anterior scleritis-associated IgAV, we suggest avoiding the long-term exposure of NSAIDs at the expense of glucocorticoids or immunosuppressive agents. Short-term use of NSAIDs in Case 1 and Case 2 did not have any adverse outcome. Interestingly, a recent study on patients with chronic kidney disease showed a modest relationship between the use of NSAIDs (30-day analgesic use reported at annual visits) and adverse outcomes.<sup>23</sup>

In our study, short-term use of NSAIDs was sufficient to control non-complicated anterior scleritis. However, anterior and posterior scleritis in one patient required methylprednisolone boluses. Moreover, in this particular case of recalcitrant scleritis, infusion therapy with rituximab, an anti-CD20 chimeric monoclonal antibody, was started with long-

lasting remission after two separated doses. Prior experience with rituximab in immune-mediated scleritis has reported favorable outcomes with a fair safety profile.<sup>21</sup> Besides, as reported by Hernandez-Rodriguez et al., rituximab should be considered in IgAV as an encouraging alternative by inducing disease remission in patients resistant or refractory to glucocorticoids or other immunosuppressive drugs and in those patients in whom these agents are contraindicated.<sup>24</sup>

Prognosis of renal involvement in IgAV shows that 20–40% will develop end-stage renal failure in 20 years<sup>25</sup>; the sooner the initial diagnosis, the better the long term prognosis, especially in young patients and those with a history of smoking. In this regard, urinalysis is a key tool in the initial assessment of suspected IgAV before other invasive procedures are performed. Regardless the stage of chronic kidney disease, renal function monitoring by a specialist should be carried out.

## 5. Conclusion

Although uncommon, IgAV should be included in the differential diagnosis of anterior scleritis alone or associated with peripheral ulcerative keratitis or posterior scleritis, even in systemically asymptomatic patients. Scleritis may be the first manifestation whose study may lead to the diagnosis of IgAV. Multidisciplinary approach is necessary to prevent irreversible organ damage.

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Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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