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ORIGINAL ARTICLE

Fine-needle aspiration specimens of 3 cases of intra-abdominal Rosai-Dorfman disease with comprehensive review of the literature

Patrick J. McIntire, MD*, Ayse Irem Kilic, MD, Hannah H. Chen, MD, Mohammed Atieh, DO, Eva M. Wojcik, MD, Stefan E. Pambuccian, MD

Loyola University Medical Center, Department of Pathology and Laboratory Medicine, Maywood, Illinois

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Review

Introduction Rosai-Dorfman disease (RDD) is a rare usually self-limited non–Langerhans cell histiocytosis of unknown etiology. Nodal and extranodal RDD appear to represent distinct conditions with different molecular alterations and prognosis. They also pose different diagnostic challenges on biopsies and fine-needle aspiration (FNA) cytology. The aim of this study was to report on 3 cases of intra-abdominal RDD and perform an extensive review of the literature on FNA findings of RDD.

Materials and methods We reviewed FNA specimens from cases diagnosed histologically or cytologically as RDD during the past 10 years. We searched the PubMed and Google Scholar databases for cases of RDD sampled by FNA.

Results We identified 3 cases of intra-abdominal RDD, involving the kidney, periportal lymph node, and pancreas. FNA of the latter was hypocellular with fibrosis and was nondiagnostic. FNA of the first 2 yielded hypercellular smears that were diagnosed as RDD due to the identification of emperipolesis occurring in large uni- or binucleated histiocytes with large nuclei, fine chromatin, and prominent nucleoli in smears and cell-block sections. Immunohistochemistry showed positive staining for S100 and CD68 and negative staining for CD1a. The large histiocytes with emperipolesis were more difficult to identify histologically and their demonstration required immunohistochemical stains.

Conclusion Our experience and an extensive review of the literature suggest that extranodal RDD can be diagnosed on FNA, and that the recognition of histiocytes with emperipolesis may be less challenging cytologically than histologically. The fibrosis frequently seen in extranodal RDD may lead to nondiagnostic aspirates, however.

*Corresponding author: Patrick J. McIntire, MD, Department of Pathology and Laboratory Medicine, Loyola University Medical Center, 2160 S. First Ave, Maywood, IL, 60453; Tel.: +708-327-2626; Fax: +708-327-2620.

E-mail address: pmcinti2@gmail.com (P.J. McIntire).

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Introduction

Rosai-Dorfman disease (RDD) is a rare, usually self-limiting non−Langerhans cell histiocytosis of unknown etiology that manifests in nodal and extranodal locations.[1,2] The disease predominantly affects children and young adults, and in the majority of cases presents with bilateral cervical lymphadenopathy. Up to 40% of the patients may have extranodal disease in addition to lymphadenopathy but isolated extranodal disease is unusual. The most common sites of extranodal disease are the skin, nose, and paranasal sinuses; bone; and the central nervous system.[3-6]

Clinically, nodal RDD usually mimics lymphoma, especially because it may present with fever and night sweats resembling the "B symptoms" of lymphomas. Fine-needle aspiration (FNA) has been successfully used in its diagnosis. Extranodal RDD is diagnostically more challenging because it often presents as a soft tissue or visceral mass lesion, clinically mimicking a variety of organ specific malignancies. The diagnosis is further complicated because extranodal RDD is often sclerotic, yields minimal material on FNA, or can be associated with autoimmune diseases, IgG4-related diseases, and hematopoietic malignancies, making the diagnosis more challenging.[4,7-10] RDD must be distinguished from mimics, especially from malignancy, because RDD is usually associated with a good prognosis and is generally treated by clinical observation,[11,12] or by surgical excision alone.[3,13] The literature describing the morphologic characteristics in FNA of extranodal RDD is limited.[14] The purpose of this paper is to present 3 cases of intra-abdominal RDD that served as a springboard for a comprehensive literature review of the disease and the differential diagnosis.

Materials and methods

We searched our institutional database (Sunquest CoPathPlus v.6.0.0041, Sunquest Information Systems, Tucson, AZ) for cases diagnosed histologically or cytologically as RDD during the past 11 years (January 2007 to December 2017). Three cases were identified, all of which had FNA cytologic material available for review. Two of these cases also had associated histological material (1 case having 2 surgical specimens). Diff-Quik and Papanicolaou stained smears and hematoxylin and eosin stained cell block sections were reviewed in all cases and the following features were evaluated: cellularity of the smears; the presence/number of large histiocytes (RDD histiocytes); and the presence of lymphocytes, plasma cells, small histiocytes, eosinophils, and mast cells, as well as the presence of atypical cells, fibroblasts, capillaries, and necrosis. The presence of emperipolesis, and the number and type of cells within the RDD histiocyte cytoplasm, were also recorded. Immunohistochemistry was performed on 4 μm-thick slides prepared from cell block specimens. Prior to staining, the slides were deparaffinized in sequential baths of xylene, transferred to sequential baths of 100% ethanol, followed by sequential baths of 95% ethanol and then rinsed in deionized water. Immunohistochemistry was performed using mouse anti-human monoclonal anti-S100 antibody (Poly, Dilution: RTU, Leica Biosystems, Cat# PA0900; Buffalo Grove, IL), anti-CD68 antibody (514H12, Dilution: RTU, Leica Biosystems, Cat# PA0273), and anti-CD1a antibody (MTB1, Dilution: RTU, Leica Biosystems, Cat# PA0235). Images of 20 to 30 consecutive well-visualized RDD histiocytes and of well-visualized tingible body macrophages from an FNA of histologically confirmed florid lymphoid hyperplasia were acquired at 100x oil immersion objective magnification with an Olympus DP73 camera mounted on an Olympus BX40 microscope using CellSens Standard software version 1.12 (all from Olympus America Inc., Center Valley, PA), which also allowed for measurements of cell size and nuclear/nucleolar size. A review of the specimens was performed in preparation of this paper.

Results

Of the total of 20,605 FNA specimens reviewed during the 11-year interval of the study, 3 were from patients with intra-abdominal RDD. The relevant clinical and imaging findings of the cases are described here and summarized in Table 1.

Case 1

A 19-year-old man with a history of atrial septal and ventricular septal defects presented with acute abdominal pain and was found to have an ejection fraction of 20%, severe mitral and aortic valve regurgitation, and atrial fibrillation with rapid ventricular response. A computed tomography (CT) scan of the abdomen showed a lobular heterogeneously enhancing soft tissue mass that appeared to partially encase the right kidney and invade into the renal cortex. It was abutting the right adrenal gland and measured 9.7 cm in craniocaudal dimension. There was no involvement of the right renal artery or vein and the lymph nodes in the abdomen and pelvis were not enlarged. The clinical differential diagnosis was a lymphoma versus a retroperitoneal sarcoma. A FNA showed a hypercellular smear with a dispersed population of small lymphocytes, plasma cells, and large histiocytes with emperipolesis. RDD was diagnosed and confirmed on a subsequent core needle biopsy. The biopsy also showed compressed renal tubules at one of its ends, establishing kidney involvement (Fig. 1A). Both the cell block sections and the core biopsy showed large histiocytes that were positive for CD68 and S100 and negative for CD1a (Fig. 1B-D). The patient was placed on a steroid taper and has been closely monitored as an outpatient for the last 2 years without complication.

