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Original article

Clinical and Diagnostic Characteristics of Rosai Dorfman Disease: A Case Series

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Abstract

Rosai-Dorfman disease (RDD) is an exceedingly rare nonmalignant histiocytic condition of unknown etiology. Immunohistochemistry reveals that RDD cells are S-100 positive and CD1a negative. Emperipolesis is a frequent histological finding that is not exclusive to RDD. Although lymph node and cutaneous signs are the most common, other organs might be affected. Regardless of therapy, the clinical course is uncertain. We describe a series of nine instances with lymph node and/or cutaneous lesions. Lymph nodes were shown to be involved in a variety of locations, including the mediastinum and retroperitoneum. The therapeutic response to steroids was varied, and the response to chemotherapy was unsatisfactory. Two individuals had associated autoimmune illnesses (Sjögren syndrome and vasculitis). In a follow-up, these individuals had a positive outcome regardless of therapeutic mode.

Keywords: ***Rosai Dorfman Disease, Diagnosis, Clinical characteristics, Pathology, Case series***

Introduction

Rosai-Dorfman disease, also known as sinus histiocytosis with large lymphadenopathy, is an uncommon type of idiopathic non-Langerhans cell histiocytosis. RDD is characterized by painless cervical lymphadenopathy, as well as fever, weight loss, and polyclonal hypergammaglobulinemia. Extranodal illness has been reported in up to 40% of instances with nodal disease, with disease locations including the epidermis, central nervous system, upper respiratory tract, orbit and eyelid, and gastrointestinal tract. Although occurrences in older persons have been described, this uncommon condition is more common in young adults (Chen et al, 2016).

Rosai-Dorfman illness, commonly known as sinus histiocytosis with extensive lymphadenopathy, is an uncommon syndrome characterized by painless, enormous cervical lymphadenopathy. A thick, mixed inflammatory infiltration with regions of emperipolesis are pathognomonic histological findings. Rosai-Dorfman illness affects the central nervous system infrequently, but when it does, it usually appears as an isolated dural lesion that looks like a meningioma. Rosai-Dorfman disease of the brain and spine with just intraparenchymal involvement and no dural involvement is extremely unusual (Hong et al., 2016).

Rosai-Dorfman-Destombes disease (RDD) is a rare non–Langerhans cell histiocytosis (LCH) initially characterized in 1965 by a French pathologist, Pierre Paul Louis Lucien Destombes, who observed lymphadenopathy with sinus histiocytosis on histologic examination of four children and young adults (Lee et al., 2017). Juan Rosai and Ronald Dorfman studied 34 cases of sinus histiocytosis with extensive lymphadenopathy four years later under the label sinus histiocytosis with massive lymphadenopathy (Garces et al., 2017). Typical lesional histiocytes include S100+, CD68+, and CD1a, with a varied frequency of emperipolesis. RDD has long been thought to be a self-limited condition with unclear origin, despite the fact that few individuals have bad outcomes (Milne et al., 2017).

Patients with typical RDD have bilateral cervical lymphadenopathy, however extranodal illness affects 43 percent of RDD patients (Milne et al., 2017). RDD is a complex condition that can develop alone or in conjunction with autoimmune, genetic, and malignant disorders. Due to the extensive clinical spectrum of RDD and the resulting diversity of professionals assessing and treating such patients, an evidence-based strategy to the assessment and treatment of this complex disorder is required.

This research study aimed to determine the clinical characteristics of Rosai-Dorfman disease patients. Also, the research objectives are (1) to evaluate the prognosis of the disease among these patients, (2) to assess body systems functioning and affection by the disease and to (3) to spot light on the way of treatment and management among these patients.

Methods

Study Design

A descriptive case series was employed for this study. Since this study aims to assess clinical characteristics of already diagnosed patients with Rosai-Dorfman disease and the disease incidence is so rare, this is the most appropriate design. This enables the researcher to measure the effect and the outcome at a single point of time. This study design gives reliable results with short time and less effort.

Study Setting
The study was conducted at Cochin Paris hospital during June 2021.

Participants
Participants in this study are patients diagnosed with Rosai-Dorfman disease admitted to the Cochin Paris hospital and their medical records.

Sample and sampling
Since the study is a case series study. Convenient non-probability sample was selected according to the availability of data in the medical records

Data collection
Data were collected from patients and their medical records at time of admission by taking baseline data.

