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Cutaneous Rosai–Dorfman disease: clinicopathological profiles, spectrum and evolution of 21 lesions in six patients

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Summary

Background An uncommon histiocytosis primarily involving the lymph nodes, Rosai–Dorfman disease (RDD, originally called sinus histiocytosis with massive lymphadenopathy) involves extranodal sites in 43% of cases; cutaneous RDD (C-RDD) is a rare form of RDD limited to the skin. The clinicopathological diagnosis of C-RDD may sometimes be difficult, with different clinical profiles from those of its nodal counterpart, and occasionally misleading histological pictures. There have been few multipatient studies of C-RDD and documentation of its histological spectrum is rare.
Objectives To identify the clinical and histopathological profiles, associated features, and the chronological changes of this rare histiocytosis.
Methods From 1991 to 2002, patients diagnosed as having C-RDD were collected in four academic hospitals. Clinical presentations, treatments, and courses of each case were documented. In total, 21 biopsy specimens obtained from these patients were re-evaluated and scored microscopically with attention to the uncommon patterns and chronological evolution both clinically and histologically.
Results We examined six patients with C-RDD, three men and three women. The mean age at the first visit was 43·7 years. The clinical presentations were mostly papules, nodules and plaques, varying with the duration and depth of lesions. Although the anatomical distribution was wide, the face was most commonly involved. Evolutional changes were identified clinically, as the lesions typically began with papules or plaques and grew to form nodules with satellite lesions and resolved with fibrotic plaques before complete remission. No patient had lymphadenopathy or extracutaneous lesions during follow-up (mean 50·5 months). At the end of follow-up, the lesions in four patients had completely resolved irrespective of treatment; two patients had persistent lesions. The histopathological pattern of the main infiltrate, the components of cells and the stromal responses showed dynamic changes according to the duration of lesions. The characteristic Rosai–Dorfman cells (RD cells) were found in association with a nodular or diffuse infiltrate in 15 lesions (71%). Four lesions (19%) demonstrated a patchy/interstitial pattern. One lesion (5%) assumed the pattern of a suppurative granuloma. RD cells were less readily found in these atypical patterns. Conspicuous proliferation of histiocytes associated with RD cells was found in three lesions, including xanthoma, localized Langerhans cell histiocytosis and xanthogranuloma. Along with lymphocytes, plasma cells were present in all lesions, often in large numbers with occasional binucleated or trinucleated cells. Variably found in the lesions were neutrophils (nine lesions, 43%) and eosinophils (13 lesions, 62%). The former occasionally formed microabscesses, while the latter were often few in number. Vascular proliferation was a relatively constant feature (90%). Fibrosis was found in 10 lesions (48%).

Conclusions Our study further confirms that C-RDD is a distinct entity with different age and possibly race distributions from RDD. Compared with its nodal counterpart, C-RDD demonstrates a wider histopathological spectrum with different clinicopathological phases depending on duration of the lesions. Awareness of these features is helpful in making a correct diagnosis. The associations of C-RDD with other histiocytoses may have important implications for the pathogenesis of this rare histiocytosis.

Rosai–Dorfman disease (RDD), or sinus histiocytosis with massive lymphadenopathy (SHML), was first described by Destombes in 1965 but was recognized as a unique entity by Rosai and Dorfman in 1969.[1,2] It is a benign disorder that primarily presents with lymphadenopathy. Extranodal involvement has been reported in 43% of cases and the skin was the most common site.[3] In 1978, Thawerani *et al.* reported a case of purely cutaneous RDD (C-RDD).[4] Thereafter, around 70 cases of RDD confined to the skin, mostly single case documents, have been reported.[5–19]

The characteristic histiocyte, the 'Rosai–Dorfman cell' (RD cell), is the diagnostic hallmark for RDD. It is histologically recognized by abundant amorphous cytoplasm, indistinct borders, and a large vesicular nucleus with prominent nucleoli. Phenotypically, RD cells uniquely express the monocyte/macrophage markers such as lysozyme, Mac-387 and CD68, as well as the dendritic/Langerhans cell marker S-100.[20]

The presence of pathognomonic RD cells remains the diagnostic criterion for C-RDD. Despite its unique characteristics, the diagnosis of C-RDD is hampered by its variable clinical presentation, misleading histopathological patterns, and the absence of lymphadenopathy. A wide variety of erroneous pathological diagnoses, e.g. granuloma annulare (GA), granulomatous diseases and inflammatory pseudotumour, has been found in the literature, especially in cases showing atypical features.[8,9,17] Owing to the rarity of this disease, there have been few multipatient studies of C-RDD.[5,16,18,19] Moreover, a systematic and quantitative documentation of its histological spectrum and evolution is still lacking.

We report our study on the clinicopathological profiles and disease spectrum of Chinese patients with C-RDD. In addition, we analysed the histological attributes and paid special attention to the evolution of C-RDD through long-term follow-up and sequential biopsies.

