SUCCESSFUL TREATMENT OF SEVERE SINONASAL ROSAI-DORFMAN DISEASE WITH THE MEK INHIBITOR COBIMETINIB

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ABSTRACT

Rosai-Dorfman Disease (RDD) is a rare form of non-Langerhans histiocytosis characterized by an accumulation of activated histiocytes in affected tissues. Sinonasal involvement occurs in 11% of RDD cases. Surgical intervention is a common form of management, but has significant limitations in terms of both safety and effectiveness. In this report, we present the case of a 76-year-old woman with severe sinonasal RDD. Over a period of about 8 years, the patient underwent multiple surgical interventions and other treatment modalities, all of which were ineffective. Ultimately, the patient was treated with a partial course of the MEK inhibitor cobimetinib and experienced remarkable clinical improvement. This case report highlights the use of cobimetinib as an effective treatment option for severe sinonasal RDD.

CASE REPORT

A 76-year old woman was referred for evaluation and management of bothersome bilateral nasal obstruction. Eight years earlier, she had presented to the referring otolaryngologist with a right nasal cavity mass. Excisional biopsy at the time yielded a diagnosis of low-grade B-cell lymphoma (marginal zone lymphoma), with associated histiocytic hyperplasia and features of Rosai-Dorfman Disease (RDD). She was treated with rituximab and bendamustine, followed by external beam radiation therapy. In the seven years that followed, the patient underwent multiple nasal polypectomy procedures for both diagnostic and therapeutic purposes, all consistent with RDD, without evidence of persistent or recurrent lymphoma (see **Figure 1**).

At presentation, the patient complained of gradually worsening bilateral nasal obstruction, with associated hyposmia, rhinorrhea, and sleep disturbance. She also noted that her nasal dorsum had become visibly wider over the course of the previous few months. Anterior rhinoscopy showed obstructive lesions bilaterally and a marginal nasal airway. On rigid nasal video-endoscopy, the patient was noted to have large, obstructive polypoid lesions bilaterally, as well as an anterior septal perforation (see **Figure 2a, b**). High-resolution computed tomography (HRCT) of the paranasal sinuses showed large polypoid lesions bilaterally as well as inflammatory changes involving the maxillary, ethmoid, and frontal sinuses (see **Figures 3 and 4**).

In an effort to relieve her nasal obstruction and rule out a recurrence of her sinonasal lymphoma, the patient was taken to the operating room for nasal polypectomy and endoscopic sinus surgery. However, due to the significant vascularity and friability of the lesions, the plan was limited to bilateral nasal endoscopy and limited polypectomy. Surgical pathology was consistent with RDD with an atypical B-cell infiltrate (see **Figure 5**). Further evaluation showed a 15% monoclonal B-cell population without detectable CD5, CD10, CD11c expression on a polyclonal background. Given her history, these findings were concerning for a lymphoma recurrence.

The patient's nasal obstruction improved somewhat. Her sense of smell remained unchanged. Subsequent PET/CT showed FDG-avid uptake in the nasal mucosa, as well as multiple lymph nodes above and below the diaphragm, further raising suspicions for a lymphoma recurrence. Excisional biopsy of an inguinal lymph node was consistent with RDD. Unremarkable blood work and regular evaluations by her hematologist provided further reassurance that her lymphoma remained in remission. However, her sinonasal symptoms worsened.

Repeat endoscopy again revealed obstructive, vascular-appearing polypoid lesions (see **Figure 2c, d**). In addition to nasal obstruction, the patient had begun to experience intermittent epistaxis. A variety of topical treatments were unsuccessful, including intranasal corticosteroid sprays, antihistamine nasal sprays, and budesonide irrigations. The patient was treated with a 7-week course of methotrexate, which resulted in peripheral neuropathy and no significant improvement in her nasal symptoms. Systemic corticosteroid bursts did not help. She declined the offer of a course of radiation therapy.

