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Review Article

A comprehensive assessment of cutaneous Rosai-Dorfman disease

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ABSTRACT

Background: Cutaneous Rosai-Dorfman (CRD) disease is a rare entity that is characterized by histiocytic proliferation in the skin. The disease has been reported to exhibit different clinical profiles and occasionally confounding histologic features that may be challenging for a correct diagnosis. The purpose of this study was to assess the pathobiology and highlight the variance in clinical and histologic spectrum of the disease based on published literature.

Methods: A PUBMED search was performed to retrieve cases of cutaneous Rosai-Dorfman disease published in the literature. A PRISMA-guided review of the included articles was performed. Three interesting case reports from our institution are also described.

Results: A total of 263 patients, of which 220 with purely cutaneous disease were identified in 152 studies. The mean age at presentation was 45.2 years with a slight female preponderance, and East-Asian, Caucasian and African populations being largely affected. Majority of the patients presented with multiple lesions, predominantly on limbs and comprising of nodules, plaques and papules that were occasionally pigmented. The classis histologic findings included large foamy histiocytes, exhibiting emperipolesis and a specific immunophenotype (S100+, CD68+, CD1a-). Inconspicuous emperipolesis, fibrosis, increased vascularity, neutrophilic microabscesses and concurrent langerhans cell histiocytosis and lymphoma in few cases highlighted the importance of immunohistochemistry for a definitive diagnosis. The disease shows an indolent and benign course with excision and chemotherapy being most effective for extensive and refractory cases.

Conclusions: This review of largest cohort of CRD patients provides an updated insight into the clinicopathologic features with possible diagnostic pitfalls and effective therapeutic options that should be useful in diagnosis, management and future research opportunities.

1. Introduction

Cutaneous Rosai-Dorfman (CRD) is a unique form of histiocytopathy that exhibits distinctive and reproducible histologic features including a proliferation of histiocytes with macrophage properties in a polymorphous inflammatory cell background rich in lymphocytes, plasma cells and neutrophils. While the plasma cells may be of the IgG4 subset, this condition is not considered part of the spectrum of IgG4 sclerosing disease. Emperipolesis of these aforesaid inflammatory cell elements by the macrophage component is characteristic. The entity was first described in lymph nodes in 1965 and later coined as 'sinus histiocytosis with massive lymphadenopathy' by Rosai and Dorfman in 1969 to emphasize the classic clinical features being in the context of cervical node enlargement, fever, leukocytosis, elevated erythrocyte sedimentation rate, anemia and hypergammaglobulinemia [1,2]. Extranodal manifestation of the disease is common with skin and soft tissue as the most common sites [3]. The first case of skin involvement in the literature dates back to 1978 but a pure form of CRD without nodal involvement is still rare [4,5]. While the disease follows a benign clinical course, cutaneous lesions are rarely suspected clinically to be CRD especially in the context of a de novo presentation in the skin. Clinical follow-up to exclude subsequent extra cutaneous involvement is recommended [3,6].

Despite many papers devoted to the topic of Rosai-Dorfman disease (RD) including cutaneous lesions, the etiology and pathogenesis of the disease remains unknown [3,5-10]. One espousal suggests that the histiocytes in CRD may be derived from circulating monocytes that are stimulated by macrophage colony stimulating factor (M-CSF) [11,12]. Association with infections including Epstein-Barr virus, Human immunodeficiency virus (HIV), Human herpesvirus-6, Herpes simplex

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virus and abnormalities of the immune system such as uveitis, Crohn's disease, Sjogren's syndrome, Factor XII Deficiency, and lupus erythematosus have also been reported [3,6,13,14]. There are also reports of biopsies showing concurrent features of Langerhans cell histiocytosis (LCH) and marginal zone lymphomas (MZL) [14-22]. The aim of this review was to enhance the current knowledge and understanding of the CRD by reviewing all cases of CRD, published in English language since 1978 and to determine any changes in their evaluation or management over time.

2. Methods

A literature search was performed on PUBMED using predetermined search string terms that included *cutaneous Rosai-Dorfman* and *cutaneous sinus histiocytosis* in May 2018. Based on PRISMA guidelines [23], articles in English language that reported cases with the histologic diagnosis of cutaneous Rosai-Dorfman disease were retrieved. Information on demographics (patient's age, gender, ethnicity), clinical characteristics of the lesions, systemic involvement, associated disease, histology, immunohistochemistry, treatment, outcome and duration of follow-up was recorded. Country of origin, institute and year of study were cross-referenced to remove any duplicated cases. A hand-search of bibliography of included studies was performed to further identify studies that met our inclusion criteria. Purely cutaneous disease (P-CRD) was defined as the presence of cutaneous lesions in the absence of lymphadenopathy and/or extra-cutaneous disease. A local extension of the disease into subcutaneous bone and soft tissue was still considered as purely cutaneous.

