Review article

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CLINICOPATHOLOGIC ANALYSIS OF "IDIOPATHIC" SCLERITIS AND SCLERITIS ASSOCIATED WITH RHEUMATHOD ARTHRITIS -MINI REVIEW

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Scleritis is a chronic, painful, and potentially blinding inflammatory disease that is characterized by edema and cellular infiltration of the sclera tissues. It can occur as isolated ("idiopathic") or associated with systemic immune-mediated diseases of connective tissue. We present two different cases of scleritis: one case was that of a female patient with diffuse "idiopathic" scleritis, and the other – that of a female patient with nodular scleritis associated with rheumatoid arthritis. Both patients underwent detailed clinical, laboratory, and immune examinations, as well as the pathohistological analysis of the biopsy sample. The first patient had all laboratory tests within normal limits. The pathomorphological substrate of diffuse scleritis showed considerable edema of the episcleral and scleral tissues, the presence of inflammatory infiltrates with abundant lymphoid cells, histiocytes, accompanied by active hyperemia of capillaries with unusual relationships of blood vessels of the sclera and episclera. The second patient had nodular scleritis associated with rheumatoid arthritis. The pathomorphological substrate of sclera showed multiple foci of mononuclear infiltration with the domination of lymphocytes, the inner zone of polymorphonuclears and histiocytes, epithelioid and foreign body type giant cells and the outer zone of lymphocytes and plasma cells. Compared to the normal sclera, the number of inflammatory cells was 10-15 times elevated in scleritis with the domination of lymphocytes and plasma cells.

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Key words: *scleritis, rheumatoid arthritis, scleromalacia perforans*

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Introduction

Scleritis is a chronic, painful, and potentially blinding inflammatory disease characterized by edema and cellular infiltration of the sclera tissues (1-4). It can occur as isolated ("idiopathic") or associated with systemic immune-mediated diseases of connective tissue (Rheumatoid arthritis-RA, Systemic lupus erythematosus-SLE, Wegner's granulomatosis, polyarteritis nodosa-PAN) (5-7). RA is the most common systemic disease associated with scleritis. The classification system first proposed by Watson and Hareh is still used today: I - anterior scleritis: diffuse, nodular, necrotizing (with inflammation), and scleromalacia perforans (without inflammation) and II - posterior scleritis (1, 2). Pain and erythema are the most characteristic subjective symptoms. Pain is severe and it is intensified during the eye movement and reading, thus making any work impossible. Most cases of scleritis (diffuse, nodular, necrotizing) affect the front part of the sclera. A special characteristic of scleritis is its recurrence. The diffuse form is described in the literature as more frequently bilateral, while the nodular one as more frequently unilateral. In literature, it can be found that nodular scleritis is more frequent in patients with rheumatoid arthritis than in patients with other systemic immune-mediated diseases (5, 6). Precise pathogenesis has not been discovered yet. The presence of microangiopathy in most cases of scleritis indicates an associated immuno-complex reaction – III-type of hypersensitive reaction, and partly the influence of the late IV-type of the hypersensitive reaction. Recent studies show a clear morphological difference between substrates in the analyzed forms of scleritis. In the diffuse form of scleritis, a strong infiltration of lymphoid cells is present.

In the nodular type of scleritis, the pathohistological finding has a formation similar to or even the same as nodules in rheumatoid arthritis with a granulomatous inflammatory reaction.

Materials and methods

This paper presents the case studies of two female patients: I – N.Z., who had diffuse scleritis of unknown etiology and II – G.M., who had nodular scleritis along with rheumatoid arthritis. Both patients underwent detailed clinical, laboratory, immune examinations as well as the pathological analysis of the biopsy material. The ophthalmological examination included: visual acuity by Snellen signs, biomicroscopy of the anterior segment, applanation tonometry and indirect ophthalmoscopy. The rheumatological examination included relating to the general and local clinical findings as well as standard biohumoral and radiological examinations. The RA diagnosis was consistent with the criteria of the American College of Rheumatology.

