British Journal of Medicine & Medical Research
10(8): 1-9, 2015, Article no.BJMMR.19161
ISSN: 2231-0614

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Idiopathic Necrotizing Scleritis, Anterior Uveitis, and Localized Retinal Detachment

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/19161
Editor(s):
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(2) Jingli Xu, College of Pharmacy, University of New Mexico, USA.
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(3) Wagner Koji Aragaki, Universidade Nove de Julho, São Paulo, Brazil.
Complete Peer review History: http://sciencedomain.org/review-history/11154

Case Study

Received 28th May 2015
Accepted 12th August 2015
Published 29th August 2015

ABSTRACT

Aim: To present clinical picture and treatment of anterior idiopathic necrotizing scleritis.
Methods: Clinical and laboratory examination; B-scan ultrasound; tissue biopsy and histological analysis, were performed.
Results: Herewith we depict a case of 74 year old man, with unilateral granulomatous, anterior, necrotizing scleritis. Etiology has, through extensive testing, both laboratorial and clinical, not been proven and thus the patient has been classified as having idiopathic scleritis. Complications on both anterior (anterior uveitis) and posterior (subretinal granulomatous infiltrates with localized retinal detachment) segments of the eye are a consequence of granulomatous necrotizing scleritis. Both tissue biopsy of granulomatous scleral infiltrates and histological analysis showed that this is the case of granulomatous, partially necrotizing scleritis with some elements of vasculitis. Progression of granulomatous scleral infiltrates into the eye has also been shown through clinical examination and B-scan ultrasound, and depicted subretinal lesion of medium reflectivity that is in contact with the epibulbar lesion. Retinal detachment in this area had progressed and required

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excessive laser photocoagulation barrage and resulted in absorption of subretinal fluid. Positive therapeutic outcome was achieved through the use Methotrexate and corticosteroids.
Conclusion: Granulomatous infiltrates that spread towards the subretinal space and result in localized retinal detachment are a rare complication that may occur during the evolution of necrotizing scleritis and require regular monitoring and followup. Treatment, both pharmaceutical and laser photocoagulation, should be adjusted in order to affect progression and prevent possible complications of the disease.

Keywords: Idiopathic necrotizing scleritis; anterior uveitis; localized retinal detachment; histology; immunosuppressive therapy.

1. INTRODUCTION

Scleritis is a scleral inflammation that is characterized by scleral and episcleral cell infiltrates. Clinical symptoms of scleritis are: photophobia; red eye; and pain. Pain can vary from mild to very intense, and can spread to the forehead, brow, jaw, and/ sinuses. Additionally, pain associated with scleritis can, upon any physical contact, worsen or diminish as response to palliative treatment. Clinical signs of scleritis include: violet–bluish scleral discolouration; swelling at sites of inflammation; and/ dilated episcleral blood vessels. Seeing that scleritis and episcleritis are both included as part of differential diagnosis, examination should be performed under both natural and artificial light [1,2]. In scleritis, as opposed to episcleritis, sclera remains bluish – reddish in colour even after phenylephrine (2.5%) has been applied. On a slit – lamp, congested blood vessels are shown to be attached to the sclera, and cannot be moved with a sticking apparatus, whilst this is not the case with episcleritis where conjunctiva is not fixed. In scleritis, all scleral changes are painful to the touch. Blood vessels are best seen under red – free light. In scleritis, all scleral changes are painful to the touch. Blood vessels are best seen under red–free light. Depending on localization of scleral inflammation, scleritis can be divided into anterior (process is localized in front of the rectus muscles), and the posterior (process is localized behind the rectus muscles). Type of infiltrates in the sclera determines type of scleritis as: diffused; nodular; and necrotizing.

