

CASE REPORT

Successful treatment of IgG4-related hypertrophic pachymeningitis with induction rituximab and dexamethasone followed by maintenance rituximab

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Abstract

IgG4-related disease (IgG4RD) with intracranial involvement is rare. We report a 56-year-old male who had an excellent response to rituximab and dexamethasone after going undiagnosed for 5 years. After 3 years of rituximab maintenance, he has no evidence of disease on brain MRI.

KEY WORDS

headache, IgG4 disease, lymphoproliferative disorder, maintenance rituximab, pachymeningitis

1 | INTRODUCTION

IgG4-related disease (IgG4RD) is a rare polyclonal lymphoproliferative disease which can involve multiple organ systems. IgG4-related intracranial manifestations include hypertrophic pachymeningitis (defined as focally or diffusely thickened dura mater) and hypophysitis.^{1,2} There is no standard treatment protocol for the management of IgG4 related pachymeningitis due to its rarity.³ Steroids and rituximab have been shown to achieve clinical remission in most cases.^{4,5} The role of maintenance rituximab has not been reported. Herein, we report a case of IgG4-related pachymeningitis successfully treated with induction rituximab and dexamethasone followed by maintenance rituximab.

2 | CASE

A 56-year-old male presented to us with history of severe debilitating headache for five years in association with painful, red, and tender nodules on his bilateral lower extremities. Headaches were described as a sharp shooting pain in the right frontal region, radiating over the entire scalp. The initial evaluation revealed cervical and pelvic lymphadenopathy which showed reactive changes on an excisional biopsy of a right jugular lymph node 5 years prior to his presentation to our institution. Biopsy of a skin lesion showed neutrophilic infiltrates and panniculitis, suggestive of erythema nodosum. The initial laboratory workup at our institution was significant for; ESR of 52 (0-22 mm/1 h), CRP of 56

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(≤ 8.0 mg/L), and serum IgG 4 level of 204 (2.4–121.0 mg/dL). Cerebral spinal fluid (CSF) analysis showed increased white blood cell with 85% lymphocytes and IgG level of 0.29 (≤ 0.21). Hepatitis B surface antibody and antigen both negative; hepatitis C antibody also negative. Extensive infectious and autoimmune diseases workup was negative. MRI of the brain showed a diffuse plaque-like thickened enhancing dura (Figure 1A, arrowheads) and obliteration of the superior sagittal sinus (Figure 1B, arrow). These findings were consistent with hypertrophic cranial pachymeningitis.

Pathology review at our institution of the old outside excisional biopsy of the right jugular lymph node showed regressed lymphoid follicles and increased plasma cells at the interfollicular region (Figures 2A, 3). CD138 highlighted the plasma cells (Figure 2B); which are polyclonal by kappa and lambda immunostains. IgG was positive for 146 plasma cells/high power field (Figure 2C); while IgG4 was positive for 143 plasma cells /high power field (Figure 2D); hence there was significantly increased IgG4/IgG ratio of approximately 98. Both the amount of IgG4 positive plasma cells and IgG4/IgG ratio are way above the diagnostic criteria for IgG4-related disease (IgG4 + plasma cells/hpf > 100 and IgG4+/IgG + plasma cell ratio $> 40\%$).

Based on his clinical, laboratory, pathological, and radiological findings he was diagnosed with systemic IgG4RD

with cranial pachymeningitis. He was treated with 8 cycles of weekly rituximab and dexamethasone, resulting in resolution of both headaches and erythema nodosum. MRI of the brain showed near complete resolution of pre-existing findings. However, he quickly developed intermittent flare-ups of headache without significant MRI changes and was managed successfully with dexamethasone as needed. He was also initiated on maintenance rituximab every 2 months for three doses followed by every four months achieving complete symptom control. Currently after three years of maintenance rituximab, he is symptom-free with MRI brain showing resolution of the dural thickening (Figure 1C, arrowheads) and improved caliber of the superior sagittal sinus (Figure 1D, arrow). IgG 4 levels continued to decrease (Figure 4). At 3-year follow-up after initiation of rituximab, the patient is in clinical and radiologic remission.

