The Canadian Journal of Neurological Sciences (2023), **50**, 907–913
doi:10.1017/cjn.2022.321

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Brief Communication

IgG4-Related Disease of the Central Nervous System: A Case Series

Ghada Abbas[1,2,3], Jason Karamchandani[4], Anthony Ciarallo[5] and Liam Durcan[2,3]

[1]Division of Neurology, Department of Internal Medicine, Faculty of Medicine, King Abdulaziz University, Saudi Arabia, [2]Department of Neurology, McGill University, Montreal, Quebec, Canada, [3]Department of Neurology and Neurosurgery, Montreal Neurological Hospital and Institute, Montreal, Quebec, Canada, [4]Department of Pathology, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada and [5]Department of Diagnostic Radiology, Nuclear Medicine, McGill University, Montreal, Quebec, Canada

ABSTRACT: IgG4-related disease (IgG4-RD) is a rare and often misdiagnosed disorder with limited literature that highlights the different neurological presentations of this treatable disease. The diagnosis of IgG4-RD could be challenging, while imaging is fundamental for the diagnosis, biopsy is considered the gold standard. Most cases respond well to steroids and immunosuppressive therapy. This is a case series study that illustrates the varied neurological presentations of IgG4-RD through three different patients that were followed at the Montreal Neurological Institute. This paper takes you through the diagnostic strategy that we followed to accurately diagnose and treat those patients.

RÉSUMÉ : Maladie du système nerveux central, liée aux IgG4. La maladie du système nerveux central (SNC) liée aux IgG4 est un trouble rare, souvent mal diagnostiqué et peu documenté, qui fait ressortir les différentes manifestations neurologiques de cette maladie susceptible de traitement. Le diagnostic de la maladie du SNC liée aux IgG4 peut être difficile à poser, mais l'imagerie joue un rôle fondamental dans le diagnostic, et la biopsie est considérée comme l'examen de référence. Dans la plupart des cas, la maladie réagit bien aux stéroïdes et au traitement immunosuppresseur. Voici une série de cas qui illustre bien la diversité des manifestations neurologiques de la maladie du SNC liée aux IgG4, observées chez trois patients suivis à l'Institut neurologique de Montréal. L'article vous fera découvrir la stratégie de diagnostic que l'équipe a adoptée afin de bien diagnostiquer de la maladie et de la traiter.

Keywords: Hypophysitis; Pachymeningitis; Supraorbital tumor; Neurological spectrum of IgG4-related disease; IgG4; IgG4-positive plasma cells; Fibrosis; Autoimmune pancreatitis; Pituitary insufficiency; IgG4-related disease

(Received 14 March 2022; final revisions submitted 16 October 2022; date of acceptance 3 November 2022; First Published online 11 November 2022)

IgG4-related disease (IgG4-RD) is a fibro-inflammatory immune-mediated entity affecting various organs with different manifestations.[1,2] It is marked by lesions abundant in IgG4-positive plasma cells that are often associated with elevated serum IgG4 concentrations.[3] IgG4-RD should be considered when pathognomonic histopathological findings are seen in organs and when good response to treatment is observed.[2]

The cases discussed in this paper showcase the central nervous system (CNS) spectrum of IgG4-RD. Herein, we report three different IgG4-related neurological presentations where diagnosis was challenging, and treatment was effective. Our case series will be helping in considering IgG4-RD among other CNS diseases of similar presentations.

Case 1

A 78-year-old Caucasian man received oral prednisone for 2 years for the diagnosis of suspected lymphoma, a diagnosis that was made in an outside institution. He was also being followed for intraductal papillary mucinous neoplasm (IPMN) with cystic lesions in the body of the pancreas. He presented with acute left orbital pain and diplopia. Diplopia was secondary to bilateral sixth cranial nerve palsy. Magnetic resonance imaging (MRI) of the sella turcica showed thickening and enhancement of the pituitary stalk with enhancing abnormalities in the left cavernous sinus and retrosellar/retroclival sheet (Figure 1A and C). These findings were suggestive of dural thickening that could be secondary to lymphoma or to other infiltrative process. Orbital MRI (−/+ gadolinium) was within normal limits with no intra-orbital lesion. Adrenocorticotropic hormone (ACTH) was low, 0.78 pmol/L (normal 1.60–12.90 pmol/L), and IGG4 level was high, 2.590 g/L (normal 0.039–0.864 g/L), constituting 26% of all IgG subclasses combined. Eighteen fluoro-deoxyglucose positron emission tomography (18-FDG PET)/CT scan revealed no areas of active neoplastic disease between the base of the skull and the thighs. These manifestations together with the cystic pancreatic disease and the high IgG4 level were suggestive of IgG4-RD for which prednisone was restarted. Initially, the radiological findings were progressive, with eventual stabilization. MRI head showed less prominent pituitary stalk thickening with stable