Three interesting cases of CRD from our institution are also described to demonstrate the phenotypic variability.

3. Results

There were 221 abstracts identified from the initial search, of which 158 full-text articles were reviewed. Ten articles were excluded due to different reasons (Appendix A) while 4 articles from the reference list of reviewed full-text studies met the inclusion criteria. A total of 152 studies were available for analysis that included 132 case reports and 20 case series, published between 1978 and May 2018 (Appendix B). Majority of the studies (n = 125) were published in the past two decades with one third of the total studies from the United States (US). The largest cohort was from China published in 2007 that included 25 Chinese patients followed in number by a second study from the US (2002) comprising 22 patients of different ethnicities [6,10].

3.1. Clinical presentation

There were 263 patients in total of which 220 patients (84%) had purely cutaneous disease. Three of these patients had direct extension of disease into underlying bone, conjunctiva and nasal cavity. Of 43 CRD cases (16%) with systemic involvement (CRD−S), 38 patients had lymphadenopathy and 6 patients had extra-nodal and extra-cutaneous involvement (epidural, pituitary, conjunctiva, nasal cavity, middle ear, larynx, trachea and thymus). A comparison of clinical features of P-CRD and CRD-S cases are shown separately in Table 1. For combined cases, there was a slight female preponderance (53.8%) with a mean age of

Table 1
A comparison of clinical, laboratory and associated findings between P-CRD and CRD−S.

	P-CRD (N = 220)	CRD-S (N = 43)
Age (range)	47.1 years (3–84)	41.6 years (6d-73)
Gender	Female 56% (121)	Female 44% (19)
percent distribution (n)	Male 44/% (96)	Male 56% (24)
	No data (3)	
Ethnicity	East-Asians 57% (96)	Caucasians 31.5% (12)
Percent distribution (n)	Caucasians 20% (33)	East-Asians 26% (10)
	Africans 12.5% (21)	Africans 21% (8)
	Hispanics 5% (9)	Middle-Eastern 8% (3)
	Middle-Eastern 3.5% (6)	Indians 8% (3)
	Indians 2% (3)	Hispanics/Mixed 5% (2)
	No data (52)	
No of lesions	Multiple 60% (130)	Multiple 88% (38)
Percent distribution (n)	Single 40% (86)	Single 12% (5)
	No data (4)	
Average duration	19 months	21 months
Site	Extremities 51.5% (113)	Extremities 64% (27)
Percent population (n)	Trunk 47% (103)	Trunk 48% (20)
	Face 35% (77)	Face 36% (15)
	Head/neck 8% (17)	Head/neck 14% (6)
	Generalized 2% (5)	Generalized 5% (2)
	Penis 0.4% (1)	No data (1)
	No data (1)	
Serum globulins	IgG 11% (24)	IgG 49% (21)
Percent population (n)	IgA 1% (2)	IgA 9% (4)
		IgM 5% (2)
		IgE 2% (1)
Increased ESR	14.5% (32)	39% (17)
Percent Population (n)		
Associated findings	Uveitis 4% (9)	Uveitis 2% (1)
Percent Population (n)	Crohns' Disease 2% (4)	
	Positive EBV titers 2% (4)	Positive EBV titers 2% (1)
	Positive HHV titers 2% (4)	Positive HIV titers 2% (1)
	Positive HIV titers 1% (3)	
	Positive HSV titers 0.4% (1)	
	Positive CMV titers 0.4% (1)	
	CRD arising in VZV scars 1% (2)	CRD arising in VZV scars 2% (1)
	Concurrent LCH in same specimen 2% (5)	
	Concurrent marginal zone lymphoma 0.8% (2)	

Table 2
Histological features and immunohistochemistry results of CRD.

Location (n):	
Dermis: 63% (167)	
Dermis + Subcutis: 32% (85)	
Subcutis: 4% (11)	
Histology (n):	
Histiocytes, lymphocytes, plasma cells: 100% (259)	
Neutrophils: 52% (135)	
Eosinophils: 11% (28)	
Fibrosis: 12% (32)	
Increased vascularity: 12% (31)	
Germinal centers: 6% (16)	
Intralymphatic histiocytes: 3% (9)	
Immunohistochemistry:	
S100+: 235	
CD68+: 150	
CD1a-: 153	
CD1a+: 1	
Combinations used	
S100, CD68, CD1a:	124
S100, CD1a:	29
S100, CD68:	24
S100:	58
CD68, CD1a:	1
CD68:	1

45.2 years (range: 6 days- 84 years) at the time of presentation. Ethnicity was reported in 205 cases of which Eastern-Asians comprised more than half (52%) of the total patient population followed by Caucasians (22%) and Africans (14%). Ninety-one patients (35%) presented with a single lesion. The lesions were described as nodules (42%), plaques (34.4%) and papules (23.5%), with the largest lesion measuring up to 30 cm in size (avg. 5.29 cm) and present for 19 months on average. Majority of the lesions were asymptomatic while few cases complained of tenderness ($n = 8$), pruritus ($n = 7$) and ulceration ($n = 2$). Sixty-six cases presented with brownish discoloration of the lesion. The most common site of involvement was extremity (54% of the patients) followed by trunk (47% of the patients). Eight patients had generalized whole body involvement while one patient had a penile lesion. Laboratory investigation revealed increased ESR in 49 patients and hypergammaglobulinemia in 47 patients.

