Rosai-Dorfman disease is a rare subtype of non-Langerhans cell histiocytosis. With the last major report published in 1990, there is a paucity of contemporary data on this disease. Our objective was to report the clinicopathological features, treatments and outcomes of patients seen at a tertiary referral center. Sixty-four patients with histopathological diagnosis of Rosai-Dorfman disease were identified from 1994 to 2017 (median age 50 years; range, 2-79). The median duration from symptom onset to diagnosis was seven months (range, 0-128), which was also reflected in the number of biopsies required to establish the diagnosis (median 2; range, 1-6). The most common presentation was subcutaneous masses (40%). Of the 64 patients, 8% had classical (nodal only) and 92% had extra-nodal disease (67% extra-nodal only). The most common organs involved were skin and subcutaneous tissue (52%), followed by lymph nodes (33%). Three patients had an overlap with Erdheim-Chester disease, which had not been described before. Two of these were found to have MAP2K1 mutations. Commonly utilized first line treatments were surgical excision (38%) and systemic corticosteroids (27%). Corticosteroids led to a response in 56% of the cases. Of those treated initially, 15 (30%) patients developed recurrent disease. The most commonly used systemic agent was cladribine (n=6), with 67% overall response rate. Our study demonstrates that Rosai-Dorfman disease has diverse clinical manifestations and outcomes. While this disease has been historically considered a benign entity, a subset of patients endures an aggressive course necessitating the use of systemic therapies.

Introduction

Rosai-Dorfman disease (RDD) is a rare non-Langerhans cell histiocytosis characterized histopathologically by the accumulation of CD68-positive, S100-positive, and CD1a-negative histiocytes with frequent emperipolesis. RDD was first described in 1965 in four African children with lymphadenopathy by Destombes, and was called “adenitis with lipid excess”, owing to the lipid-laden histiocytes in the tissue specimen. In 1969, Rosai and Dorfman reported a separate series of four patients with massive cervical lymphadenopathy with specific histopathological features, and called it “sinus histiocytosis with massive lymphadenopathy”. Since the original description, further reports, including a summary of 423 cases from an international registry in 1990, described both nodal and extranodal manifestations of the disease. In the last decade, the understanding of the biology of related histiocytic disorders such as Erdheim-Chester disease (ECD) and Langerhans cell histiocytosis...
(LCH) has been enhanced by the discovery of recurrent BRAF and related mitogen activated protein kinase – extracellular signal-regulated kinase (MAP-ERK) pathway mutations.4-6 The identification of these specific mutations in both LCH and ECD further supported their consideration as neoplastic disorders rather than reactive inflammatory conditions. Recently, mutually exclusive KRAS and MAP2K1 mutations were identified in one-third of RDD patients, pointing toward a neoplastic process in this disease as well.7 Due to the rarity of RDD, the clinical spectrum and treatment outcomes are not well defined. Hence, we undertook this study to evaluate our institutional experience with RDD patients in a more contemporary setting.

Methods

The medical records of patients with RDD evaluated at a tertiary referral center from January 1, 1994 to December 15, 2017 were identified and reviewed after approval from the Institutional Review Board. Definitive histopathological diagnosis by tissue biopsy review was necessary for inclusion in the study. All biopsies identified at our institution (n=28) were re-reviewed by two pathologists with expertise in histiocytic disorders (K.L.R. and A.R.).6-10 Data abstracted from the medical records included: demographic characteristics, symptoms at disease presentation, histopathological features, treatment modalities utilized, and outcomes. In addition, radiologic and genomic findings were captured where available. Next generation sequencing (NGS) using an oncogene panel (FoundationOne® or Tempus®) was performed on five RDD tissue samples and one blood sample (Guardant360®).11-13 All patients in the study were followed up by a medical record review until death or November 10, 2018, whichever was earlier. For patients that were lost to the follow up, additional information was acquired via a telephone interview and survey forms. To minimize errors and bias, the medical records were independently reviewed by two investigators (GG and AK).