Corresponding author: Dr. Ghada Abbas, Division of Neurology, Department of Internal Medicine, King Abdulaziz University Hospital, P.O. Box 80215, Jeddah 21859, Saudi Arabia. Email: gabass@kau.edu.sa

Cite this article: Abbas G, Karamchandani J, Ciarallo A, and Durcan L. (2023) IgG4-Related Disease of the Central Nervous System: A Case Series. *The Canadian Journal of Neurological Sciences* **50**: 907–913, https://doi.org/10.1017/cjn.2022.321

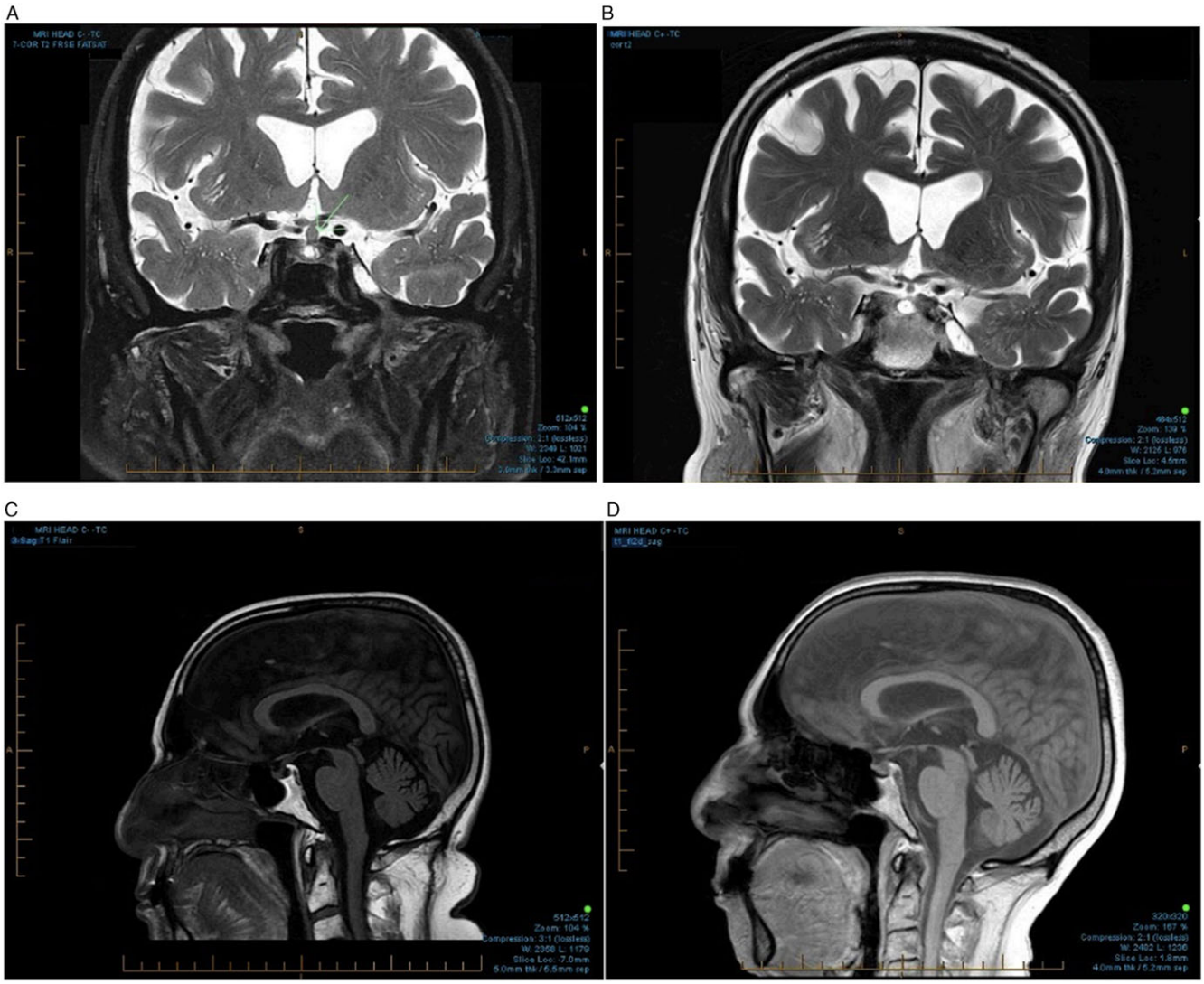

Figure 1: (A) T2-weighted images (fat sat): pituitary stalk thickening on coronal view. (B) T2-weighted images (6 months follow-up images): some improvement of pituitary stalk thickening on coronal view. (C) T1 FLAIR sag.: pituitary stalk thickening on sagittal view. (D) T1-weighted sag. Images (6 months follow-up images): some improvement of pituitary stalk thickening on sagittal view.

retrosellar/retroclival dural thinking (Figure 1B and D). This coincided with markedly reduced serum IgG4 level 1.620 g/L (normal 0.039–0.864 g/L). Remission, on low-dose prednisone, continued throughout his 5-year follow-up period.

