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CASE REPORT

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IgG4-related disease associated with the primary manifestation of recurrent cerebral venous thrombosis: A rare case report

Arsh Haj Mohamad Ebrahim Ketabforoush[1] | **Mahsa Bahadorinia**[2] | **Elahe Dolatshahi**[3] | **Zohreh Nozarian**[4] | **Nahid Abbasi Khoshsirat**[5]

[1]Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran

[2]Student Research Committee, Alborz University of Medical Sciences, Karaj, Iran

[3]Department of Rheumatology, Clinical Research Development Unit (CRDU) of Shahid Rajaei Hospital, Alborz University of Medical Sciences, Karaj, Iran

[4]Department of Pathology, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran

[5]Department of Neurology, Clinical Research Development Unit (CRDU) of Shahid Rajaei Hospital, Alborz University of Medical Sciences, Karaj, Iran

Correspondence
Nahid Abbasi Khoshsirat, Department of Neurology, Clinical Research Development Unit (CRDU) of Shahid Rajaei Hospital, Alborz University of Medical Sciences, Rajaei hospital, Ghalam St, Beheshti Ave, Karaj, Iran.
Email: nahid.abbasi.k@gmail.com

Abstract

Nervous system involvement in IgG4-related systemic disease (IgG4-RD) is rarely reported and manifests as hypertrophic pachymeningitis and hypophysitis. In this report, a 33-year-old woman with neurological manifestations was diagnosed with IgG4-RD by biopsy. The patient showed improvement in symptoms after treatment.

KEYWORDS

cerebral venous thrombosis, IgG4-related disease, pachymeningitis

1 | INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a disorder that causes chronic inflammation and fibrosis by involving a variety of organs in the body. High IgG4 serum levels have been detected in the majority of patients, and it commonly presents with mass-like swelling of an organ by dense infiltration of lymphocytes and IgG4-positive plasma cells arranged in a fibrosis storiform shape.[1] Moreover, IgG4-RD is related to mild infiltration of eosinophils and obliterative phlebitis.[2,3] This disease is seen in a wide range of ages; however, it usually manifests itself in the fifth and sixth decades of life. Two prevalent manifestations of IgG4-RD are salivary gland disease and autoimmune pancreatitis; other affected organs are the liver and biliary tract, lacrimal gland, respiratory system, lymph nodes, and retroperitoneum.[4] Due to the indolent pattern of the disease with unfocused and vague symptoms, early diagnosing IgG4-RD is challenging. To confirm IgG4-RD diagnosis, the recommended criteria by the American College of Rheumatology (ACR) would be helpful along with the consideration of clinical, paraclinical, histopathological, radiological findings, and other differential diagnoses.[5]

There are few reports of head and brain involvements of IgG4-RD in the form of hypertrophic pachymeningitis, cranial nerve impairments, pituitary gland inflammatory lesions, orbital pseudotumor, pterygopalatine fossa infiltrations, and recently central nervous system (CNS) parenchymal involvement.[6–9] Here, we established IgG4-RD diagnosis in a young woman who presented with recurrent cerebral venous thrombosis (CVT), pachymeningitis, and an orbital mass.

2 | CASE PRESENTATION

A 33-year-old woman with a history of recurrent hospitalization due to headaches with blurred vision was admitted to our neurology department. In January 2018, she had CVT in the left transverse sinus with left mastoiditis and treated with anticoagulants and antibiotics. Extensive workup to identify the etiology produced negative results, including acquired and genetic thrombophilia tests.

In December 2020, she was diagnosed with a new CVT in the sigmoid sinus. Again, she was discharged with a 5 mg daily dose of Warfarin. In her most recent hospitalization in March of 2021, she presented horizontal binocular diplopia, blurry vision, and hemicranial headache. The patient also complained of right eye proptosis, which developed over a period of 3 months. She did not report any fever, seizures, neck stiffness, or weight loss. On physical examination, her vital signs were stable (blood pressure:133/78 mmHg, pulse rate: 92 pr/min, respiratory rate: 18 pr/min, and temperature: 37.6 C), and her mental status was not impaired (Glasgow Coma Scale:15/15). An ophthalmometer established a 5 mm protrusion from the temporal orbital rim in the right eye.