The majority of the patients did not undergo positron emission tomography – computed tomography (PET-CT) scans for baseline evaluation or treatment-response assessment. Hence, we utilized data from the reports of imaging studies available — radiographs, CT scans, and magnetic resonance imaging (MRI) scans. The imaging studies selected to be included in the manuscript were reviewed independently by a radiologist with expertise in histiocytic disorders (J.R.Y.).14 RDD patients were classified into subgroups based on the location, as well as associated conditions.15 The sites of disease were based on histopathologic or radiographic findings and include those found at the follow-up as well. Based on the location, RDD involving the lymph nodes alone was classified as “classical” and others as “extranodal”. Based on consensus definitions of concomitant disorders, RDD was classified as “neoplasia-associated” RDD, “immune-related” RDD, and “IgG4-related” RDD.8

As there is no United States Food and Drug Administration (US-FDA) approved treatment for RDD, the patients were treated with various therapeutic agents/modalities. We assessed treatment response by reviewing the clinical documentation. The response criteria were defined clinically and radiologically as we have previously described in ECD.16 Because RDD is a relapsing-remitting disease, we assessed the overall response rate (ORR), which incorporated complete as well as partial remissions (complete or partial resolution of symptoms or imaging finding suspected due to RDD). Descriptive statistics were used to summarize the data.

Results

Patient characteristics and presenting features

We included 64 RDD patients in the study. Of these, 8% had classical (nodal only) and 92% had extra-nodal RDD (67% extra-nodal only) (Table 1). Overall, 47 (75%) had multi-site disease and 17 (27%) had solitary or single-site disease. The median age at diagnosis was 50 years (range, 2-79). Five patients were less than 18 years of age (age 2, 2, 11, 14, and 15 years, respectively). In the entire cohort, there was a slight female preponderance (female: male 1.5:1). The median duration from symptom onset to diagnosis was seven months (range, 0-128; mean 18 months). The most common presenting symptom was painful or painless subcutaneous masses (40%; Figure 1A). Symptoms due to lymphadenopathy were reported only in 11% of patients (Figure 1A). C-reactive protein level at diagnosis was available in 21 (33%) of patients, with a median value of 12 mg/L (range <0.3 to 198 mg/L; normal value <8 mg/L).

### Table 1. Clinical and baseline features of patients with Rosai-Dorfman disease.

| Classification                          | Total patients | RDD/ECD overlap (mixed histiocytosis) | Median age at diagnosis (years) | Female: Male |
|-----------------------------------------|----------------|---------------------------------------|--------------------------------|--------------|
| Familial                                | 0              |                                       | 50 years (range, 2-79)         | 1.5:1        |
| Classical (node-only)                   | 5 (8%)         |                                       |                                |              |
| Extranodal                              | 59 (92%)       |                                       |                                |              |
| Neoplasia-associated                    | 8 (13%)        |                                       |                                |              |
| IgG4-related                            | 3 (5%)         |                                       |                                |              |
| Immune-related                          | 5 (8%)         |                                       |                                |              |
| Race                                     |                |                                       |                                |              |
| White                                   | 40 (63%)       |                                       |                                |              |
| Black                                    | 9 (14%)        |                                       |                                |              |
| Asian                                    | 3 (5%)         |                                       |                                |              |
| Other/unknown                           | 12 (19%)       |                                       |                                |              |
| Median time from symptom to diagnosis   | 7 (range, 0-128) |                                       |                                |              |
| (months)                                |                |                                       |                                |              |
| Median number of biopsies for diagnosis  | 2 (range 1-6)  |                                       |                                |              |
| Median duration of follow-up (months)   | 31 (range 0-249) |                                       |                                |              |
| Median overall survival since onset of   | 140 (range 8-684) |                                       |                                |              |
| symptoms (months)                       |                |                                       |                                |              |
| Lost to follow up                       | 15 (23%)       |                                       |                                |              |
| Deaths                                   | 4              |                                       |                                |              |
macroglobulinemia). Immune-related RDD was diagnosed in five patients, with one case each of rheumatoid arthritis, multiple sclerosis, Sjögren’s syndrome, systemic lupus erythematosus, and warm autoimmune hemolytic anemia. Serologic evaluation was not indicated in the remaining patients due to a lack of clinical features of concomitant autoimmune disorders. Three patients had high IgG4 level expression in lesional lymphoplasmacytic cells on immunohistochemistry, but only one had elevated serum IgG4 levels. None of these patients had other features consistent with IgG4-related disease.

