Rosai-Dorfman disease and the heart

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Summary

Rosai-Dorfman disease (RDD) is a non-malignant pathology of histiocyte proliferation. The classical clinical presentation is with painless cervical lymphadenopathy, but extranodal involvement is frequent, occurring in approximately 40% of cases. The literature was systematically reviewed to identify reported cases of RDD with cardiac involvement. Eighteen cases were identified (3 pediatric and 15 adult). In adult cardiac RDD (cRDD), three patterns of disease were noted: an intra-cardiac mass, epicardial involvement, and pulmonary artery involvement. Reported cases suggest that surgical excision of intra-cardiac masses confers a good prognosis.

Keywords: Histiocytosis, non-Langerhans, cardiac
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1. Introduction

First described in 1965 (*1*) and subsequently characterized in 1969 (*2*), Rosai-Dorfman disease (RDD) is a non-malignant disease of histiocyte proliferation. Although the classical clinical presentation is with painless cervical lymphadenopathy (hence the alternative term “sinus histiocytosis with massive histiocytosis”, or SHML), extranodal involvement is frequent, occurring in approximately 40% of cases. Common sites of extra-nodal involvement include the skin, nasal cavities, and paranasal sinuses. Cardiac involvement (cRDD) has previously been documented as occurring in < 0.1% of cases (*3*).

The etiology of RDD is as yet poorly defined and is, in the absence of convincing evidence to the contrary, currently considered to be idiopathic. A viral cause has been postulated, either *via* direct infection or as a result of an exaggerated immune response to the viral agent. Human herpes virus 6 (HHV6) DNA has been detected in RDD histiocytes (*4*), but in other cases HBV6 has not been detected (*5*). Epstein-Barr virus (EBV) infection has been identified in approximately half of patients with RDD (*6*), but no evidence of EBV RNA has been found in isolated RDD histiocytes or lymphocytes (*7*). Parvovirus B19 has been found in RDD lymphocytes (but not histiocytes) (*8*). A genetic form of RDD — Faisalabad histiocytosis, mapped to a mutation in the *SLC29A3* gene on chromosome 10q22.1 (*9*) — has been identified but is isolated to 3 consanguineous families.

Definitive diagnosis is by histological assessment, the two cornerstones of which are identification of emperipolesis and appropriate immunohistochemical analysis. Emperipolesis in relation to RDD refers to the presence of histiocytes containing intact lymphocytes within their

cytoplasm. Emperipolesis is differentiated from phagocytosis due to the intact nature of the engulfed cell, which by definition is viable and can exit the engulfing cell without any structural or functional abnormality (*10*). In addition to RDD, emperipolesis is also seen in malignant disease processes, such as lymphoma, leukaemia, myelodysplasia, and myeloma. Immunohistochemical staining for S100 protein is considered diagnostic. Cells will also be positive for CD68 and negative for CD1a, helping to distinguish RDD histiocytes from Langerhans cells (*11*).

Management of RDD is greatly dependent on the extent and site of disease and also on the presence or absence of symptoms (*12*). Surgical resection is appropriate for localized disease, with radiation therapy an option for residual disease after resection. In systemic/extensive extranodal disease, first line therapy is corticosteroids. Other options include immunomodulators, and/or cytotoxic chemotherapeutic agents. Due to the infrequency of reported cases of cRDD, no current treatment algorithm has been defined. In general, RDD is considered a benign process, but extensive lymph node or cutaneous involvement can lead to disfigurement, and deaths have also been noted (*13*) (mortality 7% (*14*)). RDD tends not to have an adverse prognosis unless the disease has a profound effect on vital organs or is extensive/disseminated.

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2. Literature review

The literature was systematically reviewed (in line with PRISMA guidance) to identify cases of RDD involving the heart and/or great vessels. A search was carried out *via* PubMed using the terms “Rosai Dorfman” and “sinus histiocytosis” combined with “heart” and “cardiac". Only English language publications were considered. Nine hundred and forty-three results were obtained. Those results yielded 17 papers describing 18 individual cases of cRDD (Table 1). Of the 18 individual cases, 3 were pediatric cases (< 16 years of age) while 15 were adult (≥ 16 years of age).