Regarding the findings of her physical examination in March 2021, bilateral papilledema was detected on ophthalmoscopy. Except for a right sixth nerve palsy, other cranial nerve examinations were unremarkable. Sensory and motor examinations were unremarkable, the muscle tone was normal, and the motor strength was 5/5. Deep tendon reflexes were not impaired, and the plantar reflexes were downward. Also, the patient demonstrated a normal gait. We assessed for protonator drift and dysmetria that was within normal limits. Except for the history of recurrent CVTs, the patient did not have any specific diseases. She discontinued her medications individualistically 4 months prior due to the improvement of her symptoms. The patient was a life-long nonsmoker and never used illicit drugs. Additionally, there was no history of drugs that induced a hyper coagulated state (e.g., oral contraceptive pills [OCPs]).

Brain magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), magnetic resonance venography (MRV), and a computed tomography (CT) scan were performed. The T_1-weighted MRI with Gadolinium contrast demonstrated diffuse pachymeningeal thickening (Figure 1A,B) and an enhanced intra-orbital mass measuring 9*15*24 mm, which seems to originate from right lateral and superior rectus muscles (Figure 2A,B). Compared to the previous neuroimaging of the patient admissions in 2018 and 2020, this mass was defined as a new finding.

MRV revealed CVT within the left transverse sinuses and superior sagittal sinus (Figure 3). In addition to confirming the intra-orbital mass presence and size, orbital MRI disclosed the tortuous appearance of both optic nerves with dilation in nerve sheets, and superior ophthalmic veins were dilated.

Laboratory test findings were unremarkable, except for hemoglobulin (Hgb:11.9 g/dL), high serum C-reactive protein (CRP:52 mg/L), erythrocyte sedimentation rate (ESR:76 mm/h), serum IgG (34,6 g/L;normal range:7–16),

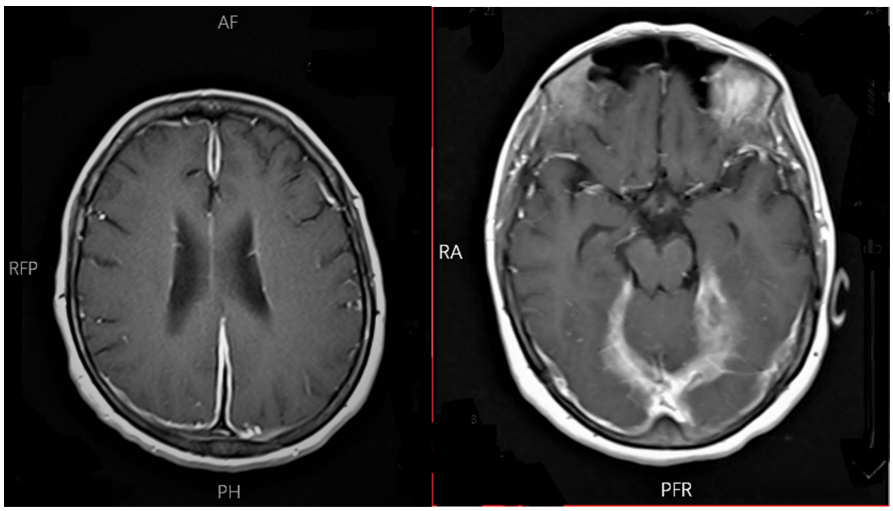

FIGURE 1 T1-weighted MRI with Gadolinium contrast showed diffuse meninges' enhancements at different levels

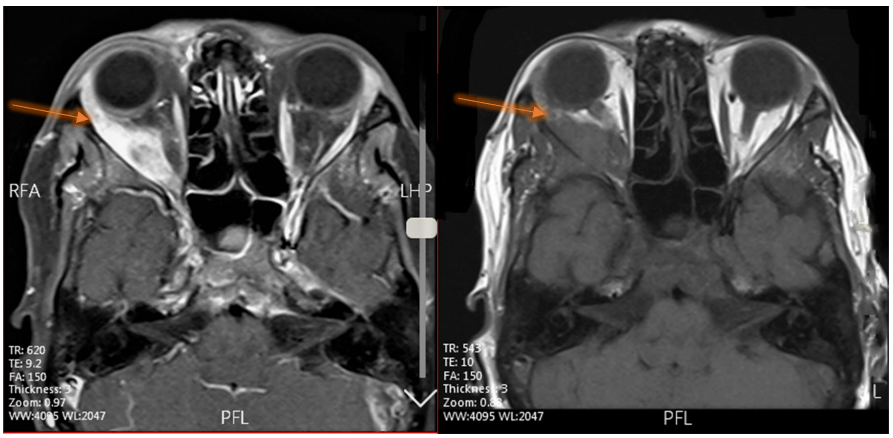

FIGURE 2 T1-weighted MRI with Gadolinium contrast (A) and T1-weighted MRI without contrast (B) revealed a right orbital mass with compression effect on the right optic nerve

