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[2], Zohreh Nozarian[3], Nahid Abbasi Khoshsirat[2], and Alberto Pepe[4]

[1]Iran University of Medical Sciences
[2]Alborz University of Medical Sciences
[3]Tehran University of Medical Sciences
[4]Affiliation not available

July 21, 2022

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 the treatment.

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 of symptoms after the treatment.

Key Clinical Message

Although there are many causes of neurological manifestations, IgG4-related systemic disease should strike a clinician in the absence of other causes. Here, we discuss a 33-year female with the disease and treatment which improved her symptoms.

Key Words

IgG4-related disease, pachymeningitis, cerebral venous thrombosis

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. IgG4-RD 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][Stone, 2012 #165]. Also, IgG4-RD is related to mildly infiltration of eosinophils and obliterative

phlebitis [2,3]. High IgG4 serum levels were detected in the majority of patients. However, this disease is seen in a wide range of ages but usually manifests itself in the fifth and sixth decades of life. Salivary gland disease and autoimmune pancreatitis are the two prevalent manifestations of IgG4-RD. Other affected systems and 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. American College of Rheumatology (ACR) recommended the criteria for confirming IgG4-RD diagnosis. Using various clinical, paraclinical, histopathological, and radiological findings and considering the differential diagnoses make ACR criteria more comprehensive and reliable[5].

There are few reports in 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]. Hypertrophic pachymeningitis characterized by dura matter inflammation in the periorbital areas, clivus, vestibular structures, brainstem, and spinal nerve roots and usually presents with focal neurological signs and symptoms [10]. Cerebral Vein Thrombosis (CVT) may be associated with the local inflammatory setting near the pachymeningitis or the formed fibrosis tissue mechanical pressure[2,11]. Lymphoma, granulomatosis with polyangiitis (GPA), and neurosarcoidosis are the differential diagnoses of IgG4-RD pachymeningitis [12]. CT-scan and MRI reveal linear thickening of the dura, and cerebrospinal fluids investigations are usually non-specific [13]. However, a meningeal biopsy is invasive and risky; it is still the gold standard for the diagnosis. In this condition, searching for other organs' silent involvements may be an appropriate guide to the diagnosis [14]. Different stages and organ involvement in IgG4-RD respond dramatically to glucocorticoids. Other treatment options in patients who are resistant or unable to use glucocorticoids are Azathioprine, Mycophenolatemofetil, or Rituximab [4,5].

Here, we established IgG4-RD diagnosis in a young woman who presented with recurrent cerebral venous thrombosis (CVT), pachymeningitis, and an orbital mass.

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 cerebral vein thrombosis (CVT) in the left transverse sinus with left mastoiditis, treated with anticoagulants and antibiotics. Extensive work-ups for finding 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 5mg daily dose of Warfarin. In March 2021, she presented horizontal binocular diplopia, blurry vision, and hemicranial headache in the last hospitalization. The patient also complained of right eye proptosis, which developed in a period of 3 months. She did not report any fever, seizures, neck stiffness, or weight loss. Except for the history of recurrent CVTs, the patient did not have any specific diseases. She had stopped using her drugs individualistically four months ago due to the improvement of her symptoms.

The patient had a smoke-free life and never used illicit drugs. Also, there was no history of drugs that induced a hyper coagulated state (e.g., Oral Contraceptive Pill or OCPs). On physical examination, the vital sign was stable (Blood Pressure:133/78 mmHg, Pulse Rate: 92 pr/min, Respiratory Rate: 18 pr/min, Temperature: 37.6 C), and the mental status was not impaired (Glasgow Coma Scale:15/15). An ophthalmometer established a 5mm protrusion from the temporal orbital rim in the right eye. On ophthalmoscopy, bilateral papilledema was detected. Except for a right sixth nerve palsy, other cranial nerve examinations were not involved. Sensory and motor examinations were unremarkable, the muscle tones were normal, and the forces were 5/5. Deep Tendon Reflexes were not impaired, and the plantar reflexes were downward. Also, the patient had a normal gait.

