• Clinical Research •

Extranodal Rosai-Dorfman disease with ocular involvement in 5 cases with a literature review

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Abstract

● **AIM:** To analyze the general profile, clinical symptoms, pathological features, and prognostic characteristics of extranodal Rosai-Dorfman disease (RDD) with ocular involvement.

● **METHODS:** This was a retrospective series of case study. Clinical data from 35 cases who had extranodal RDD with ocular involvement were collected for analysis, including 5 cases diagnosed at our hospital and 30 reported in the literature which searched *via* PubMed, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Periodical Database (VIP), and WanFang Data database from database creation to April 2023. Lesion location, clinical presentation, pathological presentation, treatment modality, follow-up time, and prognosis were recorded.

● **RESULTS:** Lesions of five cases were located in the orbit, eyelid, lacrimal gland, or conjunctiva. The main presenting features were proptosis, eyelid swelling, and conjunctival hyperemia with decreased vision. Four patients underwent surgical resection, one received surgery and adjunctive immunosuppression, and none experienced recurrence during follow-up. A total of 30 cases were retrieved from the literature. The mean age was 41.4y, and 66.7% were male. The lacrimal gland and conjunctiva/subconjunctiva were the most commonly affected sites (each 20.0%). Most patients received surgical management (50.0%) or immunosuppressive therapy (20.0%). Only one recurrence (3.3%) was reported during follow-up.

● **CONCLUSION:** When symptoms like ocular protrusion and visual acuity loss occur, RDD should be considered in the differential diagnosis. The diagnosis of RDD primarily depends on pathological histology, which serves as the key basis for confirmation. Although RDD generally has a favorable prognosis, long-term follow-up of patients is still essential to closely monitor for potential recurrence.

● **KEYWORDS:** Rosai-Dorfman disease; extranodal; orbital disease; pathology
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INTRODUCTION

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a relatively rare histiocytic disease that was first reported by Rosai and Dorfman in 1969. Mostly seen in children and teenagers, it has a favorable prognosis[1]. Clinically, 90% of RDD patients present with painless cervical lymph node enlargement, and nearly 50% have extranodal involvement[2], particularly in the head and neck[3-4]. Some patients have ocular symptoms, the orbit being the most common site of involvement. Bone destruction, intracranial or sinus involvement, and varying degrees of visual loss are frequent clinical manifestations[5-6]. The histocytology of RDD is characterized by pale microscopic histiocytes with swollen nuclei and prominent nucleoli, a great deal of plasma cell infiltrate, and occasional apoptotic lymphocytes. Immunohistochemistry (IHC) for RDD is characterized by positivity for S-100 protein levels and histiocyte markers [clusters of differentiation 68 and 163 (CD68, CD163)], negativity for Langerhans cell markers (CD1a and CD207), and emperipolesis[7].

Typically, RDD occurring in lymph nodes is usually found *via* hematoxylin and eosin (HE) sections and a few IHC parameters[8]. When it occurs outside lymph nodes, with less-

Table 1 Demographics, histology, treatment, clinical feature, and tumor recurrence for patients with Rosai-Dorfman disease

Case	Gender	Laterality	Position	Clinical feature	Immunohistochemistry	Treatment	Follow-up (mo)	Recurrence
1	Female	Left	Intraorbital	Protopsis	CD68, S-100, IgG, κ, λ, CD38, CD138(+), CK, IgG4, P53, CD1a, PAS(-)	Surgery	22	No recurrence
2	Male	Binocular	Upper and lower eyelids, lacrimal glands	Eyelid mass, ptosis, extraocular muscle thickening	CD68, S-100, IgG, SMA(+), IgG4, ALK(-)	Surgery	26	No recurrence
3	Male	Right	Lower eyelid	Eyelid mass	CD20, CD3, CD34, κ, λ, IgG, IgG4, CD38, CD138, CD68, S-100(+), CD35, CD1a(-)	Surgery	76	No recurrence
4	Male	Left	Intraorbital, genyantrum, intracranial	Inferior orbital wall mass, extraocular muscle thickening	CD20, CD3, κ, λ, IgG, IgG4, CD38, CD68, S-100(+), SMA, CD1a, ALK(-), IgG4/IgG about 20%	Surgery+ immunosuppression	-	-
5	Female	Left	Conjunctiva	Conjunctival hyperemia and decreased vision	CD3, CD20, CD68, S-100, PAX5, CD38, CD138, IgG(+), IgG4(8-12/ HPF), CD56, CK, CD1a(-)	Surgery	2	No recurrence

CD: Cluster of differentiation; PAS: Schiff periodic acid shiff; SMA: Smooth-muscle actin; ALK: Anaplastic lymphoma kinase; HPF: High-powered field; PAX: Paired box gene; CK: Cytokeratin.

distinctive cytomorphological features, it can be difficult to assess[9]. In addition, fewer studies have been conducted on ocular RDD, resulting in a lack of comprehensive, detailed data. Therefore, this study adds novelty by focusing specifically on ocular extranodal RDD and incorporating both original and literature-derived cases to generate the largest dataset to date. We report on analysis of 35 cases, including 5 cases diagnosed at our hospital and 30 reported in the literature. Clinical presentation, treatment, IHC features, and prognosis are summarized to provide information for subsequent studies.