Case 2

A 54-year-old Caucasian male patient with diabetes on oral hypoglycemics and untreated mesenteric panniculitis presented with an episode of involuntary left-hand movement. This was followed by loss of consciousness, mouth frothing, and cyanosis. In the emergency department, he was found to have left-sided hemiparesis. Computed tomography (CT) scan of the head revealed fullness over the right fronto-parietal and temporal convexity. Subsequent MRI of the brain showed a hyperintense lesion involving the right posterofrontoparietal region with associated leptomeningeal and pachymeningeal enhancement (Figure 2A and C). The electroencephalogram (EEG) disclosed interictal epileptiform disturbance of the cerebral activity over the right posterior parasagittal region. During his hospital stay, he developed generalized tonic clinic seizures, so he received phenytoin and levetiracetam. MRI brain was repeated a few days later showing marked progression of the meningeal process (Figure 2B and D). Lumbar puncture (LP) revealed normal cerebrospinal fluid (CSF) protein, glucose, and cell count with slightly elevated IgG 19.7 g/L (normal 7–15 g/L). A right parietal dural biopsy showed meningeal inflammation with IgG4-RD features (Figure 3A, B, C, D). Given the patient's past history of mesenteric panniculitis, further testing followed. Positron emission tomography (PET) scan revealed multiple areas of hypermetabolism (e.g. Figure 4). Several mesenteric biopsies showed fibro-inflammatory abnormalities. Inflammation with infiltration of the lymphocytes and plasma cells with greater than 18 IgG4 cells per high-power field was evident on a meningeal biopsy. These findings suggested the unifying diagnosis of IgG4-RD explaining his pachymeningitis. Eventually, prednisone 60 mg daily was started. Serial MRI brain (+/− gadolinium) showed progressive improvement of the leptomeningeal enhancement with eventual resolution of the meningeal

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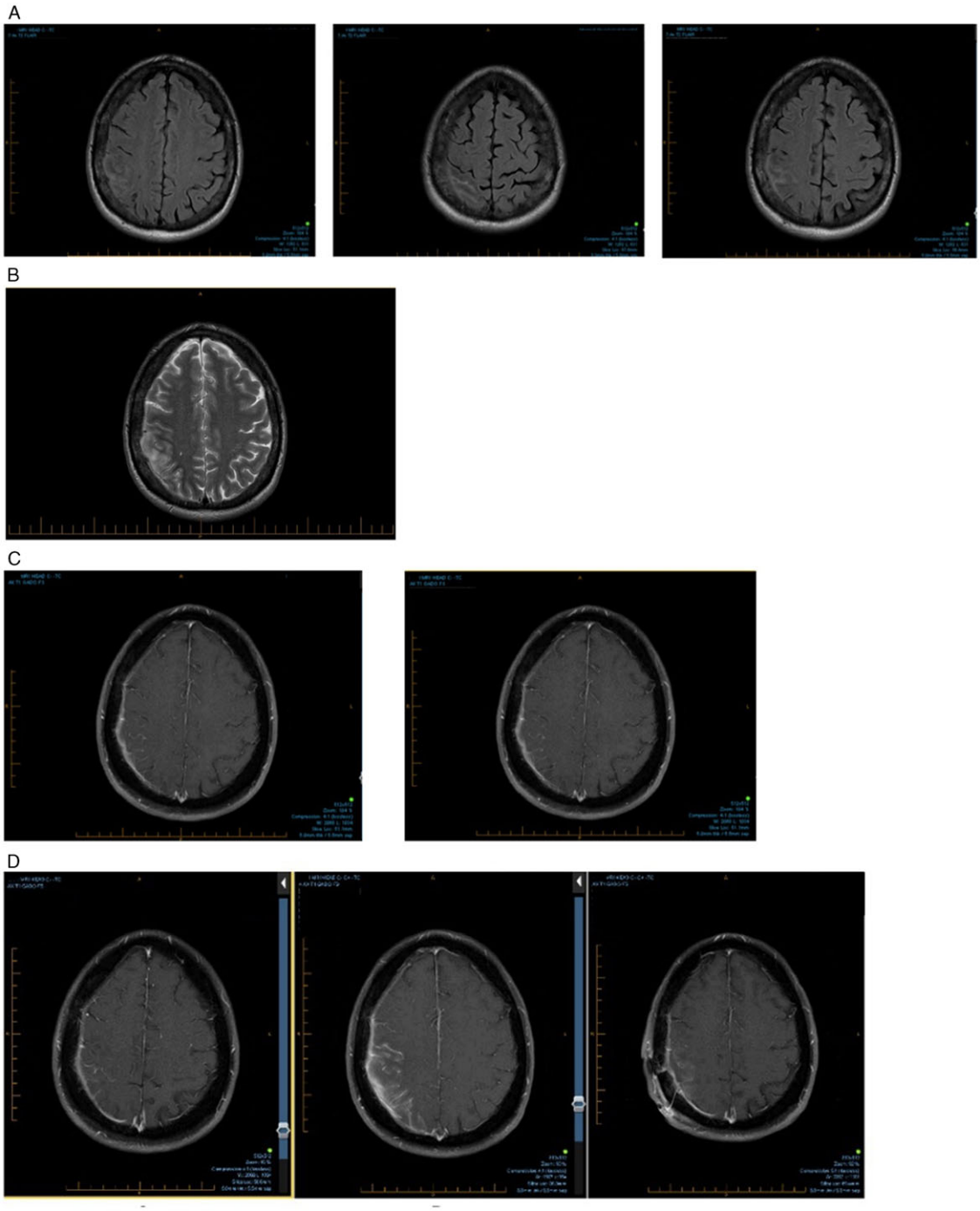

