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A Case of Extranodal Rosai-Dorfman Disease Presenting as an Isolated Mass on the Base of the Tongue in a 57-Year-old Woman

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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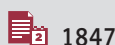
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Conflict of interest: None declared

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| Patient: | Female, 57-year-old |
| Final Diagnosis: | Rosai-Dorfman disease |
| Symptoms: | Cough |
| Medication: | — |
| Clinical Procedure: | — |
| Specialty: | Otolaryngology |
| Objective: | Rare disease |
| Background: | Rosai-Dorfman disease (RDD), is a rare, benign, proliferative, histiocytic disorder characterized by persistent massive lymphadenopathy, which mimics malignant tumors. Diagnosis of extranodal RDD without lymphadenopathy is difficult due to its unusual clinical manifestation and lack of typical histopathologic features. Hence, it requires both a high degree of clinical suspicion and careful histopathologic examination. |
| Case Report: | A 57-year-old woman presented with an isolated mass on the base of the tongue (BOT) without lymphadenopathy. Laryngoscopic examination revealed a mass on the midline of the BOT. The patient underwent complete surgical excision via suspension laryngoscopy with a CO ₂ laser. Based on the histopathologic features, including numerous histiocytic infiltrations with emperipolesis and cytoplasmic expression of S100 and CD68 in histiocytes, the diagnosis was confirmed as extranodal RDD. No further treatment was required, and follow-up evaluation revealed no evidence of recurrence. |
| Conclusions: | Because no ideal therapeutic approach is available for RDD, treatment should be tailored to the clinical manifestations. To prevent airway obstruction and recurrence, surgery is considered an appropriate option in cases of localized RDD arising on the upper respiratory tract. We report an extremely rare case of extranodal RDD without lymphadenopathy in the BOT, and provide a detailed discussion of its clinical and histopathologic features and treatment with a brief review of the relevant literature. |
| MeSH Keywords: | Histiocytosis, Sinus • Laser Therapy • Oropharyngeal Neoplasms |
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Background

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy (SHML), is a subgroup of histiocytic disorders [1]. The disease was first described by Destombes in 1965 and subsequently recognized as a distinct clinicopathological entity by Rosai and Dorfman in 1969 [2,3]. RDD is a rare, idiopathic, systemic, and nonmalignant disorder that may spontaneously resolve and usually affects younger patients [1,3–13]. It is typically characterized by enlarged, nontender, bilateral cervical lymphadenopathy often accompanied by fever, leukocytosis, elevated erythrocyte sedimentation rate (ESR), and other symptoms, depending on the sites involved [1,3–8,10–13]. RDD typically occurs in lymph nodes and coexists with at least one site of extranodal involvement in approximately 43% of diagnosed patients [1,5,8,11–15]. In the head and neck, the commonly involved extranodal sites are the sinonasal tract and major salivary glands; the larynx, trachea, pharynx, and thyroid gland are less frequently involved [11–13,15]. However, extranodal RDD without lymphadenopathy is very rare.

RDD exhibits a distinct pathologic feature called emperipolesis, in which large histiocytes contain engulfed lymphocytes and erythrocytes in their cytoplasm. Despite this, the diagnosis of extranodal RDD without lymphadenopathy can be difficult, because its clinical manifestation is uncommon and the characteristic histopathologic findings are less prominent [10,15–17]. Because ideal therapies for RDD are not available, treatment should be tailored to the individual clinical manifestations [5,11]. We report a case of extranodal RDD without lymphadenopathy that presented as an isolated mass on the base of the tongue (BOT), which was diagnosed by complete surgical excision using a CO₂ laser under suspension laryngoscopy.

