Rosai-Dorfman disease with extranodal manifestation in the head

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Abstract
The term sinus histiocytosis with massive lymphadenopathy (SHML) was introduced by Rosai and Dorfman in 1969. Although SHML was initially described as low-pain cervical lymphadenopathy accompanied by fever, leukocytosis, an increased erythrocyte sedimentation rate, and hypergammaglobulinemia, extranodal involvement is observed in 25 to 40% of cases. This pathology is very rare and involvement of the nasal fossae and paranasal sinuses is exceptional. We present two atypical cases of extranodal involvement exclusively confined to the head and review the literature. The first case showed a dramatic involvement of facial skin and muscles, orbit, and paranasal sinuses. In the second case, the disease was limited to the nasal fossae. Both cases showed exclusive extranodal involvement limited to the head region. In the absence of lymphadenopathy, diagnosing Rosai-Dorfman disease is difficult because of the lack of the most typical manifestation of the disease.

Introduction
In 1969, Rosai and Dorfman described 4 cases of a disease they called sinus histiocytosis with massive lymphadenopathy (SHML). They referred to 2 previous cases described in the literature by Azoury and Reed (1966) and by Vincent and Miercort (1967). In 1972, Rosai and Dorfman analyzed 30 additional cases, establishing SHML as a well-defined clinicopathologic entity.

Approximately 600 cases of SHML have been described in the English literature, generally children or young adults with tumoral cervical adenopathy, fever, hypergammaglobulinemia, an increased erythrocyte sedimentation rate (ESR), and leukocytosis with neutrophilia. Other lymphatic groups, such as mediastinal, axillary, and inguinal lymph nodes, can also be affected. In about 40% of cases, one or more of the following extranodal sites are affected:

- eyelids
- orbit
- respiratory tract
- salivary glands
- skin
- bone
- testis
- lung
- kidney
- central nervous system
- thyroid
- and gastrointestinal tract.

Extranodal involvement is often responsible for the most important clinical manifestations of the disease.

The cause of SHML has not been established, but two theories exist. One associates the disease with a specific infectious process; the other attributes it to a disturbance of the immune system. The course of the disease is generally benign, with spontaneous remission, but rare cases of death have been reported.

In the absence of typical tumor lymphadenopathy, the diagnosis of SHML, or Rosai-Dorfman disease, is difficult. We report 2 patients we attended at the Otorhinolaryngology Department at the University of São Paulo between 1989 and 2001.

Case reports
Case 1. A white man reported rhinorrhea and nasal obstruction since 1980, which were diagnosed as bilateral chronic sinusitis and right nasal polyposis. In 1982, the patient underwent bilateral maxillary sinusectomy through a Caldwell-Luc technique and right nasal polypectomy, which led to temporary improvement. Symptoms recurred after 4 years, and the patient underwent the same surgery in 1986. In 1990, progressive bulging occurred in his eyelids and in the maxillary, zygomatic, and bilateral masseteric regions.

In April 1991, we attended the patient for the first time. He was then 38 years old and presented with diffuse infiltration of the facial skin affecting the eyelids, mainly the right, which showed discrete exophthalmus (figure 1). Rhinoscopy showed a polypoid lesion in the right middle meatus. Computed tomography (CT) and magnetic nuclear resonance imaging of the face and cranium revealed a marked heterogeneous increase in the anterior soft parts of the face. The masseter, pterygoid, and temporalis muscles, as well as the eyelids and parotid glands, were also affected. The lesion was found to extend to the nasal fossae, maxillary sinuses, periorbital fat, and bilaterally to the extrinsic ocular musculature (figure 2).

Laboratory examination showed hypergammaglobul-
linemia (2.2 g/dL). A blood count and erythrocyte sedimentation rate (ESR) were within the normal range. Anatomopathologic examination of a facial lesion biopsy using immunohistochemistry for the detection of protein S100 was compatible with Rosai-Dorfman disease.

Corticotherapy led to important regression of the facial bulging, but because the patient suffered from gastric ulcer, this therapy had to be discontinued. Therefore, in October 1991, we opted for surgical excision of the lesion in the right side of the face. A large portion of a fibroelastic tissue infiltrating all facial tissue without limits or dissection planes was resected. It was not possible to identify fat, fascia, or muscle tissue. The immediate result was highly satisfactory; however, the surgical bed secreted large amounts of a serous fluid, which impaired the adhesion of the skin despite the use of a drain and compressive dressings. Treatment with high corticoid doses resulted in secretion control and removal of the drain after attaching the skin flap. However, 4 months after surgery and with discontinuation of the drug, the same bulging observed initially occurred again in the right hemiface. Due to the lack of an effective treatment and his intolerance to corticotherapy, the patient was kept under observation and to date has maintained a stable condition.

Case 2. An 18-year-old white man reported a progressive right nasal obstruction accompanied by frequent ipsilateral nosebleeds for 2 years. Physical examination revealed a pink mass with bulging contours filling the right nasal fossae (figure 3). CT showed a solid formation filling the right nasal fossae and extending in the direction of the middle meatus (figure 4). Laboratory tests revealed normochromic and normocytic anemia. Protein count, ESR, and immunoglobulins were within normal limits. In March 1997, the mass was excised through a degloving-type sublabial incision. During surgery, it was observed that the lesion originated from the nasal septum. Histopathologic analysis

Figure 1. Pre- (A) and postinfiltration (B) photographs show the appearance of the patient in Case 1.

Figure 2. Massive infiltration of the soft tissues of the face is evident in both axial computed tomography (A) and sagittal magnetic resonance imaging (B).
was compatible with Rosai-Dorfman disease.