Figure 2: (A) T2 FLAIR: Abnormal focal leptomeningeal and pachymeningeal dural hyperintensity and thickening along the right parietal lobe on axial view. (B) T2-weighted follow-up images: Interval increase in amount of abnormal focal leptomeningeal and pachymeningeal thickening along the right parietal and frontal lobe, with minimal extension to the right temporal lobe on axial view. (C) T1 with gadolinium injection: right-sided pachymeningeal and leptomeningeal enhancement on axial view. (D) T1 with gadolinium follow-up images: Interval increase in amount of abnormal focal leptomeningeal and pachymeningeal enhancement along the right parietal and frontal lobe, with minimal extension to the right temporal lobe on axial view.

abnormalities and stabilization of the right frontoparietal hyperintensities. That was complemented with a normal IGG4 level 0.213 g/L (normal 0.039–0.864 g/L). Later, he developed chronic cough and fever with infiltrates on pulmonary imaging and persistently high C-reactive protein (CRP) 269.49 mg/L (normal 0.00–5.00 mg/L) and erythrocytes sedimentation rate (ESR) 55 mm/h (normal 0–10 mm/hour). Although the pachymeningitis responded well to prednisone, multi-system effects of his IgG4-RD prompted the administration of rituximab. Remission remained throughout his 9-year follow-up period.

Case 3

A thirty-four-year-old Middle Eastern female patient with a history of menstrual irregularity, miscarriage, benign adrenal hypoplasia, diabetes mellitus, hypothyroidism, obesity, and metabolic

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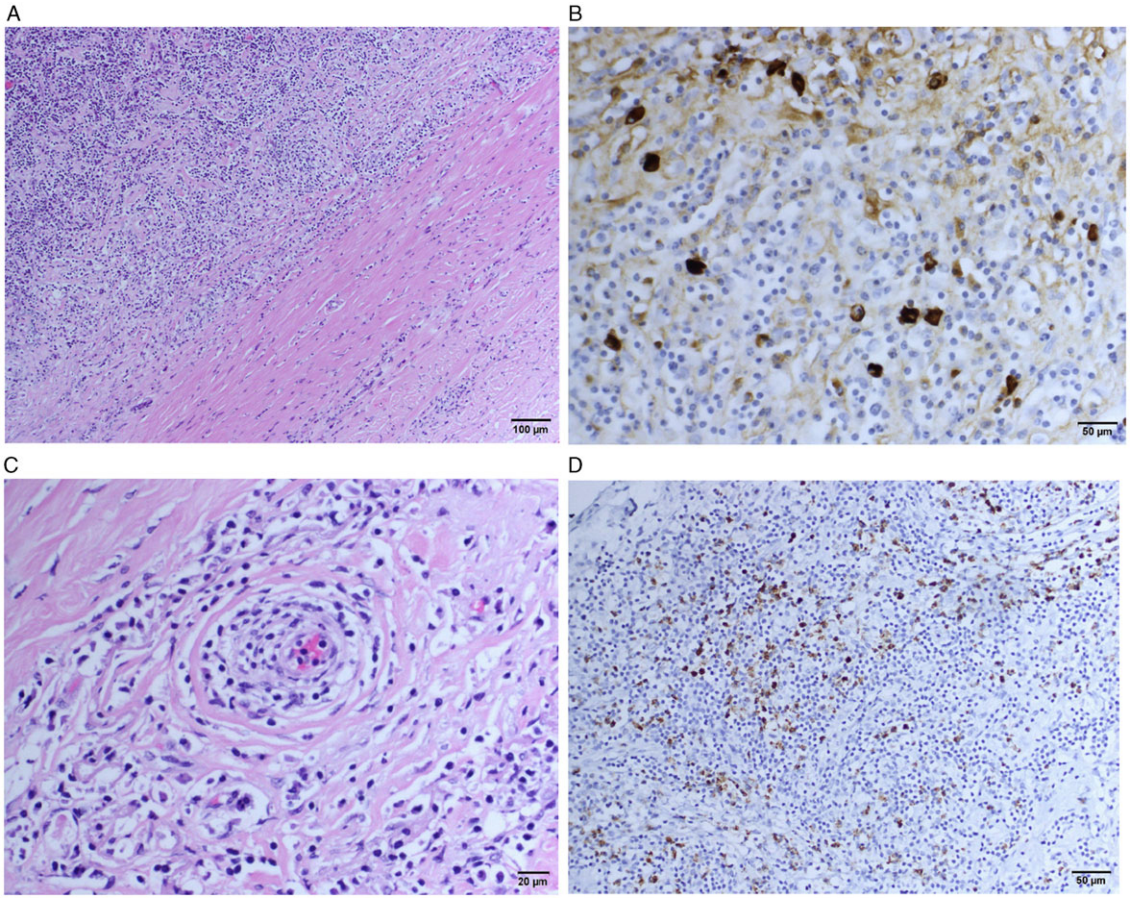

