Case Study

Idiopathic necrotizing scleritis, anterior uveitis, and localized retinal detachment

ABSTRACT

Purpose: To assess the etiology of anterior 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, projected as part of a scleral nodule. 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 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.

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. 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, 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 erythematous (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].

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 12mmHg. 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].

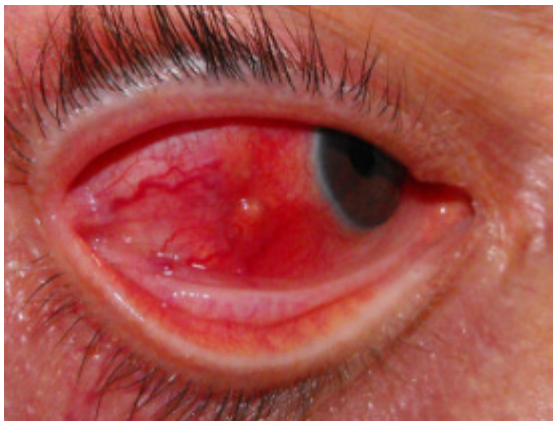

Figure 1. *Image of right eye: anterior granulomatous scleritis; initial examination.*

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. 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 pulse doses of corticosteroids (5 doses of 500mg intravenous methylprednisolone (MP)). Subsequent corticosteroid therapy consisted of prednisone (tablets) which were slowly tapered (until dosage of 10mg was reached). Adequate food plan was prepared and diet further supplemented with potassium chloride and Ranital 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].

Table 1. Test results which were outside the normal ranges

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

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.

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.

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. At the same time, there were exudates (in form of protein and cell Tyndall) in the anterior segment of the eye, and precipitates on the corneal endothelium, but there was no noted scleral nodule infiltration in the anterior chamber [Fig. 2]. Both systemic corticosteroid and nonsteroidal local and systemic therapy was applied.

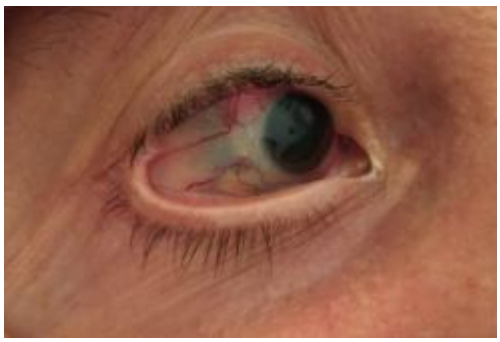

Figure 2. Image of right eye: anterior granulomatous scleritis, sectored scleral atrophy; followup examination.

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.

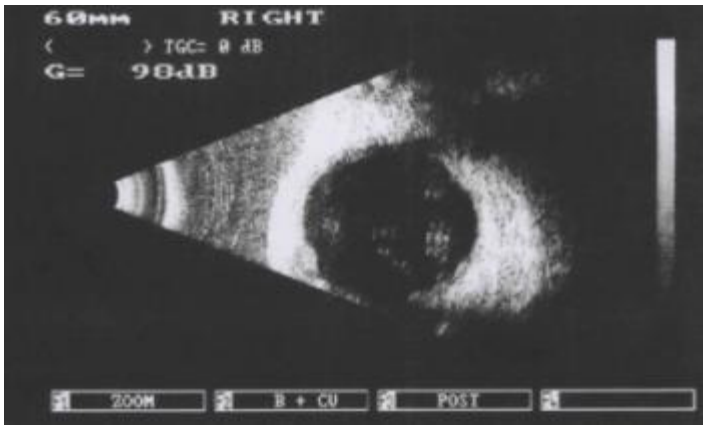

Figure 3. Ultrasound; right eye

Ultrasonography findings were as follows: OD: Lax=23.16mm; OS: Lax=22.80. Right eye examination revealed a localized subretinal mass, 7.14*2.60mm 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*1.05mm in size. Above the intra–bulbar lesion the entire bulbar wall has been thickened to 2.43mm, whilst the subretinal space has been widened to 0.90mm. 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.