Case Report

A 57-year-old woman presented to our clinic with an intermittent and nonproductive cough, throat clearing, and a sensation of having a foreign body in her throat for 3 months. Her medical and family histories were unremarkable and free of smoking and alcohol consumption. Previously, she had been in good health, and all vital signs including body temperature were normal. Laryngoscopic examination revealed a globular lobulated mass with a smooth surface on the midline of the BOT (Figure 1). There were no abnormal findings in the other regions of the upper respiratory track, including the oral cavity, oropharynx, and larynx. Enlarged or palpable lymph nodes were not detected upon physical examination of the entire neck. Results of blood testing were within normal limits. Thus, histopathologic confirmation through surgical excision was required for differential diagnosis of the various tumors

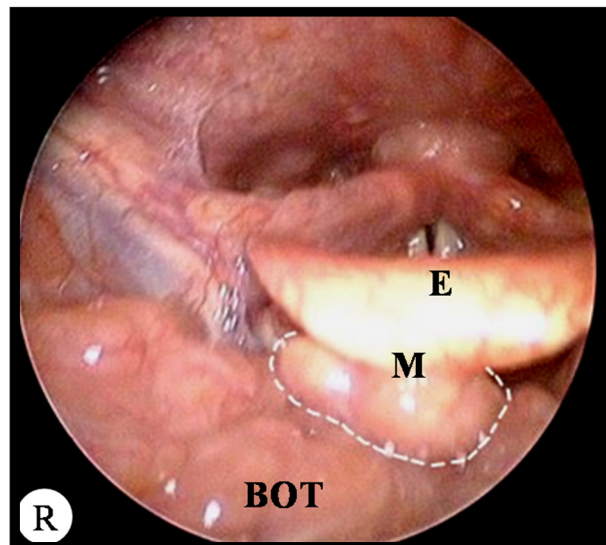


Figure 1. Representative laryngoscopic image. Laryngoscopic examination revealed a globular lobulated mass with a smooth surface on the midline of the base of the tongue. BOT – base of the tongue; E – epiglottis; M – mass; R – right.

that can arise on the BOT. After oroendotracheal intubation, the mass on the BOT was readily surgically accessible and was fully exposed under suspension laryngoscopy. The patient underwent complete surgical excision through suspension laryngoscopy using a CO₂ laser with vaporization of the implantation area at 2 watts.

No complications such as bleeding and edematous changes were observed either during or after the operation. The excised mass comprised pinkish-gray soft tissue that measured 1.5×1.2×0.5 cm. On microscopic examination, heterogeneous cellular infiltration in the subepithelial stroma was identified at low magnification (Figure 2A). There was no evidence that the lesion arose from lymph nodes; normal lymph node architecture, such as a subcapsular sinus or germinal center, were not observed. In the stroma, extensive infiltration of variously sized histiocytes, plasma cells, and occasional neutrophils was found and the overlying squamous epithelium was intact (Figure 2B, 2C). The histiocytes had indistinct cell borders, round to oval vesicular nuclei, and pale to bubbly cytoplasm. Further, enlarged histiocytes contained intact lymphocytes, neutrophils, and plasma cells in their cytoplasm, which was morphologically consistent with emperipolesis (Figure 2D). There was no evidence of either granulomas or necrosis. The histiocytes were cytoplasmic positive for CD68 and S100 (Figure 3A, 3B) and negative for CD1a (Figure 3C). Dispersed plasma cells were highlighted by the immunohistochemical (IHC) staining of CD138 (Figure 3D). Based on these observations, the pathologic diagnosis was confirmed as extranodal RDD on the BOT. A postoperative laryngoscopic image showed

