BALNEO RESEARCH JOURNAL
English Edition
eISSN 2069-7619 pISSN 2069-7597 ROMANIAN ASSOCIATION OF BALNEOLOGY

An uncommon association of dry eye syndrome with relapsing polychondritis and necrotizing scleritis

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Balneo Research Journal DOI: http://dx.doi.org/10.12680/balneo.2020.341 Vol.11, No.2, May 2020 p: 204–209

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Abstract

Introduction Relapsing polychondritis (RP) is a rare disease evolving with recurrent cartilage inflammation, but also with ocular, respiratory, cardiac and vascular involvement. Associations with various autoimmune disorders and with hematological diseases, mainly leukemia, lymphoma and myelodysplastic syndrome and rarely with hemolytic anemia, have been described. We report a 63-year patient with thyroiditis and pernicious anemia in whom a left eye necrotizing scleritis led to the diagnosis of RP and common variable immune deficiency (CVID). The necrotizing scleritis was successfully operated with scleral graft. However, the disease control was difficult to be achieved with glucocorticoids and various immune suppression regimens tried (including cyclophosphamide, cyclosporine, azathioprine, leflunomide and infliximab) along with immunoglobulin substitution. The association of RP and CVID or CVID-like diseases is rare, another 4 cases having been reported. We review the literature and discuss the diagnostic and management difficulties. A multidisciplinary team approach is necessary in this setting.

Key words: *relapsing polychondritis, dry eye, necrotizing scleritis,*

Introduction

Necrotizing scleritis is a severe ocular complication of systemic diseases, that may rarely be inaugural. Necrotizing scleritis may occur in other diseases such as rheumatoid arthritis, in systemic vasculitis as granulomatosis with polyangiitis, Crohn's disease, relapsing polychondritis (RP) etc. Relapsing polychondritis (RP) is a rare disease evolving with recurrent cartilage inflammation, but also with ocular, respiratory, cardiac and vascular involvement. Associations of RP with various autoimmune disorders and hematological diseases, mainly leukemia, lymphoma and myelodysplastic syndrome and rarely with hemolytic anemia, have been described (1).

Common variable immune deficiency (CVID) is a rare disease manifesting with low concentrations of immunoglobulins, mainly IgG and IgA, and with inefficient production of antibodies to different pathogens (2). Autoimmune diseases, including thyroiditis, pernicious anemia, rheumatoid arthritis and rarely RP, are associated in 20% of cases (2).

Case report

A 63-year female patient with a 6- year history of autoimmune thyroiditis and hypothyroidism, with pernicious anemia since 2 years, two episodes of red eye in the last 2 years, on chronic substitutive therapy with L-thyroxine, vitamin B12 and folic acid, with bronchial asthma and several episodes of pneumonia in the last 2 years, presented in the Emergency for a red painful left eye. She also complained of chronic hoarseness, non-productive cough and episodic joint pain. Family history revealed that her mother suffered from asthma and Basedow-Graves' disease and her sister was diagnosed with Hashimoto thyroiditis.

The general clinical exam was normal.

The functional ocular examination revealed a best corrected visual acuity (BCVA) of 0.9 at right eye (RE) and 0.2 at left eye (LE). Ocular refraction was -3.50 sf/ cyl -0.75 ax10º and -2.00 sf/cyl -2.25 ax100º. The intraocular pressure in the RE was 17 mmHg and 59 mmHg in the LE, measured by Goldmann aplanotonometry.The pupillary reflex at light was present in both eyes and was normal. The Schirmer test was normal for the RE and 4 mm for the LE. The break-up time (BUT) was 5 seconds, revealing a great instability of tear film. Corneal and conjunctival staining was grade III on the Oxford Grading. (Table 1)

The slit lamp examination showed a normal examination in the RE. Left eye presented a necrotizing area of 2.5/1 cm in the superior

perilimbal region with scleral and conjunctival necrosis, localized at about 1 cm from the limbus with ciliary body visibility covered with mucus secretion. At the same eye, cornea was transparent with a thin white perilimbal infiltration, a medium sized anterior chamber, ptosis and edema of the superior eyelid. (Fig.1)