Case 2

A 38-year-old woman with a history of systemic lupus erythematosus was incidentally found to have lymphadenopathy in the vicinity of the celiac axis. A positron emission tomography (PET) CT scan showed bulky lymphadenopathy with a maximum standardized uptake value (SUV) of 6.4. The lymphadenopathy involved the left paraortic, gastrohepatic, porta hepatic, and peripancreatic lymph nodes, extending inferiorly along portal hepatic space toward the level of the mid right kidney. The patient reported "fevers and night sweats" over the last 3 years. Her laboratory results were significant for a positive antinuclear antibody titer of 1:40. A FNA showed many large, pale staining histiocytes exhibiting emperipolesis within a background of lymphocytes, and plasma cells. Immunohistochemistry was performed and the histiocytes were positive for CD68 and S100 and negative for CD1a. The patient was diagnosed with RDD and is currently being followed clinically without complication for the last year.

Case 3

A 63-year-old woman with a history of diabetes mellitus presented with jaundice and pruritus. A CT of the chest and abdomen revealed a 1.2 × 0.4 cm sessile, pleural-based noncalcified nodule in the inferior right middle lobe and tiny nodules in the bilateral upper lobes. A CT of the abdomen showed an ill-defined 2.6 × 2.5 cm mass of the head of the pancreas, which was isodense with the rest of the pancreas. On PET scan the SUVs of the pleural nodule and pancreas were 6.3 and 4.6, respectively. These findings were suspicious for a pancreatic malignancy with pulmonary metastasis. A pleural biopsy was performed that demonstrated a mixed inflammatory infiltrate composed of acute and chronic inflammatory cells with numerous histiocytes and fibroblasts. The biopsy was initially interpreted as nonspecific chronic inflammation. A FNA of the pancreatic mass showed aggregates of crushed lymphocytes in a background of fibrotic material, and was interpreted as nondiagnostic. IgG4 serum levels were not elevated. A pancreatoduodenectomy was subsequently performed; the surgical specimen showed a 3-cm diameter poorly demarcated area of fibrosis with chronic inflammatory cells in the head of the pancreas (Fig. 2A). The subcentimeter peripancreatic lymph nodes showed dilated sinuses with plasmacytosis and large histiocytic cells with lymphocytic emperipolesis (Fig. 2B-D). Both the pancreas and lymph nodes showed numerous large S100- and CD68-positive, CD1a-negative histiocytes with a variable number of intact lymphocytes within their cytoplasm, and were interpreted as RDD. On retrospective review, the pleural nodule was also interpreted as extranodal RDD. The FNA of the pancreas was reviewed in preparation of this paper and the original diagnosis was confirmed. The surgical pathology of the pancreas specimen has been reported previously.[15] Since the previous report,[15] the patient developed diabetic end-stage renal disease, apparently unrelated to RDD, requiring dialysis. She was placed on the kidney transplant waiting list but died the following year.

Cytomorphologic findings

With the exception of case 1, in which the smears from the pancreatic mass were hypocellular and showed fragments of fibrotic tissue and small numbers of lymphocytes without RDD histiocytes, the aspirate smears were moderately to highly cellular.

In addition to the characteristic RDD cells and lymphocytes, they also showed numerous plasma cells, some containing Russell bodies, and small histiocytes. No naked nuclei, apoptotic bodies, or necrotic cells or debris were seen in the background, and no mitoses were identified. Occasional eosinophils and mast cells, and fragments of

Table 1 Patient clinicopathological characteristics.

Case	Age	Sex	Location	Size, maximum (cm)	Relevant clinical history	Clinical findings	Imaging findings
1	19	M	Renal/Perirenal	9.7	ASD/VSD	Heart failure	MRI: low T2 signal, intermediate T1 signal with associated restricted diffusion and diffuse enhancement PET: SUV 4.6
2	38	F	Periportal LN	2.5	SLE	Fevers and night sweats	bulky intra-abdominal lymphadenopathy (SUV 6.4)
3	63	F	Lung, pancreas	1.2 (pleural nodule) 2.6 (pancreas)	DM	Jaundice, pruritus	CT: Pleural-based noncalcified nodule; pancreatic head: mass isodense to pancreas PET: pleural nodule SUV 6.3 pancreas SUV 4.6

ASD, atrial septal defect; DM, diabetes mellitus; ESRD, end-stage renal disease; F, Female; FNA, fine-needle aspiration; IHC, immunohistochemistry; LN, lymph node; M, Male; RDD, Rosai-Dorfman disease; SLE, systemic lupus erythematosus; SUV, standardized uptake value; VSD, ventricular septal defect.

capillaries, were also seen. The RDD cells had similar cytologic features; their numbers, however, varied from about 20 RDD cells/smear in case 1, to over 100 RDD cells per smear in case 2. The RDD histiocytes were not distributed randomly within the smears but were seen in clusters of 3 to 20 cells (Fig. 3). The size and shape of the RDD cells varied within each case; they were large, ovoid or polygonal, measuring 70 to 170 μm in the largest dimension, had ill-defined cytoplasmic borders, and abundant wafer-like finely vacuolated cytoplasm that stained faintly blue to sky-blue in Diff-Quik and pale green-blue in Papanicolaou-stained smears.

The degree of cytoplasmic vacuolation was variable both between cases and within the same case, but most cells showed only few small vacuoles. The vacuoles were better appreciated in Diff-Quik-stained smears and were mostly optically clear resembling lipid vacuoles (Fig. 4). The RDD cells typically showed 1 to 2 nuclei, but occasional RDD cells were multinucleated. The nuclei were large, round, ovoid, or reniform and measured 20 to 30 μm in the largest dimension. The chromatin was typically fine and pale, but occasional cells had hyperchromatic nuclei with coarse or smudgy chromatin. Nucleoli were frequently seen and were occasionally very large, measuring 4 to 6 μm in diameter. Some of these cells showed binucleation with large mirroring nuclei, and prominent macronucleoli reminiscent of the appearance of "Reed-Sternberg" cells (Fig. 5). The RDD histiocytes contained a variable number of intact cells in their cytoplasm, characteristic of emperipolesis. The composition of the cells seen within the cytoplasm of the RDD histiocytes varied from case to case and included lymphocytes and plasma cells and occasional erythrocytes, histiocytes, and neutrophils (Fig. 6). The numbers of such cells within the cytoplasm varied from one to a handful of cells, to over 100 cells (Fig. 7A). As a rule, larger cells contained a larger number of emperipoletic cells. A clear halo was sometimes seen around the cells contained in the cytoplasm of the RDD cells (Fig. 7B). The cytoplasm and nuclei were poorly visualized in cells that showed marked emperipolesis, as the tightly packed 3-dimensional aggregate of smaller cells obscured the RDD histiocyte nucleus. In all cases, somewhat smaller (600 to 700 μm in the largest dimension) cells with similar nuclear and cytoplasmic features, and showing no emperipolesis, were also identified—but were less frequent than the emperipoletic cells. In some cells, the cytoplasm of the RDD cells appeared damaged due to smearing, and the lymphocytes appeared to spill out of the cell. In comparison with the RDD histiocytes, the tingible body macrophages containing apoptotic bodies and cellular debris (which can be confused with emperipolesis), were considerably smaller, averaging a diameter of 35.7 μm, and measuring from 28 to 60 μm in largest dimension. Their nuclei and nucleoli were also smaller, averaging 17 μ, (range: 15 to 20 μm) (Fig. 8).

Cell block sections showed scattered single RDD cells with up to 20 emperipoletic cells within their cytoplasm; the presence of emperipolesis was highlighted by S100 immunostains, which stained the nucleus and cytoplasm of the RDD cell but left the emperipoletic lymphocytes unstained (Fig. 7C, D).

Histopathology

Review of the histopathology of the renal (case 1, Fig. 1), pleural, and pancreatic (case 3, Fig. 2) RDD involvement showed similar findings: extensive fibrosis with chronic inflammatory cells with predominance of lymphocytes over plasma cells. In contrast to the cytologic preparations (smears and cell block sections), in which RDD cells were easily identified as very large dispersed individual cells, they were difficult to identify in tissue sections, in which they were inconspicuous because of their very pale nuclei and the poor demarcation of their vacuolated cytoplasm from the background fibrosis and chronic inflammation.

