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A CHALLENGING CASE SERIES OF OCULAR WEGENER'S GRANULOMATOSIS WITH DIGITAL GANGRENE OF THE LOWER LIMB TOES

Ophthalomology

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ABSTRACT

Wegner's granulomatosis is a rare multisystemic autoimmune granulomatous vasculitic disease, associated with significant morbidity and mortality. Ophthalmic involvement occurs in 28% to 60% of cases and can be the only clinical presentation prior to systemic involvement. We present a rare case series of ocular Wegener's granulomatosis based on the typical feature of nodular scleritis with uveitis along with digital gangrene of the lower limb toes. C-ANCA titer was positive on ELISA and ESR was raised. The patient showed improvement with oral cyclophosphamide and oral steroids. This case series illustrates the importance of considering a diagnosis ofocular Wegener's granulomatosis in patients presenting with digital gangrene.

KEYWORDS

Wegener's granulomatosis; digital gangrene; necrotizing nodular scleritis; Anti PR3cANCA

INTRODUCTION:

Wegener's Granulomatosis (WG) is a severe, granulomatous necrotizing vasculitis which classically affects the upper and lower respiratory tracts and kidneys. Scleritis may be the initial or only presenting clinical manifestation of this potentially lethal disorder [1].

Case 1

A 49-year-old male patient presented with pain, redness and diminution of vision in the left eye along with multiple raised swelling. It was associated with watering, photophobia and swelling of lids. The patient gave a history of fall of insect in the left eye. His right eye was normal on ocular examination with best corrected visual acuity of 6/6, N6 and left eye vision was 6/60, N24 on Snellen's chart. On Slit lamp examination of the anterior segment, the left eye sclera showed multiple nodules measuring 2 X 2mm in size present both nasally and temporally, tender, immobile bluish red in color with slit beam displaced by the nodule (Figure1,2). There was also circumcorneal congestion. The anterior chamber showed a grade 1 flare and few cells. There were also posterior synechiae at 3'0 clock position with no nodule on the iris. His pupil was irregular with a sluggish reaction to light, lens showed pigments over the capsule with Grade- III Nuclear sclerosis. The posterior segment showed no abnormality.

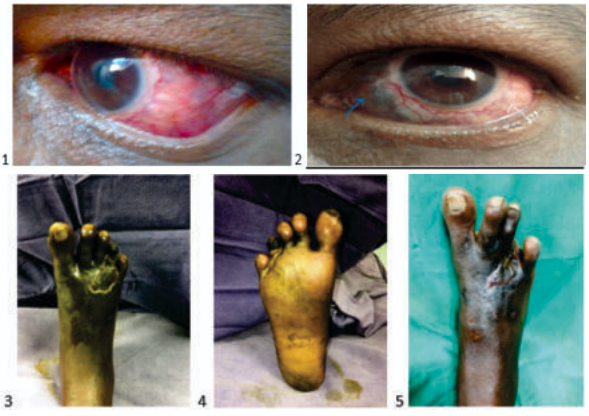
The patient had no history of similar episodes in the past. The patient did not give any history suggestive of rheumatoid arthritis, collagen vascular diseases or any other auto-immune diseases. There was no history of viral infection or chronic infections like tuberculosis, leprosy and syphilis. There was also no history of any skin affections. All other systems like cardiovascular system, respiratory system and musculoskeletal system were evaluated but no abnormality could be detected.

His complete blood count, biochemical profile, renal function test, RBS and a chest radiograph was within normal limits. Urine analysis showed proteinuria (Protein +),USG KUB was done which was normal. ESR was elevated. Mantoux was negative. Urine C/S was sterile.

The patient was started on oral and topical antibiotic drugs presuming it to be a case of infectious scleritis, as there was a history of fall of insect which was misleading along with oral steroids to decrease the inflammation. Along with protein restricted diet and to maintain adequate hydration. On follow up patient showed no improvement, rather he developed further new nodules.

Special investigations like antinuclear antibodies, c- reactive protein and Rheumatoid factor were negative. However, the c-ANCA titer was found to be raised.