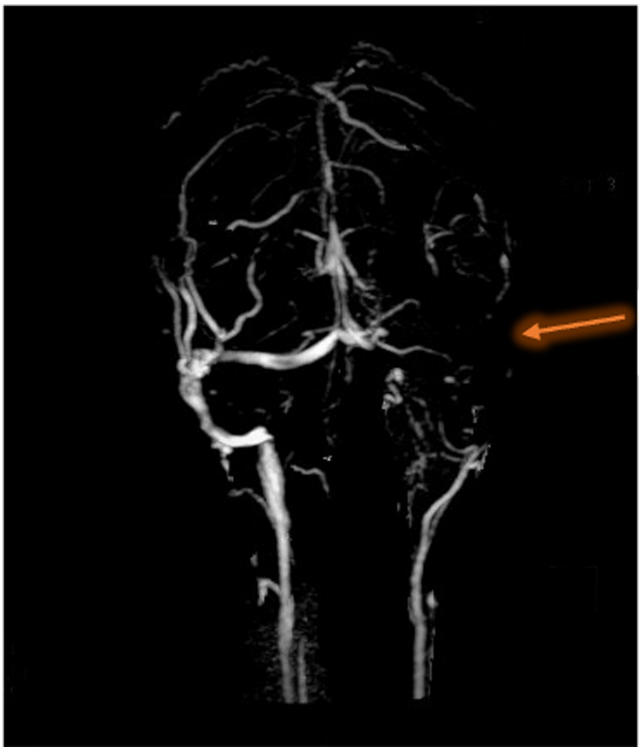

FIGURE 3 Brain MRV with Gadolinium contrast demonstrated thrombosis in the sagittal sinus and proximal of the left transverse sinus

and serum IgG4 (141 mg/dL) was above the upper limit of the normal range (4–90 mg/dL). Other specific serum rheumatological or vasculitis markers include P-ANCA, C-ANCA, ANA, Anti-dsDNA, anti-Smith, anti-RNP, anticardiolipin antibodies, β2-glycoprotein, C3, C4, RF, anti-CCP, anti-SSA/Ro, and anti-SSB/La were within normal limits. In addition, acquired and genetic thrombophilia test findings (e.g., protein C deficiency, protein S deficiency, antithrombin *III* deficiency, Factor V Leiden mutation, homocysteine level, and prothrombin 20,210 mutation) were negative. Tumor marker assessment demonstrated negative results for CA5.3, CA19.9, CA125, α-fetoprotein (α-FP), and carcinoembryonic antigen (CEA). Lumbar puncture (LP) indicated a low elevation in opening pressure (30 cm H_2O), absence of WBC and RBC, a normal protein level (33 mg/dL), and an average glucose level (63 mg/dL). Cerebrospinal fluid (CSF) isoelectric focusing showed an oligoclonal IgG banding pattern. There was no evidence of bacterial growth in CSF gram staining and culture. A surgical biopsy from the intra-orbital mass was accomplished.

In the pathology report, a microscopic examination of the specimen revealed fragments of fibroconnective tissue containing inflammatory cell infiltration, composed mostly of lymphoplasmacytic admixed with histiocytes and polymorphonuclears (PMNs). Foci of necrosis fibrosis and lymphoid follicles formation were also seen. Special stainings for acid-fast bacilli and fungi were negative. Immunohistochemistry showed approximately 60 IgG4-positive plasma cells per high-power field (HPF), of which almost more than 40 of the IgG+ plasma cells were IgG4+. Also, the IgG4+/IgG+ plasma cell ratio was more than 40% (Figure 4).

Regarding other organ workup, chest CT-scan and abdominal/pelvic MRI did not demonstrate pertinent findings. The patient received prednisolone (1 mg/kg/day) for 3 months and a 5 mg daily dose of Warfarin. She felt a rapid improvement after initiating the treatment. Azathioprine (2 mg/kg/day) was also prescribed without any interval. After 8 months, all neurological symptoms had resolved.