One year after the first surgery, a similar lesion was found in the left nasal fossae. In February 1998, the patient underwent the same type of surgery, and the mass was removed from the septum. Anatomopathologic examination of the mass again revealed Rosai-Dorfman disease. Three years after the last surgery, the nasal fossae are free of any mass and the patient remains asymptomatic.

**Discussion**

Approximately 600 cases of Rosai-Dorfman disease have been reported in the literature. Their analysis shows a worldwide distribution of the disease, which predominantly affects whites (43.6%). The disease can manifest in any age group, although 81% of reported cases occurred during the first and second decades of life, and has a 2:1 male-to-female ratio. Our patients were white males who reported the occurrence of the disease during the second and third decades of life.

The predominant clinical manifestation of the disease is tumoral cervical adenopathy (87.3% of cases) that, in most cases, is painless and bilateral, affecting one or all cervical ganglion chains. Lymph nodes are isolated, mobile, and small during the initial stages but become adherent with disease progression, forming a voluminous multinodular mass. The axillary (23.7%), inguinal (25.7%), and mediastinal (14.5%) regions can also be affected, but always to a lesser extent than cervical involvement. Extralodal manifestation of the disease is observed in 28 to 43% of cases, with preference for head and neck regions. The patients we studied presented with extralodal disease confined to head and neck regions.

Laboratory alterations are frequent and include anemia (65.7%), leukocytosis (59.1%), neutrophilia (68.4%), increased ESR (88.5%), and hypergammaglobulinemia (90%). Case 1 showed altered protein concentration resulting from an increased gamma fraction; Case 2 presented with only anemia.

In 1977, Sanchez et al analyzed 113 cases and found involvement of one or more extralodal sites in 28%. More recently, Foucar et al, in a review of 423 cases, observed extralodal involvement in 43%, but the authors emphasized that this value might have been overestimated because these cases attract greater interest for publication. The most common sites of extralodal involvement are skin (27.4%), nasal and paranasal cavities (26.8%), subcutaneous tissue (20.2%), orbit and eyelids (20.1%), and bone (18.4%). The concomitant involvement of one or more sites in the same individual is observed in up to 44.7% of cases.

According to Foucar et al, the most frequent otorhinolaryngologic manifestations are found in the nasal cavity (50%), followed by the pharynx (25%), paranasal sinuses (18.7%), amygda (12.5%), and trachea (6.3%). A second extralodal site is involved in 68% of these patients. Case 1 showed involvement of the nasal sinuses, parotid glands, subcutaneous facial skin, and orbit. In contrast, in Case 2, the disease affected only the nasal cavity, as also described by Ozunlu et al. With respect to the orbit, the most commonly affected sites are the soft tissue (84.6%) and eyelids (45.5%), which manifest as exophthalmus (53.8%), clouding of vision, conjunctival infiltration, diplopia, increased or reduced lacrimation, and slight ocular irritation. Case 1 showed palpebral infiltration and involvement of the extrinsic musculature of the eye and orbital fat, as well as ocular irritation and altered visual acuity.

The diagnosis of Rosai-Dorfman disease is made on the basis of clinical suspicion and confirmed by anatomicopathologic examination. Histopathologic findings include lymphoid aggregates intercalated with areas consisting of histiocytes, lymphocytes, and plasma cells and associated, or not, with vascular proliferation and fibrosis. These findings are less characteristic in the extralodal form of the disease.
The epidemiologic, laboratory, and histologic findings are similar among patients with ganglionic and extranodal involvement, suggesting a common biologic basis. In general, extranodal involvement does not determine a more aggressive character or poorer outcome; however, generalized lymphadenopathy, extranodal involvement of multiple organs (kidney, lungs, and liver), and immunologic alterations lead to a poor prognosis.9

The cause of the disease has not yet been established, but two theories exist. In the first theory, SHML is caused by a specific infectious process based on the generally infectious process seen at the onset of the disease (localized adenopathy, fever, leukocytosis with neutrophilia, increased ESR, and hypergammaglobulinemia), which tends to spontaneously regress at some time. However, no laboratory evidence points to an etiologic agent.5,13 In the second theory, the disease is attributed to an abnormal immunologic response, because depression of immunologic cells can be observed. However, no other clinicopathologic signs suggesting a deficient humoral or cellular immunity or phagocytic disorders have been reported.5,14,15

The clinical and microscopic manifestation of SHML should be differentiated from malignant lymphoreticular neoplasias, such as Hodgkin’s disease and mononcytic leukemia, histiocytosis, rhinoscleroma, tuberculosis, juvenile xanthogranuloma, dermatofibromas, and eosinophilic granuloma, among others. Depending on the site affected, other pathologies also need to be excluded.16-19

The best treatment for Rosai-Dorfman disease has yet to be established. Some authors defend surgical treatment with partial or total resection, radiotherapy, chemotherapy, and antibiotic therapy. Komp20 reported the following treatments for 84 patients: 39 underwent surgery because of airway obstruction, neurologic or ocular compressions, or severe deformation; 34 were submitted to radiotherapy and 67 to chemotherapy. However, the patients’ response to radiotherapy or chemotherapy was unsatisfactory.

In the present study, we opted for observation in Case 1, because surgical resection was not beneficial and the patient did not tolerate corticotherapy. In Case 2, surgery led to a satisfactory result, probably because the disease was restricted and limited and, to date, the patient has been free of signs and symptoms of disease.

Conclusion
Extranodal manifestations of Rosai-Dorfman disease are rare and range from restricted to highly extensive forms. A treatment has not yet been established, with surgical excision showing a poor outcome. Because the head region is the preferred site of the extranodal form of the disease, otorhinolaryngologists and pathologists should always be aware of SHML in making a differential diagnosis.

References