Table 1. Diagnostic laboratory testing and scleritis

Laboratory test	Identified condition
CBC	Non-specific: infection, tumor, other
Chemistry panel: includes BUN, Creatine, CO_2	Non-specific for vasculitis-induced renal disease
ESR	Non-specific for systemic inflammation
Urinalyses	Kidney or liver dysfunction, metabolic disease
Rheumatoid factor	Rheumatoid arthritis
ANA	Systemic lupus erythematosus
ANCA	Specific for Wegener's granulomatosis, PAN, and related vasculitis – associated diseases
Cryoglobulins	RA, SLE
ACE	Sarcoid
C-reactive protein	Non-specific for systemic inflammation
Circulating immune	RA, SLE, Cogan's syndrome complexes
Scleral biopsy	Infectious diseases and rare causes
Chest radiography	RA, Tuberculosis, Wegener's granulomatosis
Sacroiliac radiography	Ankylosing spondylitis
ELISA	Lyme disease, HIV
HLA-typing	HLA-related inflammatory disease, such as SLA

ESR-erythrocyte sedimentation rate, ANA-antinuclear antibody, ANCA-antineutrophil cytoplasmic antibody, ACE-angiotensin converting enzyme, ELISA enzyme-licensed immunoassay, HLA-human lymphocyte antigen
Diagnostic laboratory testing was performed in the Central Biochemical Laboratory of the Clinical Center in Niš (Serbia).

The pathohistological examination was done at the Centre of Pathology, Clinical Centre of Niš (Serbia). The biopsy samples were taken after the local application of an anesthetic (cystocain). The tissue samples were taken from the clinically most affected inflammatory area above the scleral nodule. The samples were fixed in 10 % buffered formalin and processed with a modified method for small samples in the automatic tissue processor. The samples 3-5 microns thick were colored with the hematoxylin-eosin-method, Trichrome by Mallory and Woerchef-Fe hematoxylin method.

The patients gave a written informed consent.

Results

CASE I

A 36-year-old woman came in with a two-month history of painful red eyes and an "achy" pain on the temporal sides of her left globe. The pain was

present during the day. She had experienced five similar monocular episodes that affected the left eye. The pain became stronger at each movement of the eye, at reading, so any kind of activity was impossible. The patient's ocular history was positive for diffuse episcleritis of the left eye a year before. The slit–lamp examination revealed chemosis, and deep, diffuse 3+ hyperemia of the conjunctiva vasculature was noted, being most prominent in the temporal areas. There was a bluish tinge to the sclera superior on the left eye. The cornea was clear, and the anterior was 16 mmHg. A dilated fundus examination revealed normal optic nerve, macula, and fundus. These were treated to resolution with 1 % prednisolone ophthalmic suspension four times a day.

On the one-week follow-up visit, pain symptoms somewhat resolved. Hyperemia worsened to 4+, and engorged vasculature was noted. The cornea, anterior chamber, and optic nerve were still unchanged. The diagnosis was changed to recurrent episcleritis versus anterior diffuse scleritis. The patient has been using 1.0 % topical prednisolone acetate ophthalmic suspension six times a day and systemic 80 mg prednisone per day with 150 mg ranitidine once a day.

All laboratory tests (Table 1) (CBC, chemistry panel, urinalysis, ANA, ANCA, ESR, circulating immune complex, Complement, C reactive complement, Rheumatoid factor and uric analysis, ELIA, HLA typing) were within normal limits, and the final diagnosis was idiopathic diffuse scleritis. On the four-week follow- up visit, the patient showed remarkable improvement.

The pathomorphological substrate of diffuse scleritis showed considerable edema of the episcleral and scleral tissues, Presence of inflammatory infiltrates with abundant lymphoid cells, histiocytes, accompanied by active hyperemia of capillary vessels with an unusual relationship of blood vessels of the sclera and episclera (Figure 1). The margination of erythrocytes up to the formation of microthrombosis indicated a disrupted blood flow (Figure 2). Repetitive regenerative processes were noticed with significant deposits of collagen fibers in the form of imprisoned whirlpools, which resulted in a change of the usual distribution of these and elastic fibers in the sclera. The thickening of the capillary basal membrane of focal nodular nature was also noticed (Figure 3).

