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Case Report

Mixed Diffuse and Tumoral Form of Bing-Neel Syndrome Successfully Treated with Ibrutinib

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Keywords

Bing-Neel syndrome · Waldenström macroglobulinemia · Bruton tyrosine kinase inhibitors · MYD88 L265P · Lymphoplasmacytic lymphoma

Abstract

Introduction: Bing-Neel syndrome (BNS) is a rare and heterogenous manifestation of Waldenström macroglobulinemia (WM) involving central nervous system (CNS) infiltration by malignant lymphoplasmacytic cells. Efforts to standardize diagnostic criteria have improved in recent years, as have treatment options including the use of the Bruton tyrosine kinase inhibitor (BTKI) ibrutinib. ***Case Presentation:*** Here, we present the case of a 70-year-old male with a remote history of WM previously treated with bendamustine and rituximab, who presented to medical attention with several months of left-sided weakness, headache, and ataxia. Brain magnetic resonance imaging revealed numerous enhancing masses in the bilateral cerebral hemispheres, inferior medulla, and upper cervical spine. Laboratory studies showed serum IgM lambda monoclonal gammopathy and elevated free serum kappa and lambda light chains, while cerebrospinal fluid flow cytometry revealed CD19+ B cells. Stereotactic brain biopsy of a right frontal brain lesion was consistent with lymphoplasmacytic lymphoma, confirmed by a positive MYD88 L265P mutation. He received ibrutinib 420 mg orally daily, and this resulted in appreciable clinical and radiologic responses, which have persisted over a 31-month period. ***Conclusion:*** The advent of molecularly targeted agents and novel therapies for WM has provided patients and clinicians with additional therapeutic options. The use of BTK inhibitors with their high-level CNS penetrance, in particular, offers a novel way to

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treat BNS and improve patient overall survival while maintaining a high level of quality of life. We discuss the importance of MYD88 L265P testing in the context of BNS as well as the expanding role of BTKIs in treating this disease.

Introduction

Bing-Neel syndrome (BNS) is a rare manifestation of Waldenström macroglobulinemia (WM) involving lymphoplasmacytic infiltration into the central nervous system (CNS) [1]. First described by Bing and Neel [2], approximately 1% of patients with WM will develop BNS [3]. The diagnosis remains challenging, given its variable presentation depending on the region of CNS involvement. Most patients with BNS will be diagnosed at the time of disease progression of pre-existing WM. Rarer are those patients who develop neurologic symptoms as an initial manifestation of WM [4, 5]. The most common symptoms include gait disturbances (12–48%), motor limb deficits (14–35%), and cranial nerve palsies (29–35%) of the facial and oculomotor nerves [6, 7].

The gold standard for diagnosis is the histological evidence of differentiated lymphocytes on biopsy of the affected cerebrum and/or meninges. Immunohistochemical investigations yield characteristic B-cell antigens including but not limited to CD19, CD20, CD79a, and CD70b [8]. Cerebrospinal fluid (CSF) analysis revealing elevated IgM monoclonal protein levels or clonal homogeneity on flow cytometry may further suggest leptomeningeal involvement and should match immunophenotypic features in WM-diseased bone marrow [9].

Genetic studies reveal the presence of the MYD88 L265P mutation in the CSF of 93–97% of WM patients. However, this mutation is also found in other hematological malignancies including diffuse large B-cell lymphomas [10], marginal zone lymphomas [11], and IgM monoclonal gammopathy of undetermined significance [12]. Therefore, histologic and CSF analyses, along with imaging, are critical for an accurate diagnosis.

Radiological investigations to support the diagnosis of BNS involve a T1-based brain magnetic resonance imaging (MRI) sequence before and after gadolinium enhancement with a FLAIR sequence, and abnormalities are found in approximately 80% of patients [13]. Leptomeningeal enhancement is reported in 59–80% of patients [6, 14]. Conversely, tumoral involvement can be unifocal or multifocal and is commonly found in deeper subcortical regions [15].

