Red Eye as the Primary Manifestation of Wegener's Granulomatosis☆

Ojo rojo como manifestación primaria de vasculitis sistémica

Dear Editor,

We are writing to present the atypical case of a rare first manifestation of granulomatosis with polyangiitis.

The patient is a 74-year-old woman who came to our centers' Emergency department due to 4 days with persistent headache associated to a red right eye and ptosis of the same side. The process had an abrupt onset and was not associated to fever or trauma, persisting over time and not improving with rest. Upon examination the patient had no cardiopulmonary, abdominal, locomotor, central or peripheral nervous system alterations; just the right red eye and ptosis were found. In the urgent laboratory tests requested we only found a CRP of 78 mg/l and ESR of 109 mm/h, with the rest of the serology within normal limits.

Eye examination showed unilateral proptosis of the right eye, red eye with a negative Tyndall effect, absence of cells in the anterior or posterior chamber, without retinal lesions. The patient had a 0.6 visual acuity of the right eye and of 1 on the left eye.

A cerebral magnetic resonance was performed showing an increase in the size of the right lacrimal grand with supracilliar and lateral and superior orbital affection of the right eye, compatible with dacryocystitis/infiltrative process (Fig. 1, coronal plane), leading us to the diagnosis of orbital pseudotumor with muscle affection and dacryocystitis, beginning treatment with high dose steroids and intravenous antibiotics, due to the severity of the process. A biopsy of the swollen area was performed but the result was non significant and response to medication was tapered, due to the severity of the eye manifestations.

We only found positivity to PR3 45 U/ml (normal <3), with infectious serology (HIV, Syphillis, *Brucella*, hepatitis B and C, *Toxoplasma*), autoimmunity (RF, ANA, anti-DNA negative; ANCA: MPO negative), thyroid hormones and tumor markers negative. The chest X-ray did show a nodular pattern in the lower right lobe.

Two weeks later the patient presented non specific muscle and joint pain of the upper limbs, a single ulcer on the base of the tongue and fever. We performed a thoracic computed tomography which revealed several symmetric and random nodules, mainly on the right lung base, measuring 5 and 15 mm, some of them cavitated, possibly related to granulomatosis. The lateral segment of the middle right lobe showed a condensation possibly related to the same process.

A transbronchial lung biopsy was performed showing a granulomatous vasculitic process, with segmental vascular necrosis and neutrophil and monocyte infiltration, making us reach a conclusion of granulomatosis with polyangiitis.

With respect to later treatment, once the diagnosed was reached we began treatment with: (a) pulse steroid 1.000 mg for three doses, continuing with oral prednisone 1 mg/kg for 2–4 weeks and reducing to 20 mg/day at the end of the second month, with a progressive downward adjustment for 6 months, (b) associated with cyclophosphamide boluses for 4 weeks intravenously, and (c) trimetoprim-sulphamethoxazole, orally, 3/week for *Pneumocystis carinii* prophylaxis.

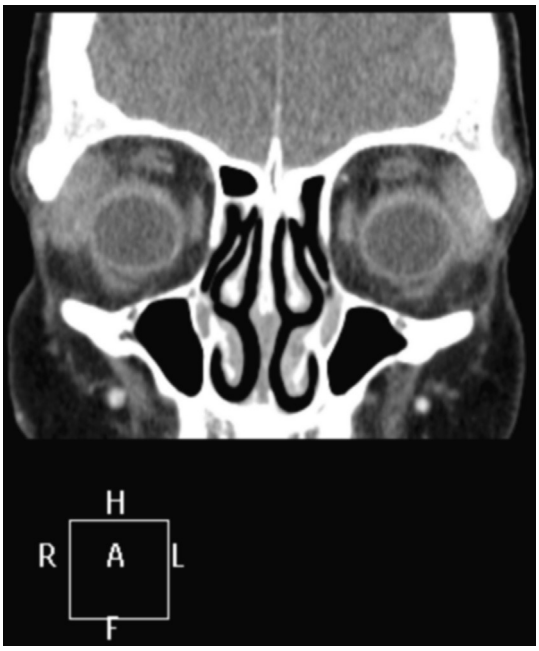

Fig. 1. Cerebral magnetic resonance: increase in the size of the superior and lateral right orbit, compatible with an infiltrating process.