3.2. Histologic features

A description of histologic findings was available in 259 cases (Table 2), of which histiocytic proliferation was present intradermally in 163 patients with a further extension into the subcutaneous tissue in 86 patients (33%). Eleven patients had localized lesion predominantly within subcutaneous tissue. The lesions were poorly circumscribed with infiltrative margins, comprised mainly of large histiocytes with granular and palely eosinophilic cytoplasm, vesicular nuclei (mononuclear/multinuclear) and prominent nucleoli. Intracytoplasmic engulfment of inflammatory cells including lymphocytes, plasma cells and neutrophils, known as emperipolesis was a constant feature in all the cases; however, their degree was variable both within and between the cases and some required immunohistochemistry for identification. The histiocytes were present in a background of mixed inflammatory infiltrate composed of lymphocytes and plasma cells with occasional neutrophils (52%) and rare eosinophils (11%). Clusters of plasma cells, predominantly around venules and neutrophilic microabscesses were noted in few cases. Other findings included increased vascularity (12%) and presence of intralymphatic histiocytes (3%). A fibrotic stromal response was recorded in 12% of the lesions, present for 13 months on average (1–36 months). Rare formation of germinal centers around periphery of the lesion was noted in 6% of the cases.

Table 3
Different treatment modalities used and their outcomes.

	N	Complete remission (%)
Excision/cryotherapy	84	56 (66)
Oral/intralesional steroids	56	3 (5)
Chemotherapy	46	10 (22)
Radiation	14	2 (14)
No treatment	51	12 (regression)
Not mentioned	42	–

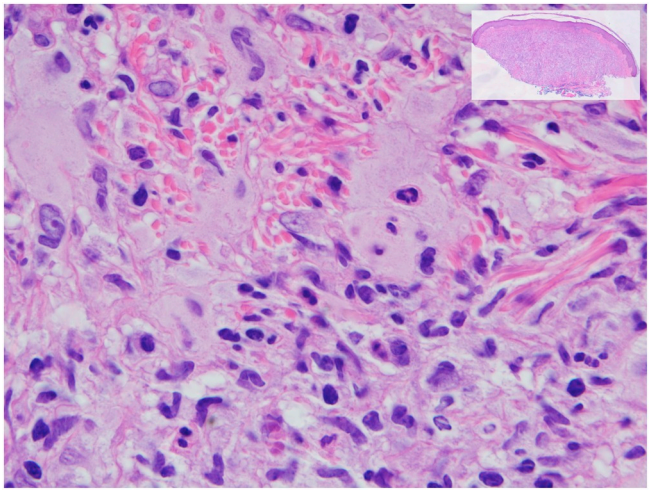

Fig. 1.1. Histologic image shows large histiocytes with gray watery cytoplasm and exhibiting emperipolesis in a background of mixed inflammatory infiltrate (H&E, original magnification 1000×). Inset image shows a dense dermal histiocytic and inflammatory infiltrate, beneath the Grenz zone (H&E, original magnification 40×).

3.3. Immunohistochemistry

Immunohistochemistry (IHC) was an important step in the diagnosis and was used in 240 cases with S-100 being most commonly used immunostain (performed on 98% of the cases), highlighting histiocytes with emperipolesis (Table 2). These histiocytes were negative for CD1a, performed on 64% of specimens. The most common cocktail was a combination of triple (S100-CD68-CD1a) immunostains that was used in little over half of the cases (52%). An isolated S100 stain was used in another one-quarter of the cases (24%).

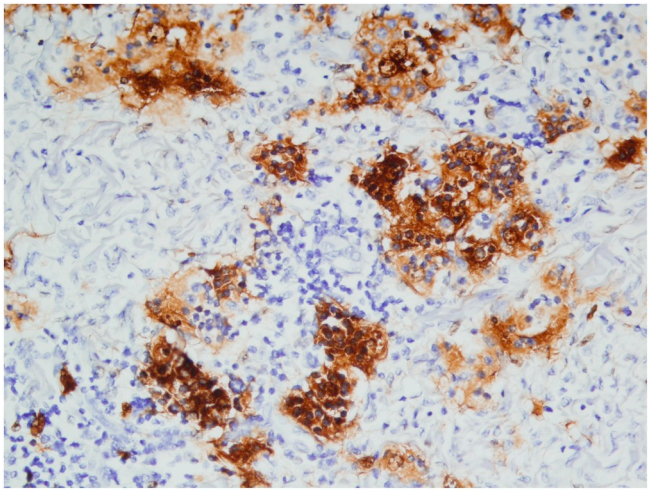

Fig. 1.2. S-100 immunostain highlighting histiocytes with emperipolesis (S-100 IHC, original magnification 400×).