Management of BNS is personalized and heterogeneous, with the goal of symptom reversal and limiting disease progression. The benefits of active therapy for asymptomatic patients are uncertain, and these individuals are often managed conservatively [16]. Treatment options have historically been limited to chemotherapy regimens with CNS penetration such as methotrexate (MTX), cytarabine, and fludarabine [17]. More recently, ibrutinib and an expanding list of Bruton tyrosine kinase inhibitors (BTKIs) have gained popularity in the broader context of WM treatment due to the improved overall survival rates compared to chemotherapy and thus have been incorporated into the latest clinical recommendations from the tenth International Workshop for WM in 2020 [18].

Here, we present a case of a patient with a prior history of WM, who was diagnosed with BNS and successfully treated with ibrutinib. We also discuss the utility of MYD88 mutational assessment and how it impacts clinical decision making.

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Case Report

A 70-year-old male initially presented in May 2012 with a 20-lb weight loss, 6 weeks of progressive dyspnea, and rectal urgency. A computerized tomographic scan of the chest, abdomen, and pelvis revealed a large right pleural effusion, as well as extensive supraclavicular, axillary, intra-abdominal, and retroperitoneal lymphadenopathy. Biopsy of a retroperitoneal lymph node confirmed low-grade lymphoplasmacytic or marginal zone B cell lymphoma on immunohistochemistry. Flow cytometry showed clonal lymphocytes in the peripheral blood. Whole-body positron emission tomography suggested bone marrow involvement in the setting of severe hypoproliferative anemia. He received nine cycles of rituximab therapy with six concomitant cycles of bendamustine. In January 2013, he reportedly achieved a complete remission based on imaging and peripheral blood flow cytometry. He was then lost to follow-up for 7 years.

In March of 2020, he presented to a local emergency department with acute-onset left-sided weakness, headache, and ataxia. He was told he had suffered a "mini-stroke," but neither further workup nor imaging was pursued. By June 2020, his left-sided weakness had progressed to a hemiparetic gait, and he experienced cognitive decline including confusion, forgetfulness, and occasional visual hallucinations. A brain MRI revealed multiple enhancing masses in bilateral cerebral hemispheres, inferior medulla, and upper cervical spine on T1-weighted FLAIR imaging. Laboratory studies included an elevated total protein of 9 g/dL (normal: 6.0–8.3 g/dL) and a normal albumin of 4.3 g/dL. Serum protein electrophoresis (SPEP) revealed a monoclonal spike of 0.3 g/dL, and immunofixation showed a monoclonal IgM lambda component. Quantitative immunoglobulin levels were notable for IgA 177 mg/dL (normal: 101–645 mg/dL), IgG 2,122 mg/dL (normal: 540–1,822 mg/dL), and IgM 513 mg/dL (normal: 22–240 mg/dL). A free serum kappa and lambda light chain ratio was 0.71 (normal: 0.26–1.65). Urinalysis did not show proteinuria, but a 24-h urine collection with immunofixation was positive for a monoclonal IgM lambda band measuring 6 mg/dL. A PET-CT in August 2020 showed areas of increased uptake within the intramedullary mass at the junction of the cervical spinal cord and medulla (maximum SUV 9.7), as well as mild cervical and inguinal adenopathy with minimal SUV avidity.

Subsequent studies included a lumbar puncture with CSF sampling showing the following: protein 672.9 mg/dL (normal: 15–45 mg/dL); glucose 46 mg/dL (normal: 40–70 mg/dL); and IgG 119 mg/dL (normal <8.1 mg/dL) with a synthesis rate of 147.87 mg/24 h (normal <12 mg/24 h). The total nucleated cell count was elevated at 21 × 10^6/L (normal <5 × 10^6/L). Flow cytometry of the CSF demonstrated 5% CD19+ B cells (7% of the lymphocyte gate) with polytypic expression of kappa and lambda light chains. An excisional biopsy of a right cervical lymph node showed clonal lymphoid cells with identical features to those seen 7 years earlier. However, given the concern for aggressive transformation of his low-grade lymphoma, he underwent stereotactic brain biopsy of a right frontal brain lesion. Flow cytometric analysis of this sample demonstrated an abnormal population of B cells (36% of the lymphocyte gate, 50% of total events) positive for CD19, CD20, CD22, CD11c, CD200, FMC7 (subset), and CD23 (dim, subset), with monotypic expression of lambda surface light chain, and negative for kappa surface light chain, CD5, CD10, CD25, and CD103. The cytospin preparation demonstrated small, mature-appearing lymphocytes including plasmacytoid forms. The lymph node cells were washed, aliquoted, and analyzed using the fluorescence-activated flow cytometer utilizing the following monoclonal antibodies: CD45, CD3, CD19, CD5, CD10, ANTI-KAPPA, ANTI-LAMBDA, CD11C, CD20, CD25, CD103, CD22, CD23, ANTI-FMC7, and CD200. Immunohistochemical studies were also performed to correlate with morphological findings and to evaluate markers not performed by flow cytometry. These demonstrated that the majority of lymphocytes were B cells positive for CD20 and CD79a. CD3