Materials and methods

Patients and clinical analysis

A search of the files in dermatology and pathology departments of Taipei Medical University Hospital, Wan-Fang Hospital, Shing-Kong Hospital and Veterans General Hospital (Taipei) disclosed six cases of C-RDD from 1991 to 2002. The diagnoses were made in either initial or subsequent biopsies, and at least 2 years of follow-up showed no evidence of extracutaneous involvement. Of six patients, five received multiple biopsies from different sites or at different time points. Some of these were performed because a definite diagnosis was still in doubt; others for the purpose of chronological follow-up and/or staged surgical removal of lesions. Clinical history, photography, type and duration of each lesion, associated abnormalities, laboratory and image studies and follow-up course were reviewed.

Histopathological and immunohistochemical analysis

Each biopsy specimen from these patients was reviewed with light microscopy on the original haematoxylin and eosin sections and some on new sections. The diagnostic criteria for RDD were: (i) the presence of large, pale-stained histiocytes with evidence of emperipolesis, and (ii) S-100 positivity of these histiocytes. Each lesion was scored for a series of histological features including epidermal changes (atrophy, acanthosis, scales/crusts), pattern of main infiltrate, number of RD cells, components of inflammatory cells (plasma cells, neutrophils, eosinophils), presence of lymphoid follicles, vascular proliferation, and fibrosis. The scoring methods were based on those used by Fung[21] and Thawenrani *et al.*[4] The quantity of lymphocytes was not evaluated as they are universally present in acute and chronic inflammatory disorders. Immunohistochemical studies included S-100 and CD1a stains in each lesion. CD68 staining was performed in 12 of 21 lesions. In addition, UCHL-1 (as a T-cell marker), CD20 (as a B-cell marker), κ and λ chains (all of the above immunohistochemical stains were from DakoCytomation, Glostrup, Denmark), periodic acid–Schiff (PAS), Gomori methenamine silver (GMS; for fungi), Gram (for bacteria), Giemsa (for protozoa), acid-fast (for mycobacteria) and alcian blue (pH 2·5, for intercellular mucin) stains were variably performed when necessary. For convenience, each biopsy was given a number and a letter. The number corresponded to the patient from whom the biopsy was taken, and the letter indicated the order of biopsy in time sequence.

Results

Clinical profiles and lesional types

The male/female ratio of our series of six Chinese patients was 1 : 1. The mean age at diagnosis was 43·7 years (range 27–56). Five patients had multiple lesions. The lesions sometimes formed coalescent nodules and pustules, causing a disfiguring appearance (Fig. 1a). One patient had a single lesion. The most common site of lesions was the face, followed by

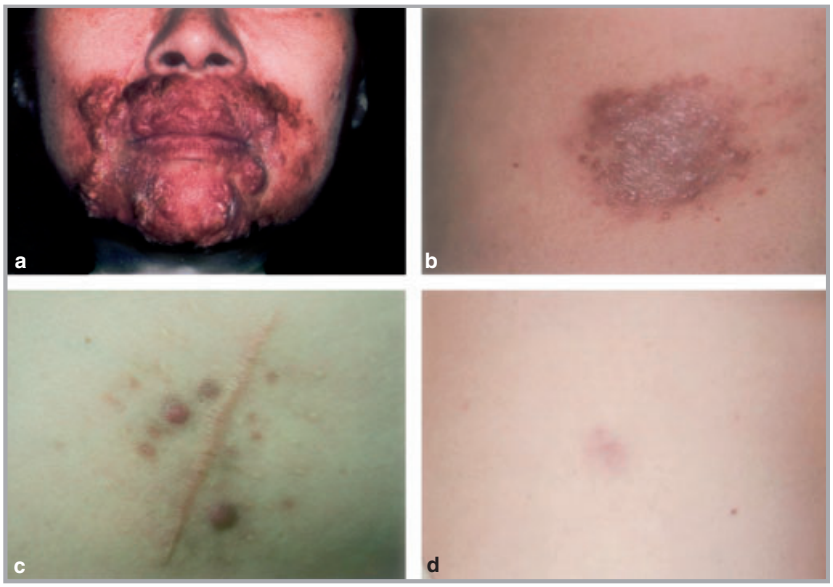

Fig 1. (a) Disfiguring nodules on the face (patient 5). (b) Dark-red to violaceous plaques dotted with papules on the main lesion and in the periphery (patient 3). (c) Recurrent lesions in the vicinity of previous operation scar (patient 2). (d) Tender subcutaneous nodule on the back (patient 2).

the thighs, back, chest, flank and shoulder. The clinical morphology of lesions ranged from papules, nodules, plaques and patches to pustules, depending on the duration and depth of lesions. Lesions were mostly erythematous, but hyperpigmented (dark red) (Fig. 1b) or yellowish lesions were also noted. Different types of lesions occurred in the same patient, and covered wide anatomical locations. The lesions were all asymptomatic except one, which was a small tender nodule on the back (Fig. 1d). One patient had iron deficiency anaemia, diabetes and hyperlipidaemia (patient 1). Others were generally in good health.

The patients were monitored clinically with a mean follow-up period of 50·5 months (range 12–122). During follow-up, two had recurrent or new lesions (Fig. 1c); the recurrent lesions were excised or resolved spontaneously in a few months. At the end of follow-up, four patients (patients 1, 2, 4 and 6) were free of lesions after excision or spontaneous resolution. Two patients (patients 3 and 5) had persistent lesions at the end of follow-up (40 months and 12 months, respectively).