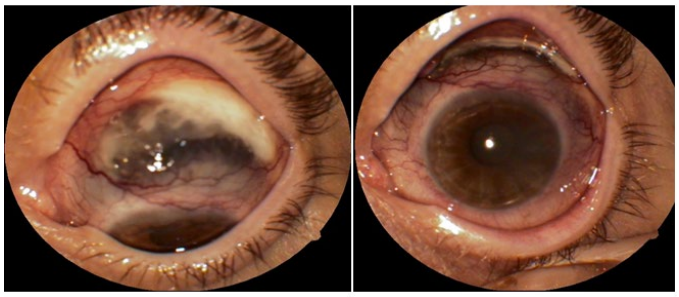

Fig. 1. The slit lamp examination - a necrotizing area of 2.5/1 cm in the superior perilimbal region with scleral and conjunctival necrosis at about 1 cm from the limbus with ciliary body visibility

Table 1. The evaluation of the dry eye syndrome

Schirmer Test		**BUT (Break – up time)**		**OSDI (Ocular Surface Disease Index)**
RE normal	**LE 4 mm**	**RE normal**	**LE 5 seconds**	**OSDI = 35**

Ptosis diagnosis was done by measuring the distance between the lid margin of the upper eyelid and corneal reflex RE= 4 mm / LE =1mm (4.5). The distance between the lid margin of both eyelids was RE=11 mm /LE =8mm (8-12), the superior rectus muscle function was RE= 7mm/ LE =7mm (12-15). The distance between the lid margin and the orbital margin of the upper eyelid was RE =10mm/ LE =10mm (10). Fundus examination revealed retinal angiosclerosis in both eyes.

An ocular ultrasound examination was performed, showing a thickening of the superior rectus muscle (tennonitis) with severe thinning of the ocular sclera (about 0,5 mm) in the superior area of the ciliary body. (Fig.2)

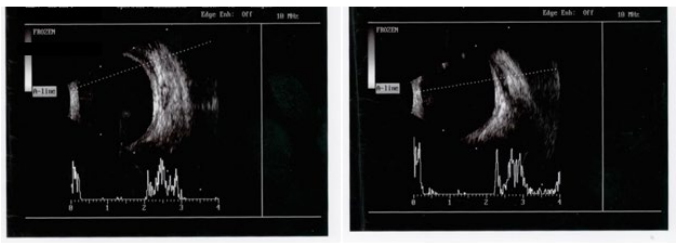

Fig. 2. Ultrasound exam at left eye – Thickening of the superior rectus muscle and thinning of the sclera in the superior area.

The screening for infection was negative (negative conjunctival secretion cultures, pharyngeal swab, bronchial secretion, hemocultures, procalcitonin, Mycoplasma, Cytomegalovirus, Epstein-Barr, hepatitis B and C, HIV). Examination revealed a deformed ear cartilage. A relapsing polychondritis was suspected, soon confirmed by the presence of florid ear chondritis. (Fig.3)

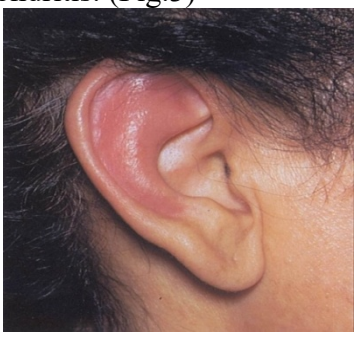

Fig. 3. Ear chondritis

Laboratory revealed an elevated ESR (85 mm/h) and CRP (2.4 mg/dL, normal<0.6 mg/dL). C3 and C4 were normal (C3 138, normal 60-150 mg/dL, C4 18, normal 16-35 mg/dL). Antinuclear, anti-Ro, anti-La, anti-neutrophil cytoplasm, anticardiolipin and anti-beta-2 glycoprotein antibodies were negative, but the anti-parietal gastric cell antibodies were positive in immunofluorescence (1/80) and the anti-TPO antibodies were positive (625 IU/mL, normal <45 IU/mL). There was a moderate anemia (Hb 8.7), with minimal hemolysis (indirect bilirubin 1,2 mg/dL, normal<1 mg/dL), LDH 512 (normal 230-460IU/L), with normal WBC with differential and platelet count (5400/mmc and 217 000/mmc respectively). The vitamin B12 (2 years previously low, 125 pg./dL, normal >210 pg./dL) and folic acid were normal under substitution, as were the T3, T4 and TSH values. Direct and indirect Coombs test were negative. The immunogram, however, repeatedly revealed low immunoglobulin titers, suggestive of common variable immunodeficiency (IgG 42 IU/mL, normal 90-120, an IgA of 61 (normal 60-240) and a normal IgM (158, normal 70-250 IU/mL). The urinary Bence-Jones proteins, the immunoelectrophoretic with immune fixation of the blood and urine for free light immunoglobulin chains was negative. Due to the low value of hemoglobin (5,6 g/dL), we suspected anemia and a hematologic consultation was performed, showing VEM: 112fl, reticulocytes =1‰, discrete leucopenia - WBC=3100/mm3, neutropenia, neutrophil 1350/mm3, discrete thrombocytopenia, PLT=120 000/mm3, blood smear: huge erythrocytes, hyper segmented neutrophils. The myelogram showed the presence of megaloblastic cells with giant metamyelocytes; there were no elements of