highlighted admixed small T cells. The plasmacytoid cells showed monotypic expression of the lambda light chain by chromogenic in situ hybridization (CISH). Scattered cells were positive for the kappa light chain by CISH. The final pathology was consistent with lymphoplasmacytic lymphoma, confirmed with a positive MYD88 L265P mutation by polymerase chain reaction, and he was diagnosed with BNS (Fig. 1).

He received 4 mg of dexamethasone orally four times daily, and he was subsequently discharged home on a steroid taper. He was seen in follow-up 2 weeks later and reported unchanged headache, left arm pain, and difficulty with ambulation. Ibrutinib therapy was initiated in September 2020 at a dose of 420 mg daily. Within 2 weeks, he noticed improved strength in his left arm and improved ambulation. A brain MRI collected at that time showed significant interval shrinkage of the cervico-medullary junction mass and bilateral CNS lesions (Fig. 2).

The patient continued to improve with resolution of palpable adenopathy and improvement in his neurologic symptoms. Repeated MRI of the brain and cervical spine at the end of October 2021, 14 months from the initiation of systemic therapy, was notable for resolution of the intraparenchymal lesions and continued diminution of the cervico-medullary junction spinal cord lesion. Additionally, there was no longer radiographic evidence of leptomeningeal disease. He continued this regimen until January 2022 when there was a 2-month period where he ran out of medication, during which he developed anemia and worsened left-sided numbness. Ibrutinib was promptly restarted with an excellent clinical response that has been sustained since his most recent follow-up in April 2023. At the time of his last blood tests, SPEP showed an IgM monoclonal spike measuring 0.1 g/dL. The completed CARE Checklist for this case report is included as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534528).

Discussion

The diagnosis of BNS remains challenging, given the wide spectrum of clinical presentation, with no specific symptomatology that can prove or exclude BNS. A combination of radiographic, laboratory, and histologic testing is thus needed. MRI abnormalities are found in up to 80% of patients with BNS and can manifest with diffuse leptomeningeal involvement or tumoral with distinct CNS masses [13]. Epidemiologically, the diffuse form is more common, with some studies estimating the frequency around 66–93% [7, 19]. In terms of clinical manifestation, the diffuse form often presents with a wide range of neurological symptoms, including cognitive dysfunction and cranial nerve deficits, whereas the tumoral form may cause focal neurological deficits related to the mass effect of the tumor. Prognosis varies with the diffuse form generally carrying a poorer prognosis due to its diffuse and infiltrative nature. Our patient exhibited signs of both leptomeningeal infiltration with headaches and visual disturbances, as well as spinal cord involvement causing sensorimotor deficits. These symptoms correlated to his radiographic findings of enhancement along the ventricular margins and a large mass at the cervico-medullary junction.

Invasion of differentiated clonal lymphocytes into the CNS is essential to establish the diagnosis of BNS and can be made via the analysis of the CSF or biopsy of the affected regions. In our patient, a lumbar puncture revealed elevated CSF protein with normal glucose levels, consistent with the reported literature [4, 7]. Biopsies of a right cervical lymph node and a right parietal brain lesion also showed involvement by a population of small B cell lymphoma with plasmacytic differentiation. Both specimens expressed CD19, CD20, and CD22 and were negative for CD5, CD10, CD25, or CD103, consistent with lymphoplasmacytic cells in WM [1].