Instruments
The data was collected using self-designed questionnaire. Study questionnaire contained three domains. First, characteristics of study participants. Second, clinical characteristics of participants. Third, management of patients.

Statistical Analysis
Data obtained from medical records of cases were entered and analyzed using SPSS program version 23 computer software. Sociodemographic data are presented using descriptive statistics as means, median, percentages and standard deviation. Disease characteristics are analyzed based on the clinical categories.

Ethical Consideration
Ethical approval was obtained from hospital administration to view the medical records. Patients' informed consent was obtained to use their laboratory results and clinical diagnoses pictures such as radiological and histological information as well as clinical manifestation pictures under anonymous considerations.

Results

The study included 9 cases with confirmed diagnoses of Rosai Dorfman disease. As reported in table 1, 2 and 3, in this cohort encompassing 8 patients, we found all age categories from 19 to 85 years of age. There was an almost equal proportion of male (n=5) and female (n=4). The median time from first clinical manifestation until the RDD diagnosis was 3.5 months (range, 1 to 12 months).

Table 1: Baseline data of patients

Sex	Age	Major Past Medical History	Medication received before the diagnosis	Cutaneous clinical features
F	19	Nothing	Nothing	Left Lumbar mass
F	58	Nothing	Nothing	Firm Erythematous Nodule on the External surface of left Arm,
M	35	Nothing	Nothing	Multiples dermo-hypodermic papules and nodules not ulcerated on the back,chest, shoulder and outer thighs
M	85	Bone pain	Gabapentine 600 mg and Doliprane	Multiples papules over the back
F	39	Sjogren's syndrome, Bilateral anterior uveitis, Retractive mesenteric panniculitis, Duodenal ulcer and meralgia	Nothing	Nodule in the right helix
M	57	Vasculitis, Periodic fever syndrome, Diabetes (Corticosteroid-induced), Hepatitis B virus, migraine and Bilateral scleritis with granulomatous anterior uveitis	Prednisone 1mg/kg/day, Methotrexate	Multiple chronic hypodermic papulonodular lesions of the anterior aspect of the left thigh
M	59	Chronic hepatitis B carriage	Nothing	Infiltrated erythematous papulonodular lesions in the left and right cheek
F	74	Nothing	Doxycycline 200 mg for three weeks	Non itchy erythematous nodule infiltrated purplish plaques of the left scapula,two pigmented macules painless lesions of the right forearm, one slightly infiltrated pigmented lesion of the right thigh and multiple yellowish papules in the nape of the neck
M	28	Nothing	Doxycycline, Dermoval and Fuicidine	Extensive non itchy granulomatous papulonodular placard over the left cheek then appearance of two lesions on the left temporal and maxillary

Table 2: Extra-cutaneous involvement

Patient	Extra-cutaneous involvement
F /19	Subcutaneous mass (Nodules) on the left buttock, Bone Hypermetabolic Foci Right Fibula and Left Inernal Condyle, Bilateral Cervical Lymph Nodes and Left Inguinal
F /58	Bone Nodule on the Dorsal Face of the feet
M /35	Supracentimetric lymphadenopathy of the axillary regions, Multiple inflammatory hypersignals from anterior corners of the thoracic vertebrates (MRI), Inflammatory of anterior dorsal enthesis and congestive arthropathy of lumbar and Hepatomegaly
M /85	Hypermetabolic mediastinal lymph nodes, Hypermetabolic multifocal bone infiltration and hematological pathology, right upper lumbar nodule, non-specific lower right nodule, right upper lumbar bronchial dystrophy, Adenomegaly of the Barety centimetric Lodge hilarious right and Cyst in the right and left kidneys
F /39	Multifocal bone lesions on the lateral edge of the right calcaneus, upper end of right tibia, right femoral diaphysis and hypoechoic nodule of liver
M /57	Nothing

M /59	Nodule of the right basal Fowler-pyramid junction(pulmonary), Bilateral frontal pseudo-nodular pachymeningeal thickening (MRI) and mild hepatomegaly with presence of small biliary cyst (abdominal ultrasound)
F /74	Nothing
M /28	Mesenteric lymph nodes of small infracentimetric axis associated with an infltration of mesenteric fat evoking mesenteric panniculitis and aspecific pulmonary micronodules