Brain Magnetic Resonance Imaging (MRI), Magnetic Resonance angiography (MRA), Magnetic Resonance Venography (MRV), and a Computed Tomography (CT) scan was performed. The T_1 weighted MRI with

Gadolinium contrast demonstrated diffuse pachymeningeal thickening (Figure $1_{A, B}$) and an enhanced intra-orbital mass measuring 9*15*24mm, which seems to be originated from right lateral and superior rectus muscles (Figure $2_{A, B}$) . 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, Orbit 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:76mm/h), serum IgG (34,6 g/L;normal range:7-16) 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, Anti-SSB/ La were normal in the results. In addition, Acquired and genetic thrombophilia tests findings (e.g., protein C deficiency, protein S deficiency, Antithrombin III deficiency, Factor V Leiden mutation, Homocysteine level, and Prothrombin 20210 mutation) were negative. The 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). 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, microscopic examination of the specimen revealed fragments of fibro-connective tissue containing inflammatory cells infiltration, composed mostly 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) . For other organ work-ups, CT-scan from chest and MRI from abdomen and pelvic were conducted, but they didn't have any specific findings. The patient received Prednisolone (1 mg/kg/day) for three months and a 5mg 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 eight months, all neurological symptoms had resolved.

Abbreviations

P-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies, C-ANCA: Cytoplasmic anti-neutrophil cytoplasmic antibodies, ANA: antinuclear cytoplasmic antibody, RF: rheumatoid factor, anti-CCP: Anti-cyclic citrullinated peptides, anti-SSA/Ro: anti–Sjögren's syndrome-related antigen A, anti-SSB/La: anti–Sjögren's syndrome-related antigen B, Anti-RNP: anti Ribonucleoprotein

Discussion

IgG4-RD is a newly recognized condition characterized by elevated serum IgG4 and tissue infiltrates of IgG4+ plasma cells [15]. IgG4-RD has been mentioned as a systemic disease since 2001 when increased serum IgG4 concentrations were reported in patients of autoimmune pancreatitis [16], but the term "IgG4-RD" was established later in 2012 to foregather some of the known conditions in patients with common characteristics [17]. 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 [15,17].

Involvement of every organ is possible, but the nervous system is not the most commonly affected site [18], and isolated CNS involvement is rarely reported [19]. Large studies of systemic IgG4-RD have shown no CNS manifestations[20,21]. The role of serum IgG4 levels in contributing to isolated neurological involvement is unclear [18], and biopsy-aided diagnosis, though invasive, may propose a help in this new entity of knowledge.

This report presents a 33-year-old female with the chief complaint of right eye proptosis, which developed in a period of 3 months. Our patient didn't 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 in our case, nervous system involvement can be the only IgG4-RD presentation.

The 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.

A minority of patients with IgG4-RD were reported to be younger than 50 years of age [22], and in a study of IgG4-related neurological disease, the mean age was 46 years [18]. It can be a real challenge to diagnose such a condition 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 a serious complication.

IgG4-RD in the nervous system most commonly manifests as hypertrophic pachymeningitis and hypophysitis (19), and we got the chance to observe diffuse pachymeningeal thickening in our case. Pachymeningitis appearing as a linear or bulging lesion along with dura matter involvement of different local areas can cause focal signs such as sensory, visual, or hearing problems and nerve palsies [23]. Diffuse symptoms, for instance, headache and seizures, may be due to meningeal inflammation extending to the hemispheric and basal dura [23].

Further studies are recommended in identifying characteristics of patients with this condition because those diagnosed with acute/subacute symptoms seem to respond well to steroids [17,18]. Although there is no definite treatment guideline to date, IgG4-RD response to immunosuppressive therapy and the history of immune-related conditions in the patients suggest the immune nature and inflammatory background for the pathogenesis of this disease [23]. Better knowledge of the pathogenesis of IgG4-RD can guide us in defining a specific treatment.