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

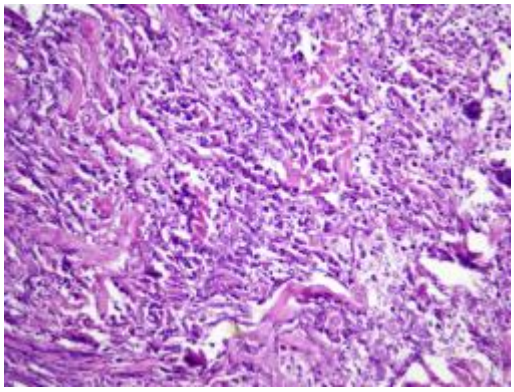

Figure 4. Necrotizing changes in the granuloma; 1400times magnification

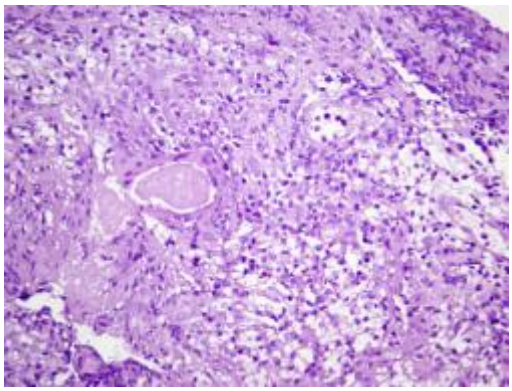

Figure 5. Cell infiltrates; vasculitis; 2400times magnification

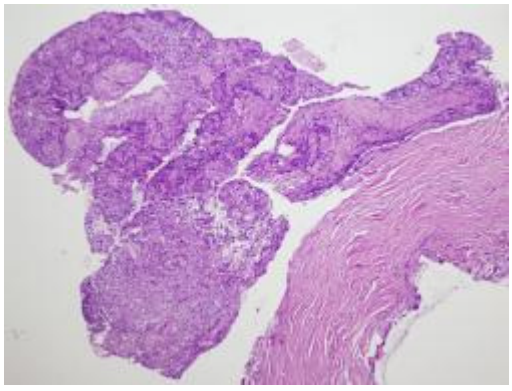

Figure 6. Inflammation of the conjunctiva and episclera; 100times magnification.

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. 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 (25mg/week); folic acid; and prednisone (60mg/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 arteritis, and thus, taking this into account; further investigation was carried out (including regular lab parameters such as C– and P–ANCA (antineutrophil cytoplasmic antibodies); CRP (C-reactive protein); etc..

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'

177 histological findings are indicative of partially necrotizing scleritis and vasculitis. Favorable
178 effects of immunosuppressive therapy can be attributed to an autoimmune reaction as part of
179 systemic vasculitis and collagenosis [9]. Whilst the most frequent complication of anterior
180 scleritis that results as consequence of evolutive processes is: keratitis (marginal corneal
181 infiltrates); the following are rarely seen: anterior uveitis; secondary glaucoma; and/ cataract
182 [10].

183 Patient presented here was, during the course of an evolutive process and scleral penetration into
184 the subretinal space, diagnosed as having anterior uveitis. Necrotizing scleritis is associated with
185 severe pain and the most complex of complications (such as retinal detachment), with poor
186 evolution and prognosis. This evolutive process can vary in rate from slow to extremely fast, and
187 thus prompt and adequate treatment and followup are of the utmost importance. In these cases,
188 besides the immunosuppressive drugs, biological therapy is also of consideration [11]. If there is
189 presence of a relatively small conjunctival and scleral necrotic tissue it can be substituted by
190 fibrous tissue, but on the other hand if there exists a large defect, a bigger scleral graft is
191 required. Posterior scleritis is a rare condition and the inflammatory scleral process is localized
192 behind the attached rector muscles. The following are also noted: choroidal folds on the fundus
193 of the eye; formation of a subretinal mass; papilloedema and ME (optic disc and macular
194 swelling); and at times retinal detachment [12].

195 Seeing that scleritis is associated with systemic diseases of the connective tissue and/ systemic
196 vasculitis, a multidisciplinary approach and immunological analysis is necessary [13–17].

197 If all of the parameters (indicative of the nature of the disease) are within normal limits, one can
198 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 Methotrexate (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). 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.

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