Scleritis is most commonly associated with systemic autoimmune diseases and systemic vasculitis [3,4]. It is assumed that systemic disease occurs in 46% of individuals with scleritis, out of which rheumatoid arthritis (RA) most commonly occurs in conjunction with scleritis [5,6]. Scleritis may be associated with numerous other disorders such as: Systemic lupus erythematosus (SLE); relapsing polychondritis (RP); polyarteritis nodosa (PAN), Wegener's granulomatosis (WG), giant cell arteritis (GCA) (temporal arteritis); spondyloarthropathies; Cogan's syndrome (CS); sarcoidosis; etc. [7]. Scleritis may be the primary sign of potentially harmful disorders such as systemic vasculitis. Besides autoimmune disorders, other factors such as infective microorganisms; endogenous substances; and/ trauma may be of importance for occurrence of scleritis. In case that association between systemic disorders and systemic vasculitis, and/ its infective nature, has not been proven, scleritis is deemed to be idiopathic in nature. Most commonly, scleritis occurs in the age group 50–60, and is more frequent in female (in association with autoimmune disorders), as opposed to male (in association with infective etiology), population.

Scleritis is a severe ocular inflammation, often associated with ocular complications, and usually treated with systemic medication. Nearly 60% of individuals with scleritis will need oral corticosteroids or immunosuppressive drugs in order to manage the disease [8].

1.1 Aim

To present clinical picture and treatment of anterior idiopathic necrotizing scleritis.

2. CASE REPORT

In June 2014, a 74 year old male, came to an ophthalmologist with signs of photophobia; red eye; tearing; and painful right eye. Pain which he was experiencing was very high and gradually moving towards his forehead and brow. Its' intensity woke him up from sleep, and only partially got better as response to various painkillers.

Right eye visual efficiency (VE) was normal, with an intraocular pressure (IOP) of 12 mmHg.

Visual acuity (visual efficiency) is the distance (20 ft in the US, or 6 m in the rest of the world) at which the test is performed, over distance at which the smallest optotype (standardized symbols for testing vision) is identified that subtends an angle of 5 arcminute. The largest letter on an eye chart often represents an acuity of 20/200 (6/60) which the value that is considered "legally blind".

Examination performed under natural light and with a biomicroscope revealed scleral changes on the meridian towards 9 o'clock along the limbus, nodular in shape, bluish–red in colour, vaguely defined, attached to the surface. Additionally, two more nodules were noted on the sclera, along the limbus, at 10 o'clock. Episcleral blood vessels were dilated, tortuous, and localized around and overlaying the nodules. They did not diminish even after implementation of phenylephrine. In this zone sclera was very painful to the touch. There were no pathological changes on the cornea. Anterior chamber of the eye had no cells and/ proteins present (both cell and protein Tyndall were at zero) [Fig. 1].

Fig. 1. Image of right eye: Anterior granulomatous scleritis; initial examination. Scleral nodule; grayish in colour; prominent and timorous in appearance

Bilateral fundus examination, with completely dilated pupils, on the ophthalmoscope and with the use of Goldmanns' three mirror contact lens, revealed that there were no pathological changes of the blood vessels or on the macula, on either the right, or the paired eye. Optical coherence tomography (OCT) (SDOCT; Copernicus +; "Optopol" Technology) was performed as part of the diagnosis. There were also no changes noted on the periphery of the fundus, in the projection of the scleral junction. Vitreous humor was clear.

Patient was diagnosed as having right eye, nodular scleritis, and both topical and systemic treatment was applied. Topical treatment consisted of: nonsteroidal antiphlogistics (Uniclophen 0.1%; 4/day), whilst systemic therapy consisted of: nonsteroidal anti-inflammatory drug (NSAID) (Ibuprofen), and due to the severity of the disease, pulse doses of corticosteroids (5 doses of 500 mg intravenous methylprednisolone (MP), as per guidelines). Glucocorticoids have been used in management of inflammatory diseases since 1969. There are no official protocols regarding pulse therapy, so that its application depends on the assessment that takes into the account localization and the degree of disease, and unofficial guidelines suggest that pulse therapy has a favorable risk to benefit ratio and that it is highly efficient in short term control of inflammation such as necrotizing noninfectious scleritis. In order to enhance therapeutic effects and reduce side effects, intravenous (i.v.), supra-pharmacological doses, i.e. high dose i.v. / "pulse" corticosteroid treatment, is used in various inflammatory and autoimmune conditions, administered with substantial variations in dose; number; timing; and duration (i.e. >250 mg prednisone or its equivalent daily, 1 – 5 days; no longer than 12 alternating days at the time). Subsequent corticosteroid therapy consisted of prednisone (tablets) which were slowly tapered (until dosage of 10 mg was reached). Adequate food plan was prepared and diet further supplemented with potassium chloride and "Ranital" (Ranitidine, ranitidine hydrochloride) tablets. In the initial phase of treatment inflammatory process subsided to some extent, and additional laboratory and clinical examination was performed in order to determine the etiology of the disease.