Approximately two-and-a-half years after her initial visit, the patient was referred by her hematologist for subspecialist evaluation at a tertiary care institution. She was prescribed a three-week course of the MEK inhibitor cobimetinib, 40 mg by mouth daily, but was only able to tolerate it for one week due to severe gastrointestinal side effects (particularly diarrhea). The patient underwent diagnostic nasal endoscopy nine days after stopping treatment. She had already noticed improvements in her nasal breathing and her sense of smell. Epistaxis had resolved. Nasal endoscopy showed remarkable improvement in nasal airway patency. The lesions were still present, but they looked smaller and considerably less vascular. Over the course of the next several visits, the lesions disappeared completely, revealing post-surgical anatomy that included a large septal perforation and multiple nasal synechiae. The nasal airways were widely patent, with the choana and nasopharynx easily visible on the right side without much effort (see **Figure 6**, images taken seven months after cobimetinib treatment).

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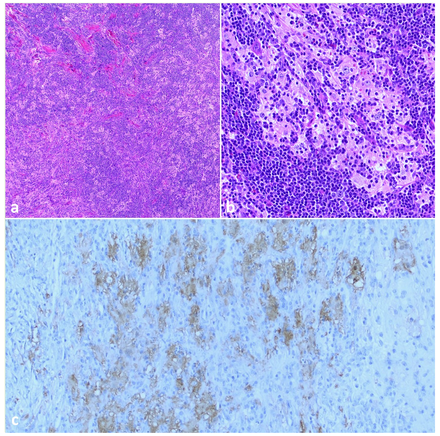

Figure 1. (**a**) Hematoxylin and eosin stain (H&E) showing a heterogeneous lymphocyte population admixed with large epithelioid histiocytes. (**b**) Large histocytes with pale cytoplasm, some with enlarged nuclei with prominent nucleoli. Intact lymphocytes and plasma cells are seen within the cytoplasm of the histiocytes (*emperipolesis*, a histologic hallmark of RDD). (**c**) Immunohistochemical stain for S100 protein shows nuclear and cytoplasmic reactivity, supporting the diagnosis of extranodal RDD.

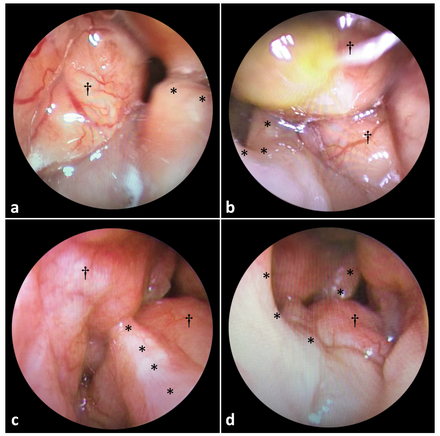

Figure 2. Rigid nasal endoscopy pictures taken preoperatively (**a**, **b**) and postoperatively (**c**, **d**), showing large, obstructive, vascular polypoid lesions (*dagger* symbol) and a septal perforation (*asterisks* denoting perforation edge). Note the minimal difference between the right (**a**, **c**) and left (**b**, **d**) nasal cavities before and after surgical intervention. Images taken with a 30-degree rigid endoscope and high-resolution video-endoscopy system.

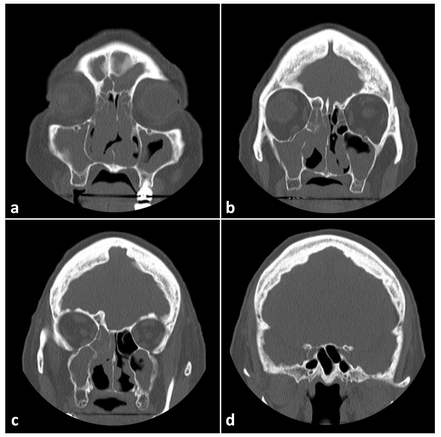

Figure 3. Preoperative coronal high-resolution computed tomography (HRCT) images showing polypoid lesions in both nasal cavities as well as bilateral frontal, maxillary, and ethmoid sinusitis. The sphenoid sinuses are spared.

