Case Report

DOI: 10.5582/irdr.2019.01061

Tumefactive fibroinflammatory lesion successfully treated with Rituximab

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Summary **Skull base pseudotumors, or tumefactive fibroinflammatory lesions (TFIL), are tumors characterized by local destruction with benign histopathology. Treatment includes surgery and steroids with varying degrees of symptom relief. A 45-year-old female presented with right otorrhea and middle ear effusion, which progressed to CN V_3 pain/numbness, trismus, headache, and autophony. MRI showed a diffuse infiltrating mass in the right infratemporal region involving the trigeminal ganglion. Biopsy revealed benign fibromuscular and adipose tissue with lymphoplasmacytic infiltrate, giving a diagnosis of TFIL. Resection would be very difficult given tumor location. Initial treatment included an extended course of steroids without response, and interval disease progression. Two courses of rituximab 375 mg/m^2 weekly × 4 given 3 months apart were then completed with excellent tolerance. With sixteen months following induction, the patient reports minimal symptoms with radiographic findings confirming continued disease regression. Rituximab is a potential treatment option for patients with TFIL without response to steroids.**

Keywords: Rituximab, tumefactive fibroinflammatory lesion, pseudotumor, immunomodulators, inflammatory pseudotumors

1. Introduction

Tumefactive fibroinflammatory lesions (TFIL) are a subset of inflammatory pseudotumors most commonly located in the head and neck that are characterized as a rare, locally destructive mass with benign findings on histopathology. Epidemiological data is limited with disease information restricted to case reports and case series from published materials (*1-2*). The historical use of various names in the medical literature further complicates our understanding of this diagnosis (*3*). Although there are no standardized treatment guidelines, therapy for TFIL typically includes a combination of surgical resection and steroids. Many patients experience recurrence once steroids are tapered, leading practitioners to explore alternative therapeutic options including immunomodulators (*1-5*).

Herein we present a case of TFIL of the infratemporal region successfully treated with rituximab following a failed response with steroids.

2. Case Report

A 45-year-old female presented with otorrhea and a right middle ear effusion for two months. The symptoms persisted despite placement of a pressure equalization tube. Five months later, she developed pain and numbness in the right CN V_3 distribution, trismus, headache, and autophony. MRI brain and CT neck demonstrated a diffuse, enhancing, infiltrative mass involving the infratemporal fossa, oropharynx, and soft palate, extending into the foramen ovale with displacement of the trigeminal ganglion, in addition to questionable involvement of the right facial nerve and right vidian canal (Figure 1A). She underwent endoscopic transpterygoid biopsy with

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image guidance and mucosal graft of the defect. Pathology revealed small lymphoid cells and plasma cells without atypia intermixed with hypocellular bands of fibrosis and entrapped atrophic skeletal muscle (Figure 2). In light of these pathological findings, she was diagnosed with an inflammatory pseudotumor, specifically a TFIL. A high dose prednisone taper was initiated at that time, which provided resolution of the headache and improved V3 sensation and pain in the immediate postoperative period. She was referred to a hematologist with experience treating similar lesions. Her symptoms returned within three weeks of her