Basic laboratory findings (haematocrit; leukocyte count; transaminase levels; creatinine; urea; glucose; urine analysis; proteins in the blood) were within normal limits. Erythrocyte sedimentation was 8. Based on general laboratory analysis, etiology of the disease could not be confirmed. Additional immunological and virological tests were performed, and their results within normal range [Table 1].

Based on various virological results it could not be said that the disease is of viral etiology, and so additional consultations were made. Consultation with a rheumatologist did not confirm existence of a systemic vasculitis; collagenosis or seronegative arthropathy.

Table 1. Test results which were outside the normal range

Analysis	Results (and their reference values)
ANA Screen IgG	0.42 (< 1.0)
ANA Hep –2	5.66 U/ml (< 12)
ANCA – P MPO	2.73 U/ml (< 10)
ANCA – C PR3	4.21U/ml (< 10)
HSV1IgG	69.51IU/L (< 16)
HSV1IgM	0.11 (< 0.8)
VZV IgG	202.98I U/L (< 80)
VZV IgM	0.24 (< 0.8)
CI inhibitor esterase	343.0 mg/L (230 – 410)
CIC – CI IgG	1.1kRU/L (< 20.0)
ACE	8.8 U/L (8.0 – 52.0)

ANA anti-nuclear antibody, IgG immunoglobulin G, Hep hepatitis, ANCA antineutrophil cytoplasmic antibodies, MPO myeloperoxidase, PR3 proteinase 3, IgM immunoglobulin M, HSV herpes simplex virus, VZV varicella zoster virus, CIC circulating immune complexes, ACE angiotensin-converting enzyme

2.1 Granulomatous Scleritis is viewed as Idiopathic

In July 2014, one month after the initial onset of the disease, there was increased scleral activity. Nodules on the sclera increased in size, one of which was grayish in colour, prominent, and timorous in appearance. Patients' pain levels had increased as compared to the previous month, so that even the slightest of touches to the top of the head caused it to worsen. Both VE and IOP were within normal limits, and there were no exudates in the anterior chamber of the eye. There was no inflammatory process in the deeper, posterior, segments of the eye including its' periphery, in the area of a scleral nodule. The patient was on treatment consisting of Methotrexate (MTX) and NSAID the entire time.

A month later, in August of 2014, existing scleral nodule enlarged to that extent that it perforated the sclera. On the retinal periphery, in the projection of a scleral nodule, a subretinal mass was noted. The noted change progressed on a daily basis and within a period of ten days resulted in localized retinal detachment which occurred as consequence of subretinal infiltrates. There was no traction and/ breaks of the retina. At the same time, there were exudates (in form of protein and cell Tyndall) in the anterior segment of the eye, and non-pigmented, mutton fat precipitates on the corneal endothelium, but there was no noted scleral nodule infiltration in the anterior chamber [Fig. 2]. Cell Tyndall is the presence of cells and proteins in the anterior chamber of the eye, and so the degree of proteins and cell tyndall determines the degree of inflammation in this part of the eye. Tyndall effect (Tyndall scattering), is light scattering by particles in colloid or those in a fine suspension, which is commercially used to determine the size and density of particles in aerosols (colloid of fine solid particles or liquid droplets, in air or another gas) and other colloidal matter. Both systemic corticosteroid and nonsteroidal local and systemic therapy was applied.

Due to progressive inflammatory process, and in the absence of other laboratory and/ clinical indicators which could confirm that scleritis is associated with an autoimmune disorder or that it is infective in nature, there was further need to exclude any timorous formations. With this in mind ultrasound [Fig. 3] and biopsy of scleral infiltrates was performed.

