<https://doi.org/10.47660/CBR.2020.17309>

GRANULOMATOSIS WITH POLYANGIITE AND HIGH SERUM IGG4 LEVELS

Ítalo Magalhães Gusmão^{1,*}, Eduardo José do Rosário e Souza¹, Marcelo Rocha Scaramussa¹, Gustavo Braga Hallais França¹, Corina Quental de Menezes Alvarenga¹, Carolina Laís Ladeira Estefani¹

1.Santa Casa de Misericórdia de Belo Horizonte, Belo Horizonte (MG), Brazil.

*Corresponding author: italogusmao23@gmail.com

BACKGROUND

Granulomatosis with polyangiitis (GPA) is a small vessel vasculitis whose pathogenesis involves the participation of anti-neutrophil cytoplasmic autoantibodies (ANCA), especially those directed against proteinase 3, present in up to 90% of cases. In addition to nonspecific constitutional symptoms such as fever, weight loss, arthralgia and myalgia, GPA is characterized by the involvement of several other organs, most common the upper respiratory tract (90%), but it can also reach the lungs and kidneys¹. It can affect all structures of the human eye, with more frequent findings of peripheral ulcerative keratitis (PUK) and scleritis². The involvement of the lacrimal gland and orbit, although rare, are described and can be confused with other pathologies, such as IgG4-related disease (IgG4-RD).

CASE REPORT

P.G., 34 years old, female, married, receptionist, born in Belo Horizonte, Minas Gerais, reported a bruised nose after her daughter hit her heel while she slept. In the following days, she developed nasal congestion, later presenting epistaxis, mainly when sneezing. Antibiotic treatment was performed on suspicion of acute sinusitis, without improvement. During this period, she observed a flattening of the nasal bridge, assuming a “saddle nose” (Fig. 1). She evolved with ocular hyperemia and edema in the upper eyelids, mainly on the left (Fig. 2), when she sought the Eye Clinic of the Santa Casa de Misericórdia of Belo Horizonte, in May 2020.

Figure 1. Saddle nose.

Figure 2. Enlargement of lacrimal glands, most notably to the left.

Orbit tomography revealed a bilateral enlargement of the lacrimal glands, more evident on the left, in addition to left maxillary sinus disease (Fig. 3).

Figure 3. (A) Left maxillary sinus disease and (B) enlarged tear glands.

Ophthalmological evaluation showed an association of bilateral necrotizing scleritis and peripheral ulcerative keratitis (PUK) (Fig. 4).

Figure 4. (A) Peripheral ulcerative keratitis (PUK) and (B) necrotizing scleritis.

In the immunohistochemical analysis of the lacrimal gland, a mixed B and T lymphoid infiltrate was found with the presence of IgG4-positive cells > 50 per high-magnification field. Laboratory tests showed nonhemolytic anemia, leukocytosis, increased inflammatory tests, elevated serum creatinine, positive rheumatoid factor, serum IgG4 > 2x the reference range and P-ANCA 1:80. In the urine test, hematuria and proteinuria of 1.74 g/day were present, estimated from the correlation between protein/creatinine in an isolated sample. The patient underwent a chest tomography that showed the presence of nine pulmonary granulomas, six of which were cavitated (Fig. 5).

Figure 5. Bilateral granulomas, some cavitated.

Thus, the diagnosis of GPA was established, associated with ocular manifestations, renal and pulmonary involvement. Treatment with methylprednisolone and cyclophosphamide was started, in addition to topical ocular corticosteroid therapy.

DISCUSSION

The case described is marked by a traumatic event as a possible trigger for GPA. Before the trauma, the patient did not present any respiratory or ophthalmological symptoms. Other cases are described in the literature in which trauma appears as possible triggers for an inflammatory response leading to GPA⁴⁻⁶. This correlation would be explained by the activation of neutrophils by ANCA from stimulation of those after trauma^{7,8}. Ocular involvement in GPA is common in about half of the patients, occurring due to sinus extension, contiguity or local vasculitis². It can occur as an initial manifestation of the disease and all structures of the eye can be affected, with scleritis, especially necrotizing, and PUK being a common association⁹, which was evidenced in the patient in question. Lacrimal gland involvement is rare, especially when bilateral, and the association with sinusopathy, as described in this case, is highly suggestive of GPA¹⁰. There are similarities in both the clinical and histological picture between IgG4-RD and GPA, in addition to high levels of serum IgG4 and in histological analysis of these patients¹¹. However, ANCA's positivity is one of the exclusion criteria for IgG4-RD¹². The ratio between IGG and IGG4 is one of the diagnostic criteria for IgG4-RD¹², but it is believed that it can still be a potential marker for assessing GPA activity, since the serum levels of ANCA, CRP and ESR have limitations in sensitivity or specificity¹³.