Figure 3: (A) Low-power H&N image shows a fragment of dura with an extensive lymphohistiocytic inflammation infiltrating into the superficial dura. (B) High-power image of an IgG4 immunohistochemically stained section highlights IgG4 expressing plasma cells which represent greater than 40% of all IgG expressing plasma cells. (C) High-powered H&E section shows perivascular inflammation with phlebitis in a background of hyaline sclerosis. (D) CD 138 immunohistochemically stained section shows brisk histiocytic inflammation with an abundance of CD 138 expressing plasma cells, set evenly throughout the inflammatory aggregates.

syndrome reported recurrent headaches and double vision with right gaze. Brain CT did not reveal any abnormalities. MRI orbits (−/+ contrast) showed right orbital apex lesion, Tolosa-Hunt syndrome was suspected. Steroids were given with relative symptoms improvement. Later, she was referred to a headache specialist who questioned the diagnosis, suspecting idiopathic intracranial hypertension instead. Therefore, steroids were stopped. As her symptoms progressed with blurred vision and worsening diplopia, her examination revealed proptosis. MRI brain showed right orbital apex tumor, which expended to the lateral cavernous sinus on follow-up (Figure 5). Consequently, the tumor was partially removed through transnasal transsphenoidal procedure. Pathologically, the resected tumor showed classical morphological features of IgG4-associated sclerosing pathology of the orbit (Figure 6A, B, C, D, E, F). IgG4 expression was seen in >80% of unequivocally IgG-expressing plasma cells. Her CSF IgG level was high at 0.0386 g/L (normal 0.0050–0.0340 g/L), and the other CSF parameters were normal. Although the symptoms generally stabilized, the follow-up annual orbital MRI showed some expansion of the residual tumor over years. However, this was not clinically significant. Preoperative versus postoperative visual field testing demonstrated improvement. Close follow-up with annual MRI, off steroids, is being provided.

IgG4-RD was reported first in Japan in 2003. Its histopathological features are the same in different organs. It includes infiltration by IgG4-positive plasma cells, lymphocytes, storiform fibrosis, eosinophils, and obliterative phlebitis resulting in tumefactive lesions in one or more organ systems. Also, serum IgG4 is often increased.[2]

The mean age of diagnosis is 67 years. It is more prevalent in males (3:1), except for IgG4-RD of the head and neck that equally affects both sexes.[2] Some environmental factors, for example, long-term exposure to solvents and industrial gases, may increase the risk. A Japanese genome-wide study identified HLA-DRB1 and FC-γ receptor IIb regions as susceptibility loci for the development of IgG4-RD. Nevertheless, several non-HLA genes have been also identified as a risk.[4]

IgG4-RD affects the pancreas and various extra-pancreatic organs.[2] It affects both the central and peripheral nervous system, through direct injury or mass effect.[5]

Cranial nerves and meninges are the most commonly affected.[3] Pachymeningitis with cranial nerve dysfunction or spinal compression symptoms were reported.[1] Recently, more ophthalmic IgG4-RD cases are being reported,[6] as seen in case 3. However, in our case, there was also an evident involvement of the cavernous sinus. Hypophysis involvement is rare; nevertheless, it is typical for

