Case Report

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Three Cases of Extranodal Rosai-Dorfman Disease and Literature Review

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Abstract: Object: To summarize the etiology, pathology, diagnosis, clinical features, and treatment of the rare extranodal Rosai-Dorfman disease (RDD). Methods: Clinical data of three cases of extranodal RDD who were admitted to the E. N. T. Department of the second hospital of Jilin University were analyzed retrospectively, and the literature was reviewed. Results: Three cases of extranodal RDD (maxillary sinus, nasal pharyngeal focus, and external auditory meatus) had a low fever and weight loss rather than painless enlarged lymph nodes. Surgical intervention was managed to clarify the diagnosis. All pathological diagnoses were extranodal RDD. Prednisone for oral use was given to all patients postoperatively. There was no recurrence in the following 3 months, except case 1 was lost 2 months later. Conclusions: RDD is a rare idiopathic histiocytic proliferative disorder defined by its unique histopathological features: a proliferation of huge histiocytic cells with emperiploleosis and S-100(+), CD1a(-). RDD is characterized clinically by bilateral cervical painless enlarged lymph nodes, while extranodal RDD is rarer and its manifestations varied. A defined therapeutic regimen has not been elucidated. RDD in about 20% of patients is self-limited. Surgical intervention is the main management of treatment, with glucocorticoids used in initial medical therapy. More clinical trials are necessary before drawing conclusions.

Keywords: Rosai-Dorfman Disease, extranodal

1 Introduction

Rosai-Dorfman Disease (RDD), also called sinus histiocytosis with massive lymphadenopathy, is a rare idiopathic histiocytic proliferative disorder. There are very few clinical cases of extranodal RDD. Therefore, in this study, our aim was to describe 3 cases of extranodal RDD enrolled in the E. N. T. Department of the second hospital of Jilin University from Sep. 2011 to Jun. 2014. We also present a concise overview of the clinical data and effects of therapy. We summarize the etiology, clinical features, pathology, diagnosis, differential diagnosis, treatments, and outcomes of RDD in order to improve the knowledge of RDD for otolaryngologists.

2 Case History

2.1 Case 1

A 47 year-old man was admitted to the hospital with the chief complaint of left nasal obstruction with left ipsilateral cheek swelling. Special examination demonstrated within the nasal mucosa of the bilateral nasal bottom and lateral wall of left nasal cavity edema and swelling with smooth surface. The left nasal cavity was significantly more narrow than the right one. CT scan of the nasal sinus is shown in Figure 1. Under general anesthesia, the mass of the left maxillary sinus was removed as much as possible with the use of a nasal endoscope. Histopathology report confirmed abundant large histiocytes with emperiploleosis, and immunohistochemical diagnostic criteria was cytoplasmic positivity of histiocytes for S-100 protein.

2.2 Case 2

A 45 year-old man presented with left headache, ipsilateral ophthalmalgia, and ipsilateral conductive hearing loss for 1 month. Auxiliary examination demonstrated secretory otitis media (the tympanic membrane was dull and
fluid level was detected). Nasopharyngoscope revealed the submucosal neoplasm extended from the fossa of Rosenmuller on the left side to the left torus, and the Eustachian tube was patent. A solid lesion measuring 38*17mm, originating from the nasopharynx, was observed in the MR images (Figure 2). Biopsy was obtained from the nasopharyngeal deep lesion under general anesthesia. We made a precise diagnosis of extranodal RDD according to the histopathology report (Figure 3).

**2.3 Case 3**

A 48 year-old woman was hospitalized and presented with purulent discharge in the left ear with left conductive hearing loss and persistent headache for 2 years. Neoplasm was found at the external auditory meatus by special examination and accessory MR examination (Figure 4). Under general anesthesia, the mass in the left external auditory meatus was removed, and auditory meatoplasty was conducted under microscopy. Histopathological and immunohistochemical findings were reported to support the diagnosis of extranodal RDD, with many of the histiocytes showing ingested lymphocytes, plasma cells, eosinophils, or neutrophils in the cytoplasm with staining positive for S100.

Though these three patients had different lesions, they all had a low fever and weight loss without any swollen lymph nodes around the whole body since onset. Their laboratory tests revealed normal results. And all of them had the same diagnosis: extranodal RDD. Oral prednisone was given to all of them with a 30 mg dose per day postoperatively for three months. The three cases all obtained curative effects, with relief of the above symptoms. There was no recurrence in the following 3 months (Figure 5), except case 1 was lost 2 months later.

**Informed consent:** Informed consent has been obtained from three individuals included in this study.

**Ethical approval:** The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors’ institutional review board or equivalent committee.

**3 Discussion**

Rosai-Dorfman Disease (RDD), originally described by Azoury and Reed, was reported and published as a rare distinct idiopathic histiocytic proliferative disorder by Rosai and Dorfman in 1969 [1]. It is characterized clinically by bilateral painless cervical lymphadenopathy (about 90%), while 43% of patients have extranodal involvement.
Figure 3A. Histopathology report of case 2 shows a proliferation of histiocytes (arrow) and emperipolesis of intact lymphocytes within the cytoplasm of the lesional histiocytes (H&E, ×200).

Figure 3B. Immunohistochemical staining against S-100, highlighting the emperipolesis in the histiocytes (×200) (arrow).

Figure 3C. Immunohistochemical stains for CD1a show negativity in the lesional histiocytes.

Figure 4A. MR of case 3 demonstrates surrounding extension of the mass in the external auditory canal with irregular shape. The mass shows isointense on T1WI (white thin arrow).