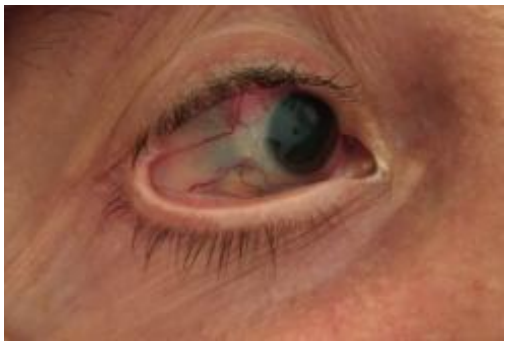

Fig. 2. Image of right eye: anterior granulomatous scleritis, sectored scleral atrophy; followup examination

Ultrasonography findings were as follows: OD: Lax=23.16mm; OS: Lax=22.80. Right eye examination revealed a localized subretinal mass, 7.14*2.60 mm in size, at 9 o'clock, on the further periphery of the eye. This lesion is of medium reflectivity and in direct contact with the epibulbar lesion, which in turn is of low reflectivity, and 5.28*1.05 mm in size. Above the intra–bulbar lesion the entire bulbar wall has been thickened to 2.43 mm, whilst the subretinal space has been widened to 0.90 mm. Retina is in place.

Clinical diagnosis of granulomatous scleritis which has breached the sclera and extended into the subretinal space was confirmed via an echograph.

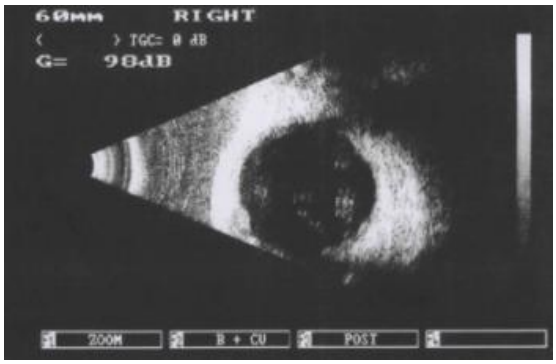

Fig. 3. Ultrasound; right eye, lesion of medium reflectivity on the fundus periphery of the eye that is in direct contact with the epibulbar lesion

Pathoanatomical finding from August of 2014 depicted that the patient described in this report had: chronic granulomatous scleritis; partial necrosis; with granulomatous necrotizing vasculitis [Figs. 4-6].

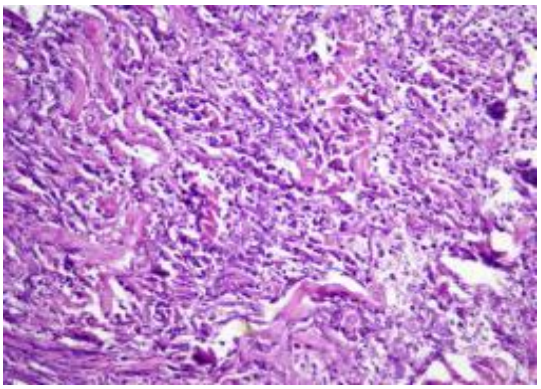

Fig. 4. Chronic granulomatous scleritis; partial necrosis with granulomatous necrotizing scleritis. Necrotizing changes in the granuloma as seen under magnification of 1400

Previously mentioned individual was adequately followed and during his followup examinations it was noted that in the zone of sclerotic nodule, there was progressive retinal detachment. With this in mind laser photocoagulation (LFC) was performed around the change, and detached retina on fundus periphery (barrage of retinal detachment: number of spots: 692; size of spots: 200; exposure: 0.14 – 0.16; power: 180 – 200). Subsequent to laser intervention, subretinal edema subsided and retina adhered. At the same time this individual was provided with immunosuppressive treatment that consisted of: methotrexate (25 mg/week); folic acid; and prednisone (60 mg/day; with gradual tapering). Objective findings as well as subjective feeling had improved following the implementation of the above mentioned treatments. Scleral change had shown signs of regression. Repeated laboratory testing did not give rise to new understanding concerning etiology of the disease, so that the patient was noted as having idiopathic necrotizing scleritis, and thus, taking this into account; further investigation was carried out (including regular lab parameters such as: C – and P - antineutrophil cytoplasmic antibodies (C– and P–ANCA); circulating immune complexes (CIC); C reactive protein (CRP); antinuclear antibodies (ANA; anti – DNA); rheumatoid factor (RF); and complements (C3; C4).