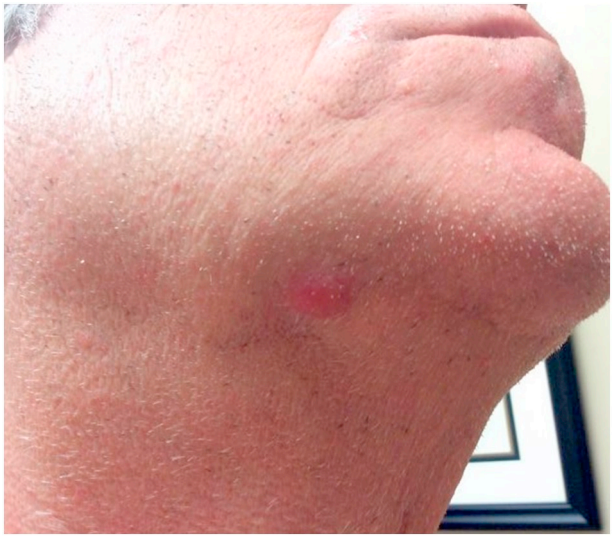

Fig. 2.1. Clinical image showing well-circumscribed, erythematous nodule on the upper neck.

3.4. Treatment, follow-up & outcome

Follow-up information was available for 202 patients with an average duration of 32.2 months (0.5–156 months). Patients underwent different treatment modalities including excision, oral or intralesional steroids, chemotherapy, radiation and cryotherapy shown in Table 3. Excision was the most successful with 59% of the cases achieving complete remission whereas steroid treatment was the least effective with only 3 cases exhibiting complete absolution. Eight patients had recurrence despite initial remission. Fifty-one patients did not undergo any treatment; 12 of which showed spontaneous regression of the lesion over an average interval of 38 months. A complete remission was noted in 85 patients while 130 patients had persistent disease.

3.5. Representative case reports

3.5.1. Case 1

A consult case regarding an HIV positive 61-year old female was received. The biopsy showed a dense dermal infiltrate of histiocytes

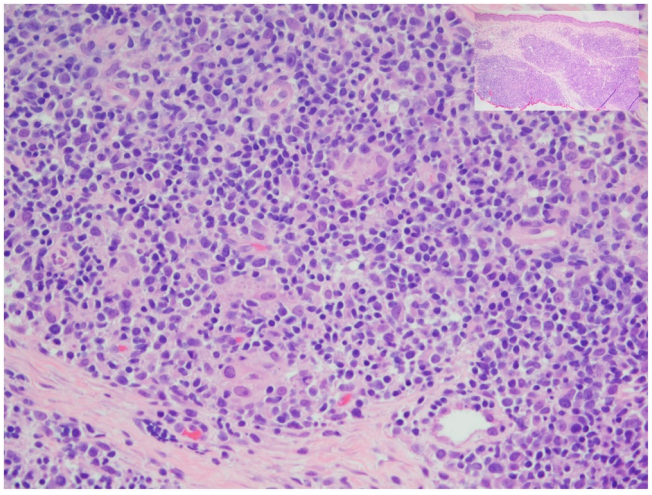

Fig. 2.2. An exuberant lymphoplasmacytic infiltrate masking the histiocytic cell populace and focal emperipolesis. Reactive, atypical immunoblasts and prominent vasocentricity can also be seen in the background (H&E, original magnification 400×). Inset image shows a dermal proliferation of inflammatory infiltrate in a nodular pattern (H&E, original magnification 100×).

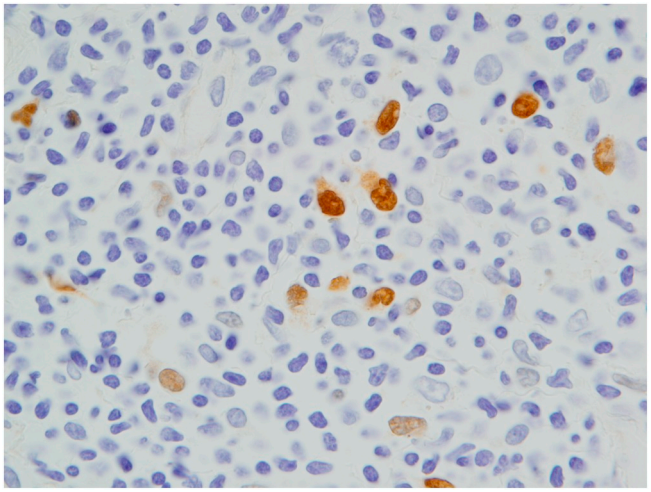

Fig. 2.3. Few histiocytes are highlighted by strong S-100 expression (S-100 IHC, original magnification 1000×).