Table 3: Treatment and Evolution among patients

Patient	Treatment	Evolution
F /19	Nothing	Therapeutic Abstention and Simple Clinical Radiological Monitoring, Asymptomatic since 12 Months
F /58	Resection of the Nodular lesion	Simple Abstention Surveillance
M /35	Thalidomide 100mg/day, Cortancyl 60mg/day, Stromectol 3 mg and Methotrexate 25 mg/week	Surveillance
M /85	Nothing	Surveillance
F /39	Aclasta 5 mg and UVEDOSE 100000 IU	Surveillance and clincal radiological monitoring (PET scan) and ophthalmological follow up
M /57	Nothing	Surveillance
M /59	Lower right lobectomy(surgical)/ Dermoval (topical corticostetroides)	Surveillance dermatology, pulmonology, Hepatology and Thoracic surgery
F /74	Nothing	Therapeutic Abstention and Simple Clinical Radiological Monitoring, Asymptomatic since years
M /28	Local injection of Kenacort 80 mg, Methotrexate 20 mg/week	Surveillance, Simple Clinical Radiological Monitoring

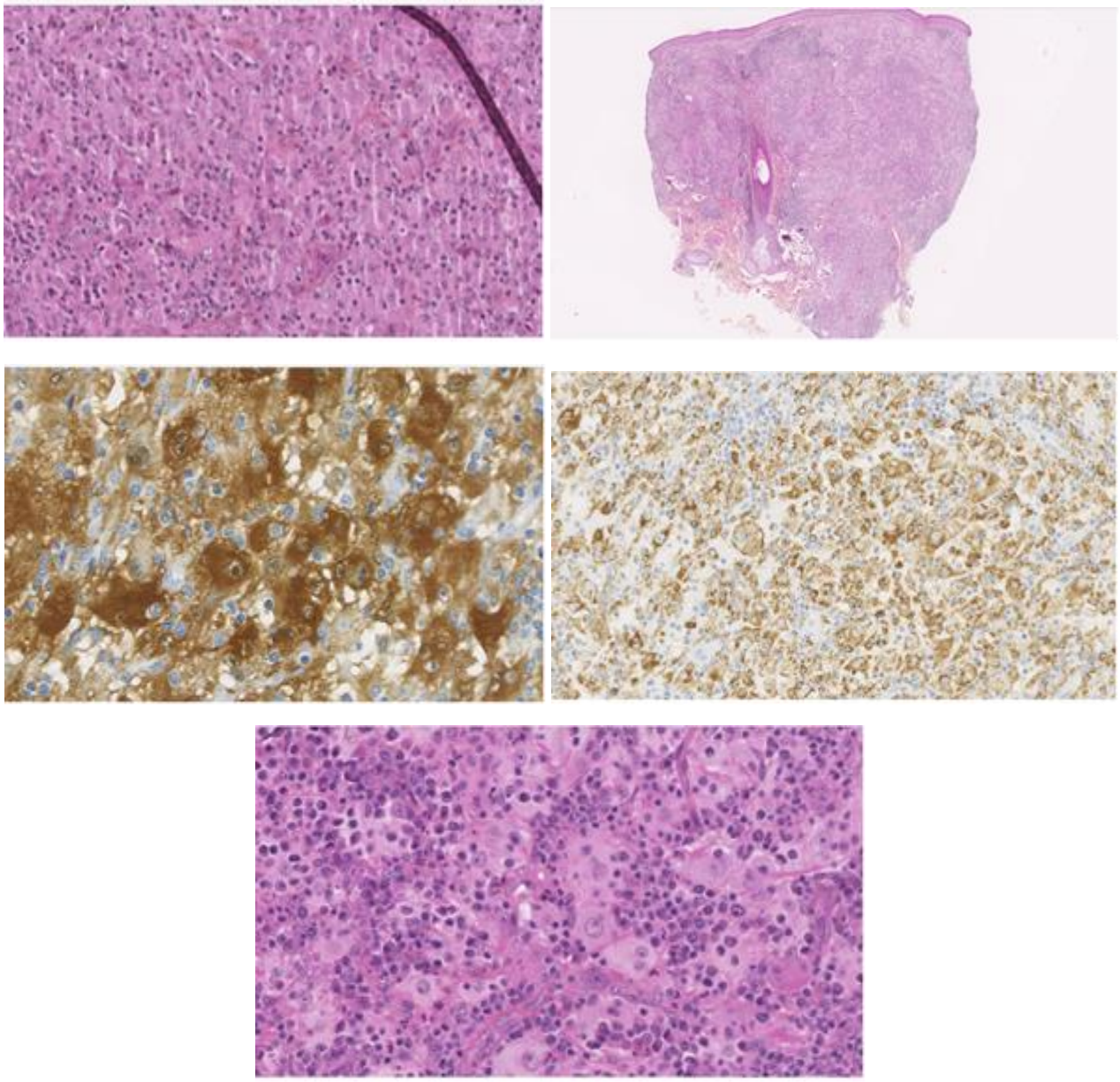

Figure 1: Representation of patients' microscopic findings

Lymphadenopathy was a predominant clinical manifestation, and was observed in 4 of the 9 patients (Table 2). These lymph nodes were often large and painful, suggesting an inflammatory reaction. Bilateral cervical (n=1), inguinal (n=1), axillary (n=1) and mesenteric (n=1). Cutaneous features of these patients is presented in table 1. The cutaneous lesions are characterized as follows: firm erythematous nodule on the external surface of left arm in patient two. Patient three had multiples dermo-hypodermic papules and nodules not ulcerated on the back, chest, shoulder and outer thighs. While patient four had multiples papules over the back. On the other hand, patient six had multiple chronic hypodermic papulo-nodular lesions of the anterior aspect of the left thigh. Furthermore, patient seven erythematous papulo-nodular lesions in the left and right cheek. Patient eight had erythematous nodule infiltrated purplish plaques of the left scapula. And patient nine had granulomatous papulo-nodular placard over the left cheek then appearance of two lesions on the left temporal and maxillary.

In this cohort, 2 patients developed an autoimmune disease. Patient five was diagnosed with Sjogren's syndrome while patient sex had vasculitis were the disease.

Microscopic examination of the biopsies from patients' lesions is presented in table 4.

Table 4: Microscopic and immune-histochemical examination of patients' biopsies

Patient	Biopsy	Microscopic findings	Immune-histochemical examination
F /19	Subcutaneous	A fibrous and adipose tissue is observed infiltrated by a florid inflammation made Polymorphic elements with lymphocyte, plasma cell, histiocyte, polymorphonuclear and numerous cell types Resorptive giants encompassing optically empty structures. Absence of granuloma. The examination in light Polarized does not reveal birefringent foreign material. These structures do not contain hair debris or Squamous flap. No signs of malignancy.	Immunostaining with cyclin D1 is positive on numerous histiocytic nuclei within the hypodermis No pathogen visualized. To be correlated with the results of the microbiological analyses.