Conclusion

In conclusion, further investigations 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 and other organs of the body due to its potential for guiding the diagnosis of other co-occurring conditions. We should include it in the differential diagnosis of possible cases because despite responding to treatments, its potential risks are as of yet unknown.

References

1. Stone JH, Zen Y, Deshpande V. IgG4-Related Disease. *New England Journal of Medicine.* 2012;366(6):539-551.

2. Nilles C, Poillon G, Deschamps L, et al. IgG4-related pachymeningitis and mastoiditis, associated with cerebral venous thrombosis: A case report. *Journal of Neuroimmunology.* 2021;360:577717.

3. Deshpande V, Zen Y, Chan JKC, et al. Consensus statement on the pathology of IgG4-related disease. *Modern Pathology.*2012;25(9):1181-1192.

4. Vasaitis L. IgG4-related disease: A relatively new concept for clinicians. *European Journal of Internal Medicine.* 2016;27:1-9.

5. Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease. *Arthritis & rheumatology (Hoboken, NJ).* 2020;72(1):7-19.

6. AbdelRazek MA, Venna N, Stone JH. IgG4-related disease of the central and peripheral nervous systems. *The Lancet Neurology.*2018;17(2):183-192.

7. Perez FA. Imaging of Nontraumatic Orbital and Neuro-ophthalmological Emergencies. Paper presented at: Seminars in Roentgenology2020.

8. Shimatsu A, Oki Y, Fujisawa I, Sano T. Pituitary and stalk lesions (infundibulo-hypophysitis) associated with immunoglobulin G4-related systemic disease: an emerging clinical entity. *Endocrine journal.*2009;56(9):1033-1041.

9. Ekizoglu E, Coban O, Ulukan C, et al. Intracranial hypertension related to cerebral venous thrombosis; and acute ischemic stroke with micro-infarcts associated with IgG4-related disease. *International Journal of Neuroscience.* 2018;128(11):1097-1099.

10. Joshi D, Jager R, Hurel S, et al. Cerebral involvement in IgG4-related disease. *Clin Med (Lond).* 2015;15(2):130-134.

11. Liu Y, Xue F, Yang J, Zhang Y. Immunoglobulin G4-related disease mimicking lymphoma in a Chinese patient. *Rheumatology International.* 2015;35(10):1749-1752.

12. Lu LX, Della-Torre E, Stone JH, Clark SW. IgG4-Related Hypertrophic Pachymeningitis: Clinical Features, Diagnostic Criteria, and Treatment.*JAMA Neurology.* 2014;71(6):785-793.

13. Fujita A, Sakai O, Chapman MN, Sugimoto H. IgG4-related Disease of the Head and Neck: CT and MR Imaging Manifestations.*RadioGraphics.* 2012;32(7):1945-1958.

14. Della-Torre E, Galli L, Franciotta D, et al. Diagnostic value of IgG4 Indices in IgG4-related hypertrophic pachymeningitis. *Journal of neuroimmunology.* 2014;266(1-2):82-86.

15. Liu A, Zhang Q, Liu B, Xu N, Li A. A case of immunoglobulin G4-related lung disease with bilateral diffuse infiltration: A case report. *Medicine (Baltimore).* 2017;96(50):e9211.

16. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med.*2001;344(10):732-738.

17. Blockmans D. IgG4-related disease. *Acta Clin Belg.*2018;73(1):11-15.

18. Sireesha Y, Uppin MS, Ganti S, et al. A Series of Biopsy-proven Patients with Immunoglobulin G4-related Neurological Disease. *Ann Indian Acad Neurol.* 2019;22(1):73-78.

19. Baptista B, Casian A, Gunawardena H, D'Cruz D, Rice CM. Neurological Manifestations of IgG4-Related Disease. *Curr Treat Options Neurol.* 2017;19(4):14.