At the time of diagnosis or during follow-up, none of the six patients had lymphadenopathy or extracutaneous involvement according to physical and imaging studies including X-ray, computed tomographic scan and echography. Laboratory tests revealed elevated erythrocyte sedimentation rate in two patients and positive Epstein–Barr virus (EBV) IgG titres in one. Other studies including serum immunoelectrophoresis, Venereal Disease Research Laboratory test, human immunodeficiency virus (HIV) and antibody against cytomegalovirus were all negative. Other relevant clinical data are summarized in Table 1. Therapeutically, one patient received intralesional corticosteroid in one lesion, which showed little response (patient 1). Another patient received liquid nitrogen therapy in some unbiopsied lesions, two or three times with a 2-week interval; this seemed to accelerate the resolution of lesions (patient 2).

Hisopathological findings

In total, 21 lesions were biopsied. Except for patient 4, multiple biopsies were performed in each patient (range two to seven). Three patients received sequential skin biopsies (patients 1, 2 and 5); sequential biopsies from the same lesion were performed in two of these patients (patients 1 and 2). Biopsies were performed from different lesions at the same time in two other patients (patients 3 and 6). The remaining patient received one biopsy only. The mean duration of the biopsied lesions was 11·8 months (range 1–30).

The histological patterns and scoring of each histological attribute are summarized in Table 2. The changes were confined to the dermis in 15 lesions, and involved both the dermis and the subcutaneous tissue in others. Subcutaneous lesions extended from the dermis, with lobular rather than septal infiltration. Three patterns of the main infiltrate were identified, namely nodular/diffuse pattern, patchy/interstitial pattern and suppurative granuloma pattern. The predominant pattern, nodular/diffuse pattern ($n = 15$) showed a dense infiltrate covering the whole or the most prominent area of the dermis/subcutaneous tissue (Fig. 2a), some cells were less cohesively arranged in a fibrohistiocytic background. The borders were often infiltrative. In the patchy/interstitial pattern ($n = 4$, biopsies 1A, 3A, 3B and 6C) the cells were scattered perivascularly or interstitially in the dermis/subcutaneous fat tissue (Fig. 2b). One lesion demonstrated a suppurative granuloma pattern ($n = 1$, biopsy 1B), consisting of multiple neutrophilic abscesses surrounded by histiocytes (Fig. 2c). In a 24-month-old lesion (biopsy 2F), no RD cells were found, showing simply a superficial perivascular infiltrate with prominent fibrosis.

In the main infiltrate, the pathognomonic RD cells were seen in variable numbers: some were scattered between the inflammatory cells, while others were present in sheets. These cells had voluminous, vacuolated cytoplasm with one or two nuclei. The cell borders were occasionally indistinct. Multi-

Table 1 Clinical features of patients with cutaneous Rosai–Dorfman disease (C-RDD)

Patient	Age (years)/sex at the time of presentation	Clinical presentation	Clinical diagnosis	Provisional pathological diagnoses before RDD was diagnosed	Number of biopsies	Site and duration of lesions at biopsy	Follow-up period and course
1	45/F	Three nodules and papules on cheeks	Lymphocytoma cutis	Xanthogranulomatous inflammation; suppurative granuloma suggestive of infection	5	1A (L cheek): 4 months 1B (L cheek): 6 months 1C (L cheek): 9 months 1D (L cheek): 11 months 1E (L cheek): 18 months	41 months. Spontaneously resolved or resolved with liquid nitrogen or totally excised without recurrence
2	41/F	Nodule on L breast. Subsequent nodules on back (tender), R flank and L thigh. Another one plaque and three papules on face	Breast cancer (breast lesion). Histiocytosis (trunk and face lesions)	Plasma cell granuloma	7	2A (L breast): 3 months 2B (nose): 6 months 2C (R back): 6 months 2D (R cheek): 1 month 2E (nose): 12 months 2F (nose): 24 months 2G (L thigh): 1 month	51 months. Most resolved spontaneously or resolved with liquid nitrogen. Others (including new and recurrent lesions) excised without further recurrences
3	40/M	Three dark- red plaques/ patches on R thigh, L flank and chest	Deep fungal infection	Cutaneous lymphoid hyperplasia; interstitial granulomatous inflammation	2	3A (L flank): 8 months 3B (R thigh): 8 months	40 months. Spontaneously resolved or persisted (L flank)
4	53/M	One nodule on R thigh	Epidermal cyst vs. dermatofibrosarcoma protuberance	RDD	1	4A (R thigh): 3 months	37 months. Excision without recurrence
5	56/F	Multiple papules and plaques with scales and tiny pustules on face	Granulomatous disease, blastomycosis	Granulomatous disease	2	5A (R face): 12 months 5B (R face): 13 months	12 months. Persistent lesions
6	27/M	Two dark-red nodules on R shoulder and upper back	Skin tumour	Primary cutaneous plasmacytoma	4	6A (R supraclavicular): 24 months 6B (back): 24 months 6C (R supraclavicular): 25 months 6D (R supraclavicular): 30 months	122 months. Spontaneously resolved or excision without recurrence

Table 2 Histological features and the types/durations of their corresponding clinical lesions in 21 biopsies