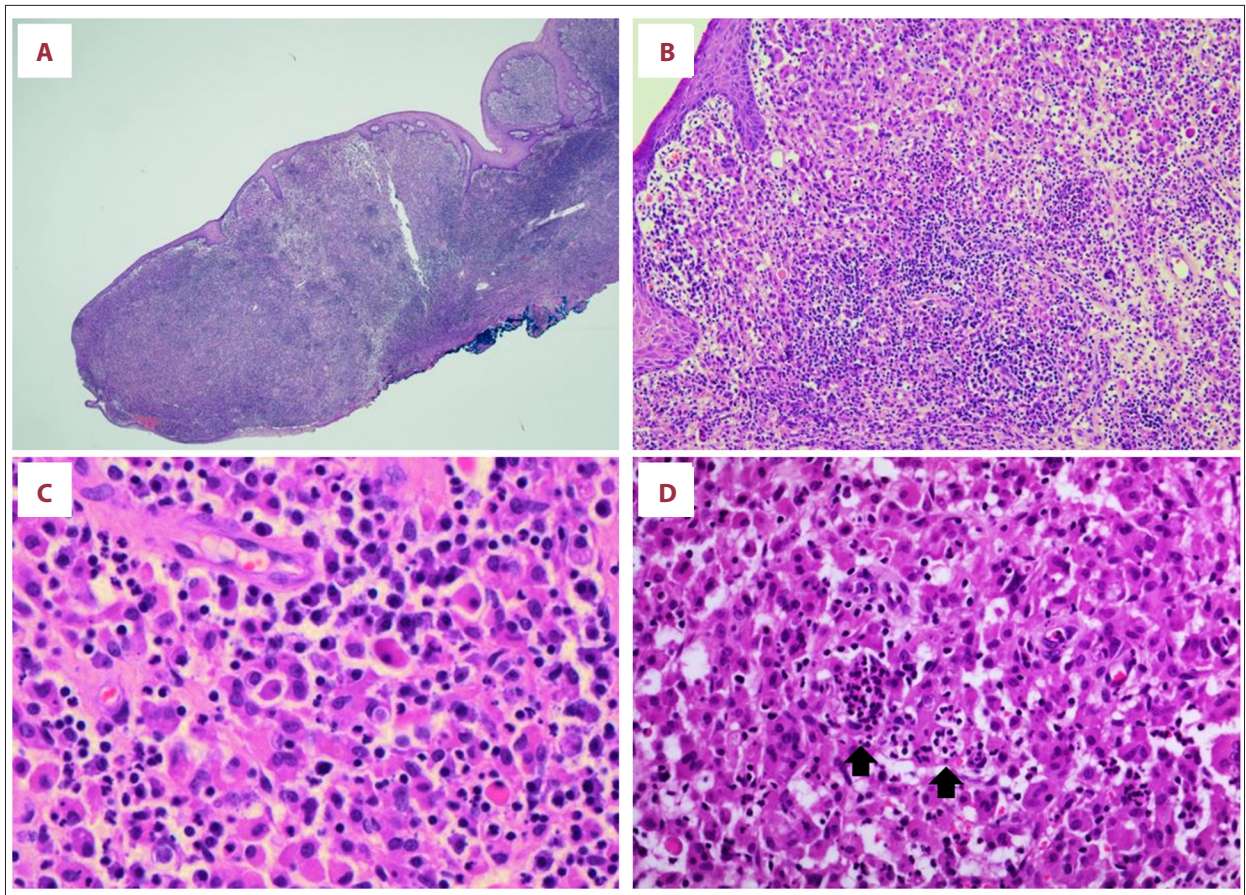


Figure 2. Histopathologic results of the microscopic examination. (A) At low magnification, a well demarcated nodular mass is seen and there is no evidence of lymph node within the excised specimen (H&E, 12.5× magnification). (B) Extensive inflammatory cell infiltration in the subepithelial stroma (H&E, 200× magnification). (C) A mixture of numerous histiocytes, plasma cells and a few neutrophils are identified (H&E, 400× magnification). (D) Enlarged histiocytes exhibiting characteristic emperipolesis (black arrow) (H&E, 400× magnification).

that the mass was completely excised and the operation site had recovered well (Figure 4). Because the surgical margins were clear and there was no evidence of lymphadenopathy, no additional treatment, including corticosteroid therapy, was recommended. The patient's symptoms resolved after surgery, and she has not exhibited any symptoms or signs of recurrence after 1 year with close follow-up.