Based on the combination of clinical and serological findings a diagnosis of limited ocular Wegener's granulomatosis with anterior uveitis and Renal polyangitis was made. The patient was then started on oral cyclophosphamide 1.5 mg/kg/day (Induction phase) along with oral corticosteroidsat a dose of 1 mg/kg/day under physician guidance until remission. Topically corticosteroid and cycloplegic eyedrops were given in the left eye. On follow-up of 4-5 months, the patient showed improvement with regression of the nodules (figure3).Urine routine microscopy showed no proteinuria. The gangrenous right 3rd toe was amputated and a soft tissue cover was provided using a split-thickness skin graft that eventually healed well.

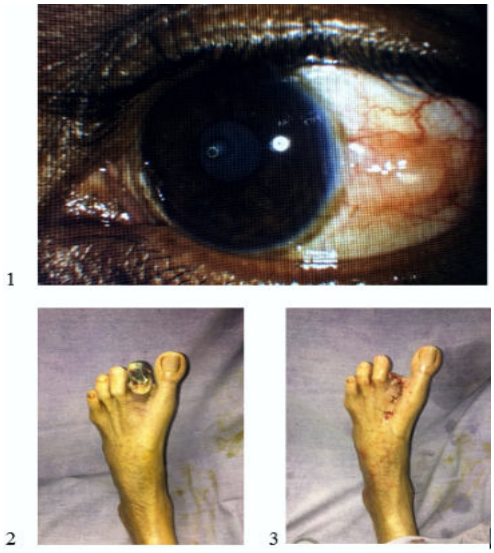


Case1: Figure 1: Left eye, showing temporal scleral nodules with scleral congestion. **Figure 2:** showing multiple scleral nodules both nasally and temporally (white arrow) with bluish discoloration of sclera due to thinning (blue arrow). **Figure 3,4,5:** Dorsal & Plantar aspect of right foot showing digital gangrene of the 4th Toe which was amputated and soft tissue cover provided with SSG

Case-2

A 35-year-old female, not a known hypertensive and diabetic came to our department with pain and redness in left eye referred from plastic surgery department with a history of left 2nd toe gangrene on treatment. She had complaints of left eye redness and pain on and off since last 6 month. Her best corrected visual acuity (BCVA) in each eye was 6/6, N6. On Slit lamp examination her left eye had nodular scleritis for which she was already using steroid eye drops from outside. Fundus evaluation was within normal limits for both eyes. Based on history she was further evaluated for scleritis. Her ESR was raised and c-ANCA titers were raised. Her complete blood count, HbA1c, routine urine analysis, biochemical profile, renal function test and USG KUB was

done, chest radiograph was within normal limits. Urine routine microscopy showed Proteinuria(Protein ++),USG KUB showed a renal cyst bilaterally and changes of cystitis She was further referred to pulmonologist to rule out any other pathology. Based on the above findings She was diagnosed as a case of ocular Wegner's granulomatosis with musculoskeletal changes and renal polyangitis and was started on oral steroids 1mg/kg/day and cyclophosphamide 1.5 mg/kg/day for 3-4 months under physician guidance. On follow up visits her scleritis had resolved. Urine routine microscopy showed no proteinuria and Renal cyst bilaterally gradually reduced in size on serial USG. The toe gangrene was managed with toe amputation followed by primary repair. The wound healed well in 2 weeks.

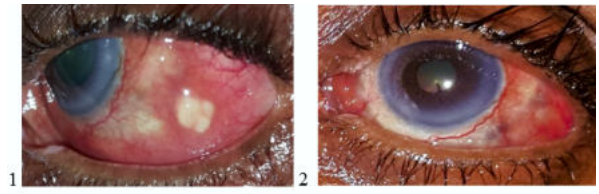


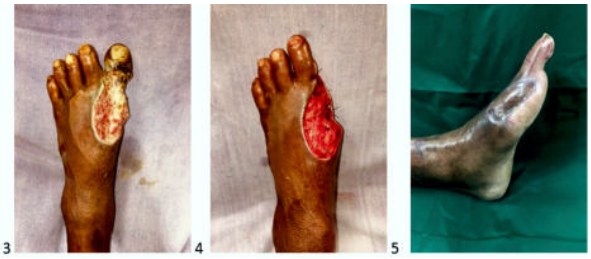
Case2: Figure 1: Left eye: Nodular Scleritis **Figure 2,3:** Dorsal aspect of the left foot with digital gangrene of the 2nd toe which was amputated and wound primarily closed