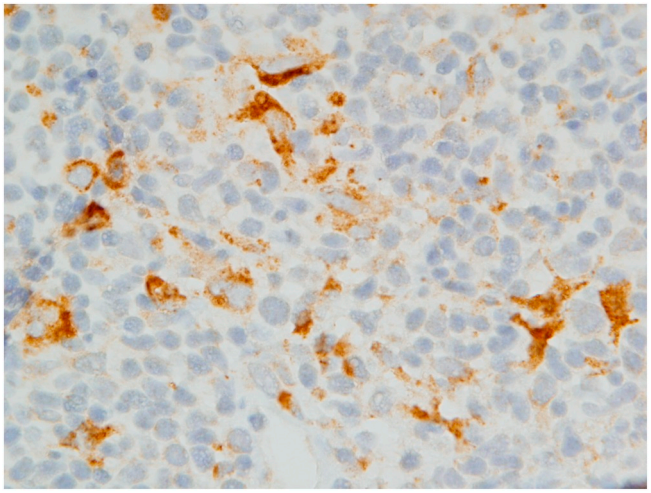

Fig. 2.4. CD68 highlighting the histiocytic cell population (CD68 IHC, original magnification 1000×).

with a background of inflammatory cells most notably lymphocytes, plasma cells and neutrophils. The histiocytes ranged in quality from being mononuclear to being multinucleated with abundant gray cytoplasm, some of which showed emperipolesis (Fig. 1.1). The histiocytic cell populace was highlighted by CD11c and Factor XIIIA corroborative of the derivation from resident dendritic monocytes with transdifferentiation features by virtue of the positivity for a scavenger macrophage cell type as revealed by CD68 and CD163 staining in concert with S-100 staining (Fig. 1.2). The cytology of the cells in RD is very distinctive and well exemplified by this case. The association of HIV disease with CRD is interesting and while a small number of cases in this series also showed HIV positivity, it is unclear if chronic HIV infection somehow stimulates macrophage activation.

3.5.2. Case 2

A 66-year old male with prior history of CRD presented with an erythematous solitary nodule on the right upper neck, measuring approximately 1 cm as shown in Fig. 2.1. The biopsy showed a multinodular lymphohistiocytic and plasmacytic infiltrate within the dermis with prominent vasocentricity. The histiocytes had both mononuclear and multinucleated forms with subtle emperipolesis that was further obscured by rich infiltrate of lymphocytes and plasma cells as seen in Fig. 2.2. There were also scattered immunoblasts, some of them were

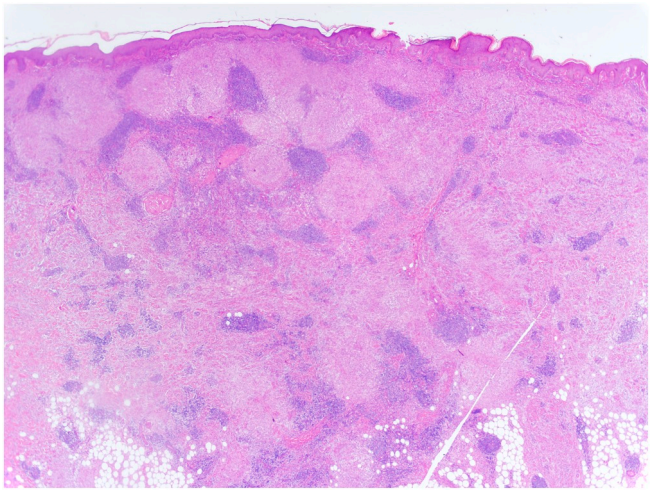

Fig. 3.1. A multinodular infiltrate of histiocytes and lymphoplasmacytic cells, involving the dermis and subcutaneous tissue (H&E, original magnification 20×).

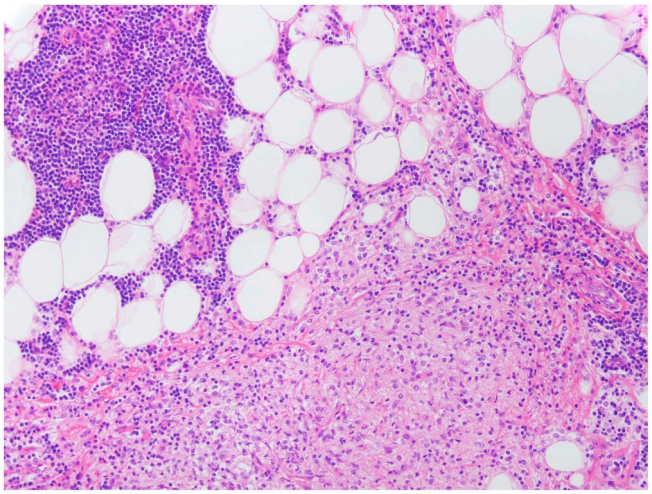

Fig. 3.2. Histiocytic proliferation with mono and multinucleated forms and emperipolesis, involving the subcutaneous tissue and infiltrating the fat lobule along with expansion of interlobular septal space. An extensive infiltrate of monomorphic lymphocytes can also be seen (H&E, original magnification 400×).