PARTICIPANTS AND METHODS

Ethical Approval This study adhered to the tenets of the Declaration of Helsinki. Ethics Committee of Beijing Tongren Hospital, Affiliated with the Capital Medical University ruled that ethics committee approval was not required for this study owing to the retrospective design. All the subjects were fully informed the purpose of this study, and obtain informed consent from the participants and their parents/legal guardians.

Participants Clinical data were collected from patients admitted to our hospital, between January 2016 and April 2023 who were diagnosed with RDD according to histopathology. Inclusion criteria were as follows: 1) RDD clearly diagnosed by histopathology; 2) lesions located extranodally, with ocular damage as the main complaint symptom; 3) cases with complete medical histories. Exclusion criteria were as follows: 1) Langerhans cell histiocytosis and other neoplastic histiocytic lesions; 2) other causes of ocular damage; 3) cases with incomplete medical histories. In addition, we searched the literature and included medical records that met the above-mentioned inclusion and exclusion criteria. Ultimately, we included 35 patients with clearly diagnosed RDD in this study, 30 of whom were discovered *via* patient data reported in the literature.

Collection of Clinical Data We recorded patient age, gender, eye laterality, lesion location, clinical presentation, pathological presentation, treatment modality, follow-up time, and prognosis. The criterion for recurrence was confirmation thereof by imaging or pathological-histological examination.

Statistical Analysis SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. The Kolmogorov-Smirnov test was used to test data normality. Variables conforming to a normal distribution were expressed as mean±standard deviations (SDs), and those conforming to a non-normal distribution were expressed as medians. Kaplan-Meier survival was used for survival analysis. $P<0.05$ was considered statistically significant.

RESULTS

Clinical Manifestations Of the five patients, three (60.0%) had involvement in the left eye, one (20.0%) in the right eye, and one (20.0%) in both eyes (Table 1, Figure 1). The lesions were located in the orbit in two cases (40.0%), the eyelid in two (40.0%), the lacrimal gland in one (20.0%), the conjunctiva in one (20.0%), the genyantrum in one (20.0%), and the intracranial region in one (20.0%). The most common clinical manifestations included proptosis in one patient (20.0%), eyelid mass in two (40.0%), ptosis in one (20.0%), extraocular muscle thickening in two (40.0%), and conjunctival hyperemia with decreased visual acuity in one (20.0%).

Imaging manifestations are varied and related to the location of the lesion. Magnetic resonance imaging (MRI) findings show significant enhancement; the dynamic-enhancement curve is of the continuous-enhancement type (Figures 2–3).

Pathological Features HE staining of all five cases revealed prominent lymphoplasmacytic infiltration with scattered large histiocytes exhibiting abundant eosinophilic cytoplasm and vesicular nuclei. Typical emperipolesis, characterized by intact lymphocytes or plasma cells within the cytoplasm of histiocytes, was evident in several cases. In some specimens, well-formed lymphoid follicles and fibrotic changes were observed in the orbital or eyelid lesions. IHC demonstrated that

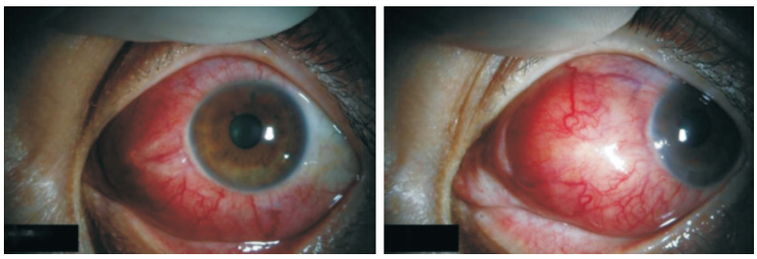

Figure 1 Case 5 The patient's left nasal and superior-inferior bulbar conjunctiva is visibly congested. A subconjunctival swelling was palpable on the nasal side, with poorly defined borders, soft texture, and movability.