F /58	Skin	A proliferation made elements with extensive epithelioid, histiocytic cytoplasm. It mixes an abundant, polymorphic population,	Histological appearance and immune-histochemical profile consistent with a diagnosis of Rosai's disease. Dorfman-Destombes. CD163 (10D6, Tebu-Novocastra), Protein S100 (Poly, Dako), SOX 10 (EP268, Epitorics) Protein S100 (Poly, Dako): + minority CD1a (MTB1, Tebu-Novocastra):- CD163 (10D6, Tebu-Novocastra): + majority
M /35	Skin	An epidermis orthokeratotic. The superficial dermis presents a pericapillary, lymphoplasmacytic inflammatory patch. The middle dermis and the deep dermis are the seat of a dense infiltrate made up of spindle-shaped elements of histiocytic appearance with cytoplasm more or less clear. These elements are distributed in clusters separated by collagen sets slightly thickened. A histiocytic infiltrate is mixed with a few polymorphonuclear cells, a few lymphocytes and above all numerous plasma cells. These plasma cells gather in clusters around the capillaries. We find a discrete capillary hyperplasia. The infiltrate surrounds the appendages especially the sweat glands. The sweat glands are essentially surrounded by a plasma cell infiltrate.	The predominantly histiocytic infiltrate is reactive in appearance and the presence of PS100+, CD1a-elements with images of emperipolele corresponds to the aspect described in Destombes Rosa Dorimann's diseases.
M /85	Skin	The bone cores are lesional, showing a preserved bone architecture with regularly distributed and discreetly remodeled bone spans delimiting spaces medullary modified by a dense inflammatory infiltrate made up of many macrophages, small lymphocytes and plasma cells. Among the macrophages, some of ex are very bulky, with an increased nucleus sometimes nucleolated or hyperchromatic and the voluminous cytoplasm often vacuolated and in which cells are sometimes observed inflammatory (emperipolesis).	The macrophage nature of the inflammatory contingent predominantly labeled with anti-CD68 antibody. It also shows many small interstitial and perivascular CD3 (+) T lymphocytes as well as quite a number of small. Perivascular CD20 (+) B lymphocytes. A fraction of macrophages, especially the very large cells are labeled with the anti-PS100 antibody. Absence of labeling by the antibody anti-CD1a.
F /39	Skin	A dense and polymorphic infiltrate, made up of lymphocytes and histiocytes and plasma cells and focally polynuclear. The infiltrate partially destroys the cartilage, which appears sub-necrotic eosinophil. In places, we find the beginnings of germinal centers. Histiocytes have cytoplasm willingly clarified, sometimes foamy and present images of emperipolesis. On some fragments there is granulation tissue	Abundant diffusely distributed CD3+ T cell population. Abundant CD20+ B lymphocyte population diffusely distributed with areas of focal reinforcement. Abundant population of CD138+ plasma cells located preferentially at the periphery of the

