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Diagnosis and treatment approach for necrotizing scleritis (NS): A clinical case

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Abstract

Necrotizing scleritis is an immune-mediated ocular inflammatory process, characterized by an area of avascular necrosis and a profound inflammation of the sclera and episclera. Necrotizing scleritis and its association with peripheral ulcerative keratitis – necrotizing sclerokeratitis (NS) – represents a serious threat for vision and eye integrity, evolves very fast if untreated, and its finding suggests the presence of a potentially lethal systemic vasculitic process. The following case is an example of the diagnostic approach and therapeutic scale in a 63-year-old woman with necrotizing sclerokeratitis. (Gac Med Mex. 2015;151:490-3)

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Introduction

The term necrotizing sclerokeratitis (NS) refers to an inflammatory process involving a limited scleral necrosis zone with visible choroid, associated with a peripheral ulcerative corneal defect and inflammatory corneal infiltrates[1,2]. Its presence is often suggestive of life-threatening systemic vasculitic process[2], and, therefore, opportune diagnosis, appropriate therapeutic approach and etiology determination must be carried out urgently, since they play a crucial role in the control of the life-threatening systemic inflammatory process that also threatens ocular globe integrity.

Case report

This is the case of a 63-year-old female patient who attended for ophthalmologic evaluation due to red eyes, ocular pain and foreign body sensation in right eye with 8 months of evolution. Previously, she was treated by the ophthalmologist with topical prednisolone six times per day and topical antibiotic (ciprofloxacin) thrice daily for 1 month with no improvement being achieved. She referred no previous family or personal history of relevant non-pathologic conditions; personal medical history consistent with facial paralysis two years previously to her consultation, hypertension

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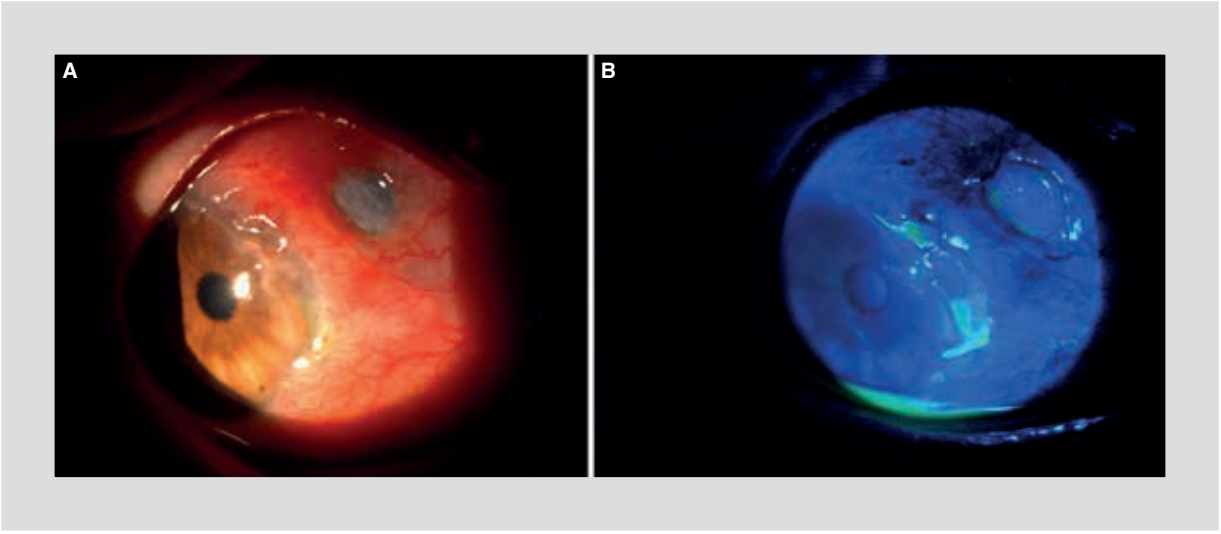

Figure 1. A: *conjunctival hyperemia and ciliary injection, 2 x 3 mm scleral necrosis area in superonasal area with visible coroid, associated with a peripheral crescentric corneal defect with thinning and stromal inflammatory infiltrates.* **B:** *fluorescein staining, cobalt light. Staining is observed in the superior portion of epithelial corneal defect, as well as fluorescein staining in scleral necrosis zone and inferior portion of corneal defect.*

of 6 years of evolution managed with metoprolol, losartan and hydrochlorothiazide, and joint pain of 5 years' evolution treated with oral indomethacin.

Best corrected visual acuity was 20/40 RE and 20/20 LE. At the biomicroscopic exam, RE with conjunctival and ciliary injection was found, as well as a 2 x 3 mm scleral necrosis area in the superonasal region with visible choroid, associated with peripheral corneal defect with thinning and stromal inflammatory infiltrates (Fig. 1 A and B). Anterior chamber was formed and ample, with no cellularity; pupils round, reactive to light and accomodation; intraocular pressure of 19 mmHg (with Goldmann applanation tonometry). LE did not show any pathological alterations at the anterior segment exam. Funduscopy was found without pathological alterations, with a cup to disk ratio of 0.3 on both eyes.

