Sinus histiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman disease (RDD), is a rare disorder with worldwide geographic distribution, recognized as a distinct clinical entity in 1969. Any organ or tissue may be affected by SHML, resulting in a broad clinical spectrum. In its classic form, it occurs predominantly in young male blacks and whites and presents with prominent bilateral enlargement of cervical lymph nodes, fever, leukocytosis, elevated erythrocyte sedimentation rate, anemia, and hypergammaglobulinemia. Extranodal involvement, most commonly of skin and soft tissue, is evident in 43% of cases irrespective of concurrent lymphadenopathy. However, RDD confined to the skin only, commonly referred to as cutaneous Rosai-Dorfman disease (CRDD), is very rare, with fewer than 200 cases reported to date.

Cutaneous Rosai-Dorfman disease more often affects middle-aged Asian and white women, manifesting with slowly growing papules, nodules, plaques, or tumors of variable size and reddish-brown, yellow, or violaceous color, often located on the torso or in the head and neck region. Unusual manifestations, such as ulcers or generalized erythema, have also been described. Occasionally, lesions are pruritic or tender, and their onset may be accompanied by nonspecific constitutional symptoms, as well as abnormal laboratory test results similar to those encountered in nodal disease. Microscopic findings consistently include S-100-positive histiocytes with abundant pale cytoplasm, many of which exhibit emperipolysis, ie, the engulfment of intact cells such as lymphocytes, plasma cells, or erythrocytes. The lesions of CRDD are indistinguishable from skin lesions occurring in multisystemic SHML, and cutaneous manifestations may precede the involvement of additional systems. Definitive diagnosis therefore requires the exclusion of systemic involvement and close clinical follow-up. Most CRDD lesions resolve spontaneously over months to years, but some patients, especially those with coexisting immunologic disorders, experience frequent exacerbations or a progressive course. If intervention is desired or necessary, excision yields the best results. Alternatively, CRDD may respond to cryotherapy or radiotherapy, steroid injections, or treatment with systemic corticosteroids, retinoids, dapsone, imatinib mesylate, or thalidomide.

The etiology and pathogenesis of RDD remain poorly understood. The most commonly reported conditions associated with RDD are arthritis, asthma, diabetes mellitus, and hemolytic anemia, generally grouped under the broad term...
immunologic disorders, as well as subclinical infections with organisms such as human herpesvirus 6, Epstein-Barr virus, or *Borrelia*. Acute or chronic uveitis has also been reported; however, it is not entirely clear whether this finding represents an involvement by RDD or an accompanying condition because uveal biopsies were not performed in approximately half of these cases. An analysis of 423 cases revealed a strong association with immunologic abnormalities, and 75% of deaths attributed to SHML occurred in patients with underlying immune disease, implicating immunologic disturbances in the pathophysiologic characteristics of RDD. The manifestations of RDD are believed to reflect an aberrant immunologic response to antigenic stimuli, such as viral or bacterial pathogens, and the typical RDD histiocytes are thought to represent defective macrophages, which have become immunosuppressive on stimulation by macrophage colony-stimulating factor (M-CSF), causing localized immunologic dysfunction. This pathogenetic model links RDD to Crohn disease (CD), in which M-CSF–activated dysfunctional intestinal macrophages lead to abnormal immune responses to commensal bacteria, resulting in the development of chronic intestinal inflammation. However, the clinical correlate to these pathogenetic similarities, ie, the coexistence of both entities in the same patient, has only been described in 2 single case reports to our knowledge.