Discussion

RDD is a rare disease characterized by sinus histiocytosis with massive lymphadenopathy. However, extranodal RDD without any lymph node involvement is very rare. Here, we described an uncommon case of extranodal RDD without lymphadenopathy on the BOT. Diagnosis of extranodal RDD without lymphadenopathy is difficult because of its unusual clinical manifestation and lack of characteristic histopathologic findings resulting from increased fibrosis, fewer histiocytes, and

reduced emperipolesis [5,10,15,17]. Extranodal involvement may be the initial clinical presentation in approximately 25% of patients with RDD, which can progress to a chronic, relapsing clinical course that has a worse prognosis than regular RDD [6,10,15–18]. RDD can occur in any age group; however, it is most common in children and young adults, and is more frequent in males [5,7,18]. The disease usually presents as a large, bilateral, painless lymphadenopathy that is often accompanied by systemic symptoms, such as fever, night sweats, fatigue, and weight loss, the severity of which depends on the sites involved [1]. These atypical symptoms make diagnosis difficult, and RDD has been reported to mimic various metastatic cancers and lymphoma [5,12]. In particular, patients with a mass on their upper respiratory tract may present with a variety of symptoms according to its size and location, such as foreign body sensation, dysphagia, voice changes, cough, stridor, and dyspnea [12,13]. In this case, the patient complained of a nonspecific cough, throat clearing, and foreign body sensation, and a mass on the BOT was identified.

