Case Report

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Immunoglobulin G4-related disease mimicking lymphoma: Challenging to diagnose

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Abstract:

Practically, all major organ systems can be impacted by an immune-mediated fibro-inflammatory condition known as immunoglobulin G4-related disease (IgG4-RD). Even though it is not unusual, the level of orbital involvement in IgG4-RD can change depending on where the lymphoplasmacytic infiltrate is located. We address a case of IgG4-RD in this study who presented with large bilateral upper and lower eyelids swelling, mediastinal lymphadenopathy, and elevated serum IgG4. It was necessary to do a histopathology examination to confirm the diagnosis of the IgG4-RD and rule out any possible mimicking hematological conditions. In conclusion, this case report emphasizes the value of clinical symptoms and imaging in reducing the number of potential diagnoses, although biopsy remains a gold standard to confirm the diagnosis of IgG4-RD.

Keywords:

Corticosteroid, immunoglobulin G4-related disease, orbital swelling, rituximab

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic immune-mediated fibro-inflammatory disease and is characterized by lymphoproliferation and tissue infiltration of polyclonal plasma cells that are IgG4-positive. IgG4-RD's pathogenesis is still not fully understood.[1] There are reports indicating the role of environmental factors such as exposure to solvents and genetics.[2,3] In view of the disease's various presentations, IgG4-RD might look such as inflammatory, infectious, or malignant conditions.[4,5] IgG4-RD frequently mimics other hematologic conditions such as multicentric Castleman disease, lymphoma, plasma cell neoplasms, and hypereosinophilic syndromes.[1] Most patients with IgG4-RD have elevated serum IgG4; however, between 30% and 50% have normal IgG4 levels.[6,7] There are numerous diagnostic criteria for the involvement of various organs in the literature, however, the IgG4-RD complete diagnostic criteria, released in 2012, are the ones that are most frequently used.[8] Japanese IgG4 team has updated the comprehensive diagnostic criteria for IgG4-RD considering in 2020, which consists of the following domains: clinical findings, radiological features, serological diagnosis, and pathological diagnosis.[9] IgG4-RD diagnosis can be difficult because of the lack of reliable biomarkers. Clinical examination, laboratory parameters, and radiological imaging are necessary for the diagnosis but frequently fall short. For these reasons, histopathology remains the gold standard.[10,11] The four histopathological pillars of IgG4-RD are storiform fibrosis, obliterative phlebitis, tissue eosinophilia, and thick polyclonally lymphoplasmacytic infiltrates with high percentages of IgG4-expressing plasma cells.[12] It is important to identify and accurately characterize IgG4-RD as soon as possible because failing to do so could result

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in serious organ fibrosis and damage.[13] Even though IgG4-RD is considered a treatable disease and responds quickly to glucocorticoids, if it goes undiagnosed, it can cause end-stage organ failure and even death. Because most patients experience relapses, prolonged courses of corticosteroids are frequently required to maintain remission. Advancement in our understanding of the mechanisms underlying diseases connected to IgG4 is resulting in the discovery of novel therapeutic targets.

Case Report

A 35-year-old male referred to our hematology outpatient clinic from an ophthalmologist with swellings over his bilateral left and right eyelids with proptosis in addition to shortness of breath. He denied having any B symptoms or any type of trauma. On examination, the swelling was non-tender and firm. There were no signs of inflammation and other ocular examinations were unremarkable per ophthalmologist's report. Imaging including brain, neck, chest, and abdomen computed tomography with contrast study was performed before referral. Contrast computed tomography of the brain revealed enlargement of the left lacrimal gland with a homogeneous enhancement postcontrast. In addition, there was an enlargement of the right inferior rectus muscle with a soft-tissue mass which was homogeneously enhancing. The soft-tissue mass protruded into the infratemporal fossa and inferior orbital foramen and into the right maxillary sinus and extending into subcutaneous tissue of the right cheek. The computed tomography (CT) scan of the chest revealed a homogeneous enhancing prevertebral posterior mediastinal soft-tissue mass extending from D4 to D11. Furthermore, a positron emission tomography CT (PET-CT) scan revealed an increased fluorodeoxyglucose (FDG) uptake in orbital regions, salivary glands, and posterior mediastinum. Apart from a slightly increased serum level of IgG4, there was nothing remarkable in routine blood tests, including blood cell counts, albumin level, transaminases, renal function, and C-reactive protein. Furthermore, the levels of C3, C4, lactate dehydrogenase, and erythrocyte sedimentation rate were within the normal range.

A biopsy was taken from the mediastinal mass for histopathological evaluation. Microscopic evaluation showed dense mixed inflammatory cell infiltrate rich in plasma cells. On immunostaining, there was strong positivity for CD3, CD20, pax5, and patchy positivity for CD10, whereas BCL-2, CD15, and CD30 were negative and Ki-67 was 25%. Histopathologist's differentials included IgG4-RD, Castleman disease, and plasma cell disorders. It is worth to mention that the opinion of more than one histopathologist was asked regarding this matter. Serum protein electrophoresis revealed monoclonal gammopathy. No remarkable findings in urine immunofixation but serum immunofixation displayed monoclonal gammopathy with IgG/Kappa pattern. In addition, a bone marrow examination was performed, and it was unremarkable.