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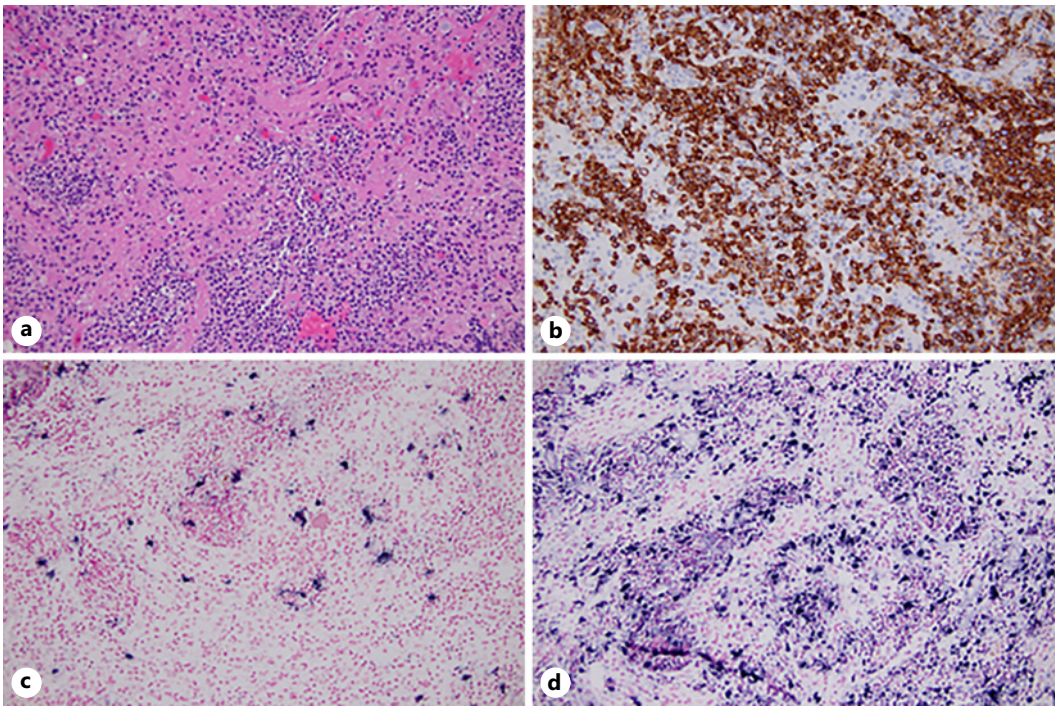

Fig. 1. Photomicrographs of stained sections from the brain biopsy sample. **a** H and E, ×20. Reveals lymphocytic infiltration into the brain parenchyma. **b** CD20 stain, ×20. Positive stain suggests the presence of B lymphocytes in tissue sample. **c**, **d** Kappa and lambda chromogenic in situ hybridization (CISH) stain, ×20. Demonstrates clonality of B-cell population in the biopsy tissue.

Whole genome sequencing has detected MYD88 L265P mutation in 93–97% of WM patients [16, 20], but importantly, this mutation is not specific for BNS. In a study examining the brain biopsy material from 18 patients with primary CNS diffuse large B-cell lymphoma, all but one harbored this mutation [21]. The right parietal biopsy from our patient also had this mutation, which provided further support for a diagnosis of BNS, given his prior history of WM and recently elevated IgM monoclonal level. Although not fully elucidated, the role of MYD88 mutation in promoting uncontrolled growth and survival of cancerous B cells is likely due to the increased NF-κB activity and JAK-STAT3 signaling. Other mutations that have been associated with WM include CXCR4 and ARID1A, which were unfortunately not obtained for our patient.

The aim of BNS treatment is to improve both clinical symptoms and progression-free survival (PFS). Published guidelines are lacking for standard treatment regimens. Conventional chemotherapy using regimens such as high-dose MTX and cytarabine is favored because of their high CNS penetrance. However, given the significant side effects that may be disproportionate to the benefits obtained, a case-by-case assessment is required in making this decision. Ibrutinib was chosen in this case because, at the time of diagnosis, only BTKI was approved by the US Food and Drug Administration (FDA) for the treatment of symptomatic WM and multiple case reports demonstrated significant clinical improvement [22–25]. Additionally, a retrospective study of 28 patients who received 3 months of ibrutinib monotherapy for BNS found symptomatic and radiologic responses in 84 and 57% of patients, respectively. The 2-year probability in this cohort of continuing ibrutinib without toxicity, progression, or death was approximately 80% [14]. Our patient also exhibited dramatic improvement in his neurologic deficits, as well as radiographic resolution of the intraparenchymal lesions, and continued to decrease in size of the cervico-medullary junction