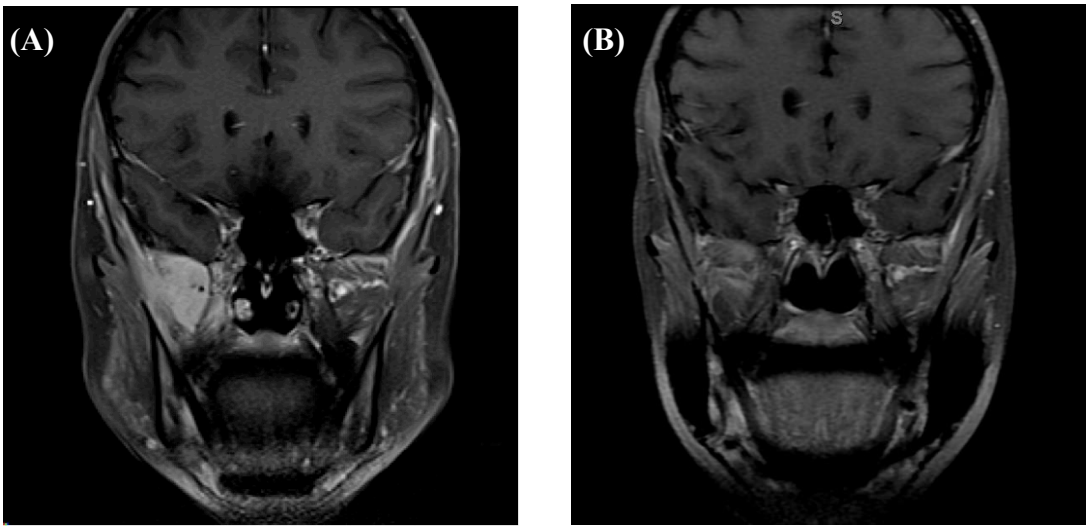

Figure 1. T1 MRI pre and post treatment. (A), Pre-treatment contrasted coronal T1 MRI showing diffuse, enhancing, infiltrative mass involving the infratemporal fossa, oropharynx, and soft palate, extending into the foramen ovale with displacement of the trigeminal ganglion, in addition to questionable involvement of the right facial nerve and right vidian canal. **(B)**, Contrasted coronal T1 MRI seven months after completion two cycles of rituximab, demonstrating significantly less enhancement in the infratemporal fossa.