### Table. Summary of All 5 Cases of Rosai-Dorfman Disease in Patients With Crohn Disease Reported to Date

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected tissues and/or organs</td>
<td>Skin, soft tissue</td>
<td>Central nervous system</td>
<td>Skin</td>
<td>Skin</td>
<td>Skin</td>
</tr>
<tr>
<td>Site of lesion(s)</td>
<td>Right volar arm</td>
<td>Left frontotemporal</td>
<td>Left buttock, right cheek</td>
<td>Right posterolateral thigh</td>
<td>Left cheek</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td>Asymptomatic 6 × 7-cm mass, hyperpigmentation of overlying skin</td>
<td>Dura-based tumor (size not specified) with seizures, Broca aphasia</td>
<td>Slightly tender 8-cm red-brown plaque with yellow nodules, 1-cm erythematous plaque</td>
<td>Slightly tender 3-cm reddish-brown nodule</td>
<td>Asymptomatic 4-mm erythematous nodule</td>
</tr>
<tr>
<td>Histopathological features</td>
<td>Dermis, subcutaneous fat, and underlying connective tissue: infiltrate of histiocytes with admixed lymphocytes, plasma cells, and neutrophils; histiocytes showed emperipolesis of lymphocytes, plasma cells, and neutrophils</td>
<td>Tumor mass contained a mixed cell population composed mainly of histiocytes, which showed emperipolesis and were S-100+, CD68+, and CD1a–</td>
<td>Cheek: dermal infiltrate of histiocytes with admixed lymphocytes and plasma cells; histiocytes showed emperipolesis of lymphocytes and were S-100+ and CD1a–; buttock: same but extending to subcutis</td>
<td>Dermal infiltrate of histiocytes with admixed lymphocytes, plasma cells, and neutrophils; histiocytes showed emperipolesis of lymphocytes and erythrocytes and were S-100+ and CD1a–</td>
<td>Dermal infiltrate containing histiocytes, some of which showed emperipolesis of lymphocytes; the histiocytes were S-100+</td>
</tr>
<tr>
<td>Means used to exclude involvement of other sites</td>
<td>Physical examination, chest x-ray, bone scan</td>
<td>Physical examination, CT/MRI of head, FDG-PET of abdomen</td>
<td>Physical examination; CT of chest, abdomen, and pelvis</td>
<td>Physical examination, chest x-ray, CT of sinuses and abdomen</td>
<td>Physical examination</td>
</tr>
<tr>
<td>Treatment and outcome</td>
<td>Biopsy and observation → subtotal enlargement; tx: debulking and split skin graft → recurrence 8 mo later; tx: excision and split skin graft → CR</td>
<td>Partial resection → relapse; tx: azathioprine → CR</td>
<td>Buttock: excision 4 y prior to initial presentation → relapse; tx: intraskeletal triamcinolone acetone injections → no improvement; cheek: biopsy and observation</td>
<td>Excision → CR</td>
<td>Excision → CR</td>
</tr>
<tr>
<td>Follow-up and disease status</td>
<td>7 mo, disease-free</td>
<td>28 mo, disease-free</td>
<td>18 mo, persistent disease</td>
<td>11 y, disease-free</td>
<td>5 y, disease-free</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>Corticosteroids, metronidazole, imatinib mesylate</td>
<td>Azathioprine</td>
<td>Mesalamine, mercaptopurine</td>
<td>Hemicolectomy, mesalamine, corticosteroids</td>
<td>Small bowel resection</td>
</tr>
<tr>
<td>Status during onset and/or recurrence of RDD, medica-tions (if any)</td>
<td>Exacerbation and tx with infliximab coincided with substantial enlargement of RDD mass</td>
<td>Diagnosed at time of RDD relapse, mild symptoms</td>
<td>Remission (8 y)</td>
<td>Remission (&gt;15 y)</td>
<td>Remission (&gt;20 y)</td>
</tr>
</tbody>
</table>

Abbreviations: +, positive; −, negative; CR, complete remission; CRP, C-reactive protein; CT, computed tomography; FDG-PET, 18-fluoro-deoxyglucose positron emission tomography; MRI, magnetic resonance imaging; RDD, Rosai-Dorfman disease; tx, therapy.

* Cases 1 and 2, previously published reports; cases 3, 4, and 5, our patients (2 men in their early 50s and 1 woman in her mid-40s); case 3, illustrative case.

#### Report of Cases

Three patients developed CRDD in the context of long-standing CD. Clinical and histological features are summarized in the Table, which also includes the 2 previously reported cases. Figure 1 and Figure 2 show an illustrative case.
On the right cheek, there was an oval, erythematous, slightly scaly and indistinct 1-cm plaque with telangiectasias (Figure 1A). This lesion appeared brownish-yellow on diascopy. On the left buttock was an approximately 6 × 8-cm red-brown, indurated plaque with a scalloped border, peau d’orange appearance, and multiple yellowish nodules scattered throughout the lesion, as well as a 0.5-cm satellite nodule with a shiny yellow center (Figure 1B). Routine hematoxylin-eosin staining revealed mild spongiosis in the otherwise intact epidermis and a dermal infiltrate composed of large histiocytes with admixed lymphocytes and loose clusters of plasma cells (Figure 2A). The infiltrate was confined to the dermis in the...
small lesion on the cheek and extended into the subcutis in the large plaque on the buttock. The pale histiocytes had abundant foamy cytoplasm and large nuclei with prominent nucleoli and occasionally contained lymphoid cells, sometimes accompanied by cellular debris (Figure 2B and Figure 2C). All histiocytes stained strongly positive for the S-100 protein (Figure 2D) and mildly positive for CD68 and were CD1a negative (not shown). This immunohistochemical profile distinguishes SHML histiocytes from S-100-negative normal sinus histiocytes and is considered diagnostic for RDD when observed in combination with emperiplois.3