Clinically, a NS diagnosis was established and diagnostic workup was started in order to determine the etiology of the condition. In view of a general physical examination without relevant findings in addition to a history of unspecific arthropathy, diagnostic auxiliaries were used in search for rheumatologic conditions and systemic vasculitic processes, with the following results:

- Blood count and general urine test within normal parameters.
- Glomerular sedimentation rate 40 mm/h and C-reactive protein 0.37.
- Negative rheumatoid factor (< 60 U/ml), citrullinated cyclic peptide and antinuclear antibodies.
- Liver function tests within limits of normal.

Since her first visit she was started on systemic antiinflammatory treatment with prednisone 60 mg (1 mg/kg/day) at weekly tapering doses and cyclophosphamide 2 mg/kg in intravenous (i.v.) bolus administered every 6 weeks, plus topical adjuvant therapy: condroitin sulfate 3% and moxifloxacin.

After initial laboratory values were obtained within normal values, determination of fluorescent anti-Treponemal IgM antibodies (FTA ABS), anti-neutrophil cytoplasmic antibodies (ANCA) and posteroanterior chest x-ray was indicated, all with negative results for pathology.

A significant clinical improvement was observed in scleral and episcleral inflammation, as well as a decrease in inflammatory and lytic activity of sclera and episclera and 20/30 visual acuity two months after the treatment was started (Fig. 2 A and B). Until the last visit, the patient continued with negative serologies, on oral prednisone with tapering dose (10 mg/day) and with 2 cycles of i.v. cyclophosphamide (1 g i.v. each cycle).

Discussion

Scleritis is an immune-mediated (autoimmune complexes) inflammatory process that affects especially patients of the female gender at the fifth or sixth decades of life[1]. Traditionally it is classified as anterior or posterior, with anterior being predominant[1]. In turn, anterior scleritis is classified into diffuse, nodular and necrotizing; 30% of the first two are associated with systemic inflammatory vascular conditions and up to 70%

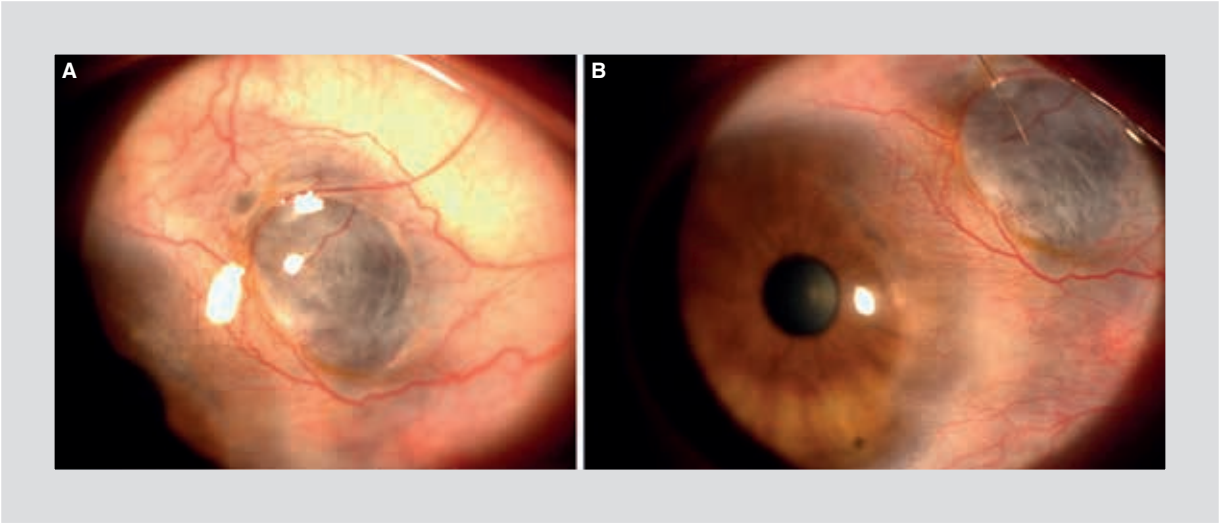

Figure 2. *Two-month evolution on systemic immunosuppressive therapy.* **A:** *important decrease of scleral and episcleral inflammation is observed, as well as tissue-remodelling zone and scleral tissue thinning (scleromalacia) with underlying uveal tissue visualization.* **B:** *epithelial defect resolution and significant improvement of corneal thinning area, as well as conjunctivalization of previously-ulcerated corneal region.*

of the latter are directly related to life-threatening vasculitic processes[1,2]. Similarly, a very clear relationship between necrotizing scleritis and peripheral ulcerative keratopathy has been established, and when the latter occurs, it tends to affect the same quadrant as scleritis. Furthermore, the presence of NS has been associated with a high rate of corneal perforation[2].