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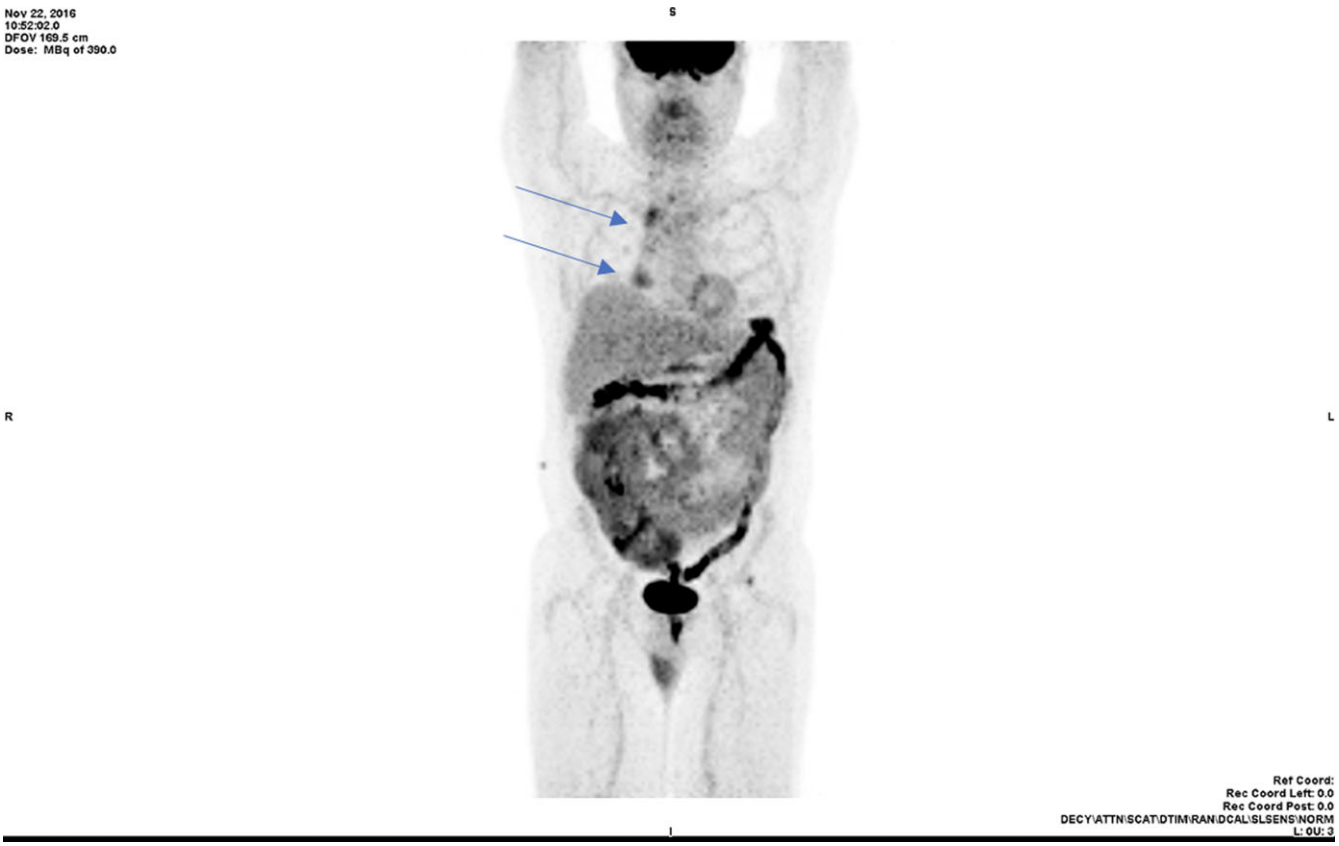

Figure 4: 18F-FDG PET-CT with transaxial CT, PET, and fusion images demonstrating the maximum intensity projection (MIP) in anterior view giving an overview of the chest findings. There are no significant extrathoracic abnormalities in this figure.