Attributes		No. (%)	No. (%)	Clinical lesional types	Mean duration of lesion at biopsy (months)
Epidermal changes		16 (76%)	Erosion/crusting 3 (14%)		10
			Acanthosis 3 (14%)		11
			Hypermelanosis 3 (14%)		6
			Attenuation of rete ridges 7 (33%)		17
Type of main infiltrate	Nodular/diffuse	16 (76%)	15 (71%)	Nodules/papules 9; plaques 6	15
			Nodular + xanthoma 1 (5%)	Nodule 1	30
	Patchy/interstitial	4 (19%)		Plaques 3; patches 1	7
	Suppurative granuloma	1 (5%)		Nodule 1	6
Cells	RD cells	20 (95%)	Few 4 (19%)		11
			Moderate 11 (52%)		11
			Many 5 (24%)		13
	Plasma cells	21 (100%)	Rare 1 (5%)		24
			Few 2 (10%)		4
			Many 18 (86%)		12
	Neutrophils	9 (43%)	Rare 1 (5%)		8
			Few 5 (24%)		8
			Many 3 (14%)		10
			Absent 12 (57%)		14
	Eosinophils	13 (62%)	Rare 4 (19%)		6
			Few 9 (43%)		17
			Absent 8 (38%)		9
	Foam cell	2 (10%)			24
Other features	Increased vascularity	19 (90%)	Present 19 (90%)		10
			Absent 2 (10%)		25
	Fibrosis	10 (48%)	Present 10 (48%)		16
			Absent 11 (52%)		6

All parameters were evaluated in haematoxylin and eosin-stained sections except Rosai–Dorfman cells (RD cells), in which S-100-stained sections were used. The numbers of RD cells were scored in a 40 × objective and the most populated focus was selected: few, < 10; moderate, 10–20; many, > 20. Inflammatory cells were scored by the approximate number of interstitial or perivascular inflammatory cells in most fields using a 20 × objective: none/rare, 0–1; few, 1–5; many, > 5.[21]

nucleated RD cells were seen in three lesions. In two lesions, RD cells were found within lymphatic spaces. Emperipolesis was variably found in 18 lesions (86%) after a thorough examination. In some lesions, RD cells were not seen in the original section and thus hampered diagnosis but the new sections showed RD cells. S-100 stain often highlighted the RD cells and helped them 'pump out' in a vacuolated background.

Notably, features of xanthoma were seen in one lesion (biopsy 6D), in which a large number of frank foam cells was seen in the infiltrate, spanning a pinkish zone of 'degenerating RD cells' from the nodular infiltrate containing otherwise typical RD cells (Fig. 3). In biopsy 1D, localized Langerhans cell histiocytosis was seen, with proliferation of histiocytes showing coffee bean-shaped nuclei and the presence of Birbeck granules. We have reported this particular finding earlier.[15] In addition, we observed sheet-like aggregates of smaller histiocytes in close proximity with RD cells in biopsy 4A (Fig. 4). These histiocytic cells, round to oval-shaped, had eosinophilic cytoplasm and showed no evidence of emperipolesis. Phenotypically, CD68 was focally positive; S-100 and CD1a were negative.

Plasma cells were seen in all lesions, often in large numbers and some with binucleated or trinucleated appearances. Some were giant or bizarre-shaped. Russell bodies were occasionally seen. Neutrophils were present in nine lesions (43%) with three forming microabscesses. Thirteen lesions (62%) had eosinophils, generally few in number. Increased vascularity, often with plump endothelium, was a fairly common finding (n = 19, 90%). Fibrosis was present in about half of the lesions (n = 10, 48%). PAS, GMS, Gram, Giemsa and acid-fast stains, performed in five lesions, did not detect any microorganisms. Other cardinal histological features are illustrated in Table 2.

Immunohistochemical studies

The large, pale-stained RD cells were all S-100+ and CD1a–. In 12 lesions stained with CD68, about 40–50% of RD cells were weakly to moderately positive. Others were negative. In some lesions, RD cells were positive for CD68 in one area and negative in another. In addition, scattered CD68+ mononuclear cells were found in 10 of 12 lesions. These cells