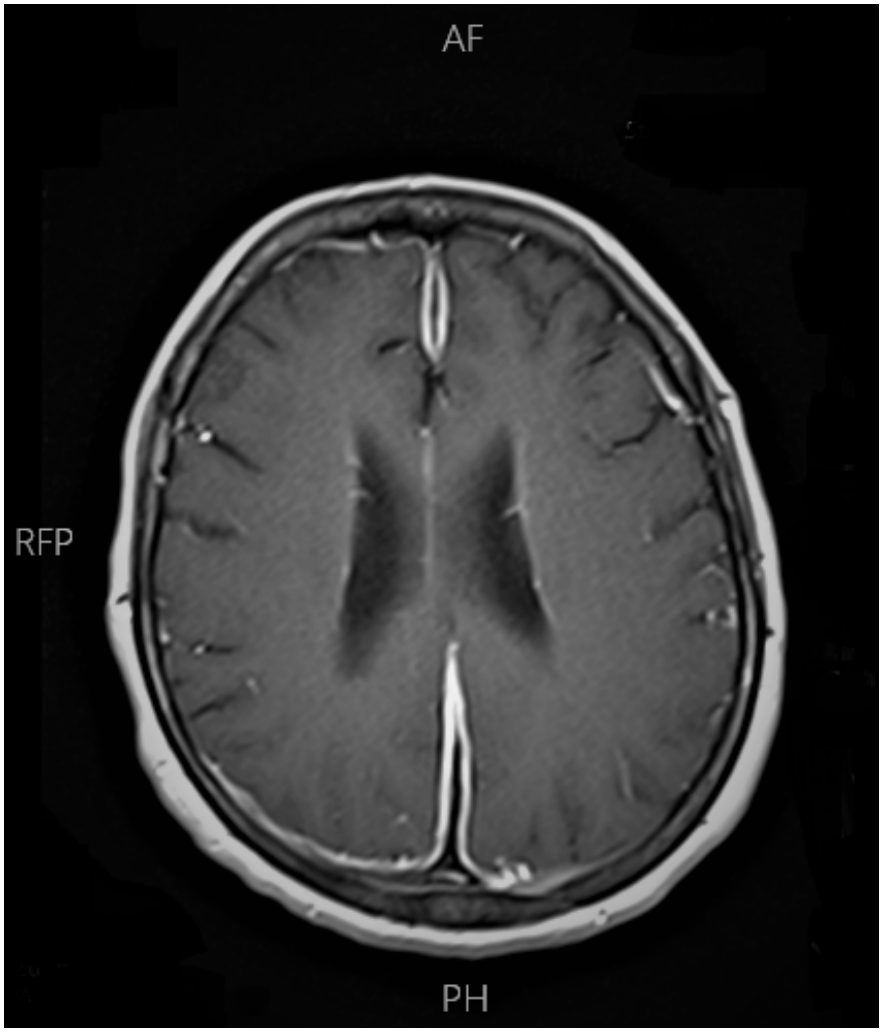
20. Inoue D, Yoshida K, Yoneda N, et al. IgG4-related disease: dataset of 235 consecutive patients. *Medicine (Baltimore).*2015;94(15):e680.

21. Lin W, Lu S, Chen H, et al. Clinical characteristics of immunoglobulin G4-related disease: a prospective study of 118 Chinese patients. *Rheumatology (Oxford).* 2015;54(11):1982-1990.

22. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med.* 2012;366(6):539-551.