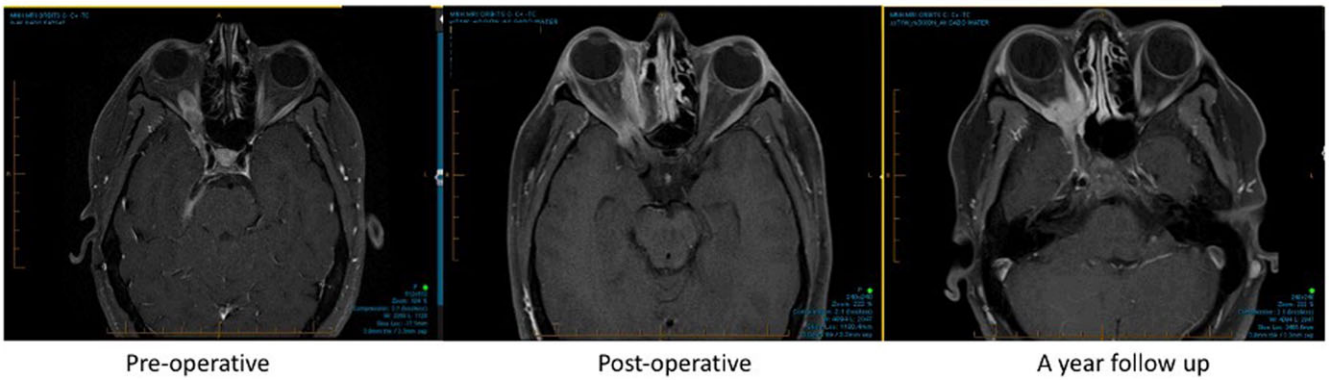

Figure 5: Comparative (pre- and postoperative) orbital MRI T1 (Fat. Sat): showing increased signal at the right orbital apex, representing a lesion.

the disease, often associated with pituitary insufficiency.[3] Moreover, the first case of IgG4-related neuropathy was recently reported.[5]

Usually, patients with IgG4-related hypophysitis, pachymeningitis, and ophthalmic disease are in good general condition with no fever, constitutional symptoms, or high CRP.[7]

IgG4-RD could be confused with malignancy presenting as mass-like lesion or dural thickening.[1] Some idiopathic hypertrophic pachymeningitis cases are thought to represent IgG4-RD, especially when associated with multifocal fibrosclerosis,[7] as in case 2. One or more symptoms dominate in IgG4 pachymeningitis, including cranial nerve palsies, visual disturbances, and seizures. Others include rapidly progressive dementia, gait disturbance, and headache. Cranial nerve involvement usually results from compression by adjacent mass, as in case 3.[1]

IgG4 hypophysitis is mostly associated with enlarged anterior pituitary gland, stalk, or both on MRI.[2]

IgG4 ophthalmic disease is of insidious-onset, painless, unilateral or bilateral, marked by eyelid swelling or proptosis. It could involve the lacrimal gland, trigeminal nerve, extraocular muscles, diffuse orbital fat, eyelids, and choroid.[6] When IgG4-RD presents with circumscribing orbital mass lesion, other diagnoses must be considered including lymphoma and idiopathic sclerosing orbital inflammation.[6,8] IgG4-related pathology in the ocular region

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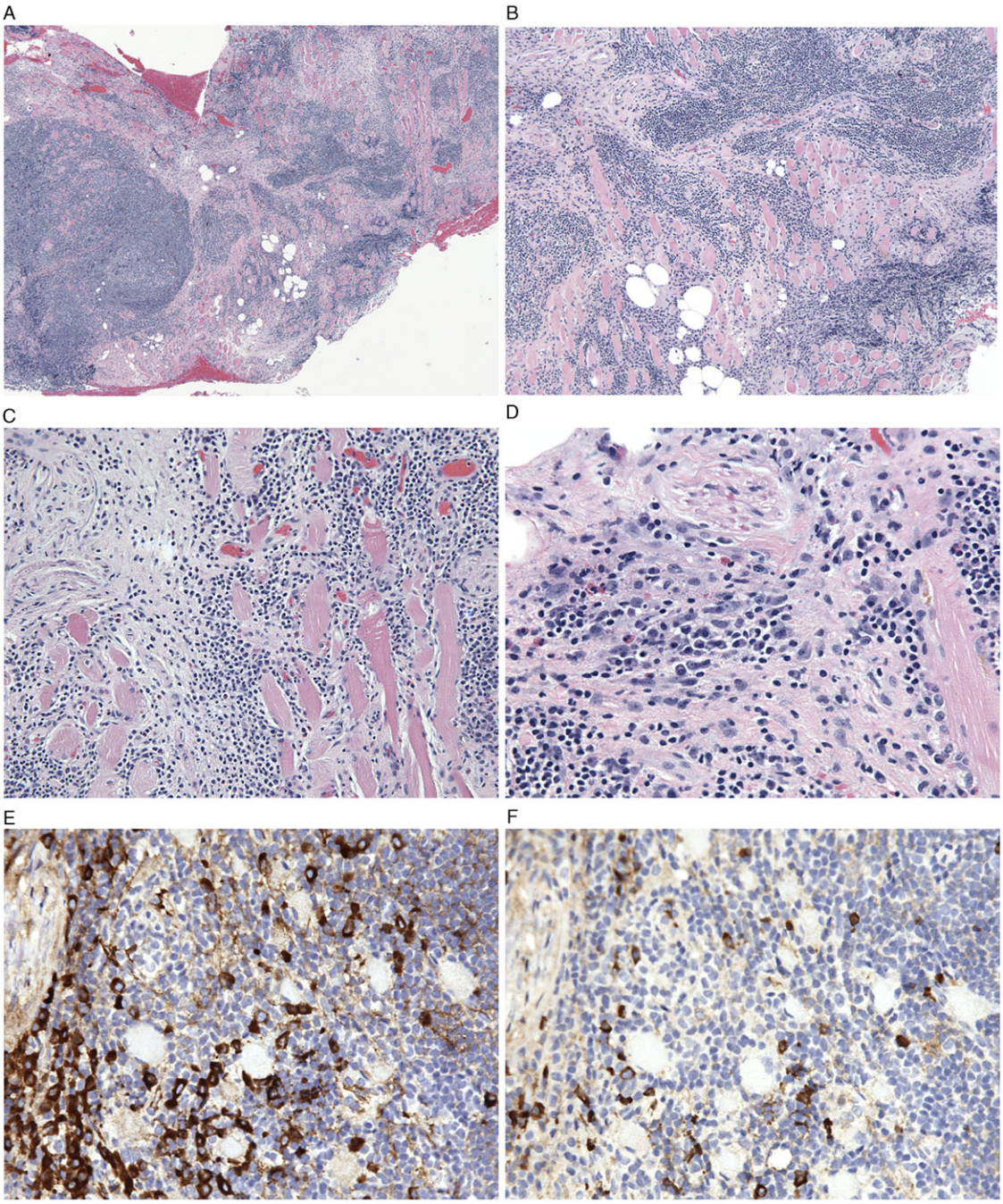