Table 1 (Continued)

Clinical diagnosis/ suspicion	FNA diagnosis	Histology	IHC	Treatment	Follow-up
Hematolymphoid neoplasms, sarcoma, renal cell carcinoma	RDD	RDD (core bx)	S100 + CD68+, CD1a-	Corticosteroids	No complications (2 y)
Lymphoma	RDD	None	CD68+, S100+, CD1a-	Observation	No complications (1 y)
Pancreatic cancer with lung metastases	Nondiagnostic	Chronic inflammation (pleural nodule) RDD pancreas	S100 + CD68+, CD1a-	Pancreatectomy (Whipple)	Died, unrelated ESRD, 1 y

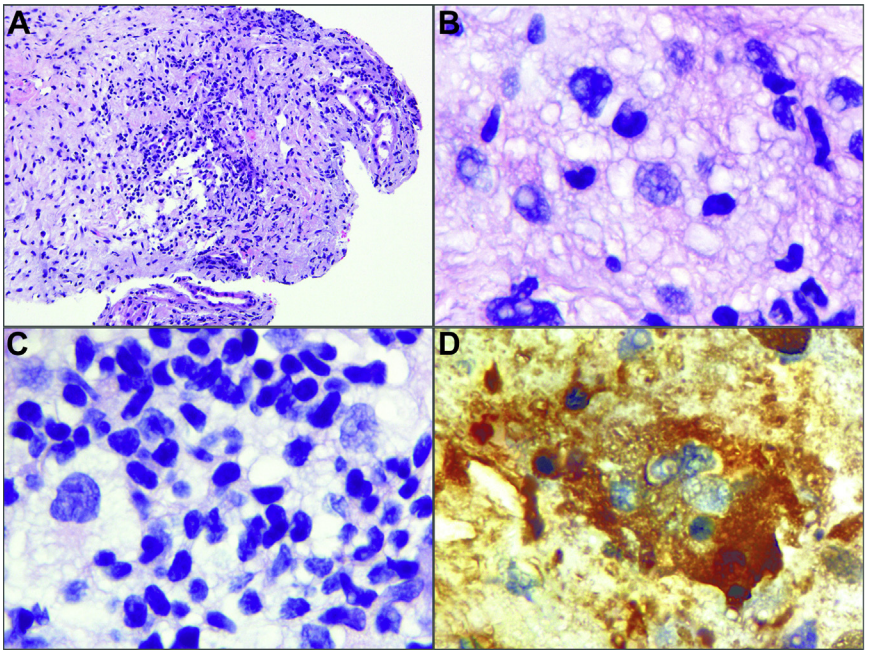

Figure 1 Histologic features of RDD in kidney core biopsy (case 1). A, Loose inflammatory tissue with aggregates of lymphocytes compressing renal tubules. B and C, RDD cells with abundant ill-defined vacuolated cytoplasm. Note the difficulty in assessing if the lymphocytes are within or surrounding the large histiocytes. D, Immunostaining for S100 helps delineate the cytoplasm of the RDD cells. (Hematoxylin and eosin, original magnification: A ×100, B and C ×1000; immunostain, original magnification: D ×1000.)

Emperipolesis was also difficult to identify within the RDD cells, because it was difficult to decide whether the lymphocytes were in or next to the large histiocytic cells. In addition, in contrast to the 3-dimensional representation of the RDD cells in the cytology smears, only a small fraction of the emperipoletic cells present in the plane of the section

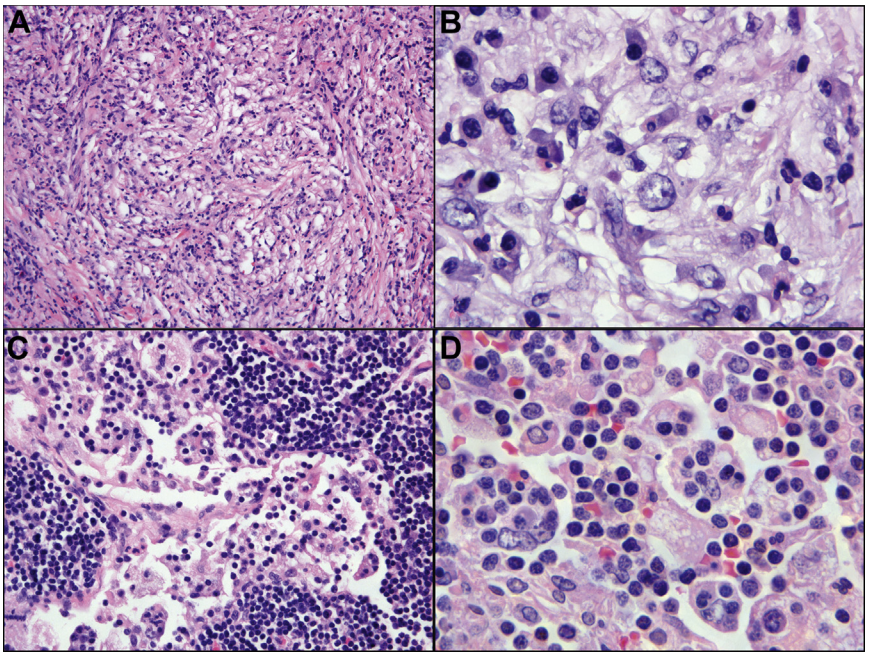

Figure 2 Histologic features of RDD in pancreatectomy specimen (case 3). A, Fibrotic tissue with sprinkling of inflammatory cells and ill-defined larger pale cells. B, RDD cells with abundant ill-defined cytoplasm. Note the difficulty in assessing whether the lymphocytes are within or surrounding the large histiocytes. C, Peripancreatic lymph node with distended sinus containing RDD cells. D, Higher power of RDD cells. Note the well-defined cytoplasmic borders, which simplify the identification of RDD cells and emperipolesis. (Hematoxylin and Eosin, original magnification: A ×100, B ×1000, C ×200, D ×400.)

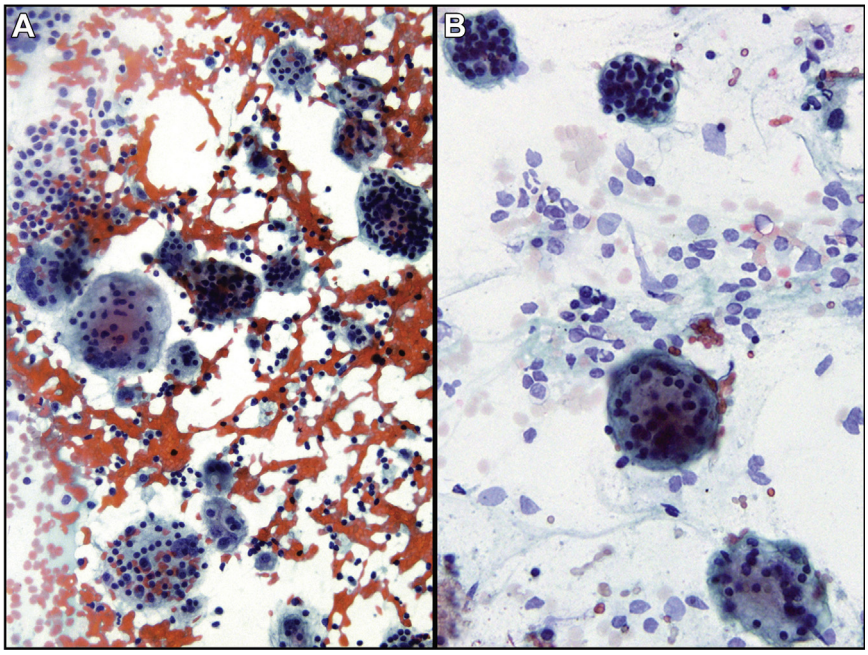

Figure 3 Variable amounts of emperipolesis. Low power (A) and medium power (B) appearance of Rosai-Dorfman disease cells in fine needle aspirate smears. Note the "clustering" of the RDD cells, and the variability of their sizes and number of cells contained in their cytoplasm. (Papanicolaou stain, original magnification: A ×100, B ×400.)

were seen histologically. Emperipolesis was somewhat easier to identify in sections stained with S100 and CD68, where the cytoplasm of the large histiocytes stained strongly, whereas the emperipoletic cells showed "negative staining" (Fig. 7D).