The incidence and prevalence of RDD and CRDD are unknown. A review of the literature, together with our findings, demonstrates that most of the 200 CRDD cases reported to date occurred in Western Europe, North America, and Asia and that 4 of these patients (2%) had a history of CD. Whereas CD is more common in industrialized vs developing countries and currently affects up to 0.2% of the population in the Western world, the incidence of CD is steadily increasing in many parts of Asia.10 Under the assumption that the 200 CRDD cases are representative of all patients with CRDD in the Western countries and Asia, an exact binominal test was used to assess whether the true proportion of CD cases in patients with CRDD (2%) is different from the assumed proportion of patients with CD in the general population (0.2%). The null hypothesis, which states that the rates of CD are the same in both groups, was rejected (P < .001), suggesting that the association of these 2 entities is not due to chance. However, additional studies will be needed to confirm this potential association because our analysis relies solely on reported cases and is therefore subject to reporting or publication bias.

Discussion

Recent findings suggest that RDD histiocytes belong to the monocyte/macrophage lineage and that their proliferation is initiated and maintained by high levels of M-CSF expressed by medium-sized monocytes, which are part of the characteristic RDD infiltrate.6,7 Proposed mechanisms of M-CSF-induced immunosuppression include diminished T-cell activation due to the production of transforming growth factor β and interleukin 10 (IL-10) by M-CSF-activated macrophages, insufficient antigen presentation due to downregulation of class II major histocompatibility complex expression on macrophages and antigen-presenting dendritic cells, and intracellular immunocompromise resulting from M-CSF-triggered phagocytosis of immunocompetent lymphocytes by RDD histiocytes.6,7

Peritoneal macrophages may become immunosuppressive on stimulation with M-CSF, and relative immunodeficiency resulting from macrophage dysfunction induced by elevated circulating M-CSF levels represents one of the primary defects in CD.10,13 Crohn disease, traditionally viewed as an autoimmune disease, is now thought to represent a disorder of autoinflammation caused by mutations in proteins involved in innate immune response.14 Whereas RDD displays some of the key features that define autoinflammatory disorders, such as activation of innate immune cells (macrophages) by presumably local tissue factors and/or aberrant antigen sensing in the absence of primary involvement of lymphocytes, additional studies would be necessary to determine whether RDD, like CD, may be included in the growing list of such disorders. Moreover, like Sweet syndrome, which has also been reported in association with CD and also exhibits discordance with CD in its clinical course, RDD can be viewed as part of the broader spectrum of cutaneous reaction patterns that are possible in patients with CD.

The pathogenetic parallels between CD and RDD form a basis for co-occurrence of these clinically unrelated entities; however, only 2 such cases have been reported to date.3,5 In case 1, the onset of CRDD was followed by multiple exacerbations of CD, which were treated with infliximab (a monoclonal antibody that causes apoptosis of TNF-activated T cells), coinciding with rapid growth of RDD mass.5 In case 2, the onset of CD occurred simultaneously with that of extranodal RDD confined to the central nervous system, and both disorders were preceded by chronic Q fever.3 In Q fever, IL-10-overexpressing macrophages promote the survival of Coxiella burnetii; the authors therefore proposed that the coexistence of these 3 entities was indicative of a common etiopathogenetic mechanism, ie, macrophage deregulation.9

In our patients, CD was in complete remission throughout the course of CRDD and remained clinically inactive for at least 3 years. The triggers required for RDD to become clinically apparent are yet to be identified and may partially differ from those in CD, which could explain the absent overlap of clinical manifestations of both disorders in our patients as opposed to the previously published cases. The course of CRDD in 2 of our patients was characterized by a single episode and complete remission following surgery, suggesting that CD, unlike other underlying immunologic disorders, may not have a negative prognostic impact on RDD. Interestingly, RDD was monosystemic and extranodal in our cases, as well as the 2 previously described patients, and was limited to the skin in 4 of 5 of these cases. Patients with underlying CD could be preferentially affected by such variants, but this finding could also be due to the fact that extranodal forms of SHML are more likely to be reported than classic nodal cases.

Cutaneous Rosai-Dorfman disease, because of its rarity, self-limiting course, and wide range of clinical presentations, may be underreported in the general population, as well as in patients with CD. Crohn disease is often complicated by perianal and perioral fissures, ulcers, or fistulae and nonspecific plaques or nodules predominantly occurring on the lower extremities.15 Cutaneous Rosai-Dorfman disease may mimic any of these conditions; thus, it is possible that unbiopsied CRDD lesions in patients with CD are falsely attributed to the intestinal bowel disease. Therefore, it may be prudent to include CRDD in the list of differential diagnoses when skin lesions are examined in patients with CD. Our observations will likely increase the awareness of this association, leading to more reports of such cases in the future.
Cutaneous Rosai-Dorfman Disease and Crohn Disease

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