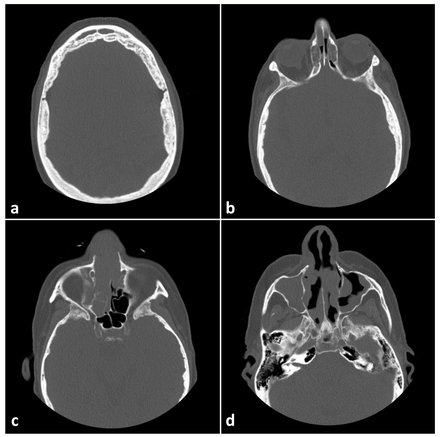

Figure 4. Preoperative axial HRCT images showing polypoid lesions in both nasal cavities as well as bilateral frontal, maxillary, and ethmoid sinusitis. The sphenoid sinuses are spared.

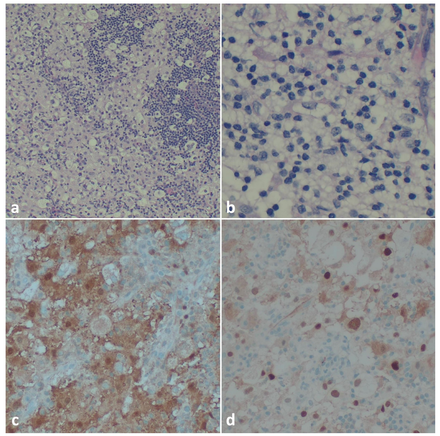

Figure 5. (**a**) RDD showing a prominent pale pink histiocytic infiltrate (light areas) in a background of inflammatory cells, predominantly comprised of lymphocytes and plasma cells (dark areas). (**b**) Sheets of large pale pink lesional histiocytes in RDD characterized by round to oval nuclei with a single, centrally located nucleolus and abundant wispy eosinophilic cytoplasm containing engulfed inflammatory cells (emperipolesis). (**c**) Histiocytic infiltrate showing emperipolesis highlighted by positive staining for S100. (**d**) Overexpression of cyclin D1 in lesional histiocytes of RDD.

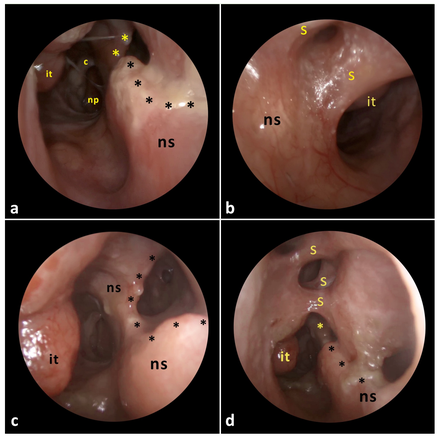

Figure 6. In-office nasal endoscopy showing the right (**a**, **c**, **d**) and left (**b**) nasal cavities seven months after a one-week course of the MEK inhibitor cobimetinib. Images taken with a 30-degree rigid endoscope and high-resolution video-endoscopy system.
Legend: *it*, inferior turbinate; *c*, choana; *np*, nasopharynx; *ns*, nasal septum; *s*, synechia; *asterisks* denote septal perforation edge.

DISCUSSION

Rosai-Dorfman Disease (RDD) is a rare form of non-Langerhans histiocytosis characterized by an accumulation of activated histiocytes in affected tissues. The prevalence of RDD is about 1 in 200,000, with approximately 100 new cases diagnosed per year in the United States.[1] Sinonasal involvement occurs in 11% of cases.[2]

RDD was first described in 1969 by Juan Rosai and Ronald Dorfman. In the initial report, the authors described four young patients presenting with prominent lymphadenopathy, fever, leukocytosis, and particular histopathologic features.[3] In 1978, Dr. Rosai and colleagues published a report of sixteen patients with otolaryngologic disease, with involvement of either upper airway, the salivary glands, or both. Nine of these patients presented initially with otolaryngologic symptoms, and a majority of them experienced significant morbidity as a result of their symptoms. A variety of treatments had been employed in these cases, including (alone or, more commonly, in combination): surgery, chemotherapy, radiotherapy, corticosteroids, and antibiotics. The authors observed that "no consistent pattern of response emerged from the study".[4]