Discussion

RDD, also known as "sinus histiocytosis with massive lymphadenopathy" (SHML), was probably first described in 1961 by Karl Lennert (1921-2012) in his monumental

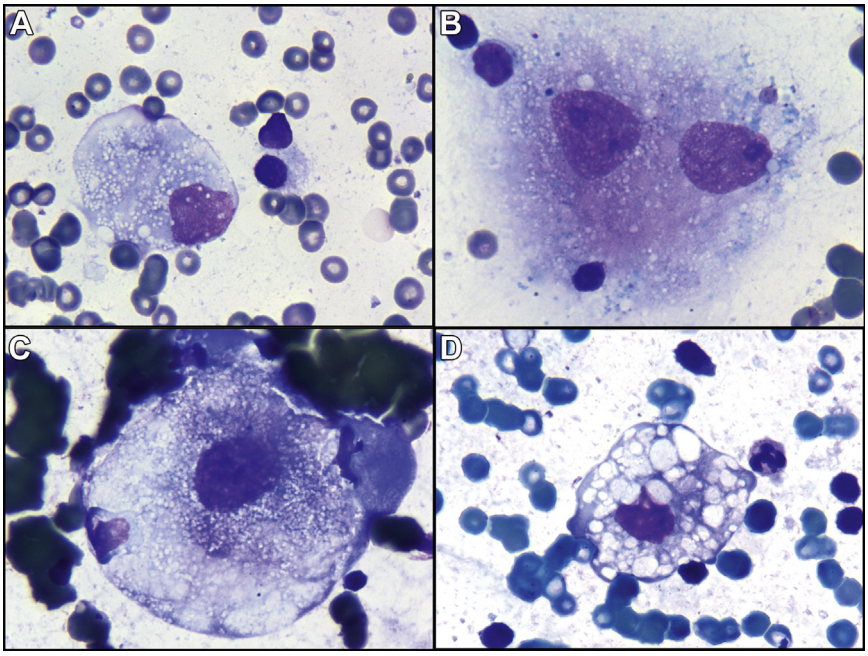

Figure 4 Rosai-Dorfman disease histiocytic cells with no or few emperipoletic cells. Note the variable amounts of "sky-blue" wafer-like finely vacuolated cytoplasm (A-C) or sharply punched-out large vacuoles (D) and ill-defined cell borders (B). (Diff-Quik stain, original magnification ×1000.)

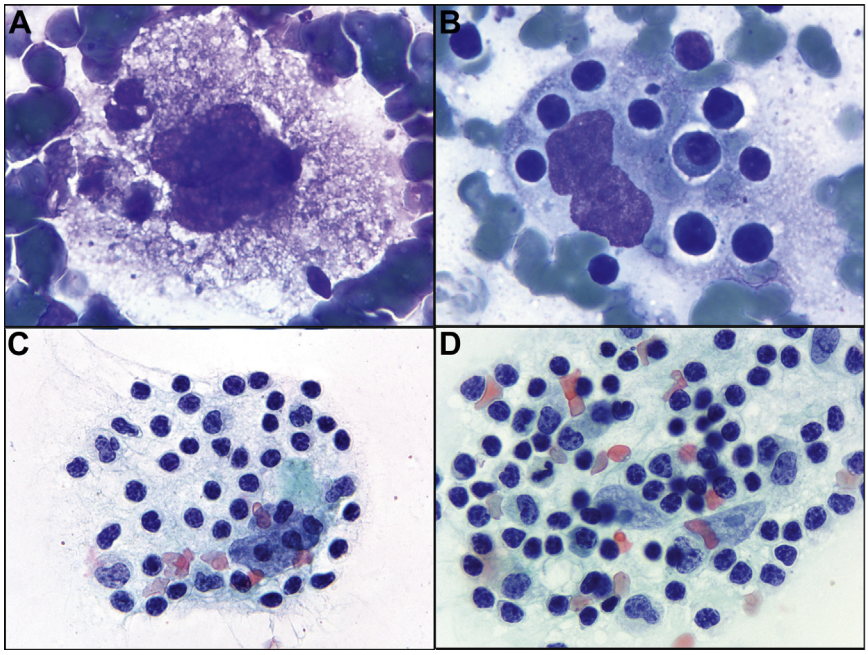

Figure 5 Emperipolesis with Rosai-Dorman disease cells with large and multiple nuclei. A-D, Binucleated Rosai-Dorfman disease cells with abundant cytoplasm and emperipolesis. (Diff-Quik stain, original magnification: A and B ×1000; Papanicolaou stain, original magnification: C and D ×400.)

monograph on the histology and cytology of lymph nodes.[16] Lennert highlighted the very large histiocytes containing fine lipid-like vacuoles in their ample cytoplasm and resembling Mikulicz cells (foamy macrophages containing Klebsiella rhinoscleromatis).[16] He also described and depicted the presence of lymphocytes, neutrophils, plasma cells, and erythrocytes in the cytoplasm of these cells.[16] Although Lennert stresses the uniqueness of this histologic pattern, he attributes it to rhinoscleroma, despite the lack of demonstrable Klebsiella organisms.[16]

SHML was first described as a distinct lymphadenopathy in 1965 by the French pathologist Pierre-Paul Louis Lucien Destombes (1912-2002).[17] He considered it a form of lipid storage in the reticulohistiocytic system of the cervical

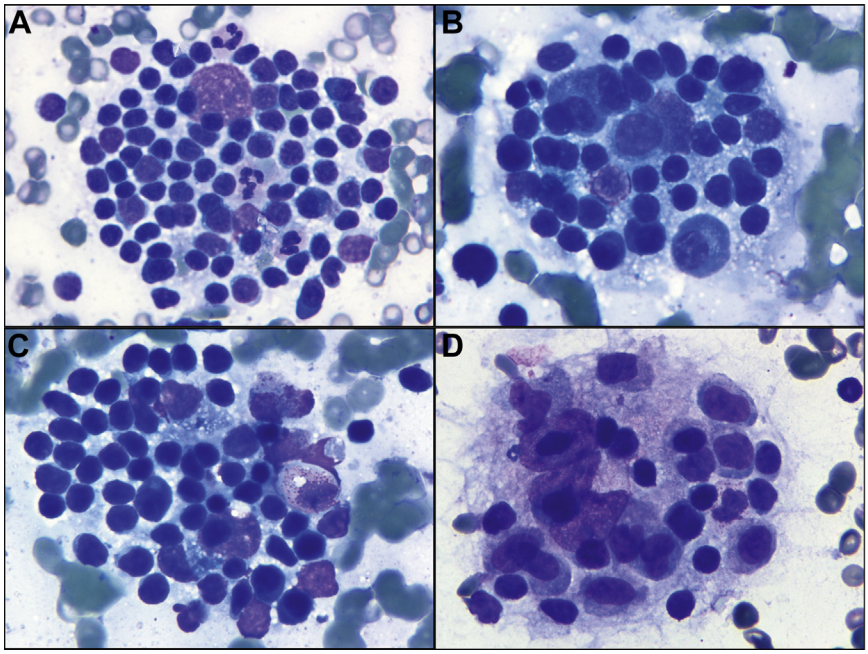

Figure 6 Rosai-Dorfman disease cells with emperipolesis. Note that, in addition to lymphocytes, the RDD cells show occasional neutrophils (A), plasma cells (B), eosinophils (C), and histiocytes (D). (Diff-Quik stain, original magnification: ×1000.)