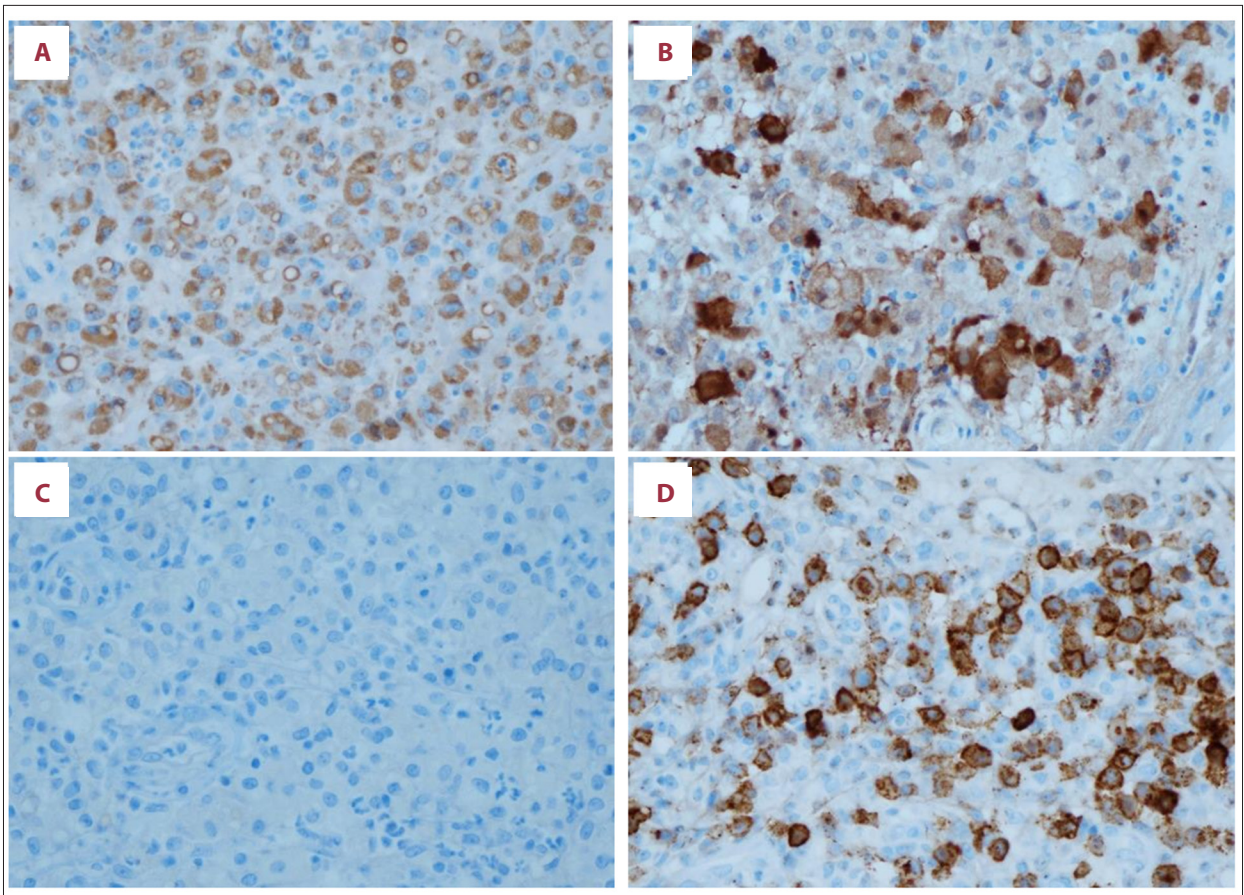


Figure 3. Immunohistochemical (IHC) staining results. Cytoplasm positive for CD68 (A) and S100 (B) in histiocytes, but negative for CD1a (C) (A–C, 400× magnification) can be seen. (D) Scattered plasma cells between histiocytes are highlighted by CD138 IHC staining (400× magnification).

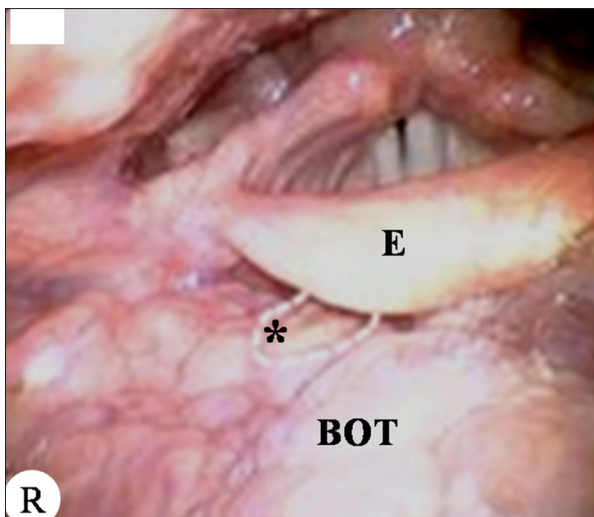


Figure 4. Representative laryngoscopic image. Laryngoscopic examination showed a postoperative lesion (asterisk) with mucosa healing in the base of the tongue at 10 days after operation. BOT – base of the tongue; E – epiglottis; M – mass; R – right.

The etiology and pathogenesis of RDD is still poorly understood; however, several theories have been proposed [5,7,12]. One theory is that the stimulation received via the macrophage colony-stimulating factor (M-CSF) leads to histiocytic proliferation due to a disturbance of cell-mediated immunity, autoimmune mechanisms, and altered immune responses [5,18]. Viral infections such as Epstein-Barr, varicella-zoster, and human herpesvirus, have also been proposed as possible causes of RDD [5,7,8,12,18,19].

Laboratory abnormalities are nonspecific, with leukocytosis, anemia, polyclonal hypergammaglobulinemia, and elevated erythrocyte sedimentation rate [1,5]. Moreover, imaging findings for extranodal RDD in the head and neck are also nonspecific; therefore, histopathologic examination is essential to confirm the diagnosis [5,6,12]. Histopathologically, RDD typically demonstrates extensive inflammatory infiltration with numerous histiocytes, lymphocytes, plasma cells and a few neutrophils. Enlarged histiocytes with phagocytosis of lymphocytes and neutrophils within their cytoplasm, which is known as emperipolesis, is a common pathognomonic finding [5–7].

Despite the distinct pathologic findings of both extranodal and regular RDD, extranodal RDD should be differentiated clinically and morphologically from other benign and malignant diseases. Differential diagnosis includes nonspecific sinus hyperplasia, Langerhans cell histiocytosis, tuberculosis, atypical fibroxanthoma, lymphoma, melanoma, and metastatic carcinoma [5,8,20–22]. Reactive sinus hyperplasia exhibits large clusters of histiocytes accompanied by reactive lymphocytes, germinal center cells, immunoblasts, and tingible body macrophages; however, emperipolesis is not observed. In Langerhans cell histiocytosis, typical Langerhans cells have irregular nuclei, intranuclear grooves, abundant eosinophilic cytoplasm, and scattered eosinophilic aggregates. Furthermore, Langerhans cells are positive for both S100 protein and CD1a, compared to our case of extranodal RDD, which was negative for CD1a. Tuberculosis has epithelioid cell granuloma with or without caseous necrosis, which are absent in RDD. Atypical fibroxanthoma can share similar morphologic features with RDD, but these malignant cells are highly pleomorphic and show frequent mitosis, including atypical form. Further, S100 protein is not expressed in most of the cells. Hodgkin lymphoma has characteristic malignant cells called Reed-Sternberg cells that do not exhibit emperipolesis [23]. These cells are S100 protein-negative, CD15-positive, and CD30-positive. Immunohistochemistry (IHC staining of HMB-45 and pankeratin can be helpful to exclude melanoma and metastatic carcinoma [20,22]. Through histopathologic examination, we identified possible diseases that may develop on the BOT and those that need to be differentiated from RDD. Extranodal RDD should be diagnosed based on clinical comprehension and histopathologic examinations, and appropriate IHC staining is mandatory for its confirmation.