Organ involvement

Among the entire cohort, 24 (38%) patients underwent a PET-CT scan, while 16 (25%) underwent body imaging with a CT scan or MRI. The most common organ involved on physical examination and imaging was skin and subcutaneous tissue (52%), followed by lymph nodes (33%) (Figures 1B and 2).

1. Skin and subcutaneous tissue

The most common presenting feature was subcutaneous nodules, either solitary or multiple, and presented at different locations on the body (chest, arm, back, and thigh). Six of the 33 (18%) cases in this group presented with primarily cutaneous lesions, either a purple or erythematous rash, or plaque-like lesions (Figure 3). Of the five pediatric cases, one patient had subcutaneous nodules.

2. Lymph nodes

Based on a clinical and radiographic record review, lymph node involvement by RDD was present in 21 (33%) cases, with isolated lymph node disease in three (5%) cases. The size of the lymph nodes ranged from 1-2 cm, with none of the patients demonstrating “massive lymphadenopathy” as described in prior reports (≥7 cm). Despite lymphadenopathy, B-symptoms (fever, drenching night sweats, weight loss) were noted only in three (5%) patients. The most common distribution of lymph node involvement was generalized, which occurred in seven (11%) cases. Isolated axillary and cervical lymphadenopathy was seen in five (8%) cases each. All of these cases presented as multiple lymph nodes (Figure 4). Thoracic lymphadenopathy was seen in the remaining four (6%) patients, and presented as mediastinal or para-tracheal lymphadenopathy. Of the five pediatric cases, three had lymph node involvement (one each of cervical, generalized, and retrocrural lymph nodes).

3. Bone

RDD of the bones was present in 16 (25%) patients, and varied in location from metaphyseal heads of the femur and humerus to the ribs, pelvis, and vertebrae. The lesions were mostly lytic in appearance and centered in the medullary space, although sclerotic lesions were seen occasionally as well. Soft tissue lesions with bone involvement were seen in four (6%) patients, with two in thoracic/lumbar spine, and one each in the mandible and acetabulum of the hip. Among the five pediatric patients, two had bone RDD involving the skull and humerus, respectively. Bone pain was not reported among patients with long-bone involvement, but common among patients with spine or pelvic bone disease.

Figure 1. Clinical manifestations and organ involvement among patients with Rosai-Dorfman disease A) Presenting features and B) Organ involvement
Figure 2. Common imaging findings of Rosai-Dorfman disease on fluorodeoxyglucose (FDG) PET/CT. (A) Maximum intensity projection depicting several FDG avid subcutaneous, lymph node and osseous lesions. (B) Coronal fusion images demonstrate FDG avid paranasal sinus (square) and lymph node (circle) disease. (C) Axial fusion image shows an FDG avid subcutaneous soft tissue lesion. (D) Sagittal fusion images of the bilateral lower extremities demonstrate several FDG avid osseous lesions.

Figure 3. Cutaneous Rosai-Dorfman Disease (RDD). (A) Petechial rash and subcutaneous nodule. (B) Nodular lymphohistiocytic infiltrates in the dermis form a dome shaped lesion. (C) Within a background of small lymphocytes and neutrophils, RDD histiocytes show round nuclei, open chromatin, central nucleoli, and abundant pale cytoplasm containing engulfed lymphocytes (emperipolesis). These cells are S100+ by immunohistochemistry (inset). (D) Enhanced coronal MRI of the left shoulder depicting a large homogenously enhancing subcutaneous mass (oval). (E) Fused FDG PET/CT of the same patient demonstrating hypermetabolism of this mass (oval).
4. **Head and neck (including orbit)**

Head and neck RDD lesions were noted in seven (11%) patients. Orbital involvement occurred in three (5%) cases, one of which was a pediatric patient. One of these also had ciliary body and scleral involvement. Other RDD sites in the head and neck region included the trachea (n=2), nose (n=1), and vocal cord (n=1).

5. **Glandular tissue**

RDD involving the glands was seen in nine cases, most common being breast tissue (n=5), with abnormalities on mammogram or MRI (Figure 5). Two patients each had involvement of lacrimal and parotid salivary gland without any evidence of dry eyes or mouth.

6. **Kidneys, adrenals, abdomen and retroperitoneum**

RDD of the kidneys was seen in six patients, most commonly as solitary parenchymal mass or nodule, and less commonly as perinephric coating, without the classic “hairy kidney” appearance as seen with ECD. None of these patients had renal failure from RDD of the kidneys. Two of these patients had adrenal nodules. Other abdominal sites included mesentery and peritoneum in one patient each.