CASE II

A 57-year-old female was referred to the Ophthalmology Clinic in Nis (Serbia). Her symptoms were: pain, decreased visual acuity and photophobia in the left eye. The patient had a history of left eye redness and pain, which had begun a year before, treated with local steroids by her local ophthamollogist. The slit-lamp examination revealed a large scleral nodule, with a 4+ injection of the overlying conjunctiva and episclera. Ten percent of phenylephrine did not affect the deep vascular engorgement, thus confirming the diagnosis of nodular scleritis. The slit-lamp examination revealed the congestion and tortuosity of the superficial and deep episcleral plexuses overlying the nodule. The cornea was clear and the anterior chamber was without cells. Intraocular pressure was 20 mmHg OD and 20 mmHg OS. The dilated fundus examination revealed normal optic nerves, maculae, and fundi.

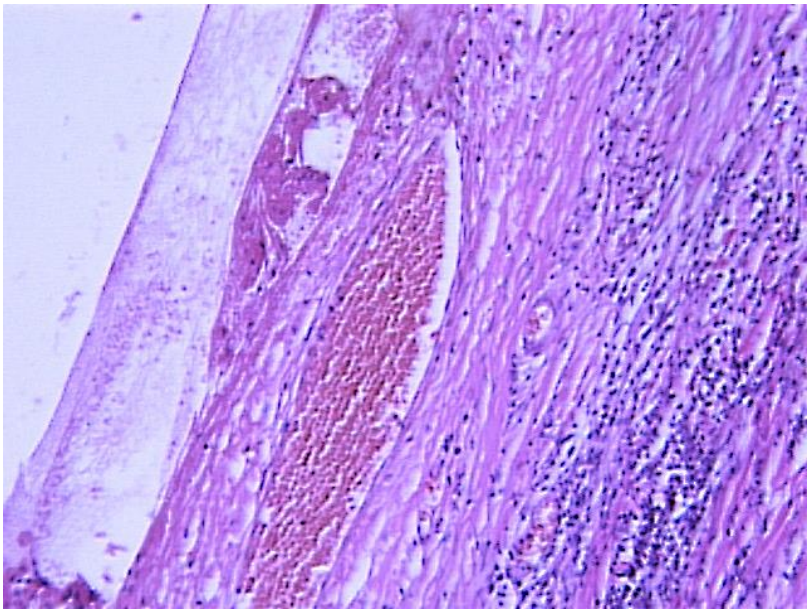

Figure 1. Inflammatory infiltrates and active hyperemia of capillary vessels with an unusual relationship of blood vessels of the sclera and episclera (HE, x 200)

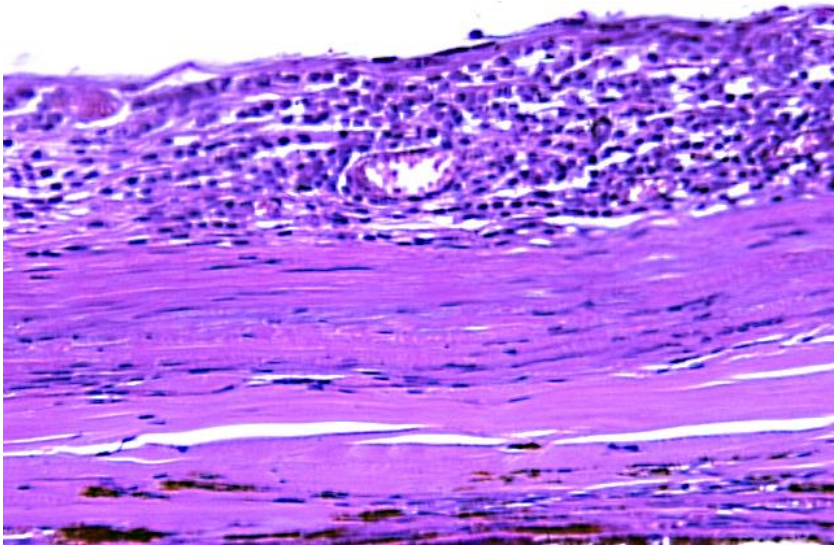

Figure 2. Significant deposits of collagen fibers in the form of imprisoned whirlpools, with distribution of these and elastic fibers in the sclera (HE, x 200)