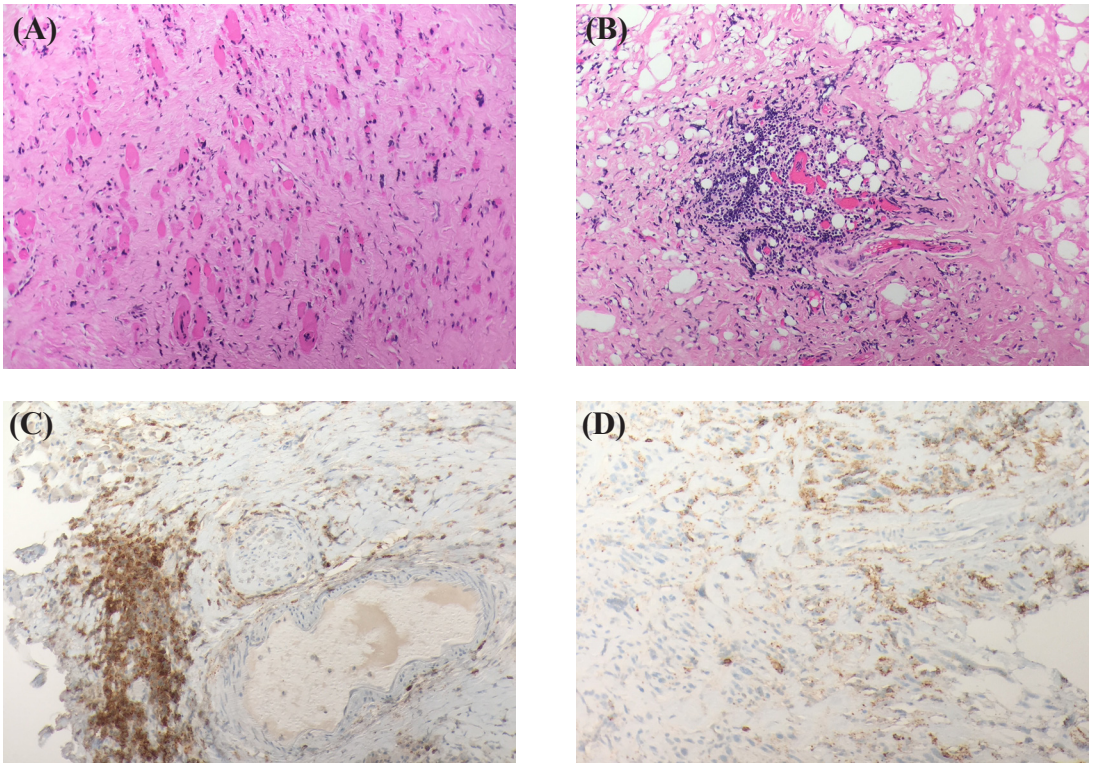

Figure 2. Histopathology report. (A), Morphologic examination of the biopsy revealed hypocellular bands of fibrosis entrapping skeletal muscle with atrophic change. (Hematoxylin and Eosin stain; original magnification 200×). **(B)**, In areas, lymphoid aggregates were seen, comprised of small lymphoid cells without atypia. (Hematoxylin and Eosin stain; original magnification 200×). **(C)**, Immunohistochemical analysis revealed predominance of CD3 positive T-cells within lymphoid aggregates. (CD3 immunohistochemical stain; original magnification 200×). **(D)**, Immunohistochemical analysis revealed few CD20 positive B-cells within lymphoid aggregates. (CD20 immunohistochemical stain; original magnification 200×).

operation while tapering the steroid dose, requiring an increase and extension of the steroid taper. She reported improvement of her symptoms with the higher steroid dosage.

Three months into the slow steroid taper, she presented with a cushingoid appearance, worsened headaches, CN V_3 pain/numbness, autophony, and a new right sided House-Brackmann 3/6 facial palsy. Repeat MRI at that time revealed interval progression of the infiltrative process with more conspicuous enhancement at the foramen ovale and extension of disease along the lateral aspect of the right cavernous sinus tracking posteriorly along the greater superficial petrosal nerve to the level of the geniculate ganglion. Due to the progression of disease, a second endoscopic biopsy was performed again confirming TFIL without evidence of malignancy. At that time, alternate therapies were explored, including rituximab, due to positivity for CD20 within a subset of the lymphoid cells. The patient was treated with rituximab monotherapy consisting of 375 mg/m^2 weekly × 4 treatments. She completed her steroid taper prior to her 3rd dose of rituximab. The MRI two months later demonstrated significant radiologic improvement with less conspicuous enhancing soft tissue fullness in the infratemporal fossa. She had ongoing improvement in symptoms and proceeded to a second course of rituximab monotherapy three months following the first cycle.

The patient tolerated her rituximab treatments without adverse events. A MRI seven months following her second course of rituximab demonstrated significant improvement with much less enhancement in the infratemporal fossa (Figure 1B). At her most recent follow up one year after completing treatment, she reports feeling very well with only faint right sided facial numbness, rare headaches in the right temple, and occasional trigeminal pain controlled with over-the-counter non-steroidal anti-inflammatory medications. Her facial paresis has completely resolved, and she notes much less autophony. No further corticosteroids have been required, and her Cushingoid appearance has resolved. A repeat MRI at that time shows further regression of disease

3. Discussion

Inflammatory pseudotumors (IP) are benign, fibrosclerosing lesions found in many organ systems including lung, gastrointestinal tract, genitourinary tract, hepatobiliary, orbit, brain, skull base, and soft tissues of the trunk and extremities, with the most common sites being lung, orbit, nasopharynx, inner ear, and skull base. Pseudotumors are found across a broad age range from newborns to patients in their 80s, with the 3rd and 4th decade of life being most common (*1*). Pseudotumors are rare and difficult to classify given the lack of clear diagnostic criteria. Prior nomenclature has included plasma cell granulomas, xanthogranulomas, or histiocytomas. Subclasses of IP include TFIL, inflammatory myofibroblastic tumor (IMT), and IgG4 related disease.