7. **Nervous system**

Central nervous system (CNS) involvement manifested as dural- or parenchymal-based lesions in four cases. Parenchymal lesions were observed on MRI imaging in three patients, manifesting as frontal or temporal solitary masses. One of these patients had pachymeningeal disease along with cerebral subcortical white matter infiltrative lesions. Additionally, one patient had optic nerve involvement causing visual disturbance.

8. **Cardiovascular and respiratory system**

Cardiovascular involvement was uncommon, noted as a right atrial mass encasing the coronary artery in one patient and aortic infiltration in two patients (Figure 5). Pulmonary RDD was seen in four patients and presented as a parenchymal nodule, interstitial pneumonitis, or solitary pleura-based lesion.

9. **Bone marrow, liver, and spleen**

Biopsy proven bone marrow involvement was seen in one patient while three others had an increased bone marrow signal on PET-CT. Liver involvement occurred in three cases and two had spleen lesions (Figure 5).

10. **Other sites**

RDD involving the testes was noted in three cases, two of which had ECD of other tissue sites (Figure 5). RDD of the maxillary and ethmoid sinuses was noted on CT scan of the head in four cases, with sinus-related symptoms in three patients. Two patients had paravertebral soft tissue nodules, one of whom presented with compression of the spinal cord from mass effect. Colon- and rectal-based polypoid lesions were found in two patients.
Histopathologic and molecular features

The median number of biopsies required to establish a diagnosis was two (range, 1-6). Eleven (18%) patients underwent ≥3 tissue biopsies. Classic histopathologic features of RDD were enlarged histiocytes demonstrating emperipolesis, expressing CD163 and S100, but not CD1a by immunohistochemistry (Figure 3). However, the pathognomonic RDD histiocytes were infrequently found within the infiltrates in some extranodal lesions, and often were obscured by the inflammatory background or fibrosis. The inflammation accompanying RDD infiltrates was characterized by secondary lymphoid follicles and abundant plasma cells. Due to these features, the histopathology was most often mistaken as non-specific chronic inflammation, with the diagnosis of RDD only recognized following a repeat tissue biopsy or review at our institution (n=11).

Among the five patients who underwent NGS, one showed a CDC73 truncation in exon 5, and another had a KRAS c.351A>T (K117N) mutation. Interestingly, two of the three patients with RDD/ECD overlap showed the presence of a MEK1 mutation, one on testicular tissue [MAP2K1 c.157T>C (F53L)] and the other on peripheral blood [MAP2K1 c.167A>G (Q56P)]. No pathogenic mutation was detected in the tissue specimen of the remaining two cases. None of these specimens demonstrated the presence of known oncogenic gene fusions on RNA sequencing. BRAF-V600E mutation testing was performed in two cases and both were negative: one by immunohistochemistry and one by cell-free DNA polymerase chain reaction.

Treatments and outcome

1. First line treatments

Treatment and initial follow-up data were available for 57 (89%) patients (Table 2 and Figure 6). Of these, eight (14%) patients were initially observed. All of the patients who were observed and with follow-up data (n=3; 38%) eventually required treatment, with a median time to treatment of 30 months. Overall, the most common first-line therapeutic modality was surgical excision in 24 (38%) patients. The duration of response to surgery was variable (median 12 months, range 2-162), with 33% relapse rate. Of the relapses, five (21%) patients under-
went subsequent surgery, and three (13%) received systemic therapy. The most common site of RDD in patients who underwent surgery was subcutaneous nodules (13 or 54%), with other single cases of isolated thyroid, bone, breast, lacrimal gland, nasal septum and dura involvement, respectively. Among the five patients who required subsequent surgery, one had a nasal septal mass that recurred, while three had other disease sites (bone, soft tissue, subcutaneous tissue) that required resection subsequently. Additionally, there was one patient with KRAS

Table 2. Treatments and overall response rates (ORR) in patients with Rosai-Dorfman disease.