Figure 6: Pathology slides of the resected right orbital apex tumor. (A) Infiltration of the periorbital soft tissue by proliferation of small, reactive appearing lymphocytes with occasional activated germinal centers (or follicles) infiltrating through the skeletal muscle and periorbital adipose tissue. **(**B) Higher magnification, showing the splaying of non-necrotic skeletal muscle fibers by small reactive-appearing lymphoid cells as well as fully differentiated plasma cells. In addition to endomyseal fibrosis. (C, D, E) High magnification images, showing an abundance of plasma cells as well as scattered eosinophils in a fibrotic background with perivascular fibrosis. In addition, CD138 highlights the abundant plasma cells within the lymphoid infiltrate which is expanding and infiltrating through the orbital periodical soft tissues. **(**F) More than 30% of the plasma cells are expressing IgG4 (normally this would be fewer than 5%).

presents an extensive morphologic overlap with reactive lesions and low-grade B-cell lymphomas, making it hard to diagnose. IgG-expressing cells in the context of sclerosis is key factor for making the diagnosis.[8] This conundrum was seen in case 3.

IgG4-RD pathogenesis is not completely understood. IgG4 is always present within involved organs.[1] A biphasic progression happens, where an "inflammatory" phase is followed by a "fibrotic" outcome.[2] Both B and T cells are central in IgG4-RD pathogenesis.[5]

In about 55–97% of cases, serum IgG4 is elevated, correlating with the number of involved organs. Nevertheless, elevated serum IgG4 can be seen in a broad spectrum of neoplastic, infectious, and autoimmune diseases. However, one meta-analysis found that when twice the upper limit of normal was used as the cutoff (range

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2.70–2.80 g/L), the specificity increased from 82.6% (81.6–83.6%) to 94.8% (94.1–95.4%).[9]

Furthermore, one study suggested that CSF IgG4 quantification and IgG4 indices could be used as alternatives to meningeal biopsy in cases of pachymeningitis. CSF IgG4 level higher than 2.27 mg/dL identified 100% of IgG4 pachymeningitis and 5% of other causes of pachymeningitis (OP). An $IgG4_{Loc}$ cutoff of 0.47 identified 100% of IgG4 pachymeningitis and no cases of OP.[10]

Histopathology (immunohistochemistry) is the gold standard test.[1]

Early diagnosis may prevent end-stage organ failure and death.[1] Steroids, disease-modifying therapy (e.g., azathioprine), rituximab (associated with remission rate of 67–83%), and infliximab were found successful. Ophthalmic IgG4-RD is of high recurrence rate, needing prolonged steroids course, rituximab, or infliximab.[6,9]

In conclusion, hypophysitis, pachymeningitis, and sclerosing ophthalmic lesions represent a large proportion of CNS IgG4-RD. This disease needs differentiation from other pathologies.[1]

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2022.321.

Conflict of Interest. All authors have nothing to disclose.

Statement of Authorship. GA contributed with review of the cases, review of the literature, drafting, editing, and reviewing the manuscript; JK contributed with providing the pathology figures and providing their descriptions; AC contributed with providing the 18F-FDG PET-CT figures and providing their descriptions; LD contributed with assessing the patients, review of the cases, review of the literature, drafting, critical review of the manuscript, editing, and approval of the final version.

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