Case-3

A 73-year-old female, not a known hypertensive and diabetic came to our department with pain and redness in the left eye, referred from the plastic surgery department with a history of left great toe gangrene associated with a non-healing ulcer of 4 weeks duration. She is a known case of glaucoma on topical medications. She had complaints of on and off redness and pain in the left eye for the past 1-1.5 years for which she was already consulting outside. Her BCVA in the right eye was 6/36, N24, left eye was 6/36, N18. On slit lamp evaluation, her both eyes were pseudophakic with glaucomatous optic neuropathy,bilateral central retinal vein occlusion with chronic cystoid macular oedema for which she had received intravitreal injections in past. Her left eye had multiple scleral nodules of 2*2 mm size both nasally and temporally with scleral congestion and thinning which was her main concern. She was further evaluated and her CBC was normal, although her ESR was raised. Renal function test were on borderline with serum creatinine level 1.8 and urine routine microscopic suggestive of microscopic hematuria and mild proteinuria, USG KUB was suggestive of early changes of chronic kidney diseases with minimal loss of corticomedullary differentiation. Her c-ANCA titers were raised.

She was started on oral steroids 1mg/kg/day and cyclophosphamide 1.5 mg/kg/day for 2-3 months and later she was tapered off from steroids and started on Methotrexate under physician guidance. Urine routine microscopy after 3 months revealed no hematuria and proteinuria, with serum creatinine level stable at 1.8.The gangrenous left great toe was amputated and VAC dressing was applied to prepare the wound bed. Eventually, a soft tissue cover was provided using a split-thickness skin graft that healed well.





Case3: Figure1; Left eye Nodular Scleritis, **Figure 2**; Resolving Nodular Scleritis **Figure 3,4,5:** Dorsal aspect of left foot with impending digital gangrene of the Great Toe with non-healing ulcer; Post amputation wound and post-split thickness skin grafting completely healed wound pictures

DISCUSSION

WG is an arteriolar vasculitis that was first documented in 1931. There are approximately 24 to 157 cases of WG per one million individuals in the United States, with 3 to14 new cases per one million individuals reported each year. [2] Ophthalmic involvement occurs in 28%[3] to 60%[4] in any form of WG .Renal involvement is seen in almost 50 percent of the patients, but most the time it is asymptomatic and diagnosed incidentally. It is more prevalent in the West and relatively rare in the East .

It is characterized by granulomatous inflammation of the upper and lower respiratory tract, necrotizing vasculitis, and nephritis. WG is classified into three forms:

Generalized form that correlates with the classic triad

Limited form which is more indolent and typically involves the respiratory tract but spares the kidneys

Very limited form as in our patient, with nodular scleritis. [5] Ocular complaints have been reported as the initial symptom in 8 to 16% of WG.[5]

Scleritis is found to be associated with various systemic autoimmune disorders, including rheumatoid arthritis, SLE, spondyloarthropathies, WG, polyarteritis nodosa, and giant cell arteritis.[1] Other rare diseases include leukemia, lymphoma & metastasis. The various ophthalmic manifestations described in the literature includes non-specific conjunctivitis, tarso-conjunctival granulomatous inflammation with scarring, episcleritis, scleritis, peripheral ulcerative keratitis, uveitis, retinitis, retinal vasculitis, exudative retinal detachment, Nasolacrimal duct obstruction, orbital inflammatory disease, proptosis, optic neuropathy and ocular motor cranial neuropathy.[6]

Renal involvement is seen in approximately 30 to 50 percent of the patients, most common presentation is Proteinuria along with microscopic hematuria ,involvement of kidney as frank nephritis is a late manifestation , involvement of glomerular vessels can manifest as Hypertension, protein losing nephropathy, on imaging most common manifestation is a hypo vascular mass .