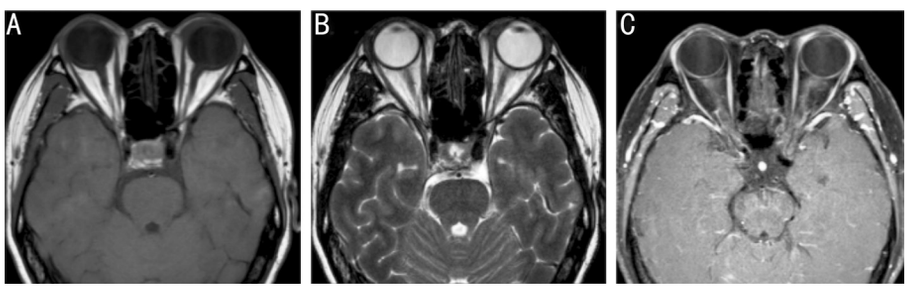

Figure 2 Case 5 The patient's orbital MRI shows a bar-shaped iso-T1 (A) iso-T2 (B) signal with blurred borders and significant enhancement visible on the anterior paranasal side of the left anterior wall of the eye (C). MRI: Magnetic resonance imaging.

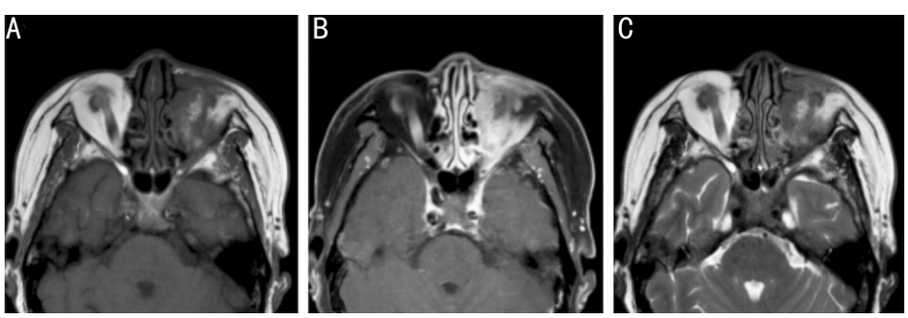

Figure 3 Case 4 Patient's orbital MRI irregularly shaped slightly long T1 (A) and iso-T2 (C) signal shadows with poorly defined borders are seen in the inner and lower quadrant of the left orbit in the interstitial space between the muscle cones. The lesion involves the internal rectus muscle, inferior rectus muscle, inferior oblique muscle and external rectus muscle, which are significantly strengthened after enhancement scan (B). The dynamic intensification curve is of a continuous strengthening type. The lesion involved the orbital apex, superior orbital fissure, inferior orbital fissure and the left cavernous sinus region posteriorly, and destroyed the orbital wall and nasolacrimal duct bone inwardly, involving the lacrimal sac region and nasolacrimal duct. Enhanced scan shows widening enhancement of the left cavernous sinus. Bone destruction of the inferior orbital wall was seen inferiorly, and the lesion was sequential to the lesion in the ipsilateral maxillary sinus. The ipsilateral subcutaneous soft tissues of the maxillofacial area were involved, with poorly defined borders and marked enhancement. The left eye was protruding, and the ocular contents did not show conduction. MRI: Magnetic resonance imaging.

all lesions were positive for S-100 and CD68, consistent with histiocytic proliferation. CD1a was negative in the examined cases, helping to exclude Langerhans cell histiocytosis. Plasma cells surrounding the lesions variably expressed IgG, IgG4, CD38, CD138, κ, and λ light chains. The proportion of IgG4-positive plasma cells ranged from 8–12 per high-power field in one case and approximately 20% of total IgG-positive cells in another, suggesting focal IgG4 reactivity rather than IgG4-related disease. Several cases showed additional positivity for CD3, CD20, and smooth-muscle actin (SMA), while staining for cytokeratin (CK) and anaplastic lymphoma kinase (ALK) was negative. Overall, the morphological and immunophenotypic features supported the diagnosis of extranodal RDD. Representative pathological features from Case 5 are shown in Figure 4.

Treatment and Prognosis All five patients underwent surgical resection, and one additionally received immunosuppressive therapy. The follow-up period ranged from 2 to 76mo. No recurrence was observed in any of the patients during the follow-up period, indicating a favorable short- to mid-term prognosis for ocular extranodal RDD.