Granulomatosis with polyangiitis is a systemic vasculitis of unknown cause that affects small and medium caliber vessels. It is characterized by respiratory system and kidney affection but may affect other organs. ANCA are frequently positive and the most important histologic characteristic is the presence of necrotizing granulomas.[1,2] Their incidence in Spain reaches 2.95 cases/million inhabitants for granulomatosis with polyangiitis, 7.91 cases/million for microscopic polyarteritis and 1.31 cases/million for Churg-Strauss' disease.[3]

Throughout the disease process, the incidence of ophthalmic manifestations described in this type of vasculitis[4,5] goes from 20 to 50% of cases. Per region, the incidence is: conjunctivitis, keratitis (12%–20%); episcleritis and scleritis (12%–27%); uveitis (2%–7%); optic neuritis (12%–16%), and proptosis (15%–57%), but being very atypical as a presenting symptom.

Eye affection is a primordial manifestation of granulomatosis with polyangiitis and it distinguishes it from other systemic or ANCA positive vasculitidies.[6,7] The most common initial manifestation is proptosis, but as in this patients case, the presence of diplopia and loss of visual acuity have also been previously described.

The differential diagnosis of orbital affection in a patient with granulomatosis with polyangiitis must include infections, fungal or bacterial, orbital lymphoma, sarcoidosis, Graves disease and orbital pseudotumor.

Treatment, based on adequate immunosuppression with steroids associated to cyclophosphamide, has led to the control of the disease in a high percentage of patients, although it is true that the loss of visual acuity is in many cases irreversible and requires a strict control by Ophthalmology as well as Rheumatology and primary care.

References

1. Schilder AM. Wegener's Granulomatosis vasculitis and granuloma. Autoimmun Rev. 2010;9:483–7.
2. Berden A, Göçeroglu A, Jayne D, Luqmani R, Rasmussen N, Bruijn JA, et al. Diagnosis and management of ANCA associated vasculitis. BMJ. 2012;344:e26.

☆ Please cite this article as: López-González R, Martínez-González O, Martín-Luquero Ibáñez M, Valdazo de Diego JP. Ojo rojo como manifestación primaria de vasculitis sistémica. Reumatol Clin. 2014;10:193–194.

3. Gonzalez-Gay MA, Garcia-Porrua C, Guerrero J, Rodriguez-Ledo P, Llorca J. The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. Arthritis Rheum. 2003;49:388–93.
4. McCluskey P, Powell RJ. The eye in systemic inflammatory diseases. Lancet. 2004;364:2125–33.
5. Tarabishy AB, Schulte M, Papaliodis GN, Hoffman GS. Wegener's granulomatosis: clinical manifestations, differential diagnosis, and management of ocular and systemic disease. Surv Ophthalmol. 2010;55:429–44.
6. Bijlsma WR, Hené RJ, Mourits MP, Kalmann R. Orbital mass as manifestation of Wegener's granulomatosis: an ophthalmologic diagnostic approach. Clin Exp Rheumatol. 2011;29 Suppl 64:S35–9.
7. Vischio JA, McCrary CT. Orbital Wegener's granulomatosis: a case report and review of the literature. Clin Rheumatol. 2008;27:1333–6, http://dx.doi.org/10.1007/s10067-008-0949-2.

Ruth López-González,[a,*] Olga Martínez-González,[a]
Miguel Martín-Luquero Ibáñez,[b] Juan Pablo Valdazo de Diego[a]

[a] *Servicio de Reumatología, Complejo Hospitalario de Zamora, Zamora, Spain*
[b] *Servicio de Medicina Interna, Complejo Hospitalario de Zamora, Zamora, Spain*

* Corresponding author.
E-mail address: lopezgonzalezruth@gmail.com
(R. López-González).