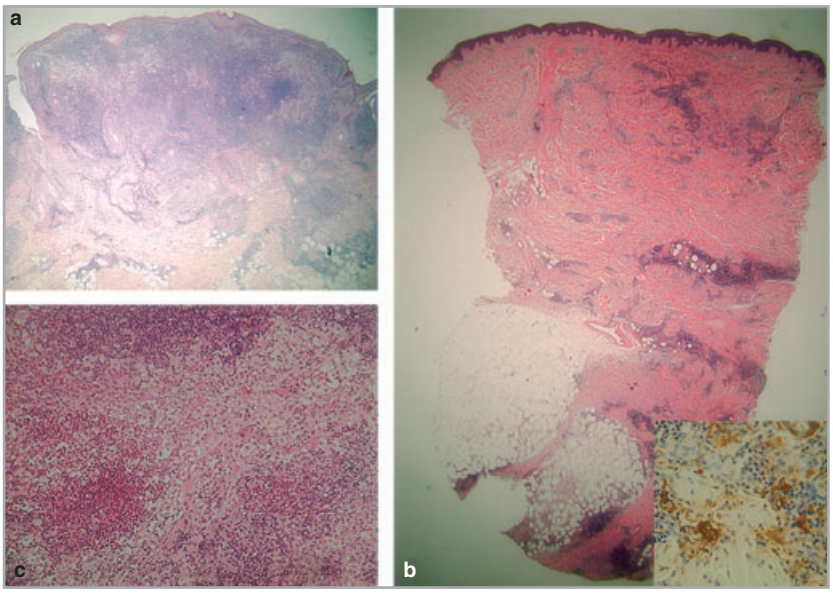

Fig 2. Main histological patterns of cutaneous Rosai–Dorfman disease. (a) Nodular/diffuse pattern (biopsy 1C); (b) patchy/interstitial pattern (inset: Rosai–Dorfman cells revealed by S-100 stain in the patchy/interstitial infiltrate) (biopsy 3A); (c) suppurative granuloma pattern (biopsy 1B).

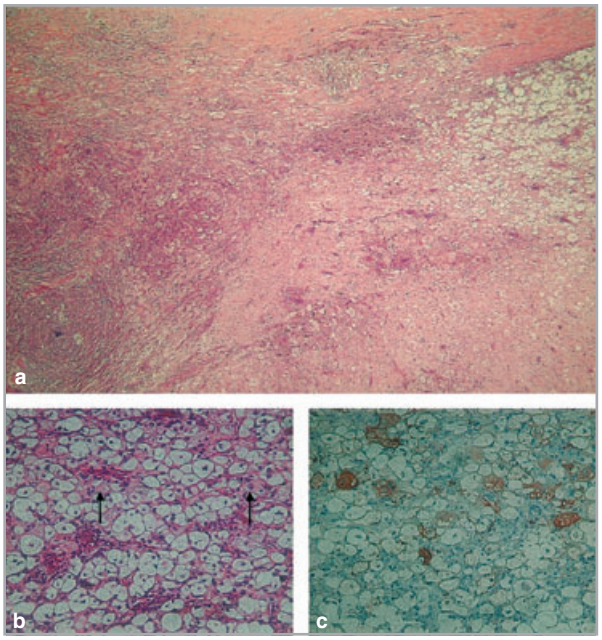

Fig 3. (a) Lesion with xanthomatous features (biopsy 6D). Collections of foam cells are on the right, and the main infiltrate containing pale-stained typical Rosai–Dorfman cells scattered within the infiltrate is on the left, spanning a 'transitional zone' where the cells are pink and 'degenerating'. (b) Close-up of the xanthoma area showing frank foam cells with centrally located small nuclei and abundant cytoplasm. Some pink cells are also seen (arrows). (c) These pink foam cells in this area are S-100+ while frank foam cells were S-100– (a,b, haematoxylin and eosin; c, S-100 stain).

were smaller than macrophages or RD cells and some showed plasmacytoid morphology (Fig. 5). In four lesions stained with UCHL-1 and CD20, both were positive in the lymphocytic infiltrates. Stains for κ and λ chains were performed in three lesions and showed the polyclonal nature of the plasma cells.

Chronological evolution and clinicopathological correlation

The chronological change of clinical lesion correlated with the lesion duration and type. In patients 1 and 2, lesions clearly 'matured' and resolved within months to 2 years irrespective of treatment. As shown in Figure 6, lesions on both cheeks of patient 1 demonstrated serial changes clinically. The lesions on the right cheek appeared 2 months earlier than those on the left cheek, and therefore resolved sooner. The histological evolution was also best exemplified in patient 1, in whom five sequential biopsies were performed from the left cheek lesion. Table 3 shows the evolution of lesional size and histological attributes from the five biopsies.

Generally, the amount of plasma cells, fibrosis and vascularity changed chronologically with the duration of lesions. The mean duration of those with few plasma cells was 4 months. The number of plasma cells increased considerably by 12 months and they were rarely seen in 'old' lesions (mean 24 months). Fibrosis was evident in lesions with a mean duration of 16 months; those without fibrosis had been present for a mean of 6 months. Increased vascularity was noted in lesions with an mean duration of 10 months and was absent in those of 25 months' duration (Table 2).

The histological patterns correlated with clinical types. The lesions showing a patchy/interstitial pattern pathologically were all plaques or patches clinically, while those of nodular/diffuse pattern appeared predominantly as nodules or papules.

Discussion

Among four series in the literature collecting more than three patients with C-RDD, three were clinicopathological studies[16,18,19] and one compared the histopathology of cutaneous lesions in cases with or without nodal involvement.[5] The

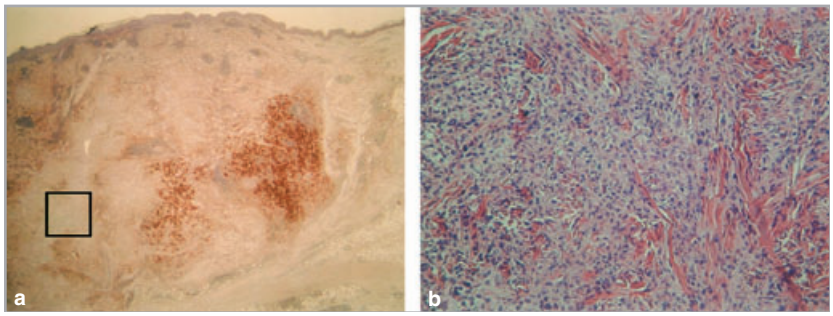

Fig 4. (a) In patient 4, proliferations of S-100– histiocytes are seen along with the S-100+ Rosai–Dorfman cells (RD cells). (b) In closer view of the square marked in (a), these histiocytes are smaller than RD cells with moderately eosinophilic cytoplasm (a, S-100 stain; b, haematoxylin and eosin; both from biopsy 4A).