Literature Review Clinical data from 30 cases of extranodal RDD were collected through PubMed, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Periodical Database (VIP), and the WanFang Data database, with a search period from database creation to

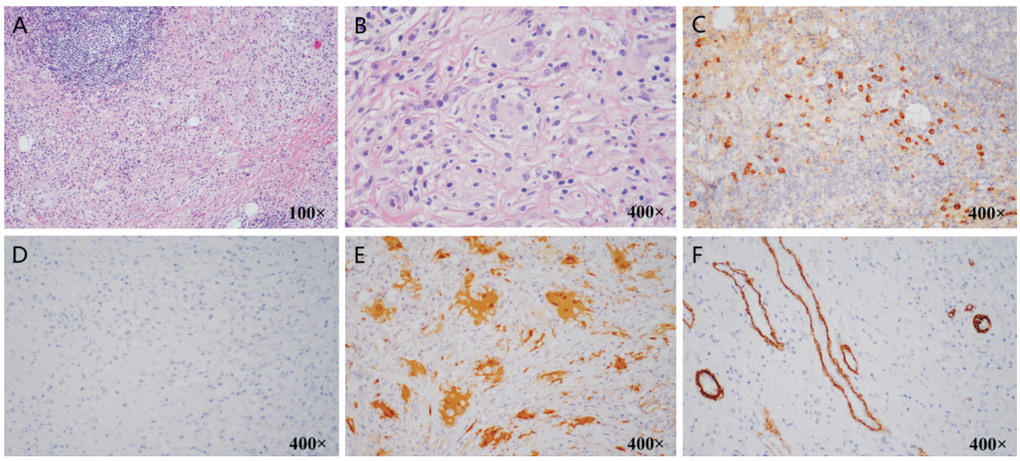

Figure 4 Pathological presentation of ocular RDD (Case 5) A: HE staining (×100). A large number of lymphocytes, plasma cells and histiocytes can be seen as a diffuse proliferative infiltrate. The bright and dark bands are clear. The dark band is lymphocytes and plasma cells; the bright band is histiocytes. B: HE staining (×400), there is an emperipolesis. C: Immunohistochemical staining shows positive expression of IgG (×400). D: Immunohistochemical staining shows negative expression of IgG4 (×400). E: Immunohistochemical staining showed positive expression of S-100 (×400). F: Immunohistochemical staining showed positive expression of smooth muscle actin (SMA) in the vessel wall (×400). RDD: Rosai-Dorfman disease; HE: Hematoxylin and eosin.

April 2023 (Table 2)[10-35]. Twenty cases (66.7%) were males, 10 (33.3%) females. Age range was 4–80y, with a mean of 41.4±21.7y.

Among the 30 previously reported patients, unilateral involvement was more common than bilateral, with 13 cases (43.3%) affecting the left eye, 10 (33.3%) the right eye, and 7 (23.3%) showing bilateral lesions. The most frequent presenting symptom was proptosis, observed in 8 patients (26.7%), followed by eyelid or lacrimal region swelling or mass in 6 (20.0%) and decreased visual acuity in 5 (16.7%). Conjunctival congestion or hyperemia was reported in 4 patients (13.3%), ocular pain or irritation in 3 (10.0%), and headache in 2 (6.7%). Diplopia and foreign-body sensation were each reported in one case (3.3%).

Lesions were most frequently located in the lacrimal gland (6, 20.0%) and in the conjunctiva or subconjunctiva (6, 20.0%), followed by the intraorbital area (5, 14.3%). Other affected regions included the eyelid (3, 10.0%), infraorbital area (3, 10.0%), and paranasal sinus (3, 10.0%). Less frequent sites of involvement were the postorbital area (2, 6.7%) and the optic nerve or its surroundings (2, 6.7%). Single cases were reported in the interorbital area, intraconjunctival area, pericorneal area, superior rectus, and sclera (each 1, 3.3%), whereas no lesions were found in the intracranial region.

HE staining showed prominent lymphoid follicles as alternating bright and dark bands under low magnification. The dark bands were a mix of lymphocytes and plasma cells; the bright ones were characteristically light-pink–stained histiocytes with fine cytoplasm and vacuolated nuclei. Emperipolesis was visible; *i.e.*, lymphocytes, plasma cells, neutrophils, and erythrocytes appeared in the cytoplasmic vacuoles of the histiocytes or were floating free in the histiocytes' cytoplasm. Twenty-five of the 30 patients were performed IHC examinations; in this subset, tissue cells were $CD68^+$ in 21 cases (70.0%), $S\text{-}100^+$ in 21 (70.0%), and $CD1a^-$ in 15 (50.0%). In addition, expression of the corresponding IHC markers of surrounding plasma cells was positive in four cases (13.3%) for CD20, in three (10.0%) for CD3, in one (3.3%) for CD38 or CD138. Two cases were negative for CK (6.67%) and one for ALK (3.3%).