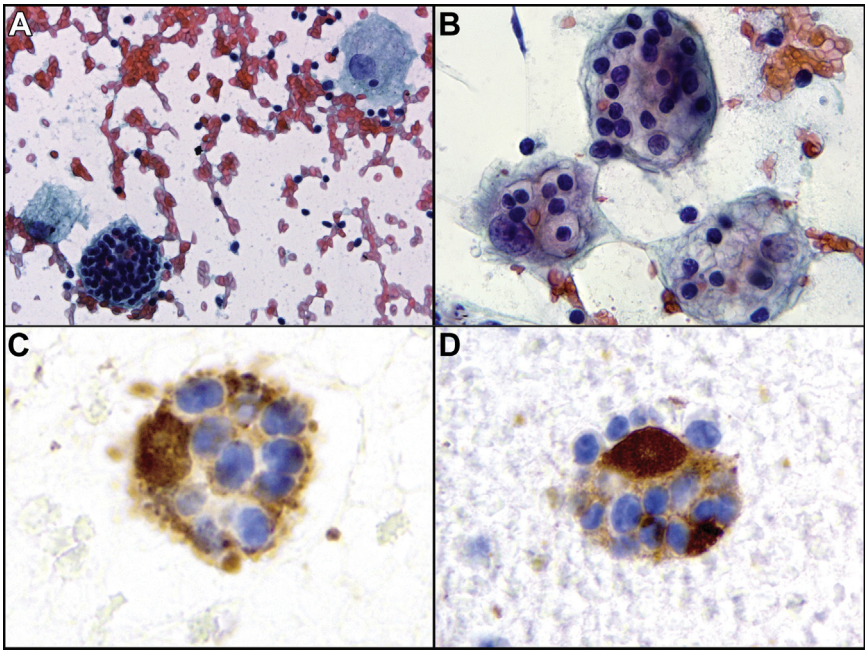

Figure 7 Rosai-Dorfman disease histiocytic cells with emperipolesis. A, Of the three RDD cells present in the field, one shows no emperipolesis, one shows a single lymphocyte in its cytoplasm, and one is filled with lymphocytes obscuring its nucleus. B, Clear halos around the lymphocytes within the cytoplasm of RDD cells. C and D, Emperipolesis in cell block sections highlighted by S100 immunostain, which shows "negative staining" of the engulfed lymphocytes, while the nucleus and cytoplasm of the RDD cells are staining. (Papanicolaou stain, original magnification: A ×100, B ×400; Immunostain, original magnification: C and D ×1000.)

lymph nodes developing after an inflammatory process and named it "adenitis with lipid excess".[17] He noted that the aggregates of histiocytes with lipid vacuoles in their cytoplasm were surrounded by abundant plasma cells and that "many of these histiocytes functioned as macrophages … still identifiable cells being observable in their cytoplasm".[18,19]

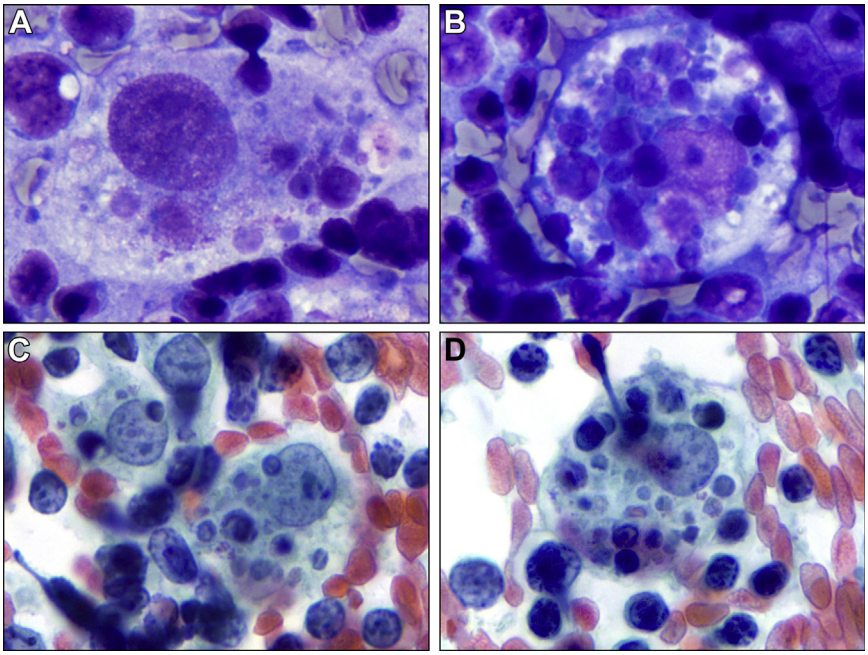

Figure 8 Tingible body macrophages from smears of florid reactive lymphadenopathy. The overall cell and nuclear size of TBM is slightly smaller than that of Rosai-Dorfman histiocytes; the partially phagocytosed cells and nuclei present in their cytoplasm appear fragmented and "dirty" and are much smaller than the cells surrounding the TBM. (A and B, Diff-Quik stain; C and D, Papanicolaou stain, original magnification ×1000.)

However, because Juan Rosai and Ronald F. Dorfman (1923-2013) definitively characterized this lymphadenopathy as a distinct entity in 2 successive papers published in 1969[20] and 1972,[21,22] the name of Rosai-Dorfman disease (or Destombes Rosai Dorfman disease or Rosai-Dorfman-Destombes disease)[2,23,24] is preferred worldwide, especially for extranodal cases.

RDD is classified among the histiocytoses, a diverse group of rare conditions with localized or disseminated manifestations and mild to progressive, life-threatening evolution.[2] In the most recent classification proposed by the Histiocyte Society in 2016, RDD is classified into its own group, the "R" group.[14] The cutaneous form of RDD, however, is included, together with other mucocutaneous histiocytoses like juvenile xanthogranuloma (JXG), in the "C" group.[14] The other histiocytoses are classified into the "L" group, which includes Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD); the "M" group of malignant histiocytosis; and the "H" group that includes the hemophagocytic syndromes.[14] Non-cutaneous RDD encompasses familial RDD and sporadic RDD, the latter including classical (nodal) RDD, extra-nodal RDD, and RDD associated with neoplasia or immune disease.[2] This classification implies that RDD is heterogenous, and that cutaneous and non-cutaneous RDD, and even the subgroups of non-cutaneous RDD, are likely to be different conditions, with different etiology, manifestations, and prognosis. The inherited cases can be associated with *SLC29A3* germline mutations (H syndrome) or *FAS* germline mutations (autoimmune lymphoproliferative syndrome).[2] Immune disease associated RDD occurs in patients with systemic lupus erythematosus (SLE), autoimmune hemolytic anemia, and human immunodeficiency virus (HIV) infection, while neoplasia-associated RDD precedes, occurs concomitantly, or succeeds Hodgkin and non-Hodgkin lymphomas, leukemia, or other histiocytoses (LCH, ECD, or malignant histiocytosis).[2]

Classical, nodal RDD with single, frequently bilateral or regional lymph node involvement generally has a self-limiting course and good prognosis.[2] This is in contrast to extranodal RDD, in which 15% of patients have a progressive course and which can be fatal.[2] Because of the prognostic differences between the two types of RDD, it is likely that classical, nodal RDD is a distinct entity from extranodal RDD. Both classical, nodal RDD and extranodal RDD can occur with or without IgG4 syndrome (ie, association with large numbers of IgG4 staining plasma cells fulfilling the diagnostic criteria for IgG4-related disease).[2]