RDD is generally considered to exhibit benign behavior that is asymptomatic, slow-growing, and spontaneous in regression without therapy in 20% of cases [5,6,12,13]. Because no uniform therapeutic approach is available, treatments should be modified according to the clinical manifestations, and corticosteroids have been preferred therapeutic options [5,10–12]. Various and combined treatment modalities, including surgery; radiotherapy; corticosteroids; chemotherapy (methotrexate, 6-mercaptopurine, clofarabine, cladribine, azathioprine); interferon; immunomodulatory therapy; and targeted therapies (imatinib and rituximab) have shown variable responses [5,10,11,19]. Surgical excision should be suggested not only for acquisition of tissue to confirm diagnosis, but also as a proper treatment for localized RDD to relieve symptoms and to preserve vital organs and functions [5,10–13,19]. Incomplete surgically excised RDD or systemic/extensively involved RDD require a variety of combined treatment modalities [5,11]. In our case, complete surgical excision was an effective treatment options to prevent airway obstruction because the mass arose on the BOT.

The prognosis of RDD is highly variable, and more than 10% of RDD cases develop progressive or multifocal and/or refractory disease [6,10,11]. Although factors and frequency related to recurrence or progression of RDD remain unknown, prognosis is known to worsen with a prolonged active phase; multiple extranodal involvements; widespread dissemination; involvement of the kidney, liver, and lower respiratory tract; and immunological disease [8,16]. Close, long-term follow-up for at least the first 2 years after complete remission is important in RDD patients for the detection of recurrence or progression [5,17].

The head and neck are the typically affected extranodal sites [7,8,10,17]. Although the pharynx and supraglottis are not considered as lymphoid organs, they have a large amount of lymphatic tissue in the submucosal region as part of the mucosa-associated lymphoid tissue (MALT) system [24], which makes them vulnerable to extranodal RDD involvement. Thus, a careful laryngoscopic examination is recommended [13]. Good outcomes have been reported in the treatment of laryngeal and tracheal RDD by surgical excision [13,19]. Further, the mass on the BOT was required for differential diagnosis from malignant carcinoma, as well as benign masses, such as vallecular cyst, thyroglossal duct cyst, and hemangiomas [7]. In the current case, the early stage of extranodal RDD without lymphadenopathy was confined to the BOT. It was completely resected through suspension laryngoscopy using a CO₂ laser to confirm the histopathologic diagnosis and to treat, because the BOT mass would possibly lead to upper airway obstruction as its size increased.

Conclusions

RDD is a nonmalignant subgroup of histiocytic disorders. Extranodal RDD without lymphadenopathy has been challenging to diagnose because of its rarity, uncommon clinical presentation, and lack of characteristic histopathologic findings. A high degree of clinical suspicion and a thorough histopathologic examination, including IHC studies, are necessary to accurately diagnose the condition, which may prevent unnecessary workups and overtreatment. There are still no available uniform treatments; therefore, treatment should be tailored to the clinical manifestations. In the case presented here, surgical resection of the localized RDD was considered the appropriate treatment option to ensure functional outcomes, a lower recurrence, and a better prognosis. After treatment, follow-up plans, including comprehensive physical examinations, should be suggested due to the possibility of recurrence.

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