Treatment modality was recorded in 28 of the 30 cases. Fifteen (50.0%) were treated with surgery, 6 (20.0%) with immunosuppressive therapy, 2 (6.1%) with radiation therapy alone, 1 (3.3%) with surgery+immunosuppressive therapy, 1 (3.3%) with chemotherapy alone, 1 (3.3%) with surgery+radiotherapy, 1 (3.0%) with surgery+chemotherapy, and 1 (3.3%) with ocular removal. Follow-up data were recorded for 21 patients for 3–60mo, with a median follow-up time of 16mo. One patient developed recurrence (3.3%), while the other 20 had no recurrence.

Comparison of Cases from Different Sources There were no significant differences in demographic information between the two types of subjects except that the mean age of our patients was higher than that of the cases in the literature. The lesion location and prognosis of the two groups are basically consistent. Of note, the main treatment modality at our hospital was surgery, supplemented by immunosuppressive therapy in the event of recurrence. In addition to surgery and immunotherapy, some of the cases in the literature were treated with radiotherapy and chemotherapy (Table 3). The 5-year recurrence-free survival (RFS) rate was 95.0% (95%CI: 0.859, 1.000; Figure 5).

Table 2 Demographics, histology, treatment, clinical feature, and tumor recurrence for patients with Rosai-Dorfman disease from literature review

Case	Gender	Laterality	Position	Clinical feature	Immunohistochemistry	Treatment	Follow-up (mo)	Recurrence
6[10]	Male	Right	Lacrimal gland	Lacrimal region swelling	CD68, S-100, CD20, CD21, CD35, CD34(+), CD1a, CD30, CK, P53(-)	Surgery	24	No recurrence
7[11]	Male	Left	Infraorbital, Interorbital	Protopsis	S-100, CD68, CD4(+), CD1a(-)	Radiotherapy	12	No recurrence
8[12]	Male	Right	Intraorbital	Orbital mass, proptosis	S-100(+), CD68(+), CD20(+), CD3(+)	Surgery	4	No recurrence
9[13]	Male	Left	Intraconical	Protopsis	CD68(+), PS100(+)	Radiotherapy	12	Recurrence
10[13]	Male	Left	Supra-lateral, lacrimal space	Tumor syndrome	-	Surgery	12	No recurrence
11[13]	Female	Left	Lacrimal gland	Lacrimal region swelling	CD68(+), PS100(+)	Surgery	-	-
12[14]	Male	Left	Lacrimal gland	Protopsis	S-100(+), CD68(+), CD1a(-)	Surgery	-	-
13[14]	Male	Right	Upper eyelid	Eyelid mass	S-100(+), CD68(+), CD1a(-)	Surgery	-	-
14[15]	Female	Left	Intraconal retroorbital	Protopsis	-	-	-	-
15[16]	Male	Left	Inferonasal part of eye	Progressive irritation	S-100(+), CD68(+), CD1a(-)	Surgery	24	No recurrence
16[17]	Male	Left	Posterior to the lacrimal gland	Conjunctival hyperemia and decreased vision	CD3(+), CD20(+), CD138(+), CD68(+), CD163(+), S-100(+), CD1a(-)	Surgery+oral corticosteroid therapy	16	No recurrence
17[18]	Female	Right	Inferior to the optic nerve	Decreased vision	S-100(+), CD68(+), CD163(+), CD1a(-), Melan-A(-)	Ophthalmectomy	36	No recurrence
18[19]	Male	Binocular	Subconjunctival	Occipital headaches, vertigo	S-100(+), CD68(+), CD1a(-)	Intravenous steroids+oral steroid, taper divalproex sodium	-	-
19[20]	Female	Right	Perilimbal	Foreign body sensation	S-100(+), CD68(+), CD1a(-), CD45(-)	Surgery	24	No recurrence
20[21]	Male	Left	Inferotemporal side of the orbit, subconjunctival	Conjunctival hyperemia and diplopia	S-100(+), IG4(+)	Prednisolone	18	No recurrence
21[22]	Female	Binocular	Eyelid	Eyelid mass	S-100(+)	Oral corticosteroids	6	No recurrence
22[23]	Male	Right	Conjunctiva	Conjunctival swelling and hyperemia	-	Immunosuppression	18	No recurrence
23[24]	Male	Binocular	Paranasal sinuses (ethmoid and maxillary)	Protopsis	S-100(+)	Surgery+radiotherapy	14	No recurrence
24[25]	Female	Binocular	Left paranasal sinuses, suprasellar region	Decreased vision	S-100(+), CD68(+)	-	-	-
25[26]	Female	Left	Conjunctiva inferotemporal side of the orbit	Protopsis	-	Short term steroid	-	-
26[27]	Male	Left	Conjunctiva	Conjunctiva swelling and pain, headache	S-100(+), CD1a(-)	Surgery+methotrexate (MTX)	24	No recurrence
27[28]	Male	Right	Optic nerve	Decreased vision	S-100(+), CD68(+), CD1a(-), langerin(-)	Surgery	-	-
28[29]	Female	Binocular	Suprarectus	Protopsis	ALK(-), SMA(+), CK(-), CD68(+), S100(+), IgG4(+), IgG(+), Ki-67(2%+), CD21(-), CD23(-)	Surgery	3	No recurrence
29[30]	Female	Right	Intraorbital	Eyelid mass	CD68(+), S-100(+), CD123(+), CD3(+), CD20(+), CD38(+), CD21(+), Ki-67(6%), CDla(-), IgG4/IgG>40%, IgG4(+)60/HPF	Surgery	-	-
30[31]	Female	Left	Intraorbital	Protopsis	S-100(+), CD68(+), CD1a(-)	Surgery	24	No recurrence
31[31]	Male	Left	Intraorbital and antrum maxillaris	Mass	-	Surgery	24	No recurrence
32[32]	Male	Binocular	Lacrimal gland	Eyelid mass	CD1a(-), S100(+), Langerin(-), CD68(+), IgG(+), IgG4(+)	Surgery	3	No recurrence
33[33]	Male	Right	Upper eyelid	Drooping of the eyelid	S-100(+), CD68(+)	Surgery	12	No recurrence
34[34]	Male	Right	Posterior pole	Decreased vision	Emperipolesis(+), S-100(+), CD163(+), CD68(+), CD1a(-)	Immunosuppression	60	No recurrence
35[35]	Male	Binocular	Sclera	Progressive pain and redness	S-100(+), CD68(+)	Chemotherapy	12	No recurrence