			infiltrate and which expresses the kappa and lambda light chains are almost superimposable. Outlines of germinal centers underlined by the CNA 42 with a discreet reinforcement of the number of elements. BCL6+ at this level and MiB1 The majority of histiocytes express PS100
M /57	Skin	Under the epidermis which is not modified, one observes on all the height of the sample, a dense infiltrate nodular and diffuse dermo-hypodermic. This infiltrate consists mainly of plasma cells and small lymphocytes with areas richer in polymorphonuclear neutrophils, especially around vessels without true vasculitis lesion. It is associated with vascular hyperplasia with vessels to cellsturgid endothelials. There is also a histiocytic infiltrate, made up of patches of large cells with extensive pale eosinophilic cytoplasm within which images of emperipolesis are identified. Others histiocytes, epithelioids, arrange themselves interstitially. There is no tuberculoid granuloma. There's no of necrosis. Numerous immunoglobulin deposits are observed. PAS, Gram, Ziehl and Grocott stains show no pathogen.	This infiltrate is made up of a mixture of small CD3+ T lymphocytes. Small CD20+ B cells (without CD21 follicular dendritic cell network) and plasma cells without one-design kappa/lambda. The IgG4/IgG ratio within plasma cells is approximately 10%. The tall pale histiocytes are PS100+, CD1a-. He has no treponema or HSV1 and HSV2 marking.
M /59	Skin	Massive lymphohistiocytic infiltrate in a nodular cluster consisting of large macrophage histiocytes with abundant clear cytoplasm and nuclei rounded oval slightly nucleolate, scattered (without granuloma) is associated with layers of lymphocytes with numerous clusters of plasmocutes and scattered PNNs, without real suppuration. Some images of emperipolesis within macrophages.	CD1a: negative, CD68 ++, PS 100 ++
F /74	Skin	Infiltrate is consisting essentially of lymphocyte and plasma cell mononuclear elements. They arrange themselves around the capillaries, around the appendages, forming confluent nodules, and diffuse between the fibers collagens.	The immune-markings carried out show the existence of a diffusely distributed T lymphocyte infiltrate, made up of small CD3 positive lymphocytes.
M /28	Skin	Superficial part of the dermis which is the site of a dense infiltrate made up of layers polymorphonuclear neutrophils or eosinophils On the periphery, there is a germinative center with a reactive appearance.	Histiocytes PS100+, CD1a- which seem to present images of emperipolesis, IgG and IgG4 are uninterpretable.

Discussion

The current work's evaluation of the literature is hampered by the short number of published publications and the small number of RDD patients involved in the medication therapy investigatory study. Furthermore, no data on case reports involving lengthy periods of time off particular therapy and relapses are known in the literature. We used the search term “Rosai-Dorfman disease” in the PubMed database. As a result, while the current research included a small number of patients, its key strength is that all eight patients were followed up on by the same group of physicians for an extended length of time. Age and gender findings in our group of cases were similar to those documented in the literature (Matter et al., 2017).