dysplasia on the granulocytic and megakaryocytic series. The bone marrow aspirate examination revealed megaloblastic cells with giant metamyelocytes with some myelodysplastic changes. (Fig.4) The patient refused the iliac bone biopsy. A gastroscopy revealed atrophic gastritis, and the rest of malignancy screening (thyroid and abdominal ultrasonography, chest CT, mammography, gynecological examination with PAP smear) was negative as well.

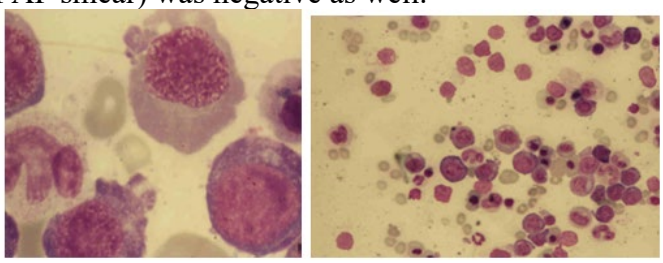

Fig. 4. Bone marrow examination – Megaloblastic cells with giant metamyelocytes

In order to confirm the polychondritis a PET –CT scan was done, which emphasized the active disease in the joints of the patient. (Fig.5)

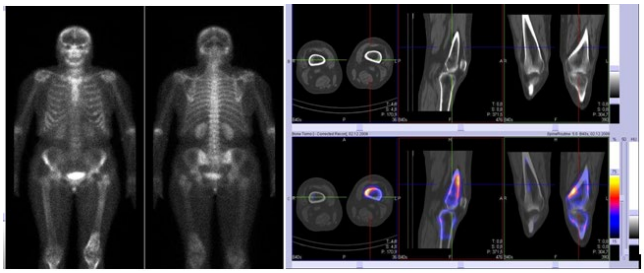

Fig. 5. Whole body PET – CT Scan – and knee section of PET-CT scan – activity of the polychondritis.

Final diagnosis was at both eyes: direct compound myopic stigmatism and at LE
necrotizing scleritis, pseudoptosis, secondary glaucoma and severe dry eye syndrome, relapsing polychondritis, common variable immune deficiency, megaloblastic anemia, autoimmune thyroiditis.

Scleritis differential diagnosis was made with anterior scleritis, purulent scleritis, scleromalacia perforans, blue scleral syndrome, ciliary body malignant taking in consideration the age, gender, clinical and paraclinical examination and causative factors.

The purpose of the treatment was to diminish the local inflammation, to decrease the intraocular pressure and to cover the wall defect and prevent the development of new necrosis. The patient was treated topical with a fixed combination of anti-inflammatory drugs and antibiotics: Tobramycin 3mg with Dexamethasone 1 mg, 5 gut/day, Ofloxacin 0,3%, 3 gut/day, Tropicamide 1%, 3 gut/day and antiglaucomatous treatment with Timolol 0,5%, 2 gut/day. For the dry eye syndrome was indicated Cyclosporin 1 mg 1 gtt/day and artificial tears. The patient was treated surgically after signing a surgical consent. It was performed a scleral and conjunctival plasty with a scleral graft recruited from the RE with the acceptance of the patient. Also, systemic therapy with methylprednisolone pulses (1g/day iv for 3 days, then 1 mg/kg/day orally one month with tapering), and cyclophosphamide monthly iv pulses of 15 mg/kg, 6 pulses, cyclosporine – stopped due to severe hypertension and renal insufficiency, azathioprine – stopped due to intolerance, then cyclophosphamide orally. The visual acuity and intraocular pressure returned to normal and she had less episodes of auricular and respiratory chondritis, but persistence of severe episodic arthritis. (Fig.6)