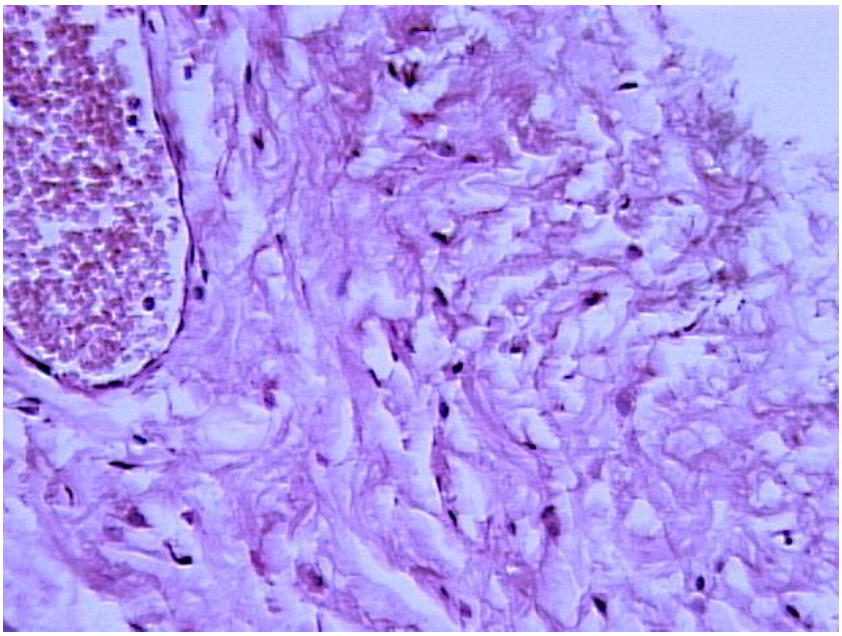

Figure 3. The thickening of the capillary basal membrane (HE, x 200)

Family history: The patient's mother and aunt had rheumatoid arthritis. Past medical history revealed rheumatoid arthritis of 10-year duration. This patient had III stage of the rheumatic disease according to the criteria of the American College of Rheumatology. The clinical laboratory test was positive for rheumatoid factor (600U; normal 40U), showed an accelerated erythrocyte sedimentation rate of 50 mm/h (Westergreen). Hand radiographs showed juxtaarticular osteopenia, marginal erosion. The topical prednisolone acetate was used four times a day. On the four-day follow-up visit, there was no improvement in symptoms. The rheumatologist offered the patient the treatment options of hydroxychloroquine or methotrexate for systemic control. The rheumatologist also recommended that we should initiate a regimen of oral steroids if an additional control of scleritis was needed. This treatment course led to slow symptomatic improvement approximately over the next 4 to 6 weeks, but scleral erythema remained.

The pathomorphological substrate of the sclera with the clinical form of nodular scleritis showed multiple foci of mononuclear infiltration with the do-

minance of lymphocytes, the inner zone of polymorphonuclears and histiocytes, epithelioid and foreign body type giant cells, and the outer zone of lymphocytes and plasma cells (Figure 4, 5). Compared to the normal sclera, the number of inflammatory cells was 10-15 times elevated in scleritis with the domination of lymphocytes and plasma cells.