RDD can affect patients with a wide age range, but affects mainly children and young adults with a mean age of onset of 20.6 years.[4] The etiology and pathogenesis are largely unknown and probably differ for the different groups of RDD. Classic (nodal) RDD is a most likely a non-neoplastic, reactive process and its relationship with infectious diseases (*Klebsiella*, polyomavirus, HHV-6, Epstein Barr virus and parvovirus B19) and other hematolymphoid neoplasms is still not settled.[25] It is thought that the accumulation and activation of RDD cells may be cytokine-mediated and could be set off by diverse infectious, immune, or neoplastic stimuli. Studies have failed to demonstrate the clonal nature of the RDD cells in the classic (nodal) type of RDD.[2]

The detection of recurrent mutations in genes of the Ras/Raf/MEK/ERK signaling pathway in the majority of cases of LCH and ECD, of which the $BRAF^{V600E}$ mutation is the most common,[14] followed by mutations of *MAP2K1, ARAF, KRAS, NRAS*, and *PIK3CA*, has led to efforts to find similar mutations in RDD.[2] Although no *BRAF* mutations were detected in RDD, mutations in other genes from the mitogen activated protein kinase (MAPK) signaling pathway, including *KRAS, NRAS, MAP2K1*, and *ARAF* have been reported in extranodal RDD,[2] challenging its assumed reactive nature and suggesting that at least some of these cases may represent neoplastic proliferations of histiocytic cells. RDD cells probably derive from circulating monocytes and their immunohistochemical staining pattern suggests an antigen-presenting cell differentiation, but the lack of HLA-DR on these cells might reflect a dysfunction in antigen presentation.[26]

Histologically, RDD is characterized by the accumulation of large histiocytic cells with round, oval or reniform nuclei, that are usually hypochromatic ("as if air had been pumped into them"), often showing conspicuous to prominent single central nucleoli and abundant pale ("watery-clear") or vacuolated cytoplasm showing variable degrees of emperipolesis.[2] RDD is also characterized by the presence of abundant polyclonal plasma cells, with numerous Russell bodies; the plasma cells may be positive for IgG4.[2] In classic (nodal) RDD, the large histiocytes with emperipolesis and plasma cells are expanding the sinuses of the lymph node; in extranodal RDD the large pale or foamy histiocytes showing less conspicuous emperipolesis are seen within a mixed lymphoplasmacytic infiltrate and may be accompanied by prominent fibrosis.[2] RDD histiocytes have a characteristic S100- and CD68-/CD163-positive, CD1a-/CD207-negative immunophenotype and may also express CD4, CD11c, and CD14.[2] The RDD histology and the above-mentioned immunophenotype are required for the diagnosis.[2,14] Careful examination and correlation with clinical and imaging findings is recommended to exclude potential associated lymphoma, leukemia and histiocytoses (LCH aor ECD).[2]

Review of the literature

Although the appearance of both nodal and extranodal RDD has been thoroughly described in the literature in surgical specimens, the literature on RDD in FNA cytology specimens is more limited and consists mostly of single case reports. A comprehensive search in PubMed and Google Scholar identified 116 cases of RDD sampled by FNA reported from India (74 cases), US (17 cases), Nepal (6 cases), Brazil (5 cases), Italy (3 cases), Spain (2 cases), Hong Kong (2 cases), and the UK, Mexico, China, Taiwan, Japan,

Malaysia and Senegal (1 case each).[27-85] Among these cases there was a slight male predominance with a male:female ratio of 1.1. The average age was 30.8 years (range: 1.5 to 79 years). Seven patients had comorbidities, systemic lupus erythematosus being the most common (5 cases), followed by HIV (1 case) and diabetes mellitus (1 case).

Most cases sampled by FNA represented nodal RDD (75.8%, 88 of 116), while extranodal RDD was less common (24.1%, 28 of 116).[27-85]See Table 2 for a summary of the literature review based on nodal versus extranodal RDD. The nodal sites sampled by FNA were mostly in the cervical region 71.6% (63 of 88), followed by submandibular or submental region 11.4% (10 of 88). In addition, there were a few reported cases involving the inguinal lymph nodes (3.4%, 3 of 88), retroperitoneal lymph nodes (2.3%, 2 of 88) or unknown of other locations (11.4%, 10 of 88). In the majority of these cases the clinical suspicion was of Hodgkin or non-Hodgkin lymphoma, less commonly tuberculosis or metastatic disease. In these cases, palpation-guided FNA of enlarged lymph nodes measuring 1 to 8 cm (mean: 3.3 cm) was performed after the mass had been present for weeks to years (average: 10 months). The cases in which extranodal RDD was sampled by FNA occurred most commonly in head and neck sites (10.3%, 12 of 116). The most common locations were the orbit (25%, 3 of 12), parotid gland (25%, 3 of 12), and thyroid gland (25%, 3 of 12), followed by mandible (8.3%, 1 of 12), nasal cavity (8.3%, 1 of 12) and subglottis (8.3%, 1 of 12). Other locations included bone (4.3%, 5 of 116), breast (4.3%, 5 of 116), skin (3.4%, 4 of 116), abdominal wall (<1.0%, 1 of 116), and rectum (<1.0%, 1 of 116). In these cases, the FNA was performed to rule out a variety of site-specific neoplasms. In some cases of extranodal RDD, the FNA was performed under imaging guidance; in a single case under endoscopic ultrasound (EUS) guidance.[52] There were no reported cases of extranodal RDD occurring in intra-abdominal or retroperitoneal organs among the reported cases sampled by FNA. There is a single report of RDD made by touch imprints.[86]

Of the 88 cases of nodal disease, 79 (89.8%) were evaluated through FNA, of which 69 cases were diagnostic of and 10 cases were found suggestive of or suspicious for RDD; in 5 cases the diagnosis of RDD was made after one or more prior FNA attempts yielded no specific diagnoses. Of the remaining 9 cases, 7 (8%) were diagnosed as negative for malignancy, receiving a descriptive diagnosis or were diagnosed as reactive lymphoid hyperplasia, and 2 were diagnosed as suggestive of Hodgkin lymphoma.[43,50] Of the 28 cases of extranodal RDD in which FNA was performed, 19 (67.9%) were evaluated through FNA, of which 15 cases were diagnostic of and 4 cases were found suggestive of or suspicious for RDD. Of the remaining 9 cases, 7 (25%) were diagnosed as negative for malignancy, receiving a descriptive diagnosis or were diagnosed as inflammation, and 1 was diagnosed as centroblastic malignant lymphoma and another as suspicious for malignancy.[64,77]

Follow-up surgical specimens were reported in 61 of 116 (52.6%) cases[27-85] and confirmed the diagnosis of RDD in all but a single case, which was histologically diagnosed as Hodgkin lymphoma.[87] Immunohistochemistry was performed on a minority of FNA specimens (13.8%, 16 of 116). There was at least partial positive staining seen in all cases for CD68 or S100 immunohistochemistry and CD1a immunohistochemistry was negative (Table 2). Early cases of nodal RDD as well as more recent cases of RDD from developing countries have been diagnosed without IHC stains, either due to lack of cell block preparations or lack of resources. Nonetheless, more recent reports generally have immunohistochemical (IHC) stains performed.