CD: Cluster of differentiation; PAS: Schiff periodic acid shiff; SMA: Smooth-muscle actin; ALK: Anaplastic lymphoma kinase; HPF: High-powered field; PAX: Paired box gene; CK: Cytokeratin.

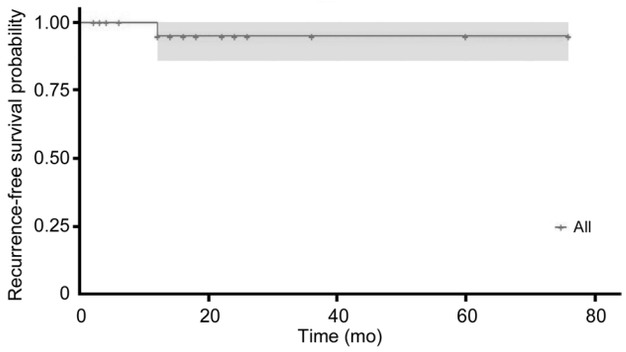

Figure 5 Overall survival analysis of Rosai-Dorfman disease The 5-year survival without recurrence was 95.0%.

Table 3 Gender, tumor position, treatment and prognosis of 35 patients with different source

Parameters	Present cases (*n*=5)	Literature cases (*n*=30)
Gender (male)	3 (60.0%)	20 (66.7%)
Laterality (unilateral onset)	4 (80.0%)	23 (76.7%)
Position		
Intraorbital area	2 (40.0%)	5 (14.3%)
Lacrimal gland	1 (20.0%)	6 (20.0%)
Conjunctiva and subconjunctiva	1 (20.0%)	6 (20.0%)
Eyelid	2 (40.0%)	3 (10.0%)
Infraorbital area	0	3 (10.0%)
Paranasal sinus	0	3 (10.0.%)
Postorbital area	0	2 (6.7.%)
Optic nerve and surroundings	0	2 (6.7.%)
Interorbital area	0	1 (3.3%)
Intracranial area	1 (20.0%)	0
Intraconjunctival area	0	1 (3.3%)
Pericorneal area	0	1 (3.3%)
Superior rectus	0	1 (3.3%)
Sclera	0	1 (3.3%)
Treatment		
Surgery	4 (80.0%)	15 (53.6%)
Immunosuppressive therapy	0	6 (21.4%)
Radiation therapy	0	2 (7.1%)
Surgery+immunosuppressive therapy	1 (20.0%)	1 (3.6%)
Surgery+radiotherapy	0	1 (3.6%)
Chemotherapy	0	1 (3.6%)
Surgery+chemotherapy	0	1 (3.6%)
Ocular removal	0	1 (3.6%)
Prognosis		
Recurrence	0	1 (4.8%)
Death	0	0

DISCUSSION

RDD, also known as sinus histiocytosis with large lymph node enlargement, is a rare nonmalignant disease characterized by a high proliferation of non-Langerhans sinus histiocyte cells in the lymphatic system[36]. First reported by Rosai and Dorfman in 1969, RDD was classified as a non-Langerhans cell histiocytic lesion by the Histiocyte Society Working Group in 1987. In 2016, the Society revised its classification, dividing non-Langerhans cell histiocytic lesions into Group R and Group C based on pathological, genetic, and molecular features. RDD was classified into Group R[1].