| Treatment                                      | First line | ORR      | 2nd/later line | ORR      |
|------------------------------------------------|------------|----------|----------------|----------|
| Surgery                                        | 24         | 24 (100%)| 7              | 6 (100%) |
| Surgery + RT                                   | 1          | 1 (100%) | 1              | 1 (100%) |
| Corticosteroids                                | 17         | 10 (56%) | 3              | 2 (67%)  |
| Rituximab                                      | 2          | 2 (100%) | 1              | 1 (100%) |
| Observation                                    | 8          |          | 0              |          |
| RT                                             | 2          | 0        | 4              | 1 (25%)  |
| Prednisone + 6-MP/azathioprine                 | 2          | 2 (100%) | 1              | 1 (100%) |
| CVP                                            |            |          | 1              | 1 (100%) |
| Cladribine                                     |            |          | 6              | 4 (67%)  |
| Mycophenolate                                  |            |          | 1              | 0        |
| Etoposide + Vinblastine + prednisone           | 1          | 0        | 1              | 0        |
| Prednisone + MTX/6-MP                          |            |          | 3              | 2 (100%) |
| Vinblastine + prednisone + 6-MP + MTX          |            |          | 1              | 1 (100%) |
| Clofarabine + vinblastine + etoposide + prednisone |            |          | 1              | 0        |
| Pegylated-interferon                           |            |          | 1              | 1 (100%) |
| Hydroxyurea                                    |            |          | 1              | 0        |

RT: Radiation therapy; 6-MP: 6-Mercaptopurine; CVP: cyclophosphamide, vincristine, prednisone; MTX: methotrexate

Figure 6. Treatments and outcomes of patients with Rosai-Dorfman disease (RDD) from diagnosis until first response where available. 6MP: 6-mercaptopurine; CVP: cyclophosphamide, vincristine, prednisone; 2-CDA: cladribine; MTX: methotrexate
c.551T>A (K141N) mutation who had a recurrence in the trachea after the resection of subcutaneous nodules. The three cases that required subsequent systemic therapy had multiple subcutaneous lesions and lymph node involvement at presentation.

Corticosteroids were used as the first-line therapy in 17 (27%) patients. Of these, responses were observed in in 56% of the cases, with a maximum response duration of 71 months and a relapse rate of 53%. The agent used in most cases was prednisone at doses of 1 mg/kg with prolonged but variably designed taper of 6-12 weeks. Responses were seen both clinically as well as radiologically, although uniform imaging re-assessment was not performed in over 50% cases. Twelve (70%) of the patients who received corticosteroids had lymph node involvement. Of these, seven responded, with a median duration of response of eight months (range, 3-25 months). There were two RDD patients with CNS involvement (dural and cerebellar, respectively) who noted improvement in symptoms after prednisone treatment. One patient had ocular (scleral) involvement and noted improvement in vision with corticosteroid eye drops. Corticosteroids were well-tolerated overall, and no major dose-limiting toxicities were reported. Radiation therapy was utilized in two cases (one subcutaneous and one bone) without any response. Other first-line therapies included combinations of rituximab, azathioprine, or 6-mercaptopurine with prednisone and resulted in universal responses in the four patients treated. The organs involved in these patients were mostly lymph nodes and subcutaneous tissues, and no relapses were noted.

The three patients with overlap RDD/ECD underwent resection of the solitary RDD lesions in the testes (n=2) and vocal cords (n=1). Two of these underwent cladribine chemotherapy that led to an ongoing response at a median follow-up of two years, and one has been observed for 2 years without ECD progression in the perinephric region.

2. Second line and subsequent treatments

Of the 49 patients that were treated initially, 15 (30%) developed recurrent disease after the first course treatment and were treated with other empiric modalities (Table 2, Figure 6). The most common chemotherapeutic agent used was cladribine (5 mg/m²/day for five days every 28 days) for 3-4 cycles, primarily used as second line therapy in six (10%) patients, with a 67% ORR. Of those who responded, no relapses were seen at median follow-up of 16 months (range, 2-26). Prednisone in combination with 6-mercaptopurine, azathioprine, or methotrexate was also successfully used in a few cases with subcutaneous and lymph node involvement. Interestingly, rituximab administered as four once-weekly doses in combination with corticosteroids resulted in a sustained ORR of 100% in the three patients who were treated, two of whom had primary lymph node involvement and third with multiple subcutaneous lesions along with lymphadenopathy. Two of these patients had immune-related RDD (warm autoimmune hemolytic anemia, multiple sclerosis). Other systemic chemotherapies that led to sustained responses utilized vinblastine and cyclophosphamide based regimens (Table 2). Radiation therapy was utilized in four patients (one each subcutaneous, tracheal, orbit, and bone), with a complete radiographic response seen in only one case of tracheal RDD, with an eventual recurrence in the multisystem distribution with an underlying KRAS mutation.