3 | DISCUSSION

IgG4RD is a rare polyclonal lymphoproliferative disorder,¹ which commonly involves the pancreas, lungs, thyroid gland, lymph nodes, extra pancreatic bile ducts, retroperitoneum, aorta, and lacrimal and salivary glands.^{6,7} Intracranial involvement is rare and most commonly involves hypertrophic

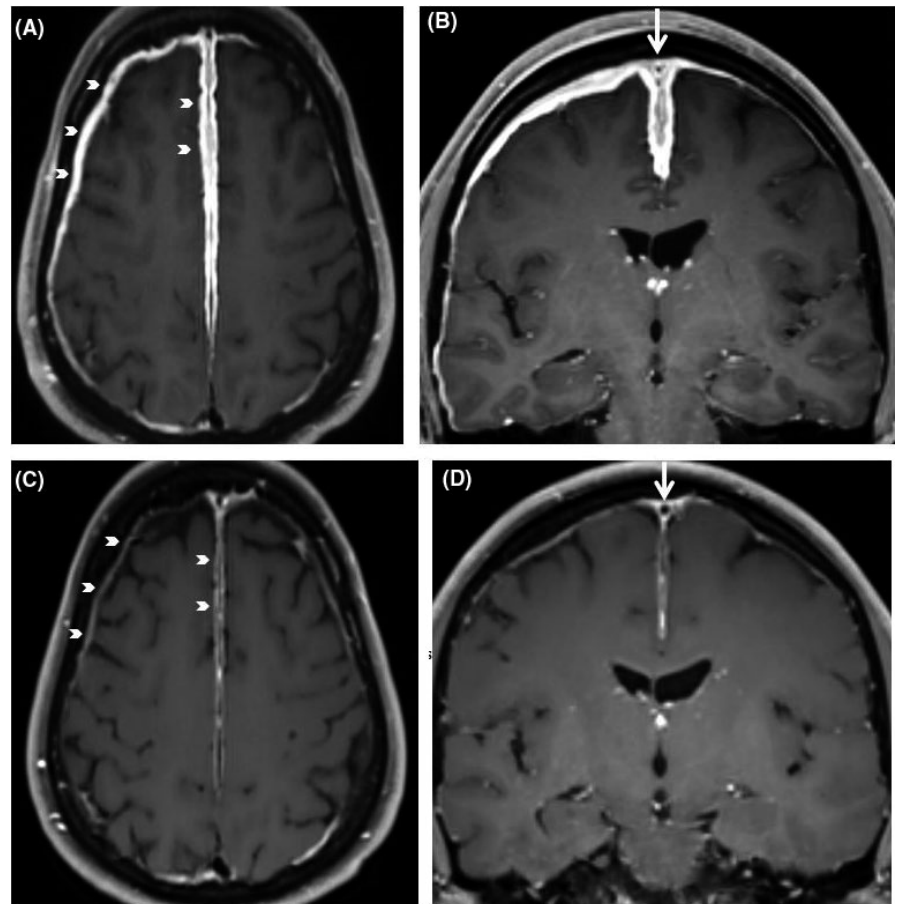


FIGURE 1 Contrast-enhanced T1 weighted MRI. Before treatment (images A and B) shows diffuse plaque-like thickened enhancing dura (A, arrowheads) and obliteration of the superior sagittal sinus (B, arrow). After treatment (images C and D) three years later, there is resolution of the dural thickening (C, arrowheads) and improved caliber of the superior sagittal sinus (D, arrow)