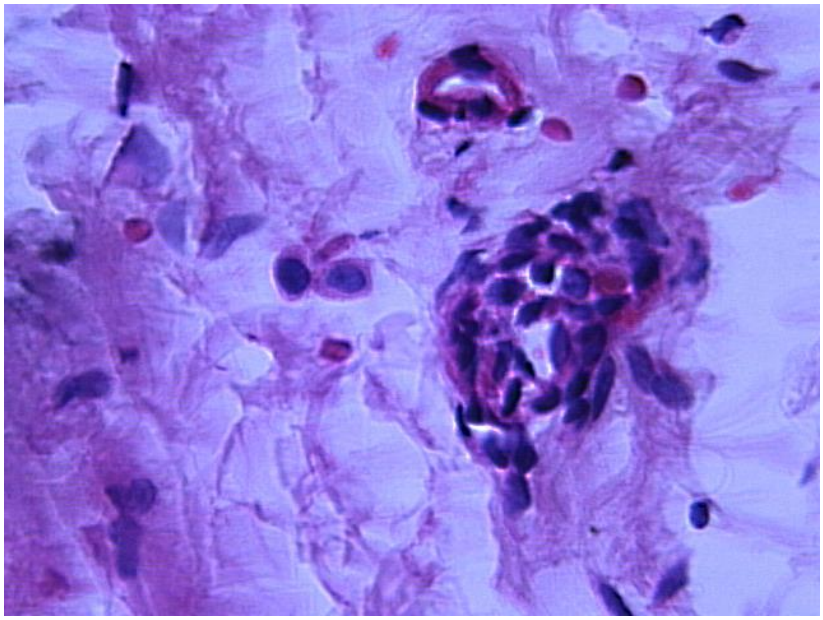

Figure 4. Nodular scleritis with multiple foci of mononuclear infiltration (HE, x200)

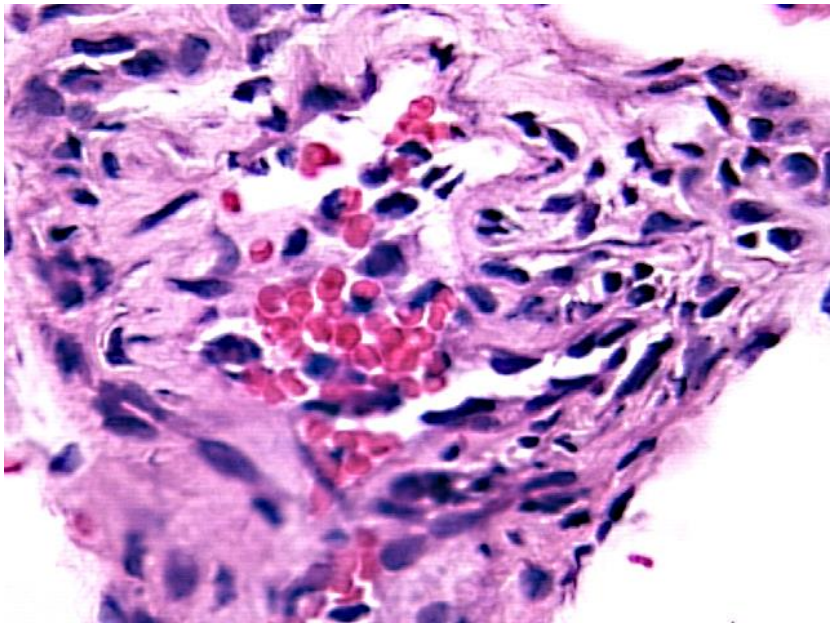

Figure 5. Elevated number of inflammatory cells in scleritis with the domination of lymphocytes and plasma cells (HE x 200)

Discussion

Scleritis is a severe inflammatory condition that is characterized by edema and inflammatory cell infiltration of the sclera. The most common symptoms present are pain and redness (1). In most cases, scleritis affects the front part of the sclera. Diffuse and nodular scleritis are equally frequent,

usually bilaterally and more common in females. While diffuse scleritis is usually bilateral with an unknown etiology, nodular scleritis and necrotizing scleritis are usually unilateral and frequently associated with systemic diseases (6).