Figure 4B. The mass shows hypointense on T2WI (white thick arrow).
Isolated extranodal RDD without lymphadenopathy is less common. The most common sites of extranodal involvement are head and neck, in the skin and soft tissue. Other anatomic sites involving soft tissue in the back, arm, buttock, thigh, groin, as well as other tissues in the upper respiratory system, genitourinary tract, eye, orbit, kidney, thyroid, breast, bone, pancreatic tail, heart, and central nervous system have been reported \[2,5\]. Here we report three rare cases diagnosed as isolated extranodal RDD, arising from the head and neck. One is in the maxillary, another is in the nasopharynx, and the third in the external auditory meatus.

The etiology of RDD has not been elucidated. Proposed mechanisms are summarized by three theories. One is related to a potential viral infection (including Epstein-Barr virus, parvovirus B19, and human herpes virus). Another is a disorder of immune regulation: stimulation of monocytes/macrophages via macrophage colony stimulating factor (M-CSF) leading to immune system suppression and production of numerous large histiocytes. The third is genetic mutation, which is confirmed by the existence of mutations in the gene SLC29A3 in familial RDD patients \[3\]. Sofia Garces found mutually exclusive KRAS and MAP2K1 mutations in one-third of cases of Rosai–Dorfman disease. She found a correlation with location (with disease manifestations being more common in the head and neck region), and a lack of correlation with disease outcome \[4\].

The hallmark of histopathological features of RDD is a proliferation of distinctive huge histiocytic cells that demonstrate emperipolesis (engulfment of different
quantities of intact lymphocytes, plasma cells, and erythrocytes by the histiocytes) against a background of a mixed inflammatory infiltrate, consisting of abundant plasma cells and lymphocytes. The emperipolesis keeps the engulfed cell structure intact, distinct from phagocytosis of monocytes or macrocytes. In terms of immunohistochemistry, the RDD histiocytes present CD68 (+), S-100 (+), CD1a (-), which helps differentiate this condition from Langerhans cell histiocytosis showing S-100 (+), CD1a (+) [3] and rhinoscleroma with S-100 (-).

There are some specific features for extranodal RDD. 1. Increased fibrosis may obscure the histiocytes. 2. Lymph node structures and sinusoids are absent. 3. Blood vessels and lymph vessels are dilated and surrounded by the lymphocyte and plasma cell. 4. Fibrotic stromal reaction is more significant [5, 6]. The three extranodal RDD cases reported here were in accord with the above description.

The diagnosis of RDD depends on histopathological examination and immunohistochemistry.

The clinical typical features of RDD are bilateral painless enlarged cervical lymph nodes mimicking lymphoma, along with a low fever, night sweats, and weight loss. The presentation of extranodal RDD is related to the size and location of the mass and the organ damage, such as in the three cases here. The extent of damage depends on the dysfunction of the involved organs. Imaging ought to be performed with a concern for malignancy, focusing on the destruction of bone, with homogeneous postcontrast enhancement in all sites of involvement [7, 8]. A biopsy is advised. In the latest report, FDG PET-CT scanning is advised to evaluate the lesions, which display high radioglucose metabolism, and the staging, FDG-avidity is usually attributed to the infiltrative and inflammatory changes caused by the disease process. Ultimately, this imaging modality may aid in the drafting of therapeutic recommendations [9].

Pure cutaneous RDD (CRDD) has its own characteristics. Samir Dalia reported that the average age at onset of patients with CRDD is 45 years old. It predominately affects females and caucasians [10]. The size of lesions in CRDD can range from 1 cm to 30 cm or more at their widest. The presentation of papules or nodules is easily palpated, and discoloration or hyperpigmentation is always visible [7]. The most common site of skin involvement is the torso followed by the head and neck region [3]. Ultrasound is more useful for CRDD. Most cases were highly suspicious for malignancy (peripheral Doppler flow), but sometimes the ultrasound appearance of CRDD is atypical [7, 10].

RDD is a benign proliferative disorder, 20% of which is self-limited. In rare cases, RDD can be locally aggressive and involve the vital organs, causing death [10]. Furthermore, generalized lymphadenopathy and immune dysfunction both are poor prognosis factors for RDD patients [12]. Systemic treatment is pursued when patients have clinical symptoms or vital organ or system involvement. At present, due to its rarity and diversity, there are no particular guidelines regarding the management of RDD. Surgical intervention is the main management of treatment, especially for CRDD and RDD located in the central nervous system or larynx and airway and involving lymph nodes. Patients achieve long-term survival, and lesions from RDD stabilize, even though recurrence has occurred in the previous reported literature. Glucocorticoids are used in initial medical therapy for all kinds of RDD. The three cases here received oral prednisone for three months and obtained curative effects. However, the reliability and durability of these responses is unpredictable. Aradhana K et al [13] concluded that low dose radiation either in combination with surgery or corticosteroids in nodal or extranodal lesions has shown better local control through a five-year retrospective analysis. Chemotherapy may be managed for the patients with disseminated and multifocal RDD or for those whom both surgery and radiotherapy have failed [14-17]. Arnao V et al [18] reported a case of an adult patient with isolated ocular and intracranial RDD, and mercaptopurine therapy stopped disease progression. They suggest that the use of purine antagonists and purine antimetabolites might be an efficacious treatment of adult forms of RDD. However, agreement is hampered by limited data.

More clinical trials and research are necessary before obtaining complete, scientific, and effective guidelines for RDD.

4 Conclusion

We summarize the etiology, pathology, diagnosis, clinical features, and treatment of RDD, aiming at increasing the knowledge of clinicians. Establishment of a standard of systemic treatment including surgery, steroids, radiotherapy, and chemotherapy is urgent for RDD patients.

Conflict of interest: Authors state no conflict of interest.
References