CONCLUSION

Physical trauma seems to be related as a trigger to the development of GPA from the activation of lymphocytes and consequent interaction with the ANCA. The wide variety of clinical manifestations in GPA should lead us to an approach directed to the differential diagnosis of other vasculitis and autoimmune diseases, with IgG4-RD having an important place in this investigation, mainly due to the histological similarity, however the typical clinical picture of GPA and the ANCA's presence are important for this differentiation. The analysis of serum IGG4 + levels and the IGG/IGG4 ratio seems to be an alternative as markers of disease activity, requiring further studies for its application.

REFERENCES

1. Garlapati P, Qurie A. Granulomatosis with polyangiitis (GPA, Wegener granulomatosis). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. [updated 2020 May 22; cited 2020 Dec 20] Available from: <https://www.ncbi.nlm.nih.gov/books/NBK557827/>
2. Sfiniadaki E, Tsiara I, Theodossiadis P, Chatziralli I. Ocular manifestations of granulomatosis with polyangiitis: a review of the literature. *Ophthalmol Ther*. 2019;8(2):227–34. <https://doi.org/10.1007/s40123-019-0176-8>
3. Karim AF, Verdiijk RM, Nagtegaal AP, Bansie R, Paridaens D, van Hagen PM, van Laar JAM. To distinguish IgG4-related disease from seronegative granulomatosis with polyangiitis. *Rheumatology*. 2017;56(12):2245–7. <https://doi.org/10.1093/rheumatology/kex335>
4. Deng S, Xing Y, Wang H, Kong X. Relapsing granulomatosis with polyangiitis provoked by trauma: A case report. *Medicine (Baltimore)*. 2019;98(3):e14189. <https://doi.org/10.1097/MD.00000000000014189>
5. Carter S, Ramjani V, Dunkley L, Salvi S. Granulomatosis with polyangiitis provoked by trauma. *Can J Ophthalmol*. 2016;51(3):E101–3. <https://doi.org/10.1016/j.jcjo.2016.02.011>
6. Bouomrani S, Dabboussi S, Belgacem N, Trabelsi S. Post-traumatic fatal granulomatosis with polyangiitis. *Clin Res Open Access*. 2018;4(4):1–3. <https://doi.org/10.16966/2469-6714.142>
7. Mortaz E, Zadian SS, Shahir M, Folkerts G, Garssen J, Mumby S, Adcock IM. Does neutrophil phenotype predict the survival of trauma patients? *Front Immunol*. 2019;10:2122. <https://doi.org/10.3389/fimmu.2019.02122>
8. Ohlsson S, Holm L, Hansson C, Ohlsson SM, Gunnarsson L, Pettersson Å, Skattum L. Neutrophils from ANCA-associated vasculitis patients show an increased capacity to activate the complement system via the alternative pathway after ANCA stimulation. *PLoS One*. 2019;14(6):e0218272. <https://doi.org/10.1371/journal.pone.0218272>
9. Salehi A, Kianersi F, Ghanbari H, Dastborhan Z, Gerami E, Pirmoazzen E. Simultaneous unilateral presentation of three different ocular manifestations of granulomatosis with polyangiitis. *J Ophthalmic Vis Res*. 2018;13(2):203–6.
10. Tan LT, Davagnanam I, Isa H, Rose GE, Verity DH, Pusey CD, Lightman S. Clinical and imaging features of lacrimal gland involvement in granulomatosis with polyangiitis. *Ophthalmology*. 2015;122(10):2125–9. <https://doi.org/10.1016/j.ophtha.2015.06.026>
11. Chang SY, Keogh K, Lewis JE, Ryu JH, Yi ES. Increased IgG4-positive plasma cells in granulomatosis with polyangiitis: a diagnostic pitfall of IgG4-related disease. *Int J Rheumatol*. 2012;2012:121702. <https://doi.org/10.1155/2012/121702>
12. Wallace ZS, Naden RP, Chari S, Choi H, Della-Torre E, Dicaire JF, Hart PA, Inoue D et al. The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease. *Arthritis Rheumatol*. 2020;72(1):7–19. <https://doi.org/10.1002/art.41120>
13. Al-Soudi A, Doorenspleet ME, Esveldt RE, Burgemeister LT, Hak AE, van den Born BJH, Tas SW, van Vollenhoven RF, Klarenbeek PL, de Vries N. IgG4:IgG RNA ratio differentiates active disease from remission in granulomatosis with polyangiitis: a new disease activity marker? A cross-sectional and longitudinal study. *Arthritis Res Ther*. 2019;21(43). <https://doi.org/10.1186/s13075-018-1806-6>