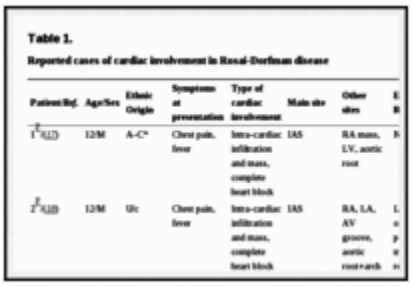

Table 1.

Reported cases of cardiac involvement in Rosai-Dorfman disease

Patient/Ref.	Age/Sex	Ethnic Origin	Symptoms at presentation	Type of cardiac involvement	Main site	Other sites	E B
1 [16]	12/M	A-C*	Chest pain, fever	Intra-cardiac infiltration and mass, complete heart block	IAS	RA mass, LV, aortic root	R
2 [16]	12/M	Ur.	Chest pain, fever	Intra-cardiac infiltration and mass, complete heart block	IAS	RA, LA, AV groove, aortic root+arch	L a p a n

Table 1.

Reported cases of cardiac involvement in Rosai-Dorfman disease

Two of the identified papers cited an additional reported case of cRDD (*15*). It was, however, impossible to obtain the full text of that report, so it has been excluded from the current analysis.

A further case report was also cited (*16*), but it has been excluded as it was not written in English.

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3. Pediatric cRDD

Of the 3 cases of pediatric cardiac involvement in RDD, 2 had very similar presentations: young male patients with sickle cell disease, presenting with chest pain and fever. Both of these patients had a mass in the interatrial septum (IAS) with infiltration of other cardiac structures. Both patients also presented with conduction disease requiring permanent pacing. Despite the similar presentations, the subsequent course was strikingly different. Patient 1 suffered from a progressive deterioration and required a cardiac transplant, while patient 2 had an indolent course. Both patients survived. The other case of pediatric cRDD involved a 14-year-old Afro-Caribbean boy with tricuspid and pulmonary valve involvement who underwent multiple surgical interventions but who ultimately died from disease progression.

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4. Adult cRDD

The 15 adult cases involved 10 males and 5 females ranging in age from 22–79 years (mean 49.5 years). Ethnic origin was reported for only 3 patients, making comment impossible. Three patterns were identified for the primary reported site of cardiac involvement: an intra-cardiac mass with or without underlying infiltration, pericardial/epicardial involvement, and a pulmonary arterial mass (Figure 1). Of the 15 adult patients, 4 had pericardial/epicardial involvement, 4 had involvement of the pulmonary artery, and 9 had an intra-cardiac mass. Of those cases involving intra-cardiac masses, 2 had a mass in the left atrium (LA), 5 had a mass in the right atrium (RA), 1 had a mass in the left ventricle (LV), and 1 had a mass in the right ventricular outflow tract (RVOT). Seven cases presented with multi-focal cardiac involvement, *i.e.* invasion/extension beyond the reported primary cardiac involvement.

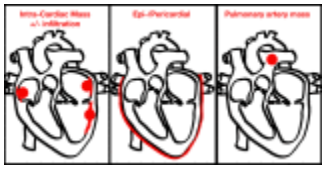

Figure 1.

Patterns of cardiac involvement in adults with Rosai-Dorfman disease.

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5. Management of and outcomes for patients with cRDD

Of the 15 adult patients, 3 received corticosteroid treatment. This resulted in stabilization of disease in 2 patients. The other patient who received corticosteroids died of multi-organ failure related to cRDD. Affected tissue/the mass was excised in 7 patients with good results. Of the 4 patients with PA involvement, three had a lesion that was successfully treated. The other patient died during an invasive examination.

Five deaths in the cohort (*18*) were reported (1 pediatric patient and 4 adults). Of the deaths, 3 were related to the cRDD itself. One patient died of other causes while 1 patient died during an invasive biopsy procedure.

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6. Discussion

Cardiac involvement in RDD is a rare manifestation of a rare disease, occurring in 0.1–0.2% of cases. The most common mode of presentation appears to be with an intracardiac mass, which in the majority of cases represents multi-focal underlying cardiac involvement. This literature review suggests that successful surgical excision of affected tissue carries a good prognosis.

This literature review has two main limitations. First, it relies on case reports, so there is very limited information on the subsequent follow-up of the patients involved. Thus, no comment can be made on the long-term clinical course, or indeed the frequency of disease recurrence in patients. Second, the condition is rare, so there are likely to be cases that have yet to be diagnosed, either due to unfamiliarity with the disease or due to lack of access to appropriate examinations.

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