Recent studies show that the percentages of patients manifesting scleritis can be classified as follows: diffuse anterior scleritis – 39 % to 45 %, nodular – 23 % to 45 %, necrotizing with inflammation – 10 % to 23 %, scleromalacia perforans – 3 % to 4 %, and posterior scleritis – 2 % to 12 % (9). Diffuse anterior scleritis manifests diffuse or sectoral hyperemic vascular congestion that includes deep scleral blood vessels and is associated with chemosis. This is the least severe class of scleritis. Nodular anterior scleritis is characterized by localized inflammation, with swelling in the form of a scleral nodule which predominantly appears in the intrapalpebral region, close to the limbus. The non-necrotizing classifications of diffuse scleritis and nodular anterior scleritis are usually far less destructive than the necrotizing types of scleritis and present a minimal risk of vision loss. However, 20 % of cases of nodular scleritis may progress to necrotizing scleritis.

Necrotizing scleritis is far more serious than non-necrotizing one due to the severity of potential sequel, including vision loss. Scleromalacia perforans usually involves the destruction of the scleral tissue with minimal to no visible inflammation. It is the most destructive form of scleritis, as it can lead to globe perforation in an asymptomatic fashion, although globe perforations are uncommon (6-8, 9).

Scleritis may be idiopathic or associated with systemic immune-mediated diseases. Rheumatoid arthritis is the most common systemic condition associated with scleritis. Several studies have demonstrated that patients with rheumatoid arthritis associated with scleritis usually have advanced joint disease and extra-articular manifestations; many of these extra-articular manifestations reflect an underlying systemic vasculitis. The most common extra-articular manifestations are subcutaneous nodules (50 %) and skin vasculitis ulcers (25 %). Other extra-articular manifestations include pulmonary disorders, cardiac abnormalities, neurological involvement, amyloidosis. Several studies have shown that the prognosis for life is poorer in patients with rheumatoid arthritis complicated by scleritis than in those without (9-11). McGavin found a 3-year mortality rate of 45.5 % for patients with rheumatoid arthritis and scleritis versus 18.2 % for patients with the disease but without scleritis (12). Foster and coworkers found rheumatoid arthritis and necrotizing scleritis in their series of 20 patients, while 7 patients died of vascular-related events within a 10-year period (13, 14).

The correct and rapid diagnosis and appropriate systemic therapy can halt the relentless progression of both ocular and systemic processes, thus preventing the destruction of the globe and prolonging survival. The treatment of scleritis requires systemic therapy such as nonsteroidal anti-inflammatory drugs (NSAID's), corticosteroids, or DMARDs. (15, 16). In the cases of necrotizing scleritis, therapy includes immunosuppressive drugs, and new data suggest that new biotech therapies, such as Rituximab, provide significant efficacy and safety (17).

The true pathogenesis of scleritis is still unknown. The presence of microangiopathy in most scleritis specimens suggests an underlying immune-complex reaction (Type I hypersensitive reaction), in which vascular injury is the result of antigen-antibody conjugation within and outside the vessel wall, with the subsequent activation of the complement, attraction of neutrophils and fibrinoid necrosis of vessels and the surrounding tissue. The antigen is usually the aberrant expression of HLA-DR on scleral fibroblasts, induced by interferon gamma (11).

Sainz de la Maza points out that microangiopathy developed through the deposits of immunocomplex, and revealed by the immunohistochemical examination of scleral biopsy, the finding of fluorescein angiography, as well as a good response to corticosteroids and immunosuppressives, suggest the autoimmune nature of scleritis. The analysis of pathomorphological substrates and establishing a clinical morphological correlation represent the basis for the understanding of disease pathogenesis (5).

The pathohistological appearance is not specified. In the diffuse form of scleritis, there is a strong infiltration of lymphoid cells. Nodules are similar to or even of the same composition as subcutaneous nodules in rheumatoid arthritis with a granulomatous inflammatory response, central necrosis, surrounded by epithelioid and giant cells as well as lymphocytes and plasma cells. In the necrotic form, prominent processes are the infiltration of mast cells and the degeneration of scleral collagen accompanied by a fibroblastic reaction.