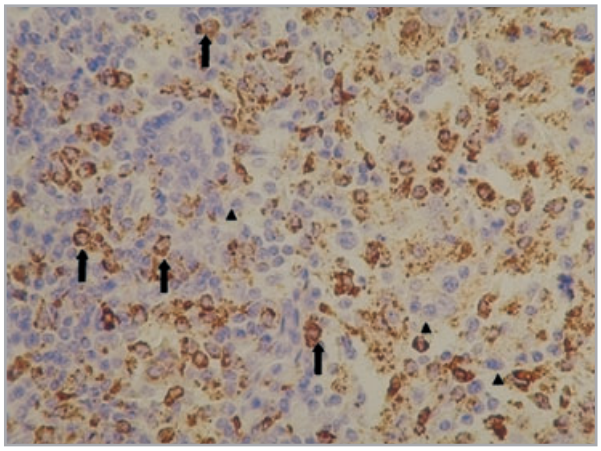

Fig 5. A significant proportion of the smaller mononuclear cells is positive for CD68 (arrows). These mononuclear cells are larger than lymphocytes with moderately abundant cytoplasm. Some plasma cells can be identified in the background (arrowhead); they are negative for CD68. The Rosai–Dorfman cells are weakly positive (CD68 stain, from biopsy 1E).

significance of our study is threefold. Firstly, to the best of our knowledge, ours is the first to analyse quantitatively all aspects of histopathological features of C-RDD and its clinical correlations. Secondly, through chronological findings, we documented a broader histopathological spectrum of C-RDD. Thirdly, we propose a unified concept for C-RDD based on its clinical, histological and immunohistochemical characteristics.

Our patients' mean age (43·7 years) and the male/female ratio (1 : 1) are basically in keeping with previous series of C-RDD: 46·7 years and 1 : 1·7. Ethnically, Asians constitute the majority in 49 patients with available ethnicity (Asian 34, white nine, black six), including the two all-Asian series of Lu *et al.*[19] and the present series. The older age group, M/F ratio and ethnic background of C-RDD are distinctly different from those of systemic RDD, which has a marked predilection for the first and second decades of life, slight male predominance (M/F 1·4 : 1) and is commonly seen in Africans.[3] In addition, systemic symptoms (fever, malaise), cervical lymphadenopathy, haematological and immunological abnormalities were commonly seen in systemic RDD but were only occasionally seen in C-RDD.[2,3]

Why are clinical profiles of C-RDD and systemic RDD broadly different? Other histiocytic syndromes showing different clinical profiles in their systemic and cutaneous forms are noted. For example, juvenile xanthogranuloma usually consists of multiple skin lesions, and occasionally involves other organs such as the eyes, central nervous system and bone, while the adult counterpart is often solitary without systemic involvement.[22] Human herpesvirus 6 (HHV-6) DNA and late antigens were frequently detected in the lesions of systemic RDD,[23,24] but not in the tissue samples of C-RDD except in one report.[9] This may suggest that HHV-6 plays a pathogenic role in systemic RDD but is less likely to be directly involved in C-RDD.

C-RDD may have associated laboratory abnormalities, including uveitis, systemic lupus erythematosus, HIV positivity,

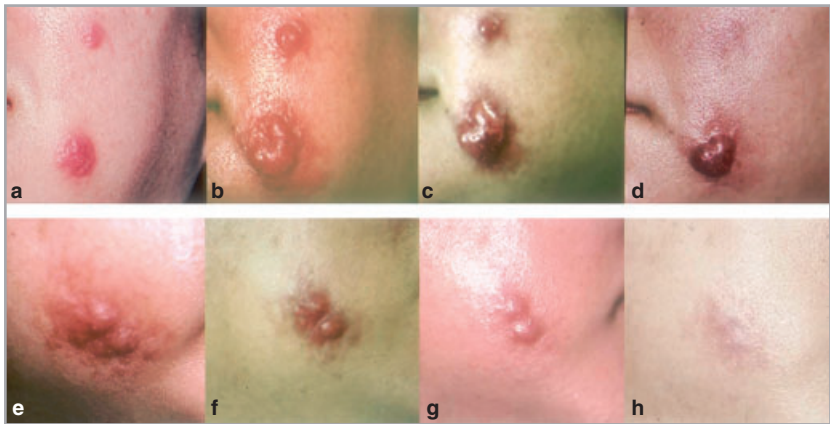

Fig 6. Upper panel (a–d): left cheek lesions of patient 1. Lower panel (e–h): right cheek lesions of patient 1. The durations of lesions at the time the photographs were taken were 4, 9, 11 and 18 months for a–d, and 6, 11, 13 and 20 months for e–h, respectively.