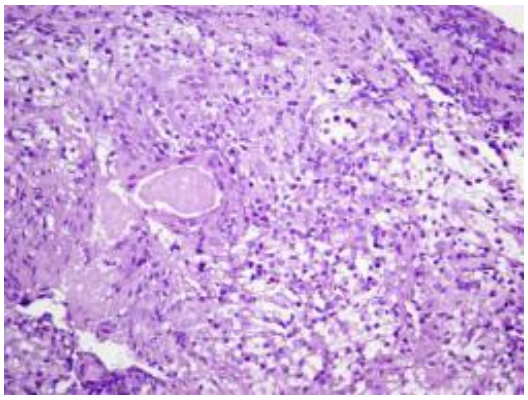

Fig. 5. Cell infiltrates; vasculitis; 2400times magnification

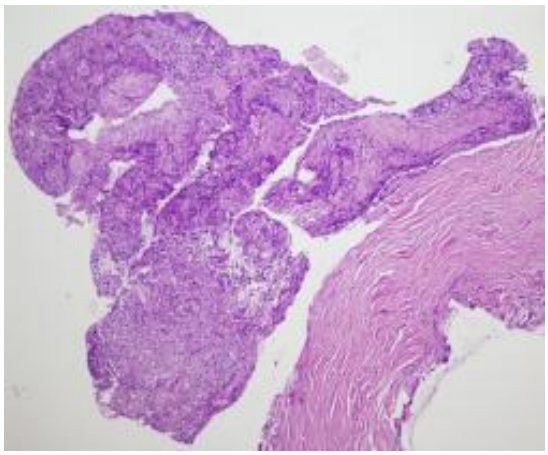

Fig. 6. Cellular infiltration of the conjunctiva and episclera; 100 times magnification

3. DISCUSSION

According to localization, scleritis is divided into anterior and posterior scleritis. Anterior scleritis can be: diffused; nodular; and necrotizing. Most common clinical form of scleritis is diffused and nodular anterior scleritis. Posterior scleritis is less common type of scleritis. The most severe and rare form of scleritis is necrotizing. Granulomatous scleral infiltrates are formed from: epithelial and giant polynuclear cells. In some cases granulomatous infiltrates can extend into the inside of the eye. Initially, reaction of type III hypersensitivity mediates the inflammatory process, only to be followed by a chronic granulomatous response, part of which are T and B lymphocytes and various cell mediators. In case of scleritis associated with systemic vasculitis, it is possible to histologically confirm vasculitis from scleral infiltrates. Our patients' histological findings are indicative of partially necrotizing scleritis and vasculitis. Favorable effects of immunosuppressive therapy can be attributed to an autoimmune reaction as part of systemic vasculitis and collagenosis [9]. Whilst the most frequent complication of anterior scleritis that results as consequence of evolutive processes is: keratitis (marginal corneal infiltrates); the following are rarely seen: anterior uveitis; secondary glaucoma; and/ cataract [10].

Patient presented here was, during the course of an evolutive process and scleral penetration into the subretinal space, diagnosed as having anterior uveitis. Necrotizing scleritis is associated with severe pain and the most complex of complications (such as retinal detachment), with poor evolution and prognosis. This evolutive process can vary in rate from slow to extremely fast, and thus prompt and adequate treatment and followup are of the utmost importance. In these cases, besides the immunosuppressive drugs, biological therapy is also of consideration [11]. If there is presence of a relatively small conjunctival and scleral necrotic tissue it can be substituted by fibrous tissue, but on the other hand if there exists a large defect, a bigger scleral graft is required. Posterior scleritis is a rare condition and the inflammatory scleral process is localized behind the attached rector muscles. Some of the signs associated with posterior scleritis are: severe pain due to ocular movement; conjunctival chemosis; swelling and retraction of the eyelids; and proposes. Due to the fact that the process extends on to both the choroidea and the retina there is associated resultant variable reduction of VE. The following are also noted: choroidal folds on the fundus of the eye; formation of a subretinal mass; papilloedema and ME (optic disc and macular swelling); and at times retinal detachment [12].

Diagnosing scleritis requires that both laboratorial and clinical analysis be performed. Seeing that scleritis is associated with systemic diseases of the connective tissue and/ systemic vasculitis, a multidisciplinary approach and immunological analysis is necessary [13–15].