23. Vasaitis L. IgG4-related disease: A relatively new concept for clinicians. *Eur J Intern Med.* 2016;27:1-9.

Figures



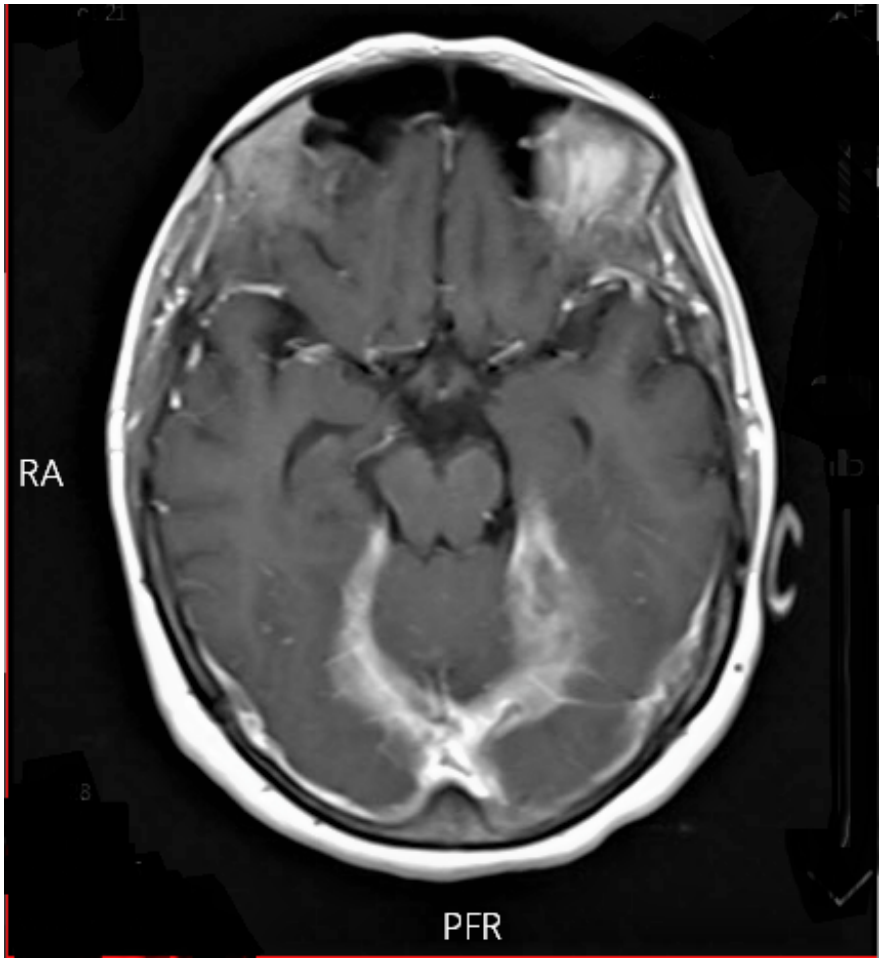


Figure 1. T1 weighted MRI with Gadolinium contrast showed diffuse meninges' enhancements at different levels.