quite atypical with nuclear irregularity and eosinophilic nucleolation. While these atypical cells were positive for CD20 and CD30, no phenotypic expression of Bcl-2 and CD43 was seen and a reactive infiltrate was favored. Few of the histiocytoid cells stained positively for S-100 (Fig. 2.3), although a greater number of the histiocytes were positive for CD68 (Fig. 2.4) whereas CD1a was negative. This case was challenging due to exuberant reactive and atypical infiltrate masking the CRD, however smattered emperipolesis and immunohistochemistry confirmed the diagnosis.

3.5.3. Case 3

A biopsy of a subcutaneous mass in the arm of a 60-year old female was received as a consult. The biopsy of the mass showed extensive histiocytic infiltrate within the dermis and subcutaneous fat, intimately associated with lymphocytes, numerous plasma cells and rare neutrophils (Fig. 3.1). There were also sheets of monomorphic appearing histiocytes with watery cytoplasm disposed singly and in nodular aggregates throughout the dermis and subcutaneous fat with expansion of the interlobular septa (Fig. 3.2). The large histiocytes exhibiting

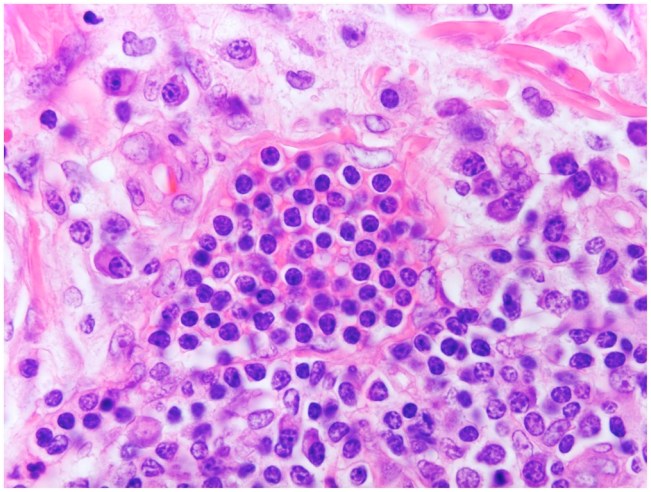

Fig. 3.3. Large histiocyte exhibiting emperipolesis (H&E, original magnification 1000×).

emperipolesis (Fig. 3.3) were highlighted by S-100, CD68 and Factor XIIIa (Fig. 3.4). There were also collections of monocytoid appearing cells that were highlighted by CD21 and CD11c, representing dendritic cells. Langerin and CD1a were negative. An extensive monomorphic B-cell infiltrate with areas of lambda light chain restriction in subcutis and without evidence of follicular center phenotype was noted. A few plasma cells were highlighted by IgM and IgG4 staining. A final diagnosis of cutaneous Rosai-Dorfman disease involving the subcutaneous tissue and concomitant marginal zone lymphoma was rendered. While this case demonstrated classic CRD phenotype including emperipolesis, this case was of much interest due to involvement of subcutaneous tissue, Factor XIIIa positivity and concurrent MZL presence.

4. Discussion

This study represents a comprehensive review of all cases of CRD patients published to date whereby 220 patients with purely cutaneous disease has been described. The goal of this study is to better define the clinical presentation, natural clinical course, and prognostic significance of CRD. The first comprehensive review of the Rosai-Dorfman disease (RD) was presented by Rosai and Dorfman themselves; they showed that skin was the most common extra nodal site involved [3]. Subsequent studies about purely cutaneous forms have been published over time with variable clinical presentation, classic histologic features and concurrent immunologic and infectious processes [6,7,10,13]. The demographics in this review are not much different from previous studies with Asian, Caucasian and African populations making the predominant ethnicities being affected. A comparison of P-CRD with CRD-S in Table 1 showed that while more than half of the pure CRD patients were Asians, those with systemic disease invariably affected Caucasians, Asians and Africans in almost equal proportions. The mean age at the time of presentation for CRD was 47 years with lesions present for an average length of 19 months. In P-CRD, there was a slight female preponderance and face was the most common site involved in contrast to a larger male population with no site predilection in CRD−S. Not surprisingly, those with systemic involvement also had a higher proportion of multifocal cutaneous disease, increased ESR and serum globulins.