NS is a rapidly progressing condition, and timely diagnosis and treatment, before the patient refers vision loss or ocular globe perforation being imminent, has demonstrated to improve ocular prognosis[3]. In view of this evidence is that it was decided to start treatment with systemic steroids and immunosuppressants at the initial visit, even without having clearly identified the etiology of the entity and after having disregarded the main infectious etiologies.

Four main etiologies of NS have been established: idiopatic, systemic disease-associated, infectious and associated with traumatic events and/or surgical procedures[4]. Sainz de la Maza, et al.[5], in a study of 47 patients with necrotizing scleritis associated with peripheral ulcerative keratopathy, found systemic vasculitic processes and collagen diseases as the main systemic associations. Within these autoimmune-origin vasculitic processes, rheumatoid arthritis and Wegener granulomatosis were more significantly correlated with NS[5]. From this evidence, and based on the patient's previous personal history (no history of trauma/surgery, history of non-specified arthtropathy), we found it necessary to perform laboratory serum tests (rheumatoid factor, anti-neutrophil cytoplasmic antibodies, erythrocyte sedimentation rate, C-reactive protein) in order to test for coexistence of immune-originating systemic disease. The importance of a good history, interrogation by organs and systems and general physical and ophthalmologic examination, are indispensable in these cases in order to determine the presence of signs and symptoms that, in the absence of previous systemic disease diagnosis, can guide us towards the diagnosis and towards the prudent selection of diagnostic auxiliary tests (imaging and laboratory).

Although the performance of initial serum testing to determine the presence of autoimmune disease initially yielded negative results, coexistence of NS with systemic disease could not yet be disregarded in this case. Karamursel, et al.[6] reported that 78% of their patients had previous diagnosis of systemic disease at initial ophthalmoligic exploration, that diagnosis was made during ophthalmologic exploration in 14% of patients and that 8% of patients were diagnosed during ophthalmologic follow-up. Relapsing polychondritis and intestinal inflammatory conditions were the two systemic diseases more commonly associated with late diagnosis in patients initially assessed for necrotizing scleritis with no evidence of systemic disease[6]. With this evidence in mind, we could not disregard an associated systemic disease in this case, since there is the probability of it being diagnosed during the follow-up; it is also important to emphasize on the importance of interrogating the patient by organs and systems at each visit in order to determine the presence of symptoms that might guide us to discover a systemic disease.

Initial management of NS, in view of the consequences, both ocular and on the patient's life, should be directed to the use of immunosuppressive agents and should be coordinated by professionals with experience in the management of these drugs. A treatment algorithm has been established for appropriate management of NS, where recommendations indicate the use of high-dose corticosteroids (oral prednisone 1 mg/kg/day) with tapering at 4-8 weeks (depending on the inflammatory response); i.v. methylprednisolone (1 g/day x 3 days) for acute control of severe inflammatory processes, and of alkylating immunosuppressive agents, with cyclophosphamide being the drug of choice (2 mg/kg/day, for up to 12 months)[7,8]. Liver enzymes, blood count and general urine tests should be periodically monitored (every 4-6 weeks) in order to screen for the most common side-effets attributed to cyclophosphamide (hemorrhagic cistitis, bone marrow suppression and drug-related hepatitis)[7,8]. The use of topical steroids has been recommended in case of coexistence with anterior uveitis, but not as main therapy[7,8]. Finally and still controversial, consensus has indicated periocular steroids contraindication in any case of necrotizing scleritis, due to an increased risk of scleral thinning and perforation[9].

Recently, tumor necrosis factor alpha (TNF-α)-inhibitor biologic agents such as infliximab, etanercept, adalimumab and rituximab, have been used with good results in some cases of necrotizing scleritis or NS refractory to standard therapy with systemic steroids and immunosuppressants[10-15]. However, its use is still limited due to the lack of experience on long-term results, potential adverse effects (tuberculosis reactivation, predisposition to infections and solid tumors), as well as to its high cost[16].

The only surgical indications in scleritis/NS are biopsy for histopathological investigation purposes, corneal/scleral repair or repair of imminent uveal prolapse in corneal perforation (with the use of fascia lata, periosteum, GoreTex®, autologous/homologous scleral tissue)[15]. For the latter two surgical indications, strict ocular inflammation control should be established[15].

Conclusions

NS is an ocular disease associated with life-threatening systemic autoimmune processes. Timely diagnosis and treatment are indispensable for preservation of the ocular globe and, more importantly, of the patient's life. Medical and personal history, interrogation by organs and systems, as well as general and ophthalmologic exploration are essential tools to guide us in etiologic diagnosis and to order auxiliary laboratory and imaging tests that help us to confirm it. Treatment should always be intended to be systemic, through the use of high-dose corticosteroids and alkylating immunosuppressive agents such as cyclophosphamide. The success of systemic immunosuppressive therapy will depend on the rational use of medications and monitoring of their adverse effects by experienced professionals.

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