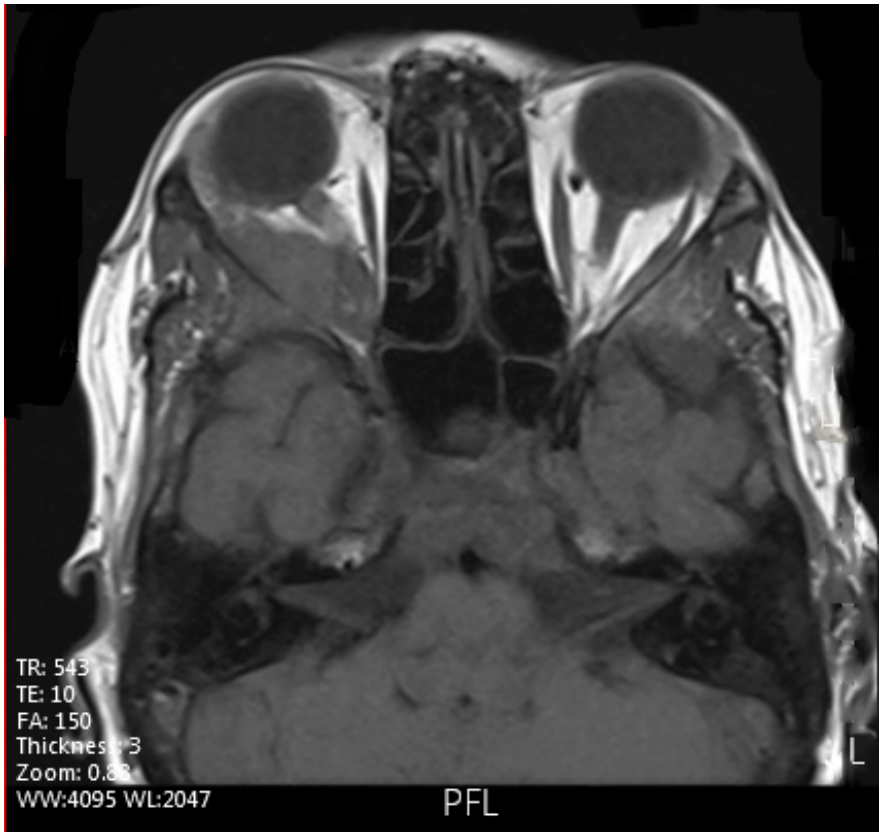


Figure 2. T1 weighted MRI with Gadolinium contrast (a) & T1 weighted MRI without contrast (b) revealed a right orbital mass with compression effect on the right optic nerve.