The lesions of CRD on clinical examination, irrespective of extracutaneous involvement are heterogenous in their clinical presentation and may be indistinguishable from other histiocytic, inflammatory and tumorous proliferations. Underlying clusters of large foamy cells and multinucleated histiocytes causing effacement of the epidermis gives a yellowish-hue suggestive of a xanthomatous lesion while increased

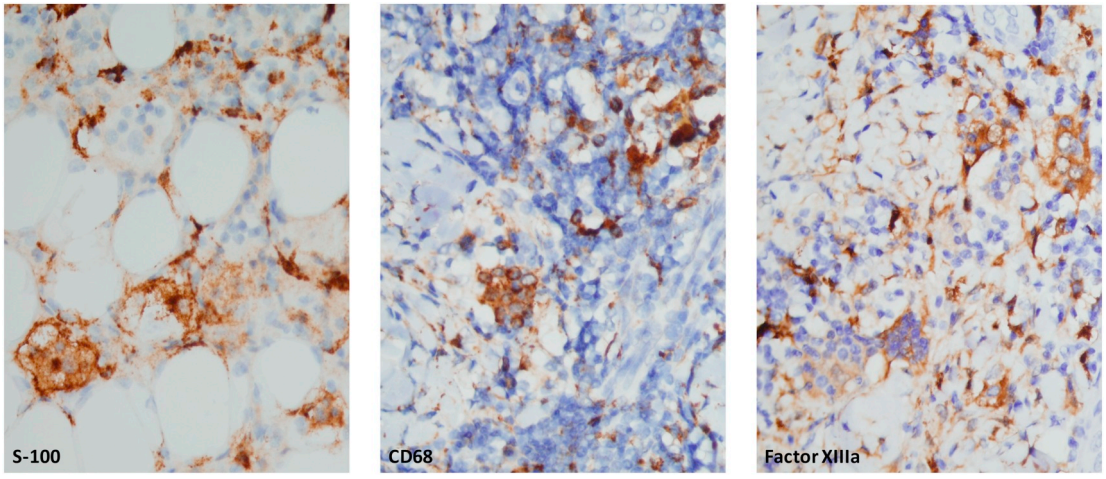

Fig. 3.4. Immunostains S-100, CD68 and Factor XIIIa highlighting histiocytes and emperipolesis (IHC S-100, CD68, Factor XIIIa, original magnifications 400×).

vascularity can be confused with hemangioma, vasculitis or pyogenic granuloma. Increased stromal reaction can give the resemblance to fibrous soft-tissue tumors [8,24]. Rarely, increased inflammation can cause ulceration, necessitating a histologic diagnosis to rule out a malignant process [8]. On histology, CRD exhibits classic findings of clusters or sheets of pleomorphic, large, foamy histiocytes with emperipolesis in a background of mixed inflammatory infiltrate [6]. However, inconspicuous emperipolesis, increased vascularity, plump endothelial cells and fibrosis along with an obscuring dense nodular lymphocytic infiltrate can result in a challenging diagnostic picture where the diagnosis of RD may not be initially apparent. It is important to remember that histiocytes seen in CRD are tissue macrophages that are mononuclear or multinuclear giant cells with immunoreactivity to S100, CD68, CD163 but negative for CD1a. Histiocyte progenitors are derived from bone marrow stem cells (CD34 positive) that differentiates into either CD14 positive or negative cells, depending on cellular microenvironment and presence of various cytokines [25]. CD14 negative cells acquire CD1a positivity and develop into Langerhans cells while CD14 positive cells are negative for CD1a and differentiates into either dermal dendrocytes (Factor XIIIa+, CD68+, CD163+, S-100-) or monocytes/tissue macrophages (CD68+, CD163+, S100+, Factor XIIIa-) [25]. With any histiocytopathy syndrome derived from terminal cells such as CRD, transdifferentiation to other histiocytic cells is not uncommon resulting in histiocytopathies exhibiting an overlapping mixed morphology and phenotype. We have seen a number of CRD cases at our institution that are positive for Factor XIIIa, an example of which is shown in Fig. 3.4. Cases of CRD manifesting an overlapping reticulohistiocytoma are also seen at our institution. The prognostic implications of distinguishing concurrent disease from overlapping phenotypic features cannot be overstated as cases of concurrent LCH and CRD are also reported in the literature [10,16-19].

This immunohistochemical profile is easily verifiable to differentiate CRD from LCH based on the positivity of the infiltrate for langerin and CD1a in the setting of LCH, a potentially fatal disease. In the closely related indeterminate cell proliferative disorder where these cells do not express langerin and may not express S100, the positivity for CD1a would support the diagnosis of indeterminate cell proliferative disorder. Although one case showed aberrant positivity for CD1a, electron microscopy in such a scenario could be useful; elaborate Golgi and interdigitating cytoplasmic protrusions support a diagnosis of CRD while Birbeck granules are consistent with LCH [26,27].