RDD is now understood to comprise a broad spectrum of clinical manifestations. In fact, a recent effort to reclassify the histiocytoses has proposed that RDD be considered as a distinct class with multiple subclasses, including: familial RDD, classical (or nodal) RDD, extranodal RDD, neoplasia-associated RDD, and immune disease-associated RDD.[5] Although the exact etiology is unknown, gene mutations involving the MAPK/ERK pathway have been implicated (including NRAS, KRAS, MAP2K1, ARAF and, less commonly, BRAF).[6]

In this report, we present a case of extranodal RDD with sinonasal involvement in a background of low-grade lymphoma. At the time of her presentation, she had already undergone more than a half-dozen surgical procedures. Over the years, surgical interventions became more difficult, riskier, and less successful. This is not uncommon. In a 2012 review of the English language literature from 1969 to 2010, Chen, et al., noted that 69 of the 126 sinonasal RDD patients studied (54.8%) had either persistent, recurrent, or progressive RDD. They also observed that 6 patients (4.8%) died from the disease.[7]

Evidence suggests surgical intervention to be a common form of management of RDD with upper airway obstruction, but there is currently no standard of care regarding systemic therapy.[8] Moreover, the effectiveness of systemic treatments has been variable and often limited to specific presentations of the disease. These treatment modalities include: corticosteroids; surgical resection; sirolimus; radiotherapy; chemotherapy; and immunomodulatory drugs (e.g., rituximab, imatinib). As we observed with our patient, systemic and topical corticosteroids tend to be of limited utility. Surgical resection of morbid lesions, if feasible, could theoretically lead to symptom improvement or resolution in unifocal disease; however, in our patient, an attempt at surgical resection was aborted due to extreme friability and vascularity of the lesions. Even though the plan to debulk these lesions was abandoned and limited, conservative biopsies were taken instead, the patient experienced protracted postoperative crusting and moderate to severe epistaxis with the slightest attempt at debridement.[9]

Once surgery proved to be a dead end, non-surgical treatments were considered, including systemic corticosteroids and methotrexate. All proved ineffective. She was offered a course of radiotherapy, but she declined given her past history of radiotherapy for lymphoma. Finally, the patient was treated with cobimetinib, a novel MEK inhibitor, and after only a partial course she experienced remarkable clinical improvement, with near complete resolution of her RDD lesions and significant improvement in all of her sinonasal symptoms.

Cobimetinib is an inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase (MEK) pathway, specifically MEK1 and MEK2. MEK proteins regulate the extracellular-signal related kinase (ERK) pathway, which promotes cellular proliferation. Cobimetinib was first studied in combination with vemurafenib for the treatment of unresectable or metastatic BRAF-V600-mutated melanoma.[10] In 2022, cobimetinib was approved as a single agent for the treatment of histiocytic neoplasms, including Erdheim-Chester disease, Langerhans cell histiocytosis, and RDD, on the basis of a single-institution phase 2 trial (NCT02649972) conducted by Memorial Sloan Kettering Cancer Center. This trial included a total of four patients with RDD.[11] In this trial, 15% of patients experienced an adverse reaction that resulted in permanent discontinuation of cobimetinib. Common adverse reactions included diarrhea (62%), nausea (46%), infections (62%, including urinary and pulmonary infections), and acneiform dermatitis.[12]

In our report, the patient was given a 3-week trial of cobimetinib but could only tolerate one week of treatment due to gastrointestinal effects, particularly severe diarrhea. Nevertheless, her improvement was profound and long-lasting—more so than any prior surgical intervention. This case report highlights the potential of cobimetinib as a novel treatment option for RDD with sinonasal involvement. It is important for otolaryngologists to be aware of cobimetinib as an option for refractory cases—and, perhaps, as an alternative to surgery in initial presentations. We believe that our findings contribute to the small yet growing body of literature on sinonasal RDD.

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