3 | DISCUSSION

IgG4-RD is a newly recognized condition characterized by elevated serum IgG4 and tissue infiltrates of IgG4+ plasma cells.[10] IgG4-RD has been mentioned as a systemic disease since 2001 when increased serum IgG4 concentrations were reported in patients with autoimmune pancreatitis (AIP)[11]; later on in 2004, by learning that AIP was seen with the involvement of other organs, the term "IgG4-related autoimmune disease" was proposed,[12]

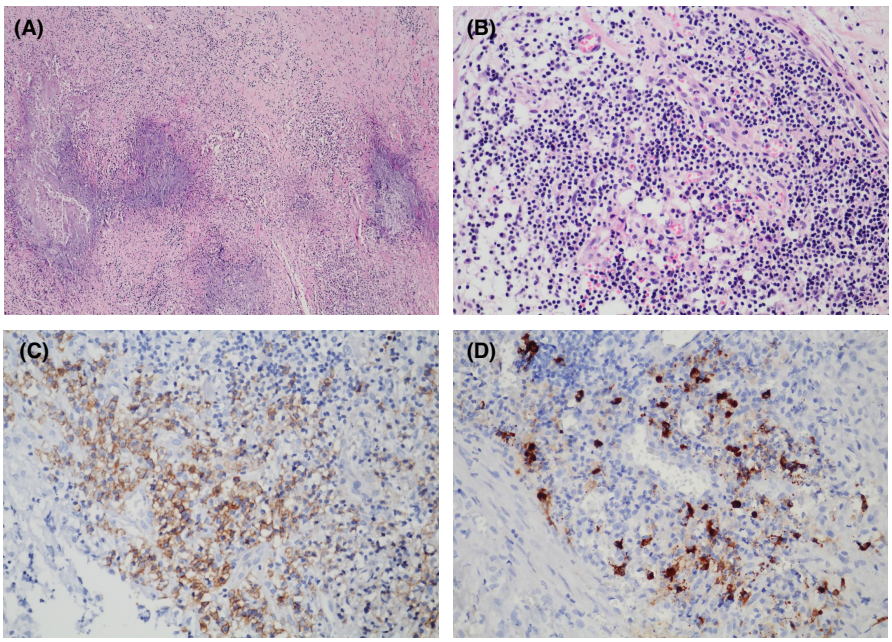

FIGURE 4 Low power field H&E staining revealed a fibroconnective tissue containing inflammatory cell infiltration, composed mostly of lymphoplasmacytic admixed with polymorphonuclears (PMNs) and foci of necrosis(A); also, in the HPF(*400), lymphoplasmacytic infiltration was seen (B). Immunohistochemistry showed approximately 60 IgG+ plasma cells (C), of which almost more than 40 of the IgG+ plasma cells were IgG4+(D).(IgG+/IgG4+>40%)

but the term "IgG4-RD" was established later in 2012 to foregather some of the known conditions in patients with common characteristics.[13] IgG4 is proposed to unify and be the link to individual fibro-inflammatory reactions in different organs of a patient and is found in high amounts in the serum of IgG4-RD patients[10,13] (except for about 30%–50% of patients who have normal serum levels[12]).

Involvement of every organ is possible, but the nervous system is not the most commonly affected site,[14] and isolated CNS involvement is rarely reported.[15] Large studies of systemic IgG4-RD have shown no CNS manifestations.[16,17] The role of serum IgG4 levels in *contributing to* isolated neurological involvement is unclear,[14] and biopsy-aided diagnosis proposes help in this new entity of knowledge. A meningeal biopsy, though invasive, is still the gold standard to establish the diagnosis, and searching for other organs' silent involvements may be an appropriate guide to the diagnosis.[18] Lymphoma, granulomatosis with polyangiitis (GPA), and neurosarcoidosis are the differential diagnoses of IgG4-RD pachymeningitis.[19] CT-scan and MRI reveal linear thickening of the dura, and cerebrospinal fluids investigations are usually non-specific.[20]

This report presents a 33-year-old female patient with the chief complaint of right eye proptosis, which developed over a period of 3 months. Our patient did not have any specific history except for the recurrent CVTs treated with anticoagulants. Other organs were clear of abnormalities, and upon further investigations, the diagnosis of IgG4-RD was considered. As exemplified by our case, it is possible for nervous system involvement to be the sole symptomatic presentation of IgG4-RD.