Table 3 Sequential clinicopathological changes in patient 1

Biopsy number	1A	1B	1C	1D	1E
Site	L cheek	L cheek	L cheek	L cheek	L cheek
Duration of lesion (months)	4	6	9	11	18
Lesional sizes (cm)[a]	1·2	N/A	2·8	2·5	1·3
Pattern of main infiltrate	P/I	SG	Diffuse	Diffuse	Nodular
RD cells[b]	Moderate	Moderate	Moderate	Many	Many
Plasma cells[b]	Few	Moderate	Many	Many	Many
Neutrophils[b]	Absent	Many	Few	Few	Few
Germinal centre	Absent	Absent	Present	Present	Present
Lipidization	Absent	Absent	Absent	Absent	Present
Vascularity[c]	+	++	++	+++	++
Fibrosis[c]	–	–	+	+	++

P/I, patchy/interstitial; SG, suppurative granuloma; N/A, not available; RD cells, Rosai–Dorfman cells. [a]The distance of the longest dimension of the lesion. The decrease of size in 1D and 1E was attributed partly to previous biopsies. [b]The numbers of RD cells were scored in a 40 × objective and the most populated focus was selected: few, < 10; moderate, 10–20; many, > 20. [c]Scoring of fibrosis and vascularity: –, normal or not increased; +, scantly increased; ++, moderately increased; +++, markedly increased.[4]. Inflammatory cells were scored by the approximate number of interstitial or perivascular inflammatory cells in most fields using a 20x objective: none/rare 0–1; few 1–5; many >5.

diabetes, hyperlipidaemia, aortic stenosis, positive serology for *Borrelia*, elevated EBV IgG titres and anaemia.[16,18,19] Orbital involvement is not uncommon in systemic RDD (12%) and may manifest years before lymphadenopathy.[25] Thus, uveitis found in several reports of C-RDD may represent systemic RDD with skin and orbital involvement rather than true C-RDD.[11,14,16,19]

We demonstrate the nodular/diffuse pattern (76% of lesions) as the main histological pattern. By carefully evaluating all the biopsies of six patients, we characterized other histological patterns of C-RDD, namely patchy/interstitial, suppurative granuloma (neutrophil-rich), and xanthomatoid patterns. Recognition of these nonspecific or atypical patterns or features prevents misdiagnosis of C-RDD and the ensuing inappropriate treatments.[8,9,17]

Patchy/interstitial pattern (19%) correlates as plaques or patches clinically. In three lesions, we did not consider RDD initially. The RD cells were 'hidden' within the interstitial lymphohistiocytic cells and the patchy lymphoid aggregates, or were only present in a small focus of the lesions (Fig. 2b, inset). Repeated sections or subsequent biopsies made the diagnosis possible. C-RDD of patchy/interstitial pattern should be differentiated from cutaneous lymphoid hyperplasia (CLH), GA, lymphocytic infiltrate of Jessner, or interstitial granulomatous dermatitis. The presence of plasma cells is a helpful clue, as it is a common feature of C-RDD, but not of the above conditions. A case of RDD carrying the diagnosis of GA and CLH for 10 years has been reported.[9] Thus, GA-like histopathology is within the spectrum of RDD.

In the 'neutrophil-rich' scenario, we observed a suppurative granuloma pattern in one lesion and foci of neutrophilic microabscess in two other lesions. While the latter were reported previously,[6,16,18] the architecture of suppurative granuloma is rarely encountered. The RD cells with indistinct cell borders and vacuolated cytoplasm are easily masked by the florid neutrophilic responses. Notably, neutrophils presented in 43% of lesions: the numbers were ranked as 'many' in one-third and were generally more than eosinophils, which presented in 62% of lesions but were all few or rare in number (Table 2).

Plasma cells were constantly found in all the lesions, forming a lymphoplasmacytic infiltration, and this may explain the polyclonal hypergammaglobulinaemia, a serological abnormality occasionally found in C-RDD and commonly seen in systemic RDD.[2,3,19] In some lesions, the plasma cells were the predominant infiltrating cells. Plasma cell-rich lesions may lead to the diagnosis of plasma cell granuloma (inflammatory pseudotumour) or plasma cell dyscrasia, as in patients 2 and 6. Presence of S-100+, large histiocytic cells and expression of both κ and λ chains in the plasma cells help differentiate C-RDD from the latter conditions. We observed binucleated and trinucleated plasma cells which have been described in cutaneous lesions of RDD as well as in other benign and malignant conditions.[4,26,27] Ultrastructural study suggested that these cells formed by cell fusion.[27]

Xanthoma or aggregates of foamy histiocytes was seen in biopsy 6D, a 30-month-old lesion. Prominent xanthomatous changes were observed in a 10-year-old lesion of C-RDD, and these were suggested as a regressing phenomenon.[10] Conspicuous aggregates of xanthomatous macrophages were also found in a case of C-RDD in follow-up biopsies at 24 and 30 months.[18] In our case, the foamy histiocytes were mostly negative for S-100, as observed previously,[10] but a few scattered cells showed S-100 positivity. Spanning the xanthomatous area and the mixed cellular area containing otherwise typical RD cells was a 'transitional zone' where the cells were granular-looking but retained S-100 positivity (degenerating RD cells). These features strongly support that these foamy histiocytes were derived from 'ageing' RD cells through a degenerating process.