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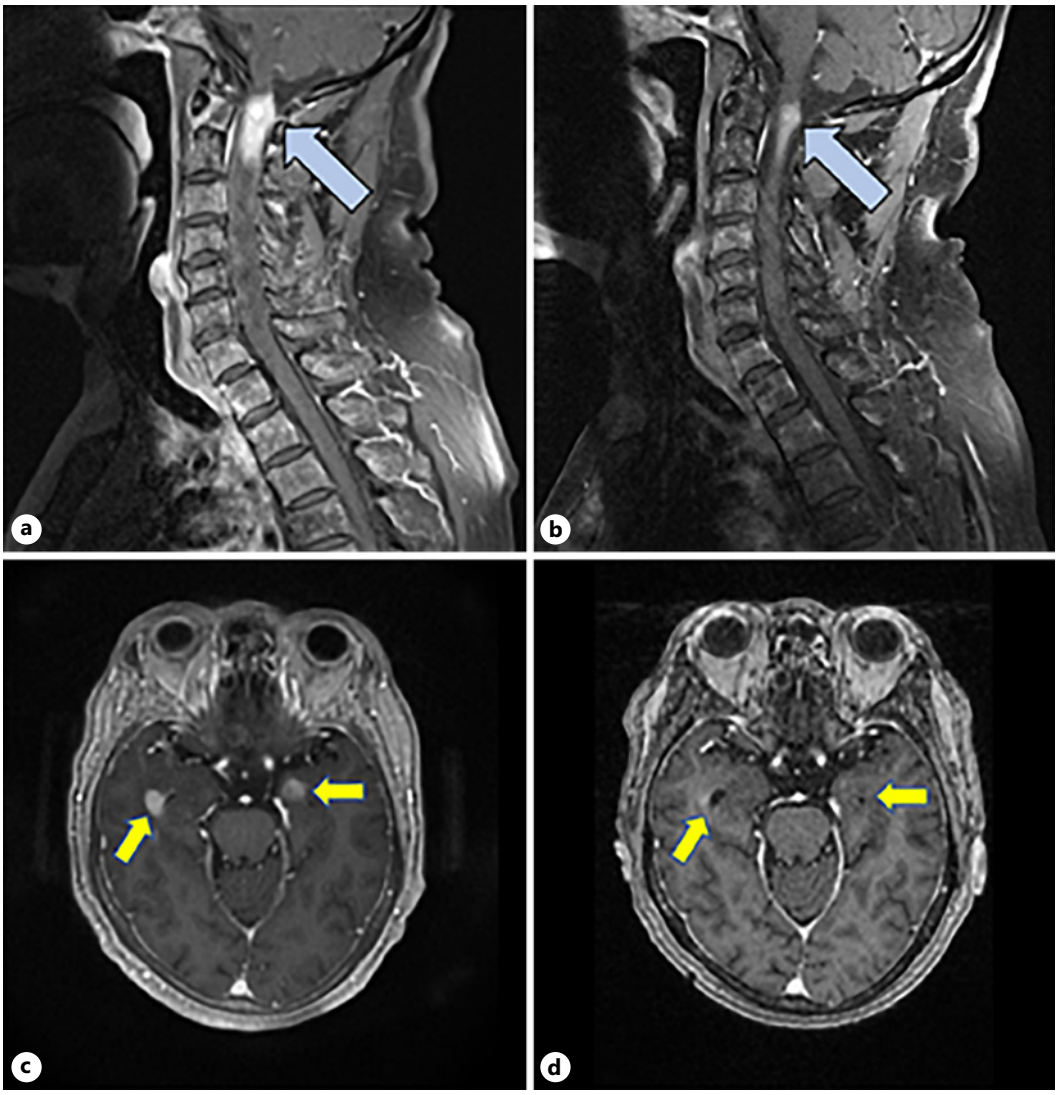