The cytomorphologic features reported in both nodal and extranodal RDD were similar and showed many similarities with our cases.[27-55 56-85] They included foamy appearing histiocytes with variable emperipolesis, ranging from 1 to >50 cells (usually 5 to 15 cells). The histiocytes usually contained intact lymphocytes and sometimes also plasma cells and neutrophils.[2] A clear halo was seen surrounding the emperipoletic cells, and large numbers of emperipoletic cells obscured the nuclei of the RDD cells. The RDD histiocytes were 2 to 10 times the size of normal histiocytes with large nuclei with smooth contours and visible to prominent nucleoli.[2] The histiocytes were binucleated or

Table 2 Summary of literature review: split based on nodal versus extranodal Rosai-Dorfman disease.

Variable	Nodal RDD	Extranodal RDD
Total FNA cases %, (n)	75.8 (88/116)	24.1 (28/116)
Age: average (range) years	27.5 (1.5-79)	40.0 (7-71)
Sex, M:F	1.5	0.5
Location, % (n)	Cervical LN — 71.6 (63/88)	Head and Neck — 42.9 (12/28)
	Submandibular/mental LN — 11.4 (10/88)	Bone — 17.9 (5/28)
	Inguinal LN — 3.4 (3/88)	Breast — 17.9 (5/28)
	Retroperitoneal — 2.3 (2/88)	Skin — 14.3 (4/28)
	Unknown/Other — 11.4 (10/88)	Other — 7.1 (2/28)
IHC performed	12.5 (11/88)	17.9 (5/28)
Diagnostic/suggestive of RDD by FNA alone, % (n)	89.8 (79/88)	67.9 (19/28)

RDD, Rosai-Dorfman disease; FNA, fine-needle aspiration; LN, lymph node; IHC, immunohistochemistry.

multinucleated, and in some cases resembled Reed-Sternberg cells.[2]

The 3 cases of RDD described herein, all in unusual locations, not previously reported in the cytology literature, including the kidney (sampled by CT-guided FNA), and the pancreas and celiac lymph nodes (sampled by EUS-guided FNA), add to the understanding of RDD. As previously reported, we found that the diagnosis of extranodal RDD can be difficult to establish on FNA, especially in the presence of extensive fibrosis due to difficulties in obtaining a diagnostic FNA sample.[2] Nonetheless, we found that extranodal RDD can also be very difficult to diagnose histologically, because the extensive fibrosis and apparently nonspecific lymphoplasmacytic infiltrate are frequently, at least initially, interpreted as chronic nonspecific inflammation. In the first case included herein, showing RDD involving the kidney, the initial FNA was diagnosed as RDD based on the characteristic cytology and immunostaining pattern on cell block sections, while the subsequent core biopsy could only be diagnosed by identifying the pale histiocytic cells as RDD cells after demonstrating their strong staining for S100, and also recognizing the rare emperipoletic lymphocytes present within their cytoplasm. In our third case, in which the FNA was nondiagnostic, the extranodal RDD involving the pleura was initially interpreted as nonspecific inflammation and a firm diagnosis of RDD could only be made on the pancreatoduodenectomy specimen due primarily to the presence of peripancreatic lymph nodes showing sinus histiocytosis with emperipolesis.

The differential diagnosis of RDD includes florid lymphoid hyperplasia with abundant tingible body macrophages, infectious lymphadenopathies, granulomatous and xanthogranulomatous inflammation, proliferations of histiocytic cells (histiocytoses), including Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), hemophagocytic syndrome, and malignant histiocytosis/histiocytic sarcoma (Table 3), and lymphomas (especially Hodgkin lymphoma).[2,14] Some of these conditions are characterized by cell-in-cell phenomena, either phagocytosis of other cells, like erythrophagocytosis or hemophagocytosis in hemophagocytic syndrome, phagocytosis of apoptotic debris in tingible body macrophages occurring in reactive lymphoid hyperplasia or high-grade lymphomas, cellular cannibalism or hemophagocytosis seen in histiocytic sarcoma and other malignancies, or emperipolesis.[14] Emperipolesis, the most characteristic feature of RDD, is different from phagocytosis in that the engulfed cell remains viable with intact normal structure within another cell.[2] The word emperipolesis or "inside round about wandering" is derived from the Greek (em = inside; peri = around; polemai = wander about) and was coined in 1956 by Humble, Jayne, and Pulvertaft[88] for "the active penetration of one cell by another which remains intact." Despite the fact that over 60 years have passed since they described this "peculiar relationship between lymphocytes and malignant cells, cells in mitosis, and megakaryocytes", the mechanisms and consequences of emperipolesis have not yet been elucidated. Emperipolesis occurs not only in RDD,[2] but also in a variety of normal situations and diseases in thymic epithelial "nurse" cells, megakaryocytes, Kupffer cells, histiocytes, and neoplastic cells. The internalized cells are frequently lymphocytes and plasma cells, but may also be neutrophils, histiocytes or eosinophils. In fine-needle aspirates, emperipolesis has been described, in addition to RDD, in dendritic cells of Castleman disease[89] and in Langerhans cells of LCH, which may contain eosinophils.[90] Identification of emperipolesis in smears may be difficult in thick areas of the smear, in which histiocytes showing emperipolesis may be overlooked or interpreted as lymphocytes overlying the histiocytes. Smeared slides are 3-dimensional and some may find it difficult distinguishing between scattered lymphocytes overlaying histiocytes and true emperipolesis. Ideally, emperipolesis should be evaluated in thinner portions of the smear; however, if no RDD cells are present in these areas, large cells with numerous lymphocytes that overly their cytoplasm usually stand out even in thicker areas. If only few such cells are present it may not be possible to be sure that it is emperipolesis; however, the very large size of the histiocytes argues in favor of RDD histiocytes. Conversely, in thin areas of the smears, the fragile cytoplasm of the histiocytes may be disrupted, resulting in spilling of the emperipoletic lymphocytes, which may appear to lie around rather than in the cytoplasm of the histiocytes.

Reactive lymphoid hyperplasia, especially when plasmacytosis is present, is one of the most difficult differential diagnoses[28] and relies on the identification of histiocytes with emperipolesis.[41] Aspirates show lymphohistiocytic aggregates and numerous tingible body macrophages (TBM), which may superficially resemble RDD cells. TBM, however, are smaller, have smaller nuclei (as noted previously), and their cytoplasm contains apoptotic or karyorrhectic debris and partially digested nuclei or cell fragments that are smaller than the surrounding lymphocytes (Fig. 8). In contrast, RDD cells exhibiting emperipolesis show intact cells that are the same size as their counterparts seen in the background, have well-defined nuclear and cytoplasmic details, and are sometimes surrounded by a clear halo.[2]

Infectious and granulomatous diseases also enter the differential diagnosis,[91] especially those associated with a xanthogranulomatous response (xanthogranulomatous cholecystitis and pyelonephritis) or with foamy histiocytes (like Whipple disease), rhinoscleroma (which shows Mikulicz cells), and leprosy (which shows "lepra cells" or Virchow cells). However, unless associated with RDD, the histiocytes of infectious and granulomatous diseases do not show emperipolesis, are smaller, have smaller nuclei, may be cohesive, and can be associated with Langhans, foreign body, or Touton giant cells.[91] In addition, special stains (Giemsa, periodic acid−Schiff, acid-fast bacilli) may be positive for infectious organisms (*Tropheryma whipplei,*

Table 3 Rosai-Dorfman disease and differential diagnoses.