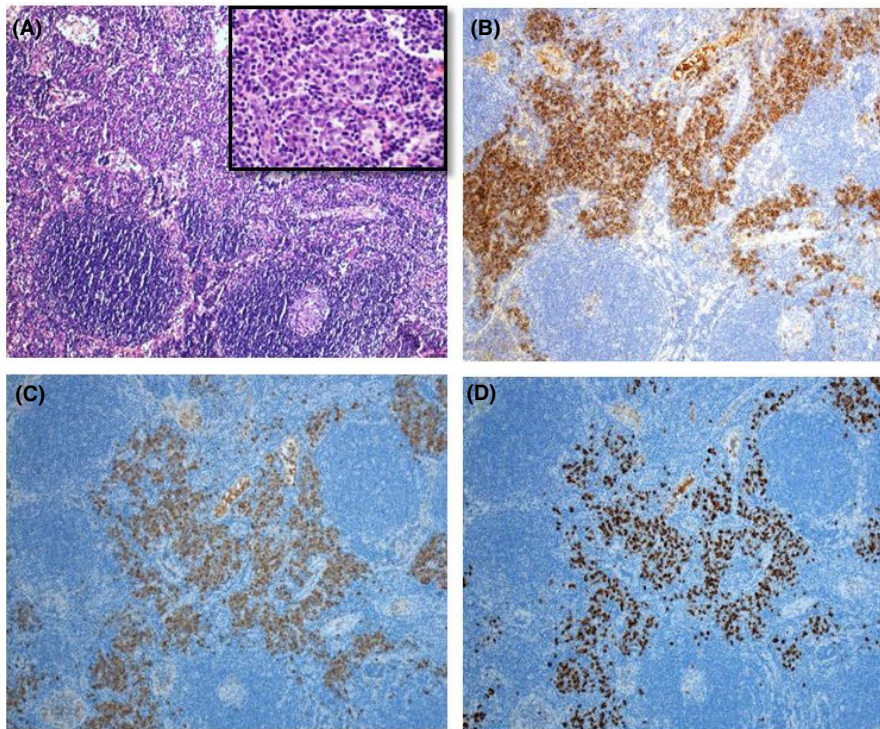


FIGURE 2 Excisional biopsy of the right jugular lymph node: A: H&E section showed regressed lymphoid follicles and markedly increased plasma cells. The increased plasma cells are better appreciated at higher magnification in the inset (H&E, $\times 10$; inset, H&E $\times 60$). B: Plasma cells in the lymph node sinuses were highlighted by CD138 (IHC, $\times 10$). C: IgG was positive for majority of the plasma cells (IHC, $\times 10$). D: IgG4 was also positive for many plasma cells (IHC, $\times 10$)

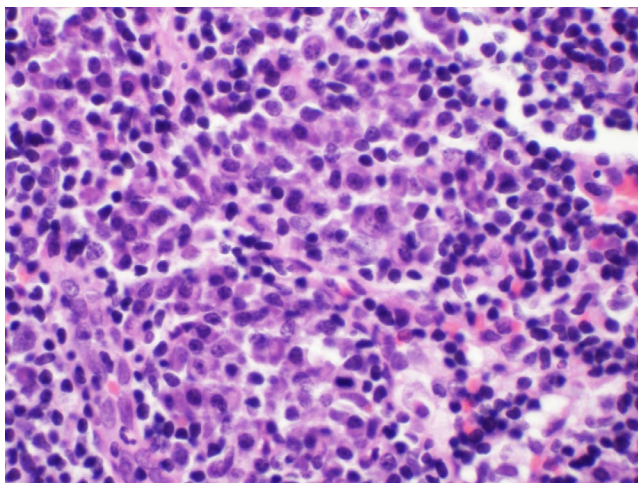


FIGURE 3 Excisional biopsy of the right jugular lymph node: Showed markedly increased plasma cells at higher magnification (H&E $\times 60$)

pachymeningitis and hypophysitis.⁸ In a Japanese survey, the prevalence of hypertrophic pachymeningitis was about 1 case per 1 000 000 with 8.8% of the cases having IgG4RD as the underlying etiology.⁹ Similar to our patient, it is more commonly seen in males, at a median age of 53 years.⁴ The diagnosis is based on histologic analysis of appropriate tissue biopsies, demonstrating lymphoplasmacytic infiltration with IgG4 + plasma cell proliferation, storiform fibrosis, and obliterative phlebitis.¹⁰

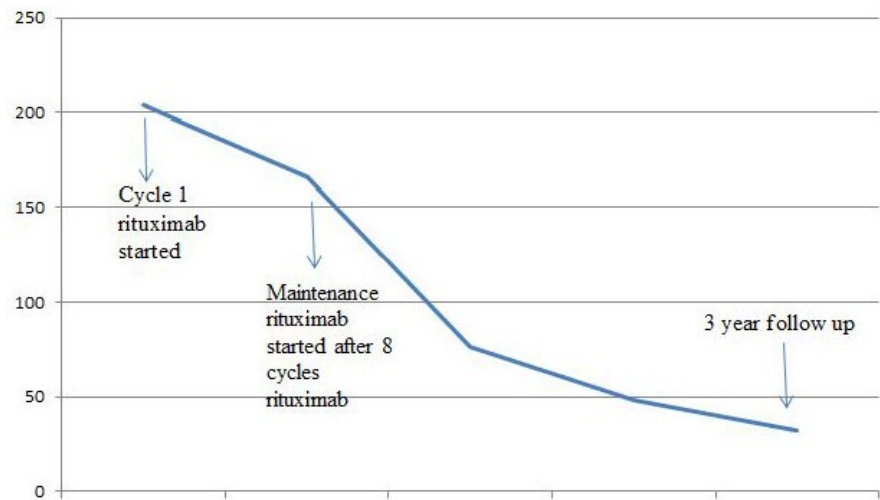
There is no specific treatment protocol for IgG4 related pachymeningitis.¹¹ High-dose steroids are the initial