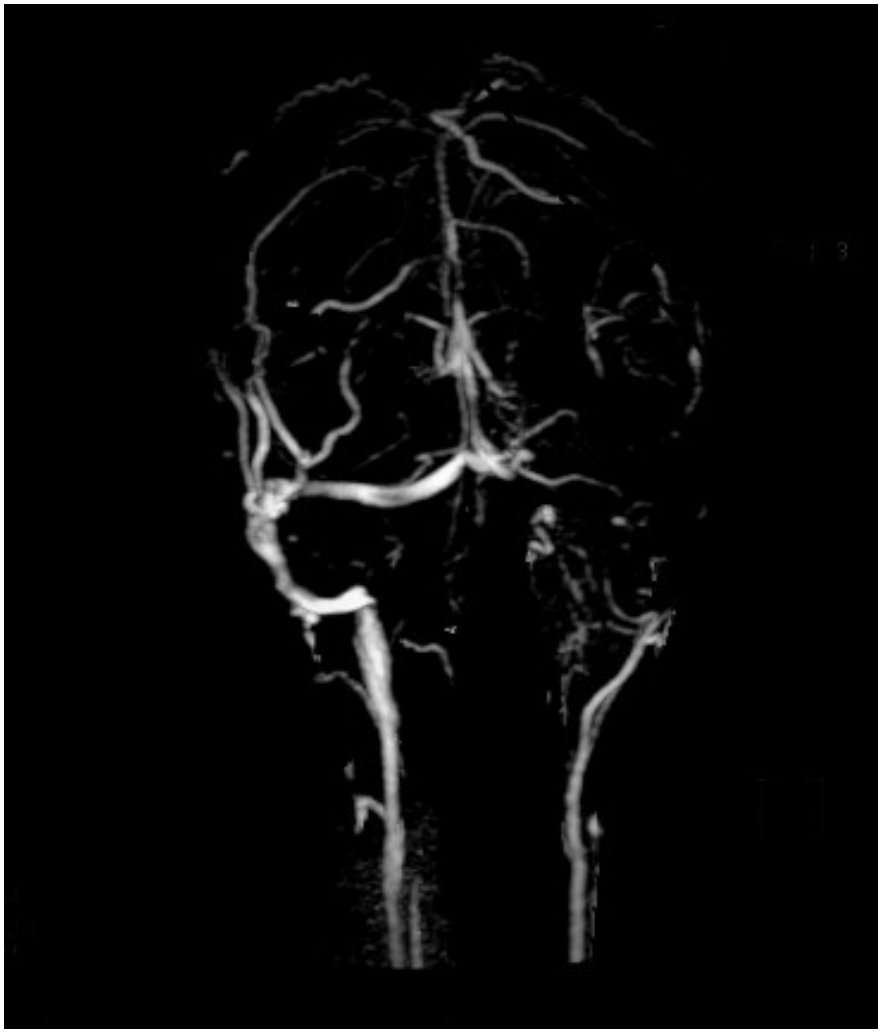
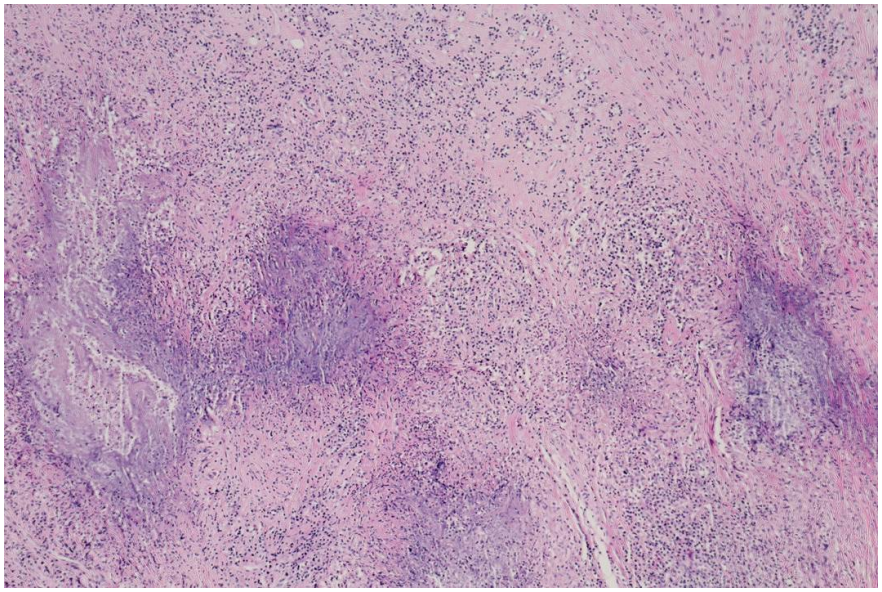
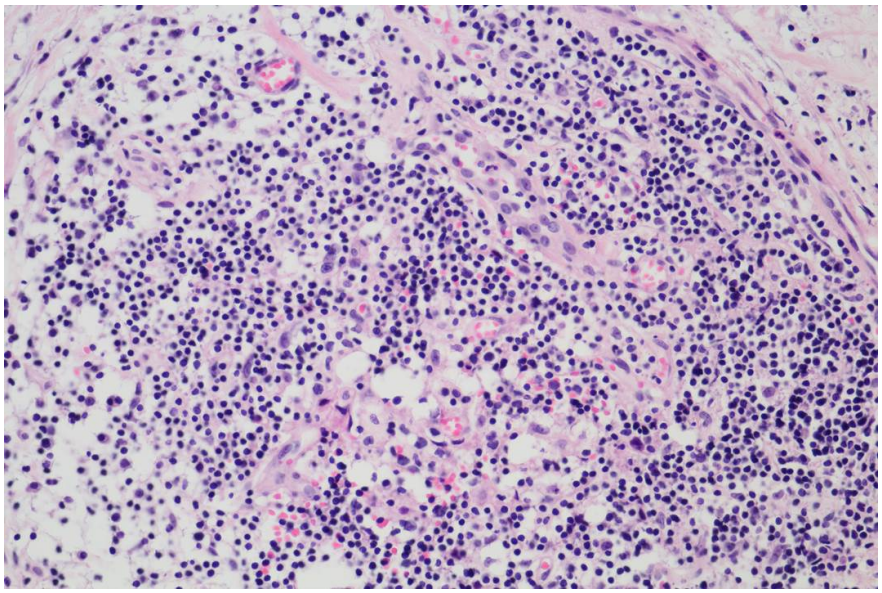
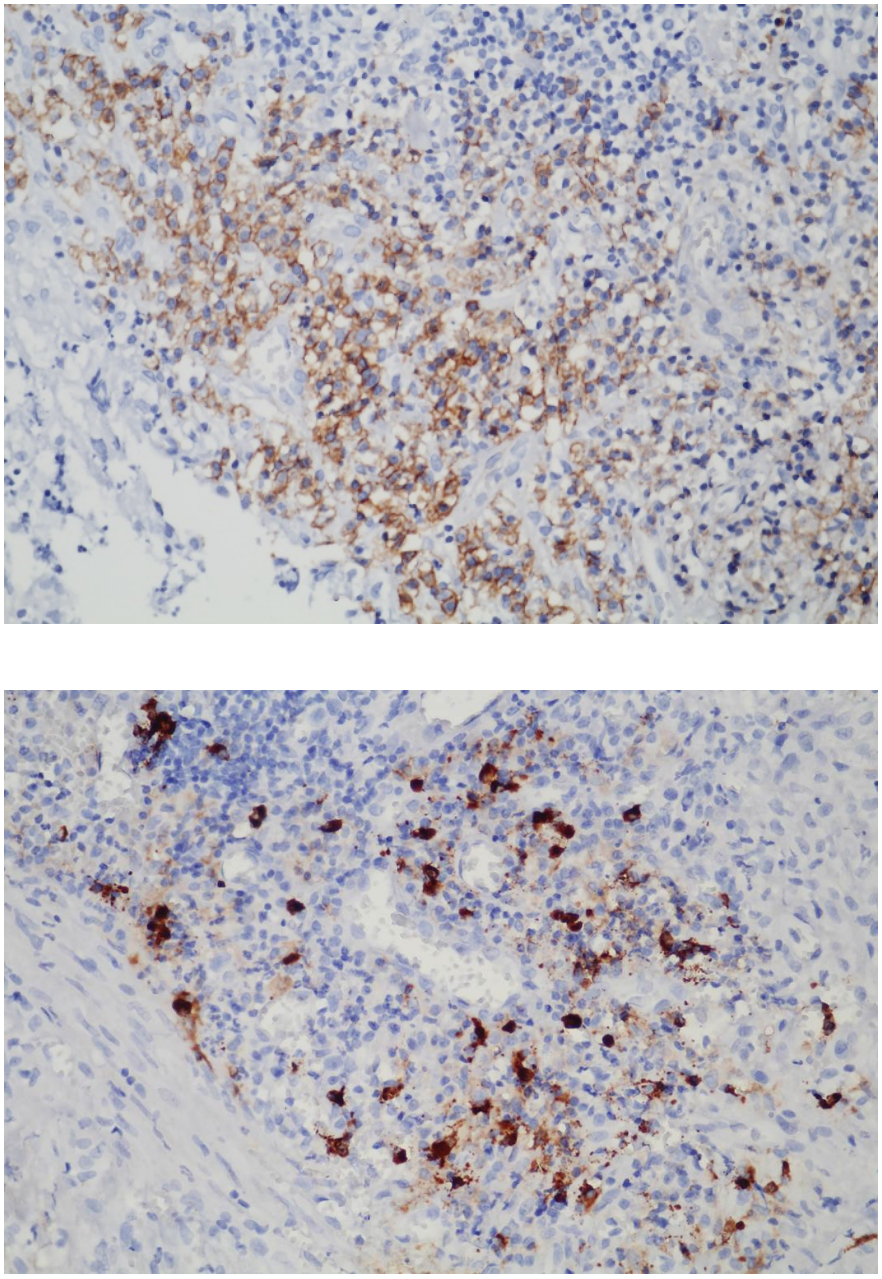


Figure 3. Brain MRV with Gadolinium contrast demonstrated thrombosis in the sagittal sinus and proximal of the left transverse sinus.





a b



c d

Figure 4. A low power field H&E staining revealed a fibroconnective tissue containing inflammatory cells infiltration, composed mostly 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%)