Tumefactive fibroinflammatory lesion was first described in 1975 as sclerosing cervicitis and the term TFIL was first used in 1983. TFIL is characterized by an aggressive, locally destructive lesion, usually of the head and neck region, resembling neither malignancy nor infection (*4*). Lesions can invade adjacent soft tissues, muscles, and neurovascular structures, and can also erode bone, leading to meningeal and CNS involvement (*2*). Clinical symptoms are site dependent and tend to be rapidly progressive with headache, otalgia, vision changes, and hearing loss being among the most common complaints at presentation (*1*). In up to 20% of cases, mediastinal or retroperitoneal fibrosclerotic lesions, orbital pseudotumor, or Riedel's thyroiditis may be found on the staging evaluation (*5*). While the etiology of the disease is unknown, proposed mechanisms include an exaggerated response to chronic infection or an autoimmune reaction to a previous viral infection (*4*). Histopathology shows sclerotic fibrous inflammatory tissue with plasma cells and lymphocytes without cytologic atypia, necrosis, significant mitotic activity, or pleomorphism that would be seen in malignant counterparts such as fibrosarcomas (*1,6*). TFIL lacks significant numbers of IgG4 positive plasma cells and storiform pattern of fibrosis as seen in IgG4 related disease. TFIL lacks the ALK positivity and intranuclear eosinophilic inclusions as seen in IMT (*7-9*).

No standardized guidelines for treatment for IP and TFIL are available given the rarity of the diagnosis. Treatment is guided by the location and severity of disease. Past treatments have included combinations of steroids, surgical resection, radiation, and/or immunomodulators. Treatment with immunomodulators have included cyclophosphamide, mycophenolate mofetil, methotrexate, alpha interferon, azathioprine, and rituximab (*1,2,4,8-13*). Complete resection is preferred; however, tumor location may prevent a safe and tolerable approach (*2*). Lesions generally demonstrate good initial response to steroids, but many patients experience recurrence as the steroid is tapered, as seen in our patient. A meta-analysis of inflammatory pseudotumors of the skull base by Alyono *et al*. reported that 76% of patients had no recurrence or progression after the first course of steroids with/without partial resection. However, only 33% of patients had complete symptom resolution, and even less had radiologic resolution (*1*). A separate case series cited the recurrence rate > 20% for head and neck cases, with only 40-50% of patients achieving complete remission (*9*).

Rituximab has recently emerged as a successful treatment option for patients who have failed prior surgical and steroid treatment. While the exact mechanism of rituximab is not clear, the tumor response

is likely due to induction of apoptosis secondary to antibody dependent, cell-mediated toxicity, and complement activation (*9*). Several case studies have shown successful use of rituximab for inflammatory pseudotumors in the jaw (*8*) and temporal bone (*9*) in addition to IgG4 related disease in the orbit (*10-11,13-14*) and temporal bone (*15*). No reports to date have used rituximab for successful treatment of TFIL specifically. Reported dosing regimens of rituximab have included 1,000 mg Q2wk × 2 doses versus 4 weekly doses at 375 mg/m^2 (*8,13-15*). The weekly schedule was chosen for our patient based on experience treating indolent non-Hodgkin B-cell lymphomas and other non-malignant inflammatory diseases like vasculitis, graft-versus-host disease, immune thrombocytopenia, and pemphigus vulgaris.

The most common side effect of rituximab is an infusion reaction consisting of urticaria, fever, chills, angioedema, and hypotension, occurring in about 18% of patients, but rarely severe. Reversible myelosuppression occurs in 2-4% of patients, but increases in frequency when combined with chemotherapy (*16*). However, effects of long term steroid use include osteoporosis, adrenal insufficiency, hyperlipidemia, and hyperglycemia, which increase in severity with increasing dose (*17*). High dose steroid regimens have been found to cause adverse effects in up to 33% of patients, even with short term treatments (*18*). Similarly, the incidence corticosteroid-induced lipodystrophy has been found to be 65% in patients on daily steroid therapy for 6 months (*19*). The frequency and severity of these adverse effects suggests therapy with rituximab could be a promising alternative.

Our patient continues to show symptomatic and radiographic improvement now sixteen months out from initiation of treatment with rituximab. Our report suggests that for patients with TFIL who have an unresectable lesion and/or have failed treatment with steroids, rituximab has the potential to be an effective steroid-sparing treatment option. We propose that more research is needed to explore the role of rituximab in the treatment of all classes of inflammatory pseudotumors.

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(Received May16, 2019; Revised May 28, 2019; Accepted May 30, 2019)