treatment of choice; other immunosuppressive agents have shown variable efficacy in reducing meningeal hypertrophy and mostly used in disease relapse setting.³ Steroids together with rituximab have also been shown to achieve an initial clinical remission in most cases.^{3,12} Rituximab is a monoclonal antibody against CD 20 that can induce killing of CD20 + cells.¹³ It has been reported to result in substantial reduction in serum IgG4 levels and clinical improvement.³ Other immunosuppressants such as cyclophosphamide, mycophenolate mofetil, or methotrexate have been used in cases refractory to rituximab and steroids.¹⁴

After an initial response to steroids or rituximab, most cases reported in the literature were followed without maintenance therapy, with the goal to reinstate treatment with steroids and/or immunosuppressive agents when the disease relapses.³ The role and choice of maintenance therapy after an initial response is not well defined. A consensus guideline from Japan recommended maintenance steroids for up to 3 years.³ Reports indicate a relapse rate of about 42.1% after stopping steroid therapy; and about 40% after initial treatment with rituximab without maintenance.^{4,15} The benefit of maintenance rituximab has been reported in patients with systemic IgG4 disease, maintenance rituximab following the initial rituximab treatment was associated with a prolonged relapse-free survival.¹⁵

Our case highlights a patient with IgG4-related pachymeningitis who was successfully treated with induction rituximab and dexamethasone followed by maintenance rituximab. We suggest the use of the combination rituximab

FIGURE 4 IgG4 levels during treatment and follow-up



and dexamethasone in the initial treatment as rituximab alone may not have a significant impact on the plasma cell component of the disease. Maintenance rituximab was justifiable in our patient due to the debilitating nature of his headaches. The optimal duration of maintenance rituximab for IgG4RD is unknown.¹⁶ One interesting observation in our patient is the resolution of pachymeningeal thickening in spite of delayed diagnosis and treatment. It appears that IgG4-related fibrosis can be reversed.

While we have described the potential benefit of maintenance rituximab, one should keep in mind the risks associated with prolonged use of rituximab such as neutropenia, low immunoglobulin levels, progressive multifocal leukoencephalopathy, reactivation of hepatitis, infection, intestinal perforation, and interstitial pneumonitis.^{17,18} These are rare; furthermore, long-term safety data of rituximab show no evidence of an increased safety risk or increased reporting rates of any types of adverse events with prolonged exposure.^{17,18}

One aspect of our patient is that he went without definitive diagnosis of IgG4RD for five years. We recommend that IgG4RD should be considered with high index of suspicion in patients presenting with MRI features of pachymeningitis. Extensive diagnostic workup should be performed including IgG4 immunohistochemistry on all the available tissue biopsies and serum IgG4 level.

4 | CONCLUSION

Hypertrophic pachymeningitis is a rare manifestation of IgG4RD and is associated with severe debilitating headache. The diagnostic possibility of IgG4RD should be explored in patients with radiologic evidence of pachymeningitis. It appears to be quite responsive to treatment with rituximab and dexamethasone. Maintenance rituximab appears to be effective for long-term disease control.

5 | ETHICS APPROVAL

Not needed.

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None.

CONFLICT OF INTEREST

All other authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

Karan Seegobin: have made substantial contributions to conception and design, acquisition of data, and drafting the manuscript. Muhamad Alhaj Moustafa: have made substantial contributions to acquisition of data and drafting the manuscript. Nicole Gannon: have made substantial contributions to conception and design, acquisition of data, and drafting the manuscript. Katelyn Keller: have made substantial contributions to conception and design, acquisition of data, and drafting the manuscript. Jacquelyn Hastings: have made substantial contributions to conception and design, acquisition of data, and drafting the manuscript. Vivek Gupta: have made substantial contributions to conception and design, and revising it critically for important intellectual content. Han W Tun: have made substantial contributions to conception and design, and revising it critically for important intellectual content. Liuyan Jiang: have made substantial contributions to conception and design, and revising it critically for important intellectual content.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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