Detailed clinical assessments, entire body work up, as well as consultations with specialists from various fields of medicine, are all part of the required diagnostic procedure. It is also necessary to assess the arterial tension as well as renal and liver functions. Besides the basic laboratory tests additional testing includes further immunological analysis such as: CIC; CRP; ANA; anti – DNA; RF; C – ANCA; P – ANCA; C3; C4. Likelihood of patients with idiopathic scleritis RA and WG increased if they were RF or ANCA positive, which supported the need for immunologic marker testing in patients with no systemic disease [16]. On the other hand some ANCA positive patients suffering from scleritis are more likely to have a severe ocular disease associated with an undiagnosed primary vasculitic one, and so require more aggressive therapy [17].

In order to prove sarcoidosis and exclude the viral nature of the disease it is also necessary to perform an ELISA test for human immunodeficiency virus (HIV) and varicella zoster virus (VZV) (immunoglobulin G; immunoglobulin M). Additionally, in order to exclude sarcoidosis concentrations of angiotensin converting enzyme (ACE) in the blood; calcium levels in blood and urine (24 h); and tuberculosis (TB) skin prick test, are to be performed.

If all of the parameters (indicative of the nature of the disease) are within normal limits, one can deduce that scleritis is idiopathic in nature. However, if one excludes the infective nature of the disease, in presence of etiologically confirmed and/ idiopathic scleritis, treatment procedure is the same and is based on severity and progression of the disease. In some instances, as is the case with necrotizing or posterior scleritis, B–scan ultrasound is also one of the required tests.

Tests which are required in order to view the entire state of the macula are: fluorescein angiography (FA); indocyanine green angiography (IGA); and/ OCT (especially in case of there having been lesions on the macula).

Certain forms of necrotizing scleritis can, due to their appearance and propagation into the posterior structures of the eye, look like a malignant choroidal melanoma; choroidal hemangioma; or metastasizing tumor. In these cases it is recommended to perform a biopsy of the affected tissue and analyze the material. Patient described herewith had clinical appearance of a possible ocular tumor and was thus sent for a biopsy and histological testing which pointed towards/confirmed a tumor and the infective nature of the disease. Polymerase chain reaction (PCR) test is utilized in order to assess the infective agents, whilst immunohistochemical examination of the provided sample can be of use in those instances in which other methods do not provide adequate data on the nature of the disease itself.

Treatment of scleritis is aimed at reducing the inflammation and minimizing tissue damage. Drug choice as well as treatment duration are both dependant on the severity and progression of the disease. As it has already been described, noninfectious scleritis is treated by nonsteroidal anti-inflammatory medication (topically) in conjunction with corticosteroid drugs (tablets/injections). Due to high risk of possible damage to the sclera, subconjunctival injection of corticosteroids is not advised. Primary treatment consists of nonsteroidal antiphlogistics, applied topically and systemically. If the previously described treatment doesn't provide adequate results, medication of choice is MTX in combination with folic acid. MTX seems to be well-tolerated medication which can, in treatment of chronic, noninfectious, and nonnecrotizing scleritis, successfully reduce inflammation and decrease the need for corticosteroids [18].

As is the case with our patient, an improvement was achieved subsequent to MTX and corticosteroids having been implemented. Other medicaments that are to be considered are: Azathioprine (Imuran); Mycophenolate mofetil (MMF) (CellCept); Cyclophosphamide (Endoxan) [19–23]. Systemic cyclosporine A (CsA) is utilized in cases of severe forms of uveitis which are associated with other systemic disorders. They can be used alone or in conjunction with corticosteroid therapy [24]. If treatment doesn't provide adequate results, scleritis is treated with biological agents such as: Adalimumab (Humira), Inflixmab (Remicade), etc. [25–27].

Scleral graft is performed only in severe cases where there is appearance of large scleral defects, and they generally have poor outcome (result in visual loss or even removal of an eye).

4. CONCLUSION

Granulomatous infiltrates that spread towards the subretinal space and result in localized retinal detachment are a rare complication that may occur during the evolution of necrotizing scleritis and require regular monitoring and followup. In cases where retina has detached due to subretinal infiltrates of necrotizing scleritis which has perforated the scleral wall, LFC can be utilized as a method of treatment for securing the retina. Treatment, both pharmaceutical and laser photocoagulation, should be adjusted in order to affect progression and prevent possible complications of the disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/11154