The pathogenesis of RDD is unclear. Previously, it was widely considered as an immune-responsive disease. However, RDD tissue cell proliferation has since been revealed to be polyclonal and to have tumorigenic features[37]. Recent studies have found point mutations in the neuroblastoma Ras (*NRAS*), mitogen-activated protein kinase kinase 1 (*MAP2K1*), and A-Raf proto-oncogene, serine/threonine kinase (*ARAF*) genes in some RDD patients[38], which might be associated with the occurrence of tumorigenic clonal proliferation. Further studies are needed to characterize the molecular biology of proliferating tissue cells.

Patients in this study were age 4–80y, with a mean age of 43.1y. We found that incidence was significantly higher in males than in females and also significantly higher in one eye than in both. RDD most often occurs in the lymph nodes of the head and neck but can also be found in any extranodal site; frequent extranodal sites include the skin and soft tissues, central nervous system, eyes, bones, and gastrointestinal tract[39]. Main clinical manifestations of the disease are fever, leukocytosis, and painless cervical lymph node enlargement. Patients with RDD at different sites of onset have correspondingly different clinical symptoms. For this study, we collected cases with ocular involvement; clinical manifestations were mainly ocular, with eyeball protrusion (25.7%), decreased visual acuity (17.1%), eyelid mass (14.3%), and conjunctival congestion (14.3%) being the most frequent. Thickening of the extraocular muscles, ptosis, swelling of the lacrimal region, headache, and eye pain were also present. Lesions frequently occurred in the orbit (20.0%), lacrimal gland (20.0%), conjunctiva and subconjunctiva (20.0%), and eyelid (14.3%). RDD can also involve the infraorbital, paranasal sinus, pars plana, intracranial, and pericorneal areas. Lesions in the orbit are more likely to present with protruding eyeballs, those in the lacrimal gland with localized swelling, those in the eyelid with eyelid mass or ptosis, and those in the conjunctiva or subconjunctiva with conjunctival hyperemia and swelling.

RDD is generally considered to be a self-limiting disease[36]. When patients receive early diagnosis and treatment, prognosis tends to be positive, but late diagnosis and systemic lymph node involvement can lead to poor prognosis[37]. Therefore, early detection and definitive diagnosis of RDD are essential. IHC and pathological examinations are important for confirming diagnosis.

RDD can be divided into intranodal, extranodal, and mixed types, with different pathological features seen at different

sites[38]. The intranodal type is mostly characterized by thickening of the lymph node perithelium, structural disruption, and varying internal shades: lymphocytic and plasma cell infiltration in dark areas, and lymphocytic or erythrocytic infiltration in dilated lymph sinuses in light areas. More-intact lymphocytes, plasma cells, and inflammatory cells within the cytoplasm of the tissue cells, *i.e.*, emperipolesis, can be seen. Extranodal RDD is very similar to the intranodal type. It is characterized by a foamy sinus histiocytic infiltrate with more-pronounced lymphoid follicles, germinal centers, fibrosis, and sclerosis. Microscopically, extranodal RDD mainly appear as bright and dark nodules within soft tissues, with less emperipolesis than the intranodal type[39]. Diseases such as Langerhans cell hyperplasia and Hodgkin lymphoma have similar pathological features, making diagnosis of extranodal RDD more difficult. In this study, the pathology of RDD was found to be characterized by prominent lymphoid follicles at low magnification. We observed alternating bright and dark bands, while lymphocytes, plasma cells, neutrophils, and erythrocytes appeared within the cytoplasmic vacuoles of the histiocytes or within the cytoplasm of the histiocytes (emperipolesis). IHC test results are an important basis for diagnosis of RDD; positivity for S-100 protein and histiocyte marker (CD68) and negativity for Langerhans cell marker (CD1a) are the main characteristics. Surrounding plasma cells can be positive for corresponding IHC markers, including CD20, CD3, CD38, and CD138.

