

## A Challenging Case of IgG4-Related Disease with Multiple Relapses: Effective Treatment with Bendamustine and Rituximab

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### 1. Abstract

Immunoglobulin G4-Related Disease (IgG4-RD) is characterized by increased IgG4 serum concentrations, tissue infiltration by IgG4-secreting plasma cells, and fibrosis. Steroids and rituximab are effective therapeutic agents for front line treatment. However, a relapsing and remitting course is expected with this disease. A number of immunosuppressive agents have been evaluated for such patients with sub-optimal responses and no clear guidance on a standard approach. We describe the use of lympho-depleting chemotherapy with bendamustine and rituximab and show efficacy with this approach in a patient with multiple relapses.

### 2. Introduction

Immunoglobulin G4-Related Disease (IgG4-RD) is a fibroinflammatory syndrome that is characterized by increased IgG4 serum concentrations, tissue infiltration by IgG4-secreting plasma cells, and fibrosis [1, 2]. IgG4-RD can affect almost all organ systems and affected organs often present with enlargement. Early awareness and treatment is essential to avoid serious organ damage though diagnosis can be challenging due to IgG4-RD mimicking many other prevalent diseases. In order to prevent organ deterior-

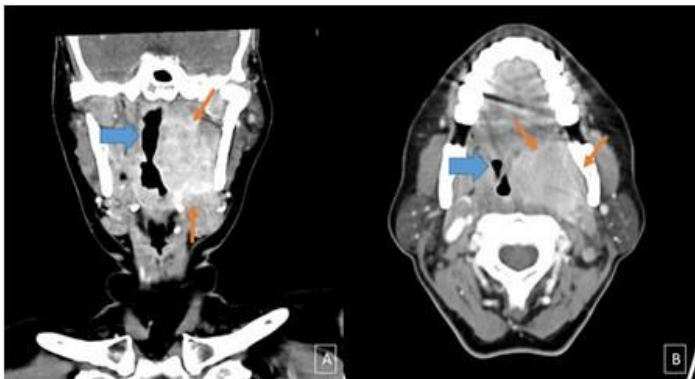
ation, treatment and maintenance of remission is necessary. Steroids, specifically glucocorticoids, are the recommended first-line therapy for many patients [1,3,4]. Another challenge faced with IgG4-RD is that patients can have a relapsing and remitting course with relapses frequently detected in patients during or after steroid tapering; some patients may even be refractory to treatment. [1] Maintenance steroids may reduce relapse rates in some patients and can be effectively transitioned to methotrexate (MTX) as a steroid sparing agent [5]. Rituximab is also highly effective as an induction therapeutic for IgG4-RD and can be combined with a low dose of maintenance prednisone to sustain remission in patients [3]. Despite such measures, relapses should be anticipated. A number of systemic agents have been evaluated for relapsed IgG4 disease including rituximab, azathioprine (AZA), and cyclosporine (CsA) [1, 6, 7]. However, options for treatments reported to date for patients with multiple relapses IgG4-RD are suboptimal with low response rates [4, 6, 7]. Alternative therapeutic strategies should be established. Herein, we present the first case of a patient to be treated with bendamustine + rituximab successfully with durable response.

### 3. Case Summary

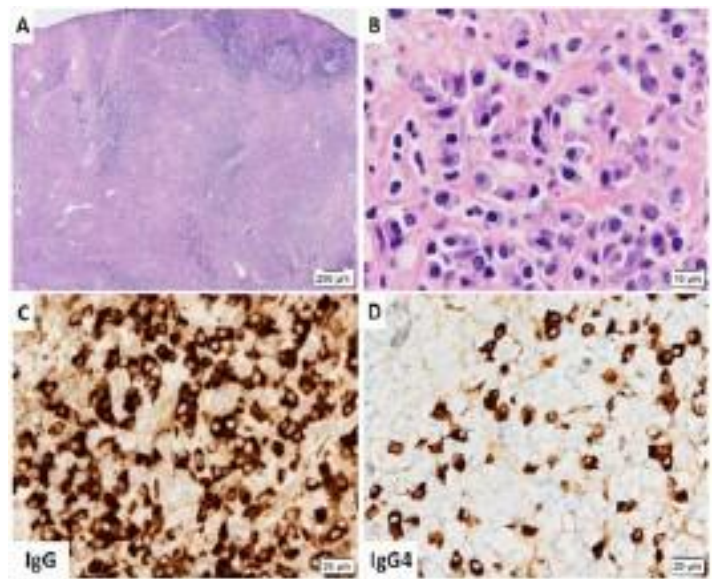
Our patient presented at age of 52 with total right sided hearing loss and facial numbness in September 2014. Evaluation by Magnetic Resonance Imaging (MRI) scan revealed a mass involving the medial pterygoid muscle in the pterygomaxillary space. She was referred to an ear-nose-throat specialist and underwent a biopsy that showed chronic inflammation with concern for lymphoma raised, but ultimately non-diagnostic. Given equivocal results, a biopsy was reattempted in October 2014. Findings again were suggestive of chronic inflammation, but notably labs demonstrated high normal levels of IgG4 and decreased Immunoglobulin M (IgM).