The finding of conspicuous monomorphous, mildly lipidized histiocytes within biopsy 4A was interesting; they actually outnumbered the RD cells as shown in the S-100-stained

section. The histological and immunohistochemical features of these cells were not specific but were reminiscent of early xanthogranuloma.[22] Xanthogranuloma may take several forms histologically and has been considered a prototype of non-Langerhans cell histiocytosis.[22] This extraordinary finding, together with our previous report of localized Langerhans cell histiocytosis in one of the lesions,[15] and the expression by RD cells of both macrophage and dendritic/Langerhans cell lineage markers, implied that they are 'unstable' histiocytes/macrophages which may undergo morphological and phenotypic changes to form either non-Langerhans cell histiocytosis or Langerhans cell histiocytosis. Local cytokine environment, which activates and modulates the macrophages and is considered crucial for the multiple variants of non-Langerhans histiocytosis,[22,28] may trigger the transformation.

In C-RDD, RD cells retain the characteristic morphology. We observed multinucleated RD cells as reported by others.[16] Intralymphatic RD cells, considered a constant feature in both C-RDD and systemic RDD by Chu and LeBoit,[5] were found only in two lesions of our patients. In fact, their presence is variable, identified by some[15] but not others,[27] and they therefore may not be viewed as a constitutive feature of C-RDD. We hypothesize that in C-RDD, the abnormal histiocytes are activated and proliferated *in situ*, rather than migrate from the regional lymph nodes.

CD68 reactivity, a reliable marker for the monocyte/macrophage system,[29] is expressed variably in RD cells in our series. Echoing the recent large series,[16] the differential staining results with CD68 may reflect the unstable phenotype of RD cells. Found in the infiltrate, there were a number of CD68+ mononuclear cells that were smaller than RD cells with moderately abundant cytoplasm. We performed double immunostaining on one of these lesions with CD68 and CD138 (a marker for plasma cells; Serotec, Oxford, U.K.): some of these cells were positive for both antigens, while others were labelled by CD68 only (data not shown). We speculate that these CD68+ mononuclear cells represent two populations, monocytes and plasma cells. The latter have been shown to express CD68 in some reactive conditions.[30]

There are three other notable features: increased vascularity (90% of lesions), stromal fibrosis (48%) and epidermal changes (76%). There were plump (but not hobnailed) endothelial cells surrounded by dense inflammatory cells, particularly plasma cells. As shown in Tables 2 and 3, the occurrence of vascularity was noted early and became conspicuous as lesions grew larger, and decreased as lesions aged. The high incidence of increased vascularity is also reflected in the literature.[5,6,13] Whether there are increased angiogenic factors in the lesions remains to be elucidated. Fibrosis is deemed one of the differentiating features from nodal disease.[6,10,12,16] We found that the mean age of lesions showing fibrosis was 16 months, whereas that of lesions showing no fibrosis was 6 months. We did not observe the storiform fibrous response.[16] Epidermal changes were generally mild. Attenuation of rete ridges (33%) was mainly seen in nodular/diffuse patterns. Erosion, acanthosis and hypermelanosis were seen in equal frequency (14%). Peudoepitheliomatous hyperplasia, documented as one of the features of C-RDD,[5] was not found.

Our cases, together with those of previous reports,[10,18] outline a general process of clinicopathological evolution for C-RDD. There are three phases in the spontaneously resolving cases: growing, full-blown and regressing. In the first 0·5–1 year of the growing phase, RD cells and other inflammatory cells were incorporated with time, beginning as patchy/interstitial and becoming nodular/diffuse with infiltrating borders. This process manifests as erythematous patches or plaques initially and turns to nodules with satellite lesions at the full-blown phase. Between 12 and 24 months, the polymorphous infiltrating cells and RD cells gradually decrease; fibrosis and foam cells occur. Thus, in the regressing phase the clinical lesions are noduloplaques or plaques imparting a yellowish hue, and finally scar-like tissue. Different histological patterns and cell components come into play according to the duration of lesions.

While spontaneous resolution is a rule, various therapeutic modalities have been proposed, including surgery,[6,8] corticosteroids,[14] liquid nitrogen[9] and radiotherapy.[7] In one of our patients (patient 2), lesions treated with cryotherapy decreased in size more rapidly than those left untreated. Thalidomide, a potent inhibitor of phagocytosis and neutrophil chemotaxis, has been shown to be effective in some cases.[19]

In summary, our study further supports that C-RDD is a distinct entity from systemic RDD (SHML): confined to the skin without lymphadenopathy, and with different demographic features. The histological picture of C-RDD can be variable and dynamic, correlating with the clinical presentation and duration of lesions. Recognizing the many faces of C-RDD is essential for making a correct and timely diagnosis. Based on the unique phenotype of the RD cell and its associations with other histiocytic cells, we suggest a unified concept that RDD is a dynamic entity in the spectrum of histiocytosis with non-Langerhans cell histiocytosis at one end and Langerhans cell histiocytosis at the other. Further studies will clarify the aetiology and pathogenesis of RDD/C-RDD.

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