Granulomatosis with Polyangiitis (GPA), previously known as Wegener's, is a variant of ANCA vasculitis that is usually associated with cANCA. The spectrum of clinical manifestations of GPA can involve almost any organ system, but the classic organ systems affected include the upper respiratory tract, lower respiratory tract, and kidneys. One of the rarer manifestations is digital ischemia and gangrene which was seen in our case series.

In a study, cytoplasmic antinuclear cytoplasmic antibody (c-ANCA) was found to be positive in 7 out of 8 patients. Cyclophosphamide was started which alleviated the symptoms in 6 patients. It was observed that scleritis with peripheral corneal involvement was the most common ocular manifestation of WG. [7]In our study, there was history of fall of insect which led to a diagnosis of infective scleritis with uveitis which was misleading. However, on further evaluation and workup, patient was diagnosed as a case of very limited ocular WG with no renal or pulmonary involvement.

Anti -Proteinase3 (PR3) cANCA form a useful adjunct in the diagnosis of WG [8,9,10,11]. 80% to 95% of all ANCA found in WG is cANCA.

ANCA specificity in WG is about 98% but the sensitivity depends on the extent of the disease activity. [12] Our patient was cANCA positive. A study from the Massachusetts Eye & Ear Infirmary showed that cANCA is highly specific and sensitive for WG in patients with scleritis. Out of 23 patients ,16 patients presented with scleritis, of which 7 patients with positive ANCA titers had limited or generalized WG, and none of the 16 patients with negative titers had WG. [5]

In a study done at Bangalore 6 out of 7 patients reported with ocular involvement and later the diagnosis of systemic WG was made. [13]A case of very limited Wegener's Granulomatosis and Scleritis has been reported in which histopathology had confirmed the diagnosis [5]. Ours is a case of very limited ocular WG with Uveitis with no systemic involvement which is rare.

Treatment of WG is multidisciplinary approach.The first-line induction regime for WG is cyclophosphamide and prednisolone. This is supported by the European Vasculitis Study Group (EUVAS) in the two landmark studies: pulse vs. daily oral cyclophosphamide in ANCA-associated vasculitis (CYCLOPS) [14] and cyclophosphamide vs azathioprine for early remission phase of vasculitis (CYCAZAREM)[15] Oral corticosteroid of 1 mg/kg/day and IV cyclophosphamide of 15 mg/kg are initiated two-weekly for three cycles, and then IV cyclophosphamide 15mg/ kg pulse three-weekly or 2mg/kg/d daily orally until remission. This regimen is continued for three more months after remission (consolidation phase). [14] For maintenance regimen based on CYCAZAREM study, azathioprine was used as maintenance of remission with fewer side effects. [15] Azathioprine should start at 2mg/kg/d for 18 months (reduced to 1.5mg/kg/d at 1 year from the time of initiation of continuous cyclophosphamide induction therapy). Prednisolone is given at 10mg/d until one year, then 7.5mg/d until month 18. Methotrexate (EUVAS-NORAM & French Vasculitis Study Group (FVSG)–WEGENT could be used as an alternative to azathioprine. [16, 17]Our patient responded well to Oral Cyclophosphamide in a dose of 1.5 mg/kg/day and oral corticosteroids in a dose of 1 mg/kg/day for 3-4 months.

CONCLUSION

This case series highlights that an ophthalmologist could be the first clinician to encounter such a case. Ophthalmic affectation prior to systemic manifestations is much less frequent and could delay final diagnosis leading to postponed treatment and possible adverse outcome. Involvement of digital arteries causing ischemia or gangrene is very rare and though it is a very rare manifestation of Wegener's granulomatosis, its possibility should still be considered while evaluating a patient of digital gangrene with pulmonary and renal involvement to avoid diagnostic pitfalls and mismanagement. Aggressive and early medical treatment results in good outcome, hence early diagnosis is crucial for the patient. In such a case a high index of suspicion of WG should be kept in mind and c-ANCA should be done along with urine routine test. Diagnostic dilemmas can be supported by biopsy. Prompt treatment with immunosuppressive and corticosteroids reduces both ocular and systemic morbidity and renal manifeststion.

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