Fig. 2. a, **b** Magnetic resonance imaging (MRI) of the cervical spine at initial diagnosis (**a**) and 2 weeks after (**b**) ibrutinib therapy. **c**, **d** Brain MRI at initial diagnosis (**c**) and 2 weeks after (**d**) ibrutinib therapy. Light blue arrows indicate the cervico-medullary junction mass. Yellow arrows indicate lesions in the bilateral cerebral hemispheres.

spinal cord mass. He did not experience any major side effects on this regimen and continued ibrutinib on a dose of 420 mg daily as of April 2023, corresponding to PFS of 31 months. His most recent laboratory tests showed a small and stable M-spike on SPEP consistent with an ongoing partial response. Notably, ibrutinib is associated with a higher bleeding risk compared to standard chemotherapy with rates of major hemorrhage ranging from 4–8% [26–30]. It has also been associated with fluid retention, atrial fibrillation, easy bruising and bleeding, and worsening hypertension.

The treatment landscape for low-grade lymphoma continues to expand [31]. A phase II study (ONO-4059-05 study, JapicCTI-184057) evaluated monotherapy with the second generation TKI tirabrutinib in patients with treatment-naïve or relapsed/refractory (R/R) WM. The results demonstrated a major response rate of 88.9% and a tolerable safety profile [32]. A 24-month follow-up analysis of the data revealed durable response rates [33], and

tirabrutinib is now approved in Japan for the treatment of WM. Multiple case reports have also demonstrated the efficacy of this agent in patients with BNS, often after the relapse of WM, subsequent to traditional chemotherapy regimens [34–38].

The FDA also recently approved zanubrutinib for the treatment of WM based on the ASPEN trial, in which patients were randomized to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily until disease progression or unacceptable toxicity. This phase III study showed a higher rate of very good partial response with zanubrutinib compared to ibrutinib (28% vs. 19%, respectively) and fewer treatment-related adverse effects, especially cardiovascular toxicity [39]. The efficacy of this agent specifically in the context of BNS, to the best of our knowledge, has only been reported in one case study wherein a 75-year-old woman with a history of previously treated lymphoplasmacytic lymphoma presented with progressive difficulty in walking. She was diagnosed with BNS by imaging and started on 12 cycles of high-dose intravenous MTX with only a partial symptomatic response. She was switched to zanubrutinib with significant improvement in lower limb weakness and complete resolution of the previously seen contrast-enhancing lesions in the cervical and thoracic cord on MRI [40].

Another promising BTKI that is currently only FDA-approved for the treatment of chronic lymphocytic leukemia and mantle cell lymphoma is acalabrutinib. This drug has been shown in a single-arm, multicenter trial to lead to an overall response rate of 93% in treatment-naïve WM patients and 95% in R/R cases. The estimated 66-month PFS rate in the TN group was 84% and 52% in the R/R group [41]. Although data on the use of these novel therapies in BNS are currently limited, they will likely play a much larger role in future treatment given their overall efficacy and improved side effect profile among patients with hematologic malignancies.

Conclusion

Our case demonstrates the importance of having a high clinical suspicion for BNS, especially in WM patients presenting with neurological deficits. It also highlights the need for histologic confirmation with subsequent genetic analysis, such as the use of MYD88 L265P testing, in cases of diagnostic uncertainty and to allow for the use of targeted therapy with BTKIs. More research is needed to explore novel mutations that may aid in further narrowing the diagnosis and providing newer targets for therapeutic agents. Finally, additional studies with longer follow-up are needed to assess the durability of response to these agents.

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Statement of Ethics

Written informed consent for the publication of this case report and any accompanying images was obtained from the patient. This retrospective review of patient data did not require ethical approval in accordance with Virginia Mason Medical Center guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Junid Naveed Ahmad was primarily responsible for drafting of the abstract, case presentation, and discussion sections of the manuscript, as well as procuring images. Brett A. Schroeder and David M. Aboulafia were responsible for critically reviewing and providing feedback on the manuscript. John Paul T. Yun was responsible for the primary draft of the introduction section.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its accompanying figures. Further inquiries can be directed to the corresponding author.

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