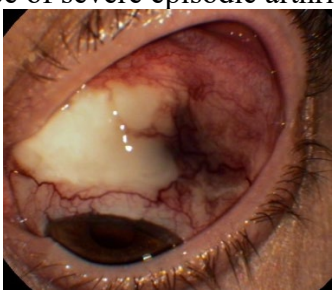

Fig. 6. – Postop follow-up – integrated scleral graft

She also received intravenous immunoglobulin monthly substitution (0.4 g/kg/month). However, while on immunosuppression therapy, two years after the first episode of necrotizing scleritis, she developed another similar episode, in the same eye. The cerebral MRI and the repeated workup for vasculitis (ANCA, ANA, C3, C4, cryoglobulins) were negative. Methylprednisolone and cyclophosphamide pulses were restarted. Due to the incomplete disease control, a course of high-dose immunoglobulins (0.4 g/kg for 5 days) was given, with ocular improvement, but minimal alleviation of joint symptoms. She developed tibiae-tarsal and subtalar bilateral arthritis evolving to dissecting osteochondritis. Leflunomide 20 mg/day and a single infusion of infliximab 3 mg/kg were given, stopped because of prolonged diarrhea revealing an E. coli sepsis. She was transferred to the Infectious disease department, where after imipenem and ciprofloxacin the hemocultures and stool cultures became negative and the general status improved. Echocardiography did not show valvular

vegetations, nor cordage papillary dysfunctions or thoracic aorta aneurysms. However, arthritis was severe, and she developed florid nasal and laryngeal chondritis. She was continued on low-dose glucocorticoids and leflunomide 10 mg/day, along with immunoglobulins. When she did not show up for the regular admission, we found out that she had a non resuscitable cardio-respiratory arrest, and no autopsy was performed, at family's wish.

Discussions

RP polychondritis is a rare disease involving mostly the cartilage. The McAdam criteria required for diagnosis include auricular chondritis, nasal chondritis, non-erosive inflammatory polyarthritis, ocular inflammation, laryngo-tracheal involvement, and audio-vestibular dysfunction (3). RP is associated with hematological pathology. RP is strongly associated with myelodysplastic syndrome (MDS) (4). MDS are clonal disorders of hematopoiesis characterized by peripheral cytopenia and a dysplastic bone marrow, usually hypercellular (5-50% erythroid precursors in the marrow) (5). Although suggestive for an MDS, our patient did not have enough diagnostic criteria, and she refused medullar biopsy. The megaloblastic anemia was attributed to pernicious anemia, in the context of antiparietal gastric cell antibodies and low vitamin B12. The differential diagnosis between MDS and pernicious anemia solely on bone marrow biopsy is difficult (6,7,8). Although in the assessment of a megaloblastic anemia a MDS and a pernicious anemia are considered mutually exclusive, they may rarely co-exist (8,9,10). Moreover, pernicious anemia may mimic MDS when falsely normal vitamin B12 levels are found, in the presence of anti-intrinsic factor antibodies (11). A nonrandom 7q- chromosomal abnormality has been observed in cases of severe vitamin B12 and folate deficiency (12). In our patient cytogenetic studies have not been performed.

Common variable immune deficiency (CVID) is a rare immune deficiency characterized by low levels of serum levels of IgG, IgA and often IgM and reduced or absent antibody production after exposure to pathogens (2,13). The serum IgG is always reduced, generally less than 400 mg/dL. The disease is often diagnosed in adults between 20-40 yrs., although it may present in children and older adults as well (2). Most CVID patients can be classified in 2 groups by diseases phenotypes that are stable in time: predominantly with infection, or with infection and predominantly inflammatory/autoimmune conditions (2). Autoimmune diseases appear in up to 20% of patients (14) including thyroiditis and pernicious anemia (13,15). CVID and other primary B cell immunodeficiencies, such as protein C kinase delta deficiency, with a CVID-like picture, have been rarely associated with RP (Table 2).