Because some studies have discovered $IgG4^+$ cells in lesions in certain cases of RDD[40], this study focused specifically on expression of IgG4 in the lesion area. The results showed that of the 30 patients who underwent pathological examination, 5 (16.7%) were positive and 3 (10.0%) negatives for IgG4. In addition, we noted that although IHC showed some patients to be $IgG4^+$, the $IgG4^+$ cell count in the high-magnification field often did not meet the diagnostic criteria for IgG4-related disease (IgG4-RD). For example, in Case 5, the patient had 8–12 $IgG4^+$ cells per high-powered field (HPF) and about a 20% IgG4/IgG ratio, whereas the pathological criteria for the diagnosis of ocular IgG4-RD are an IgG4/IgG of ≥40% or >50 $IgG4^+$ cells at high magnification. Therefore, whether RDD is an IgG4-RD remains controversial.

IgG4-RD is an immune-mediated systemic disease characterized by diffuse infiltration of plasma cells expressing positive IgG4[41-42]. Although RDD and IgG4-RD share some overlapping histologic features, RDD typically demonstrates emperipolesis and S100 positivity, which are not features of IgG4-RD[43-44]. In our study, the IgG4-positive RDD cases did not meet the comprehensive diagnostic criteria for IgG4-RD, but the partial immunophenotypic overlap may reflect a shared inflammatory pathway or secondary IgG4 involvement. Notably, no significant differences were observed between IgG4-positive and IgG4-negative patients in terms of anatomical involvement, clinical manifestations, or recurrence rates. Given the limited number of IgG4-positive cases, further studies with larger cohorts and serum IgG4 level evaluation are needed to elucidate whether IgG4 expression represents a distinct subtype of RDD or a reactive phenomenon within the spectrum of orbital inflammation. Due to the small number of IgG4-positive cases and the low recurrence rate in our cohort, subgroup comparisons or treatment-specific outcome analyses were not statistically feasible. Future multicenter studies with larger sample sizes are needed to more thoroughly investigate these potential associations.

In our analysis, only one patient relapsed after 12mo, and the 5-year RFS rate was 95.0%. Therefore, RDD has a favorable prognosis. Some patients with the intranodal form are in remission without treatment, but because ocular damage significantly affects patients' quality of life, RDD involving the eye and ocular appendages is often treated with appropriate interventions. The main options include immunosuppressive drugs, surgical resection, and enucleation of the orbital contents if necessary. Adjuvant treatment modalities include radiotherapy and chemotherapy[45]. In this study, 20 patients were treated with surgery, 6 with immunosuppressive therapy, 2 with radiotherapy, 1 with chemotherapy, 1 with surgery+radiotherapy, 1 with surgery+chemotherapy, 1 with surgery+immunosuppressive therapy, and 1 with eye removal. Although the recurrence rate is low, we should note that cases of recurrent attacks after treatment are nonetheless reported[1]. Case 4 suffered recurrence after immunosuppressive therapy before coming to our hospital; the patient's condition was basically stabilized after surgery and transfer to the immunology department for treatment. This might suggest that surgery+immunotherapy is a good means of controlling recurrent RDD, but further conclusions need to be corroborated by additional cases.

In this study, we included 5 patients from our hospital and 30 from literature searches. Aiming to reduce potential information bias and better clarify the cohort structure, we stratified these reports. Since RDD has a good prognostic profile, the different treatment modalities did not show a difference in prognostic outcome. Etiological studies have not yet clarified the nature of the disease, which also makes it difficult to reach consensus on the best treatment modality for RDD, and still needs to be improved by subsequent studies. Patients who experienced recurrences were treated with radiotherapy, but no statistically significant conclusions were reached due to the insufficient amount of data and the favorable prognosis of RDD. Future studies could include additional cases. Although we attempted to analyze the heterogeneity of

cases from both sources, heterogeneity in diagnostic criteria, treatment regimens, and follow-up time between sources may limit generalizability, especially with respect to treatment effectiveness and recurrence rates. We will continue to pay attention to and collect relevant medical records of institution in the future, with the aim of reaching more comprehensive conclusions.

In conclusion, we summarized and analyzed the clinical features of 35 cases of extranodal RDD with ocular involvement. The results showed that the infraorbital, lacrimal, conjunctival, and subconjunctival areas were the most common sites of onset for ocular RDD, and clinical symptoms were closely related to site of onset. Pathological and IHC tests are important for diagnosing RDD, which often must be differentiated from Langerhans cell histiocytosis and tumorigenic lesions. Our results showed surgical resection, immunosuppressive therapy, and radiotherapy, all of which are in current use for this disease, to be effective, but there is no authoritative fixed treatment modality.

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