Less commonly utilized therapies included pegylated interferon alfa (135 mcg subcutaneous weekly in one patient) leading to regression of subcutaneous nodules and stability of the optic nerve lesion, and hydroxyurea (1000 mg oral daily in one patient) which initially resulted in some in the vision from orbital masses, but eventually progressed within three months. One of the patients received CVP (cyclophosphamide, vincristine, prednisone) regimen for RDD involving multiple subcutaneous sites, and achieved a sustained partial response.

The median duration of follow-up after diagnosis for the entire cohort was 31 months (range, 0-249). Of the cohort with complete follow-up information (n=49), four patients had died at the time of last follow-up. Of these, three patients died from other malignancies: concomitant peripheral T-cell lymphoma (n=1), acute myeloid leukemia 1 year subsequent to RDD with concomitant myelodysplastic syndrome (n=1), and metastatic gallbladder carcinoma 12 years subsequent to RDD (n=1). The cause of death for the fourth patient was unknown.

Discussion

In this study, we report a large contemporary series of RDD patients. Over the study period of 23 years, our referral center saw RDD patients at an average rate of three cases per year. However, the recognition of this disease appears to be increasing, with 29 (45%) cases seen within the last 5 years of the study. Contrary to the historically reported RDD cohort with massive lymphadenopathy, we found that the majority of cases presented as subcutaneous lesions. Lymphadenopathies were the second most common manifestation. However, they were not massive or limited to cervical lymph nodes alone as described by Foucar et al. in the initial landmark series of RDD. The reason for this difference in organ involvement is unclear, but may be related to a difference in the study population between the two studies. Compared to the historical cohort reported by Foucar et al., our cohort had more patients who were older (mean age 48 years versus 30 years), from the United States (97% versus 38%), and Caucasians (63% versus 43%). Moreover, our center is a tertiary referral center; hence it may not include some classic RDD cases that received treatment in the community. It may also be biased towards incidentally found RDD when being extensively evaluated by means of imaging studies for other unrelated disorders. However, the majority of the patients in our cohort were referred to hematology for primary RDD diagnosis and received systemic treatments. Our findings highlight that RDD is syndromic in nature with a wide spectrum of manifestations, and our experience may be more representative of RDD in the United States.

The histopathological diagnosis of RDD can be challenging due to its rarity and non-specific histologic findings, especially in the extranodal forms. In contrast to LCH and ECD, the RDD tissue may harbor very few lesional cells, and often shows a prominent inflammatory background with plasma cells, or lymphoid follicle formation and neutrophilic infiltrates. The difficulty in diagnosing RDD histopathologically is exemplified by the numerous biopsies required to achieve the diagnosis of RDD in our patients. On some occasions, a histopatholog-
The pathogenesis of RDD is not well understood, and it is unclear whether it should be classified as a neoplastic or benign disorder. Historical studies found the RDD cells to be polyclonal in nature.21 However, there are recent reports of MAP-ERK pathway alterations in about a third of RDD patients, which suggests that at least a subset may be neoplastic in nature.22,23 We recently reported on tissue NGS results of 10 RDD patients that demonstrated oncogenic alterations among four (40%), including the one patient with a RDD/ECD overlap and the one with KRAS-K117N included in the report herein.22 Interestingly, in the series, only 1 of 5 RDD cases without any oncogenic mutations required systemic therapy while all patients with molecular alterations (PTEN copy loss, SMARCA4 frameshift loss, KRAS-K117N) had progressive disease requiring chemotherapy.22 Furthermore, about a third of the patients in the current series had a disease behaving more like a malignant hematological neoplasm, requiring second line systemic treatments. We also report a novel finding of a RDD/ECD overlap in three patients, two of whom were found to harbor MAP2K1 mutations. In the past, a RDD/LCH overlap has been described as well.21 These findings, in conjunction with the accumulating molecular and clinical data, add further evidence to the contention that a subset of RDD may be neoplastic and related to the other histiocytic neoplasms.