The application of the morphological analysis shows clear differences between substrates in the analyzed forms of scleritis. These differences in the morphologic changes in scleritis associated with systemic autoimmune diseases, compared with morphological changes occurring in idiopathic scleritis, could be caused by differences in the pathogenesis of the two types of scleral inflammations (8, 9). Rheumatoid arthritis is an autoimmune vasculitis disease associated with a circulating immune-complex. The histopathological findings of scleritis associated with a systemic immune disease - that is, the presence of vasculitis associated with zonal granulomatous inflammation surrounding the central necrotic sclera - support an immune-complex mediated immunopathogenesis for scleritis associated with a systemic autoimmune disease (14-20). Idiopathic scleritis, on the other hand, is less likely to be an immune-complex mediated process; its immunopathological findings are rather consistent with a delayed type of the hypersensitivity reaction. This is supported by the absence of vasculitis and the presence of the reactive proliferation of connective tissue (21, 22).

Conclusion

There are numerous abnormalities in the immune status of patients with both idiopathic scleritis and scleritis associated with rheumatoid arthritis. The analysis of the pathomorphological substrate shows clear differences in analyzed forms of scleritis.

Acknowledgments

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Conflict of Interest

There are no conflicts of interest.

References

1. Watson PG. The diagnosis and managament of scleritis. Ophthalmology 1980; 87:716-20. [CrossRef]
2. Watson P, Hayreh S. Scleritis and episcleritis. Br J Ophthalmol 1976; 60:163-91. [PubMed] [CrossRef]
3. Denk PO, Thiel HJ, Zierhut M. Episcleritis and scleritis. An overview of modern diagnostic and therapeutic concepts. Klin Monatsbl Augenheilkd 1997; 211(30): 140-50. [CrossRef]
4. Denk PO, Roshrbash JM, Thiel HJ. New clinical and epidemiologic aspects of episcleritis and scleritis. Ophthalmologe 1997; 94(3):202-5. [PubMed] [CrossRef]
5. Sainz de la Maza M, Foster CS, Jabbur NS. Scleritis associated with systemic vasculitis diseases. Ophthalmology 1995; 102(4):685-92. [PubMed]
6. Sainz de la Maza M, Foster CS, Jabbur NS. Scleritis associated with rheumatoid arthritis and with other systemic immune-mediated diseases. Ophthalmology 1994; 101(7):1281-6. [PubMed] [CrossRef]
7. Reddy SC, Rao UR. Ocular complications of adult rheumatoid arthritis. Rheumatol Int 1996; 16(2):49-52. [PubMed] [CrossRef]
8. Widiarti P, Riono MD, Ahmed A, Hidayat NA, Rao A. Clinicopathologic Study of 55 cases. Ophthalmology 1999; 106(7):1328-33.
9. Rao NA, Marak GE, Hidayat AA. Necrotizing scleritis. A clinicopathologic study of 41 cases. Ophthalmology 1995; 102:687-92. [PubMed]
10. Akpek EK, Uy HS, Christen W, Gurdal C, Foster CS. Severity of episcleritis and systemic disease association. Ophtalmology 1999; 106(4):723-31. [PubMed] [CrossRef]
11. McGavin D, Williamson J, Forrester J, Foulds W, Buchanan W, Dick W, et al. Episcleritis and scleritis. A study of theirclinical manifestations and association with rheumatoid arthritis. Br J Ophtalmol 1976; 60: 192-226. [PubMed] [CrossRef]
12. Jabs D, Mudun A, Dunn J, Marsh M. Episcleritis and scleritis: clinical features and treatment results. Am J Ophthalmol 2000; 130:469-76. [PubMed] [CrossRef]
13. Foster CS, Forstot SL, Wilson LA. Mortality rate in rheumatoid arthritis patients developing necrotiying scleritis or peripheral ulcerative keratitis. Effect of systemic immunsuppression. Ophthalmology 1984; 91: 1253-63. [PubMed] [CrossRef]
14. David C. Anterior scleritis: three case reports and review of the literature. Optometry 2004; 75(7):430-44. [PubMed] [CrossRef]
15. Ashok D, Ayliffe W, Kiely P. Necrotizing scleritis associated with rheumatoid arthritis: long-term remission with high-dose infliximab therapy. Rheumatol 2005; 44:950-1. [PubMed] [CrossRef]
16. Ahn S, Oh J, Kim M, Wee W. Treatment of refractory scleritis with infliximab. Jpn J Ophtalmol 2009; 53: 286-7. [PubMed] [CrossRef]
17. Chauhan S, Kamal A, Thompson R, Estrach C, Moots R. Rituximab for the treatment associated with rheumatoid arthritis. Br J Ophtalmol 2009; 93:984-5. [CrossRef]
18. Keystone E, Kavanaugh A, Sharp J, Tannenbaum H, Hua Y, Teoh L, et al. Radiographic, clinical, and functional outcomes oftreatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004; 50:1400-11. [PubMed] [CrossRef]
19. Zlatanović G1, Veselinović D, Cekić S, Zivković M, Dorđević-Jocić J, Zlatanović M. Ocular manifestation of rheumatoid arthritis-different forms and frequency. Bosn J Basic Med Sci 2010; 10(4):323-7. [PubMed] [CrossRef]
20. Sokolović S, Kasumagić S, Mackić-Durović M, Aganović-Musinović I. The impact of Rituximab therapy on the chromosomes of patients with rheumatoid arthritis. Bosn J Basic Med Sci 2010; 10(2):121-4. [PubMed] [CrossRef]
21. Artifoni M, Rotchild PR, Brezin A, Gullevin L, Puéchal X. Ocular imflammatoty diseases associated with rheumatoid arthritis. Nature Reviews Rheumatology 2014; 10:108-16. [PubMed] [CrossRef]
22. Levy-Clarke G, Jabs DA, read RW, Rosenbaum JT, Vitale A, Van Gelder N. Expert panel recommendations for use of anti-tumor necrosis factor biologyc agents in patients with ocular inflammatory disorders. Opthalmology 2014; 3:785-96. [PubMed] [CrossRef]