Variable	RDD-LN	RDD-extranodal	LCH	ECD	JXG	XG INFL	HIST SARC	Lymphoid hyperplasia	Granuloma (sarcoid, infectious)
Sites involved	LN neck	Any organ	Bones	Bones	Skin	Kidney, gallbladder	LN, any organ	LN, any organ	LN, lung, skin
Prognosis	Usually good	Can be progressive and fatal	Usually good	Progressive disease with high fatality rate	Usually good	Usually good	Poor	Good	Usually good
FNA cellularity	med/high	low	med/high	low	low	med/high	high	high	low/med/high
Cell composition									
Histiocytes	+	-/+	++	+	+++	+	+	++	+ TO +++
Epithelioid cells	-	-	-	-	+++	-	-	-	+ TO +++
Atypical histiocytes	+	+	+++	+	+/−	-	+++	-	-
Lymphocytes	+	+	+++	+	+++	+	+	+	-
Eosinophils	-	-	+++	-	++	-	-	-	-
Fibroblasts	-	+	−/+	+	-	+	-	-	−/+
Lesional cell size	+++	+++	+	++	++	++	++/+++	+/++	+
cytoplasm									
Foamy	+ to +++	+	−/+	+++	+++	+++	+/++	+	+
Cell-in-cell	Emperipolesis	+/-Emperipolesis	-	-	-	-	Hemophagocytosis	TBM	-
Multinucleated giant cells	−/+	−/+	Osteoclast-type	Touton	Touton	+	Tumor giant cells	-	Langhans type
Nuclei									
Number	1-2	1-2	1	1	1	1	1-4	1	1
Shape	round, oval, reniform	round, oval, reniform	round	round	round	round	round/bizarre	round/ovoid	ovoid, boomerang
Size	large	large	medium	medium	medium	medium	very large	medium	medium
Chromatin pattern	open	open	open	open	open	open	can be hyperchromatic		
Grooves	-	-	+++	-	+	-	-	-	-
Nucleoli	+ to +++	+ to +++	-	-	-	-	+ to +++	-	-
Background necrosis	-	-	-	-	-	−/+	+	-	−/+
IHC stains									
CD68/CD163	+/−	+/−	+/−	+	+	+	+	+	+
CD1a/CD207	-	-	+	-	-	-	-	-	-
S100	+	+	+	−/+	-	-	−/+	-	-

ECD, Erdheim-Chester disease; HIST SARC, histiocytic sarcoma; IHC, immunohistochemistry; JXG, juvenile xanthogranuloma; LCH, Langerhans cell histiocytosis; LN, lymph node; med, medium; RDD-LN, Rosai-Dorfman disease, lymph node type; TBM, tingible body macrophages; XG INFL, xanthogranuloma infiltrative.

Klebsiella rhinoscleromatis, Mycobacterium leprae). Storage disorders, which may show large histiocytes with abundant foamy or vacuolated cytoplasm ("mulberry cells" in Niemann-Pick disease, or cells with wrinkled tissue paper-like cytoplasm in Gaucher disease) may also be considered in the differential diagnosis, as are foreign material accumulations (silicone or joint prosthesis material) within histiocytes, but none of these conditions shows emperipolesis.

Among the histiocytoses, LCH can be differentiated by the smaller LCH cells demonstrating smaller amounts of cytoplasm lacking emperipolesis, characteristically grooved ("coffee-bean") nuclei with contorted shapes and inconspicuous nucleoli, the characteristic association with eosinophils rather than plasma cells, and the positivity for CD1a and CD207 (Langerin), in addition to S100 and CD68.[14]

JXG and ECD show similar cytologic findings with bland, medium-sized foamy (xanthomatous) macrophages with round nuclei and inconspicuous nucleoli, occurring singly and in clusters and fragments of fibrous tissue, possibly admixed with lymphocytes, and occasional Touton-type giant cells.[14] Their diagnosis relies in large part on clinical and imaging findings: JXG typically involves the skin and subcutaneous tissue of young children, whereas ECD typically affects middle-aged adults with bilateral symmetric involvement of the diaphyseal and metaphyseal regions of the long bones.[14] Both JXG and ECD can be differentiated from RDD by the smaller size and striking fine vacuolation of the histiocytic cells, lack of emperipolesis and of cytologic atypia as well their variable, only weak, S100 staining.[14]

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal disorder that can be primary (genetic) or secondary to infections or malignancy, and is characterized by tissue infiltration with histiocytes showing hemophagocytosis, and in particular erythrophagocytosis.[14] Hemophagocytic syndrome is a clinical diagnosis with specific criteria, and the demonstration of hemophagocytosis is not absolutely required for the diagnosis if the other diagnostic criteria are met.[14] Erythrophagocytosis predominates and the activated histiocytes of HLH are typically engorged with red blood cells, in contrast to RDD cells that typically contain lymphocytes, plasma cells, and other nucleated blood cells, but no erythrocytes.[2] Malignant histiocytosis or histiocytic sarcoma can be differentiated from RDD by the frankly malignant cytologic features, including nuclear pleomorphism, mitoses (including atypical mitoses), and the presence of hemophagocytosis rather than emperipolesis.[92] Molecular studies can also aid the differential diagnosis, because the *BRAF*^{V600E} mutations can be found in other histiocytoses, but not in RDD.[2]

One of the potentially more difficult differential diagnostic considerations is Hodgkin lymphoma, which was entertained since the earliest description of RDD.[16,18] Both entities may demonstrate large, binucleated cells with nuclear atypia. However, RDD cells show more abundant cytoplasm, emperipolesis, cytoplasmic vacuolation, and are not associated with eosinophils.[43] The large pale epithelioid or foamy ("balloon") occasionally binucleated melanoma cells, which stain for S100, and sometimes with CD68 too, may be confused with RDD cells or vice versa.[93] However, melanoma cells do not show emperipolesis and have a different immunostaining pattern, frequently also showing SOX10, MART1, HMB45 or MITF expression.

Most patients with classic (nodal) RDD have a good prognosis and do not require treatment.[2] Approximately 20% to 40% of patients with RDD will remit spontaneously, and many of the remaining patients have persistent but stable disease. Therefore, observation is the preferred management for patients with cutaneous or nodal RDD and some patients with asymptomatic extranodal RDD.[2] Approximately 10% of patients suffer from progressive disease that can result in death.[2] Features associated with poor prognosis include the presence of immune-mediated disorders, extensive nodal disease, or extranodal disease—especially with involvement of the kidneys, lower respiratory tract and liver.[25] For these patients there is currently no uniform approach to therapy; the treatment is usually tailored to the patient's individual circumstances, and may include surgery, radiation therapy, corticosteroids, immunomodulatory drugs (thalidomide, lenalidomide, methotrexate, azathioprine, cyclosporine A, mycophenolate mofetil, cyclophosphamide, imatinib, infliximab and rituximab), and chemotherapy (Vinca alkaloids, 6-mercaptopurine, vincristine, cladribine, clofarabine, chlorambucil, etoposide).[2] The identification of targetable mutations in genes of the MAPK pathway offers hope for targeted treatments with MEK inhibitors like cobimetinib[94] in cases with widespread extranodal involvement or progressive disease.[2]

In conclusion, RDD is a rare disease that can clinically mimic a variety of malignancies, but typically has a good prognosis and is often managed with observation alone. As such, definitive diagnosis on FNA is imperative for proper patient care. Cytologic diagnosis of RDD is possible even in cases from unusual locations, like RDD affecting intra-abdominal/retroperitoneal locations and can be accomplished through CT-guided and EUS-guided FNA. Nevertheless, the data from the literature and our experience demonstrate that, compared with the FNA diagnosis of classic (nodal) RDD, the diagnosis of extranodal RDD is more difficult, especially in the presence of extensive fibrosis. We found that in extranodal RDD, a cytologic diagnosis is more straightforward than a histopathologic diagnosis, because the large pale histiocytes with emperipolesis are more readily identifiable on aspirate smears than in tissue sections. The rarity of the disease and the unfamiliarity with its cytologic features are the main obstacles to a prompt diagnosis; once the diagnosis is considered and the differential diagnostic considerations are ruled out, the diagnosis can be confirmed with the use of immunohistochemical stains for S100, CD68/CD163, which are both

positive in RDD and CD1a/CD207, which are negative in RDD.

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