One aim of our report was to show how IgG4-RD can mimic typical symptoms of other diseases. Also, co-occurring conditions in other organ systems of the body may be present with IgG4-related neurological disease (IgG4-RND) even though the disease might need time to develop, and all of the symptoms might not be found simultaneously. Previous reports have indicated that nearly every aspect of the body can be affected by pathological changes of this disease, including skin, peripheral nerves, and intracranial structures.[12]

A minority of patients with IgG4-RD were reported to be younger than 50 years of age,[1] and in a study of IgG4-related neurological disease, the mean age was 46 years.[14] Diagnosing such a condition is a current medical challenge due to its rarity and non-specific symptoms, particularly early in life, as in our case. We must *recognize these patients as* being at risk of other clinical issues and take appropriate measures to reduce the likelihood of serious complications.

IgG4-RD in the nervous system most commonly manifests as hypertrophic pachymeningitis and hypophysitis, and we got the chance to observe diffuse pachymeningeal thickening in our case. In two small studies, one from Italy and another from Spain, pachymeningitis was reported 3/41 (7%) and 2/55 (4%) of patients, respectively.[21,22] Pachymeningitis appearing as a linear or bulging lesion along with dura matter inflammation of different local areas can cause focal signs such as sensory, visual, or hearing problems and nerve palsies[4] (for instance, involvement of periorbital areas, clivus, vestibular structures, brainstem, and spinal nerve roots[23]). IgG4-RD may be the most common cause of noninfectious hypertrophic pachymeningitis.[24] CVT may be associated with the local inflammatory setting near the pachymeningitis or the formed fibrosis tissue mechanical pressure.[2,25] Diffuse symptoms, for instance, headache and seizures, may be due to meningeal inflammation extending to the

hemispheric and basal dura.[4] Our patient presented with recurrent CVTs, and we could not identify any hypercoagulable state or large cerebral vessel disease. Therefore, we hypothesized that the increased level of IgG4 tagging neural cells of the central nervous system probably induces an immunological activity against vascular structures, which finally may activate the complements and coagulation cascade. Besides, further studies will be necessary to confirm this association, since it has been rarely reported in IgG4-RD. There are no specific laboratory tests except pathological biopsy investigations for IgG4-NRD, but it should be considered if there are recurrent CVTs without a clear cause.

Further studies are recommended to identify characteristics of patients with this condition because those diagnosed with acute/subacute symptoms seem to respond dramatically to steroids.[13,14] In fact, its response to steroid therapy proposed its autoimmune nature.[12] Other treatment options in patients who are resistant or unable to use glucocorticoids are Azathioprine, Mycophenolatemofetil, or Rituximab.[4,5] Although there is no definite treatment guideline to date, IgG4-RD response to immunosuppressive therapy and the history of immune-related conditions in patients strengthen the suggestion of the immune nature and inflammatory background for the pathogenesis of this disease.[4] Better knowledge of the pathogenesis of IgG4-RD can guide us in defining a *specific treatment*.

4 | CONCLUSION

In conclusion, further investigation on IgG4-RND patients should be performed, focusing on the diagnosis. Early recognition of IgG4-RND can help avoid system dysfunction and disability in the nervous system due to its potential for guiding the diagnosis of other co-occurring conditions. IgG4-RD should be considered in the differential diagnosis of possible cases because despite responding to treatments, its potential risks are as of yet unknown.

AUTHOR CONTRIBUTIONS

AHMEK and MB contributed in study concept and design, data collection and interpretation, drafting the main article, supervising of study, and final approval of the submission; ED, ZN, and NK contributed in patient record, diagnosis of the patient, drafting the main article and revised the manuscript for important intellectual content, and gave final approval for the version to be published. All authors verify that the manuscript is original.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

All procedures conducted herein were in accordance with the ethical standards of the institutional and national committees on human experimentation and the 1964 Helsinki Declaration, and later versions.

CONSENT

Written and orally informed consent was obtained from the patient to publish images and case report.

DISCLAIMER

The full article is not under review or published elsewhere.

ORCID

Arsh Haj Mohamad Ebrahim Ketabforoush https://orcid.org/0000-0002-2773-3170
Mahsa Bahadorinia https://orcid.org/0000-0003-0292-6491
Nahid Abbasi Khoshsirat https://orcid.org/0000-0001-6978-6644

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