The clinical history is used to make the diagnosis of RDD, which is then confirmed by histological investigation. Open surgical biopsy or fine needle aspiration can be used to acquire specimens. Many believe the latter to be a sensitive and reliable diagnostic approach, with the added benefit of being available in an outpatient situation. Lymph nodes that have been excised are frequently grey due to capsular fibrosis or pericapsular fibroadipose tissue. In individuals with long-standing lymphadenopathy, the architecture of the lymph node is subverted and modifications are detected. Due to lymphatic stasis, the sinusoids of the lymph nodes are usually substantially enlarged and include a mixed cell population that includes lymphocytes, plasmocytes, and histiocytes. Histiocytes with an exaggerated phagocytic appearance are the most distinguishing cells in the sinuses (Hassani et al., 2016).

These cells are big and irregular, with abundant eosinophilic and occasionally vacuolated cytoplasm and a round or oval nucleus with well-defined and delicate membranes and a single conspicuous nucleolus. Mitosis is an uncommon occurrence. Histiocytes with foamy cytoplasm, on the other hand, may predominate in the cellular environment. Histiocytes with a varied number of phagocytosed cells, mainly lymphocytes, plasmocytes, or erythrocytes, are the most prominent histological finding in RDD. Some cells, particularly lymphocytes, stay alive inside the vacuoles, resulting in lymphophagocytosis or emperipolesis, which is described as the presence of intact lymphocytes inside other cells, in this case histiocytes (Chakraborty et al., 2014).

The expression of protein S100 is the most effective marker of histiocytes in RDD. Pan-macrophage antigens (CD68, HAM 56, CD14, CD64, and CD15) as well as phagocytosis-related antigens (CD64 or the Fc receptor for IgG) and lysosomal activity may be expressed by histiocytes (lysozyme and alpha-1-antitrypsin). Furthermore, histiocytes are CD1a negative and lack Birbeck granules. (5) Our patient's anatomopathological assessment indicated emperipolesis, positivity for PS100 and CD68, and negative for CD1a. Histiocytosis of Langerhans cells, histiocytic sarcoma, lysosomal storage illnesses (such as Gaucher's disease),

classic Hodgkin's lymphoma, melanoma, and metastatic carcinomas, and infections caused by Histoplasma and mycobacteria affecting the lymph node are among the differential diagnoses of RDD (Sasaki et al., 2014).

Because of its rarity, no standard therapy for RDD has been established. However, because the illness is self-limiting, intervention is frequently unneeded, unless the airways are clogged or essential organs are crushed. Corticosteroids, chemotherapy mixed with periwinkle alkaloids, anthracyclines, antimetabolics and alkylating drugs, interferon, antibiotics, radiation, and partial or whole surgical resection have all been mentioned as treatments (Bruce-Brand et al., 2020). According to a study of the literature, 50 percent of people with RDD do not require therapy, and 82 percent of untreated patients undergo spontaneous and full illness regression. Some accounts describe illness management in children without the use of treatment. After thorough examination of the biopsied material, a cautious strategy with steady decrease of the lymphadenomegaly was taken in this patient (Pulsoni et al., 2002; Stones and Havenga, 1992; Dearth et al., 1980).

Conclusion

To summarize, there is currently no optimal paradigm for treating the many forms of RDD lesions in a comparable manner. Because the condition is self-limiting, treatment should be customized to the specific lesion or patient. Chemotherapy does not provide a positive outcome. Steroids can create long-term plateau stability and may even cause an adverse reaction on the first try. The literature and our examples show that RDD and immunological deregulatory diseases can coexist due to simultaneous onset or temporal decoupling.

These data show that RDD may be the result of an immune response to an unknown stimulus. Given that RDD can resemble numerous diseases or appear before, simultaneously, or after immune dysregulation disorders, it is critical that these patients be closely monitored for an extended length of time. Given the rarity of RDD and the scarcity of research utilizing novel therapeutic techniques, it is critical to find centers of excellence for innovative therapy to be employed in clinical trials.

Ethics approval and consent to participate

Ethical approval was obtained from hospital administration to view the medical records. Patients' informed consent was obtained to use their laboratory results and clinical diagnoses pictures such as radiological and histological information as well as clinical manifestation pictures under anonymous considerations.

List of abbreviations

RDD: Rosai Dorfman Disease
LCH: Langerhans cell histiocytosis

Data Availability

Data are available upon reasonable request

Conflicts of Interest

Authors has no conflict of interest

Funding Statement

None

Authors' contributions

All authors contributed in the data collection process as well as manuscript preparation.

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