She was closely observed over the following months until she developed further difficulty swallowing and right sided facial pain in February 2015. Scans displayed progression of her known lesion and she ultimately underwent endoscopic biopsy with pathology demonstrating IgG4 disease. A workup for IgG4-related clinical sequelae including amylase, lipase, autoimmune work-up, lactate dehydrogenase (LDH) and Computerized Tomography (CT) scans was unrevealing. There was little concern for concurrent lymphoma. The patient was started on 40 mg of prednisone in May 2015 with initial improvement. However, a repeat MRI in June 2015 demonstrated a mixed response and the patient noted increase in facial pain. She went on to receive treatment with rituximab x 2 doses in July 2016. Her course was complicated with vision changes attributed to a rare side effect of uveitis caused by rituximab and further treatment was held. Repeat imaging showed improvement of disease.

Unfortunately, the patient relapsed in November 2018. She developed a sore throat with trismus, dysphagia, fevers/chills, and voice hoarseness. CT neck demonstrated a mass in the region of left tonsil with concern for recurrent IgG4 disease (Figure 1). She underwent biopsy in January 2019 with equivocal pathology (Figure 2). However, an elevated serum IgG4 level (144.5 mg/dL; lab range 4-86 mg/dL) was captured on labs and a diagnosis of recurrent IgG4 disease was made.



**Figure 1:** Contrast enhanced CT images with coronal (A) and axial (B) planes show an enhancing solid mass centered in the region of the left palatine tonsil (orange arrows) and extending to the mandibular condyle laterally. The mass was causing at least moderate narrowing of the oropharyngeal airway (blue arrow).



**Figure 2:** A and B. Histologic section of the oropharyngeal biopsy on low power magnification showed squamous mucosa with underlying lymphoid tissue with relatively preserved architecture, increased fibrosis and inflammatory infiltrate (A: Hematoxylin-Eosin, x40). Higher power magnification showed increased plasma cells (B: Hematoxylin-Eosin, x1000). Plasma cells were polytypic (kappa and lambda immunohistochemical stains not shown in this figure). C. IgG immunohistochemical stain highlighted the vast majority of plasma cells (x600). D. IgG4 was only positive in approximately 20% of plasma cells (x600).

The patient was started on a 2-week course of MTX but with rapid escalation of symptoms and growth of neck mass with encasement of carotid arteries on imaging. She was transitioned to high dose steroids in February 2019 with rituximab induction in March 2019. The patient demonstrated measurable improvement after 4 doses of rituximab with high dose steroids with mounting intolerance to steroids. However, repeat scans after 8 doses of rituximab with steroid taper indicated progression of disease. The decision was made to switch to bendamustine + rituximab, which was started in May 2019. She completed 4 cycles of treatment with remission and no disease progression at one-year post-completion of therapy.

#### 4. Discussion

IgG4-RD is a fibroinflammatory condition recognized as a systemic disorder in 2003 [8, 9]. Three key features for IgG4-RD diagnosis are lymphoplasmacytic infiltration, obliterative phlebitis, and storiform fibrosis [9]. Patients can also present with pseudotumors, like our patient, and display symptoms similar to other established disorders which can make accurate diagnosis of IgG4-RD difficult.

The recommended front line therapy of IgG4 is high dose steroid treatment, typically glucocorticoids, that are tapered and discontinued in patients who respond well [8]. In a clinical trial with prednisolone in Japan, 61% of patients displayed complete remissions after 1 year of treatment [10]. For patients with recurrent disease or who are refractory to steroid treatment, rituximab is the

recommended approach. In an open-label trial, 30 patients were treated with 2 doses of 1000 mg of rituximab resulting in 77% of patients achieving remission within 6-12 months [11]. Rituximab has been noted to result in a swift response in patients targeting the IgG4 serum level and demonstrating reduction of IgG4 concentration within a few weeks of initial treatment [8]. However, rituximab may not entirely attenuate IgG4 concentrations and remissions may be elusive in some [9].

Relapses, defined as disease exacerbation after a period of improvement, are frequent occurrences with steroid treatment either during or after glucocorticoid tapering [1, 10]. Relapsed patients may be treated with another course of steroids or rituximab [1]. In a review encompassing 62 studies, among the relapsed patients, 100% of those retreated with rituximab reported therapeutic efficacy [10]. Following a relapse, it is recommended that a steroid-sparing agent is used in the remission maintenance period [1]. This is because long term toxicities of steroids pose significant risks to patients and will ultimately fail to control the disease as was the case in our patient [3, 4, 12]. Mycophenolate, MTX, AZA, and CsA are conventional steroid-sparing agents that have been evaluated in several small studies with variable results and some studies showing no effect [5-7, 12-15]. Notably, prospective data that evaluates the efficacy of these agents is entirely lacking and experience with these agents in patients with multiple relapses is limited. As such, patients with multiple relapses of IgG4-RD pose a major therapeutic challenge and represent a population with an unmet need.

Potential novel treatments may be found in thoroughly examining the cellular pathways of IgG4 molecules such as the role of basophil activation in the pathology of IgG4 [10]. Therapeutics that target b-cell depletion also represent a rational approach as supported by clear efficacy of rituximab in decreasing IgG concentrations corresponding with response [9]. We chose to treat our patient with a combination of bendamustine and rituximab given its b-cell lympho-depleting effects which we expected would result in decreased IgG4 antibody production and better disease control. To our knowledge, this is the first report demonstrating the efficacy of bendamustine-rituximab for IgG4-RD with durable response achieved. This approach represents an effective option for patients with multiple relapses and warrants further evaluation.

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