There is a paucity of systematic studies analyzing first-line treatments and outcomes in RDD. Historically, it was reported that about 50% of the RDD cases with involvement of lymph nodes or cutaneous disease may experience spontaneous remissions.22,24 In our series, about 40% of the patients who were observed subsequently required treatment. This suggests that there is a role for monitoring without therapy in a subset of RDD patients who are asymptomatic and have no internal organ involvement. Surgical resection has been suggested as a curative option for some isolated RDD cases.15,26,27 In our series, one-third of the patients who underwent initial surgery required subsequent therapy. Our series also suggests that corticosteroids may be considered as a treatment option for nodal only disease, or to relieve symptoms from CNS/ocular involvement. However, the duration of response may be short-lived. The optimal duration of therapy is unknown and the patients need to be monitored for the adverse effects from steroids.

Although several RDD patients were treated adequately by corticosteroids or surgical resection, about a third in our series had recurrent disease. The most commonly used therapeutic agent was cladribine and resulted in high overall response rates (~70%). This is similar to that reported in previous case reports.6,28 Some other empirically used agents that led to sustained clinical responses were prednisone in combination with other immunosuppressive therapies (6-mercaptopurine, azathioprine, and low-dose oral methotrexate) or anti-CD-20 monoclonal antibody, rituximab, especially in immune-related RDD. These agents have been reported to provide benefit in RDD in the past as well.29,30,31 Vinblastine in combination with other immunosuppressive agents led to partial response in the lymphadenopathy, consistent with prior reports of its benefit.31,32 Although the second-line regimen were heterogeneous, our study suggests that patients with immune-related RDD may benefit from rituximab or immunosuppressive agents, and others may be treated with cytotoxic agents such as cladribine as used in ECD.

Prior reports suggested the potential role of radiation therapy in refractory disease causing imminent symptoms such as airway obstruction or vision loss.33,34 In our experience, radiation therapy resulted in a response in only one of six patients. This patient had an isolated trancheal lesion. Hence, there might be a potential role for radiation therapy in patients who have a single site of disease.

Our study’s major strength is that it is the largest contemporary case series among adult patients with RDD. We show that the most common manifestation of RDD may be dermatologic in nature, and the lymphadenopathy may not be massive as previously thought to be. We also report the unique entity of a “hybrid” RDD/ECD overlap, which has not been previously reported. A major limitation of our study is the lack of uniform imaging and response assessment in all patients. However, the charts were independently reviewed by two investigators to minimize bias. Another limitation is the lack of genetic sequencing data on all the patients, and our focus was primarily on the clinical manifestations, treatments and outcomes. Additionally, one of the challenges in conducting a study of a rare and chronic disease such as RDD is the lack of long-term follow-up data on the patients. Of the patients that had complete follow-up data (n=49), no one died from RDD. In the previous largest reported series, 4 of 238 (~2%) patients with sufficient follow-up died from effects of RDD.27,29 Although the mortality from RDD appears low, it may cause significant morbidity through end organ damage, and is potentially lethal if left untreated.

Despite the progress made in the understanding of the biology of LCH and ECD, our knowledge regarding the ontogeny and pathogenesis of RDD has lagged behind. Our study provides important information regarding the clinical spectrum and natural history for this entity. Due to the varying outcomes with similar histopathology, RDD may be considered a syndrome rather than a single disease entity. On one end of the spectrum are patients with “benign” single-system unifocal RDD such as a solitary subcutaneous nodule that can be observed or excised, and may lead to sustained remissions. On the other end, however, are the patients who are truly “neoplastic” and may need closer monitoring or systemic therapy. Although both these entities demonstrate similar histopathologic features to be diagnosed as RDD, there may be differences in the molecular/genetic architecture that differentiate benign from neoplastic RDD. Hence, more studies are needed to appropriately correlate phenotypic and molecular characteristics of RDD. Further studies focused at the hematopoietic stem cell compartment are also needed to ascertain the cell of origin of RDD, as that may provide insights into the pathogenesis and therapeutics. As discovery of MAP-ERK mutations in other histiocytic neoplasms has enabled successful targeted therapy with MEK-
inhibitors, the ongoing study of cobimetinib in histiocytic disorders (NCT02649972), which includes RDD, will hopefully provide the first FDA approved treatment for this disease.  

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