CRD has also been associated with different types of lymphomas with one representative case from our institution and two cases in this series, presenting with synchronous or metachronous marginal zone lymphoma at the same site [20,28]. One of these cases underwent chemotherapy for CRD which could have played a role in the development of secondary neoplasm. However, many cutaneous lymphomas develop in a background of reactive lymphoid hyperplasia when there is a state of iatrogenic and endogenous immune dysregulation. We have seen cases of CRD with evidence of light chain restricted plasma cells but no other conclusive features of MZL. Hence, we would offer the espousal that cases of concurrent CRD and MZL likely represent the development of MZL in a background of lymphoid hyperplasia associated with CRD.

The question also arises as to whether or not one should consider CRD as a form of cutaneous IgG4 sclerosing disease. At least in some cases there are increased numbers of IgG4 positive plasma cells and in fact the extent of plasma cell infiltration would qualify as being consistent with the number of plasma cells seen in IgG4 positive sclerosing disease. IgG4-related disease has a myriad of manifestations. There is a primary cutaneous form of the disease which could be morphologically very similar to CRD including a dense lymphoplasmacytic infiltrate, oftentimes accompanied by patterned fibrosis and a characteristic fibrosing plasma cell rich phlebitis and arteritis in the subcutaneous fat [29]. The main distinguishing feature supportive of CRD would of course be the extent of histiocytic infiltration, the presence of emperilopolesis and the classic phenotypic profile. However, the distinction between a form of IgG4 sclerosing disease and an inflammatory cell rich histiocytopathy is not always very straightforward, best exemplified by case of adult onset orbital xanthogranulomatous disease [30]. These cases exhibit significant fibrosis and as well as many IgG4 positive plasma cells.

H-syndrome, an autosomal recessive syndrome has also a similar histopathology as CRD, attributable to mutations in SLC29A3 gene [31]. The molecular alteration can be helpful in distinguishing with overlapping clinical and histologic phenotypes. However, the mutation in SLC29A3 gene is also reported in Faisalabad histiocytosis, also an autosomal recessive syndrome with skin lesions and overlapping clinical and histologic characteristics with H-syndrome and RD. [32] Interestingly, familial form of RD is also noted to harbor mutation in SLC29A3 gene, creating a “SLC29A3 spectrum disorder” [32]. The protein encoded by this gene is ENT3 and when deficient leads to defective apoptotic clearance resulting nucleoside buildup, elevated intralysosomal PH and defective macrophage function. Although more studies are needed to gain further insights in clinical variability and molecular pathogenesis, these syndromes highlight the importance of clinicopathologic correlation for correct categorization of histologic lesions similar to RD.

Mycobacterium kansasii infection of the skin can manifest a morphology that closely parallels CRD including emperipolesis and a similar phenotypic profile with S100 and CD68 positivity and lack of staining for CD1a [33]. Half of the cases in this review showed striking

neutrophilic infiltration with frank abscess formation which could be confused with an infectious based trigger [34].

Despite the recognition of RD for almost six decades, the pathogenesis is still unclear. The presence of functionally activated histiocytes is thought to be a triggered response due to frequent occurrence of RD with immune disorders, lymphomas and infectious triggers. However, no evidence of a direct link exists. Recently, three different studies have shown mutually exclusive mutations of ARAF, NRAS, KRAS and MAP2K1 in a proportion of RD cases by next generation sequencing [35,36,37]. These genes are involved in the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway which is one of the key regulatory pathways required for survival and proliferation [38]. Cases harboring MAP2K1 mutations also showed over-expression of downstream p-ERK by immunohistochemistry, further supporting activation of MAPK/ERK pathway [36]. One of these cases also showed a substantial response to treatment with MAPK-inhibitor drug [37]. Although more studies are needed, these genomic alterations leading to production of inflammatory molecules such as macrophage colony-stimulating factor (M-CSF), IL-1β, IL-6, and tumor necrosis factor-α through signal transduction are proposed to play a pivotal role in development of this disease [39]. Diminished T-cell activation through cytokines production, decreased antigen presentation due to downregulation of class II major histocompatibility complex on macrophages and phagocytosis of competent lymphocytes produces dysfunctional macrophages and intralesional immunosuppressed environment [11,12]. This proposition was further supported by assessment of CRD cases found in conjunction with Crohn's disease that share the similar macrophage dysfunction and immunosuppression due to elevated circulating M-CSF [15].

The findings of genomic analysis while opening doors for targeted therapy can be particularly useful in extensive and refractory cases. Generally, CRD is an indolent and benign disease that has a favorable outcome, even in those not treated. However, majority of the cases in this review were treated with one or more options with excision being the most effective for both solitary and multifocal disease. High dose thalidomide, vincristine, methotrexate, acitretin, isoretinoid and dapsone have also been used with measurable success for aggressive and refractory disease. Steroids have shown to be least effective with at least 2 cases undergoing remission after stopping its use.

5. Conclusions

This review provides a detailed assessment of CRD with updated information on demographics, clinical variability, diagnostic pitfalls, pathogenesis and newer treatment options. The cognizance of these features should be helpful in correct diagnosis of this rare entity.

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Conflicts of interest

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