Nodular Regenerative Hyperplasia of the Liver as a Complication of Long-standing Systemic-onset Juvenile Idiopathic Arthritis☆

Hiperplasia nodular regenerativa hepática como complicación tardía de la artritis idiopática juvenil de inicio sistémico

To the Editor,

Hepatic nodular regenerative hyperplasia (HNRH) is an entity characterized by a diffuse, benign transformation of the hepatic parenchyma into small regenerative nodules, which can lead to the development of non-cirrhotic portal hypertension (PH). It has been associated with several disorders, mainly autoimmune and hematologic diseases and immunosuppressive drugs, including azathioprine and cyclophosphamide.[1] The HNRH has been described in RA/Felty's syndrome, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), Sjögren's syndrome, systemic sclerosis, sarcoidosis, polyarteritis nodosa and mixed cryoglobulinemia.[1–3] However, only one case has been reported in systemic onset juvenile idiopathic arthritis (JIA).[4]

A 33-year-old male was diagnosed with systemic onset JIA at 5 years of age based on fever, evanescent rash, joint pain, recurrent pericarditis, elevated acute phase reactants (C-reactive protein 22.5 mg/dl and erythrocyte sedimentation rate 39 mm/h) and negative for rheumatoid factor, antinuclear antibodies and HLA-B27. He was initially treated with low doses of corticosteroids and methotrexate 10 mg/week, but the latter was suspended at 20 years of age due to neurotoxicity. Since then, he has received varying doses of corticosteroids alone, maintaining an active disease, with a mild increase in alanine aminotransferase (ALT) (72 U/l), gamma-glutamyl transferase (GGT) (171 U/l) and alkaline phosphatase (AP) (146 U/l), in addition to thrombocytopenia ($117\times10^3/\mu l$) with normal bone marrow study. Ultrasonography and abdominal computed tomography showed mild splenomegaly with no signs of PH. Tocilizumab (8 mg/kg every 14 days) was initiated in January 2011, with rapid improvement of systemic symptoms and standardization of the reactants. However, after the third infusion he presented worsening liver function, doubling previous levels of ALT and GGT, increasing aspartate aminotransferase (AST) (79 U/l) and total bilirubin (TB) (3.51 mg/dl) levels, presenting hypofibrinogenemia (122 mg/dl), abnormal INR (1.5) and an increase in the severity of thrombocytopenia ($57\times10^3/\mu l$). He was admitted to the hospital with suspected Macrophage Activation Syndrome. The patient had not concomitantly received NSAIDs or other potentially hepatotoxic drugs. Serologic testing for hepatitis viruses B and C, Epstein Barr virus and human immunodeficiency virus were negative, and a bone marrow biopsy showed reactive changes and no hemophagocytosis. Endoscopy revealed the presence of grade I–II esophageal varices and a biopsy confirmed the diagnosis of HNRH (Fig. 1A and B). Tocilizumab was suspended permanently, with normalization of AST, TB, fibrinogen and INR, but the levels of ALT, GGT, AP and thrombocytopenia remained unchanged. In successive imaging controls, an increased diameter of the portal vein (17 mm) was observed (Fig. 1C), with no evidence of thrombosis. Currently, the patient receives only steroids at a variable dose, with mild to moderate activity of JIA and without developing other complications of PH.

HNRH pathogenesis is unknown, but it is considered a non-specific tissue adaptive response to an altered distribution of hepatic vascular flow with a multifactorial cause.[5] Among the identified factors which can cause this condition are thrombosis (thrombophilia, malignancies, myeloproliferative disorders, APS) and endothelial cell injury in the portal venules and hepatic sinusoids (drugs, autoimmune diseases, and viruses).[1] In this case, the underlying disease and drug therapy could have been involved. The chronic inflammatory state secondary to the long duration of systemic onset JIA is associated with high circulating levels of proinflammatory cytokines such as interleukin 6 (IL-6), which has been implicated in the development of HNRH.[6] This cytokine is important in the proliferation of hepatocytes and liver regeneration.[7] However, transgenic mice expressing high levels of IL-6 and its soluble receptor (sIL-6R) exhibit hepatocellular hyperplastic nodules around the portal tracts, as do patients with HNRH.[6] There is also clinical evidence that the increase in IL-6 is associated HNRH in Castleman's disease.[8] Other HNRH related disorders, such as SLE and hematological malignancies, have high levels of the IL-6/sIL-6R complex.[6] Although patients

☆ Please cite this article as: Sifuentes Giraldo WA, Burdaspal Moratilla A, Moreno Caparrós A, Gámir Gámir ML. Hiperplasia nodular regenerativa hepática como complicación tardía de la artritis idiopática juvenil de inicio sistémico. Reumatol Clin. 2014;10:194–195.