Ocular inflammation is present in 2/3 of patients with RP (4). Scleritis may be the sole manifestation of RP but rarely is an inaugural sign. (16,17). In CVID, uveitis was found in 1.6% of cases, generally chronic, bilateral and often granulomatous, sarcoid-like (18). Other ocular types of involvement reported are keratoconjunctivitis, retinal vasculitis and retinal vein occlusion (19). Keratitis may be infectious and/or inflammatory (19). Bilateral consecutive sterile central corneal perforations were reported in a CVID patient, responsive to topical glucocorticoids. (20). However, patients with CVID may develop ocular infections even while on iv Ig substitution and without the typical clinical picture of infection (19).

Both RP and CVID are associated with decreased life expectancy, often through association of a hematologic malignancy (2,14). The median age of death in a series followed up for 4 decades was 44 years for females and 42 years for males, due to respiratory failure from chronic lung disease, lymphoid or other malignancy or infections, much higher in patients with inflammatory complications than in those with infection only (14). Lymphomas in CVID are more commonly extra nodal and appear in unusual locations, such as lungs or mucosal-associated lymphoid tissue (2). In our case the direct cause of death could not be established as the autopsy was not permitted, but no malignancies were apparent at the initial screening.

To our knowledge, the case is unique in the presence of recurrent necrotizing scleritis with secondary glaucoma, dry eye syndrome and of the common variable immune deficiency associated with a pernicious anemia. This association is clinically challenging. It is possible that the cytokines from tear film as a mark of the inflammation associated with dry eye could increase the local inflammation. (21,22,23,24,25,26). Nevertheless, Ciclosporin was recommended as a local immunosuppressant agent which blocks the activity of T cells combined with artificial tears to supply the deficit. The diagnosis of RP in CVID may be delayed in the absence of characteristic ear chondritis, as respiratory involvement and bronchiectasis may be found in

Pt no		Age of CVID dg	Age of RP diagnosis		Reference
1 (?)	Recurrent otitis media, auricular chondritis bilateral, polyarthritis	15 mo	4 years	Methotrexate, NSAIDs, Ig iv substitution	Karaca et al, 2009 (Int J Dermatol)(15)
2 (M)	23-year male, RP (auricular chondritis, costal chondritis, bronchomalacia) esophagus-like bronchus	23 yrs	23 yrs	Prednisone 60 mg/day	Zhao et al, 2016(5)
3 (M)	14-yrs, ear chondritis, epiglottitis, costovertebral and TT joint *decreasing IgG2		14 yrs	Steroids, methotrexate, Ig iv monthly	Goldman et al, 2015(12)
4 (M)	Nephrotic syndrome, membranous GN, RP, hypothyroidism, antiphospholipid syndrome (aseptic endocarditis, pulmonary thromboembolism) *PRKCD mutation	15 mo	>3 years	Low-dose steroid, anticoagulation, IG substitution, anti-CD20 (2 courses), MMF	Salzer E et al, 2016(24)
PRKCD – protein C kinase delta; * CVID-like syndrome					

Table 2. Table 1: CVID and CVID-like diseases in RP

both. Moreover, the commonly found splenomegaly and adenomegaly may mislead with regard to a hematological malignancy often associated to RP. Another pitfall is granuloma finding on tissue biopsies in CVID, that may lead to confusion with polyangiitis with granulomatosis in the presence of chondritis (13). The dramatic sight-threatening ocular involvement always needs an urgent intervention and a balance between the immunosuppression-associated benefits and risks, in the presence of immunodeficiency. When a certain manifestation is alleviated by immunoglobulin substitution, an infectious etiology is more likely (13). Nevertheless, severe immunosuppression is often complicated by infections, even under immunoglobulins substitution, like in our case. Also, cyclophosphamide may not prevent the development of recurrent necrotizing scleritis. Anti-TNF agents have been used successfully in necrotizing scleritis complicating RP, and also with improvement in granulomatous diseases in CVID (13); however, in our case, despite ocular involvement alleviation, a single dose was complicated by an E coli sepsis. Rituximab, an anti-CD 20 antibody, is a logical and very useful alternative (2), although not universally successful (27,28). The association of RP with CVID requires frequent consultations and a multidisciplinary team approach.

Declaration of conflict of interests/Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this article.

Informed consent

Informed consent was obtained from the patient included in this study.

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