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KLINIČKO PATOHISTOLOŠKA ANALIZA SKLERITISA – PRIKAZ DVA SLUČAJA

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Skleritis je hronična bolest sklere koja može biti povezana sa sistemskim bolestima vezivnog tkiva, a koju karakterišu bol, otok, crvenilo i potencijalni gubitak vida. Skleritis se može pojaviti kao samostalan ("idiopatski") ili kao udružen sa sistemskim bolestima vezivnog tkiva. U radu su prikazana dva različita slučaja skleritisa: prvi prikaz predstavio je ženu koja je imala "idiopatsku" formu sa difuznim tipom, i drugi ženu sa nodularnim tipom skleritisa udruženim sa reumatoidnim artritisom. Obe bolesnice podvrgnute su detaljnom kliničkom, laboratorijskom i imunološkom ispitivanju, urađena je patohistološka analiza biopsiranog uzorka. Prva bolesnica koja je imala difuznu formu skleritisa, imala je laboratorijske analize sa normalnim parametrima. Patomorfološki supstrat pokazao je edem episkleralnog i skleranog tkiva i prisustvo inflamatornih infiltrata sa obilnim limfocitima i histiocitima praćenih aktivnom hiperemijom i kapilarima sa neuobičajnim vezama između krvnih sudova sklere i episklere. Druga pacijenkinja imala je nodularni skleritis udružen sa reumatoidnim artritisom. Patomorfološki supstrat sklere pokazao je multiple fokuse mononuklearne infiltracije sa dominacijom limfocita, unutrašnjom zonom od polimorfonuklearnih ćelija i histiocita, gigantskih ćelija tipa stranog tela, i spoljašnom zonom sačinjenom od limfocita i plazma ćelija. U poređenju sa normalnim tkivom sklere, broj inflamatornih ćelija bio je 10-15 puta veći kod ove vrste skleritisa sa dominacijom limfocita i plazma ćelija.

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Ključne reči: *skleritis, reumatoidni artritis, scleromalacia perforans*