Concluding all these investigation results with the diagnostic criteria from the comprehensive diagnostic criteria developed by Umehara *et al*., this patient was given the diagnosis of definite IgG4-RD. Treatment with prednisolone was initiated, and subsequent follow-up PET-CT scan after 3 months revealed no evidence of abnormal FDG uptake, and patient symptoms were improved. The steroid was continued but at the lower dose. Three months later, there was nothing remarkable both clinically and per imaging study, and treatment was reduced to a very low dose. A year after starting of steroid, the patient came back for follow-up with the same symptoms, but the patient admitted that he was not very compliant with the treatment. Low-dose steroid in combination with azathioprine was initiated and patient disappeared. When he visited us again after a year, he was having recurrent orbital swelling and had a lumbar vertebral fracture and neurosurgery team claimed that it is steroid related. A PET-CT scan was performed and revealed same findings as time of diagnosis. This time rituximab weekly for four doses was given and the patient demonstrated good response both clinically and radiologically after 3 months of treatment. Afterward, the patient was kept on azathioprine to prevent disease relapse. Two years after receiving rituximab, the patient was quite well and a follow-up PET-CT scan displayed no evidence of hypermetabolic activity. The patient is currently on regular follow-up and doing well.

Discussion

This case emphasizes the difficulties in diagnosing IgG4-RD cases. The overlap of clinical and laboratory symptoms of IgG4-RD with other hematological diseases make diagnosing IgG4-RD more difficult.

For active disease, an induction course of corticosteroids is still the go-to initial treatment, followed by a gradual reduction.[14] Maintenance of steroid might be needed to prevent relapse. In line with the previous case report, our patient demonstrated a very good response to steroid.[15,16] Although most IgG4-RD cases respond to induction therapy, relapse rates are still high and disease remission without medication is uncommon.[17] Various steroid-sparing immunosuppressants have been used in situations of resistant or recurrent diseases, with rituximab showing the most encouraging outcomes.[14] The reason we did not start directly with rituximab was that we wanted to have a line of treatment reserved for last. Patient's response to rituximab goes hand in hand with previous studies.[18] It is worth

to mention that maintaining the patient on a low dose of immunosuppression after rituximab was the French study where they revealed that around 42% of responders to rituximab were relapsed.[19] A crucial component of providing the patient with comprehensive care is prompt diagnosis and referral for thorough investigation and management. Rituximab may prove to be potent therapeutic alternatives to corticosteroids.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Chen LY, Mattman A, Seidman MA, Carruthers MN. IgG4-related disease: What a hematologist needs to know. Haematologica 2019;104:444-55.
2. Ishikawa Y, Terao C. Genetic analysis of IgG4-related disease. Mod Rheumatol 2020;30:17-23.
3. de Buy Wenniger LJ, Culver EL, Beuers U. Exposure to occupational antigens might predispose to IgG4-related disease. Hepatology 2014;60:1453-4.
4. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet 2015;385:1460-71.
5. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 2012;366:539-51.
6. Umehara H, Kawano M. IgG4-related disease. JOP 2015;16:217.
7. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. Ann Rheum Dis 2015;74:14-8.
8. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, *et al.* Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol 2012;22:21-30.
9. Umehara H, Okazaki K, Kawa S, Takahashi H, Goto H, Matsui S, *et al.* The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. Mod Rheumatol 2021;31:529-33.
10. Weindorf SC, Frederiksen JK. IgG4-related disease: A reminder for practicing pathologists. Arch Pathol Lab Med 2017;141:1476-83.
11. Maritati F, Peyronel F, Vaglio A. IgG4-related disease: A clinical perspective. Rheumatology (Oxford) 2020;59:i123-31.
12. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, *et al.* Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012;25:1181-92.
13. Katz G, Stone JH. Clinical perspectives on IgG4-related disease and its classification. Annu Rev Med 2022;73:545-62.
14. Detiger SE, Karim AF, Verdijk RM, van Hagen PM, van Laar JA, Paridaens D. The treatment outcomes in IgG4-related orbital disease: A systematic review of the literature. Acta Ophthalmol 2019;97:451-9.
15. Hirata Y, Fukae J, Nishida A, Fujioka S, Hamasaki M, Nonokuma M, *et al.* Longstanding IgG4-related ophthalmic disease dramatically improved after steroid therapy. Intern Med 2018;57:2879-83.
16. Peng T, Hu Z, Xie T, Jiang B, Zhen J, Yang X. IgG4-related disease: A case report with duration of more than 16 years and review of literature. Springerplus 2016;5:804.
17. Brito-Zerón P, Kostov B, Bosch X, Acar-Denizli N, Ramos-Casals M, Stone JH. Therapeutic approach to IgG4-related disease: A systematic review. Medicine (Baltimore) 2016;95:e4002.
18. Carruthers MN, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, *et al.* Rituximab for IgG4-related disease: A prospective, open-label trial. Ann Rheum Dis 2015;74:1171-7.
19. Ebbo M, Grados A, Samson M, Groh M, Loundou A, Rigolet A, *et al.* Long-term efficacy and safety of rituximab in IgG4-related disease: Data from a French nationwide study of thirty-three patients. PLoS One 2017;12:e0183844.