Case Report

Extranodal Rosai-Dorfman Disease Involving Colon A Case Report with Review of the Literature

Haiying Chen, MD, Jianlan Sun, MD, PhD, Lalarukh Aftab, MD, Amy Sands, MD

Abstract

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare, idiopathic and non-neoplastic histiocytic disorder. The most common presentation of RDD is painless cervical lymphadenopathy in a young patient. However, in about 25% of cases there is no lymph node involvement, and the disease presents as a mass in skin, soft tissue, nasal cavity, eye, bone, or other extranodal sites (extranodal type). This can pose a diagnostic challenge if RDD is not considered in differential diagnoses. Gastrointestinal (GI) involvement of RDD is extremely rare; only 15 cases had been reported.

We report a case of extra-nodal RDD involving the GI tract of a 24-year-old African-American woman who presented with chronic lower abdominal pain, constipation and an 8 cm mass involving her colonic wall. Microscopically, the mass was well demarcated, partially covered with serosa and extended into the muscularis propria and submucosa of the colon. The lesional cells consisted of spindle-shaped and epithelioid histiocytes intermixed with plasma cells and lymphocytes. Rare histiocytes showed emperipolesis. The histiocytes were positive for S100 (strong) and CD68, and negative for c-kit and CD1a. The above morphological and immunohistochemical features are diagnostic for RDD, extra-nodal type. The related literature was reviewed and compared with this case.

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Introduction

RDD or SHML is a rare histiocytic disorder, considered by most clinicians as an idiopathic, non-neoplastic disease. In 1969, Rosai and Dorfman recognized it as a distinct clinicopathologic entity.[1] It occurs worldwide and is primarily a disease of childhood and early adulthood. Mean age of onset is 20 years. It is characterized by slowly progressive painless lymphadenopathy and usually involves the cervical region.[2,3] However, in about 25% of cases there is no lymph node involvement, and the disease presents as a mass in skin, soft tissue, nasal cavity, eye, bone, or other extranodal sites (extranodal type). This can pose a diagnostic challenge if RDD is not considered in differential diagnoses. Although about a thousand publications related to SHML can be found in the literature, GI involvement of SHML is very rare, only 15 cases had been reported in English literature.[1-6]

Case Report

The patient is a 22-years-old African American female, who was in good health until 3 years ago when she presented with vomiting, stomachache and lower back pain. X-ray computed tomography (CT) and MRI revealed a large irregular pelvic mass. Biopsy of the mass showed fibroblastic proliferation with mixed inflammatory cells. There was no evidence of malignancy. Ten months later, the patient was admitted to surgically remove the mass. During the operation, the mass was found to adhere extensively to pelvic organs, making complete resection impossible. Since the mass adhered tightly to the colon, two segments of colon were resected together with parts of the mass.

Follow Up

Since the diagnosis of RDD, the patient had multiple hospitalizations and surgeries. Fourteen months after initial presentation, she received a second debulking surgery, which again failed to completely remove the RDD mass. A year later, due to the long term compression of the left ureter by the RDD mass, she developed left hydronephrosis and underwent left nephorectomy. At last follow-up, the patient was alive and doing well.

Pathologic Findings

The specimen consists of two segments of colon, each having an attached firm nodule. Both nodules (measuring 9.2 cm and6.0 cm respectively) are at the serosal surface, invading

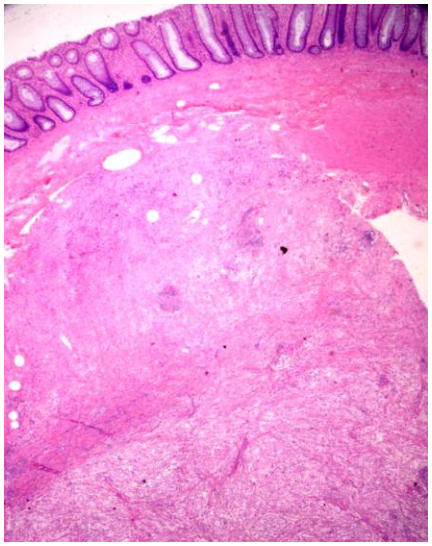

Figure 1. The mass is well demarcated, and extends to the submucosal layer. The colonic mucosa is not involved. (H&E, x20).

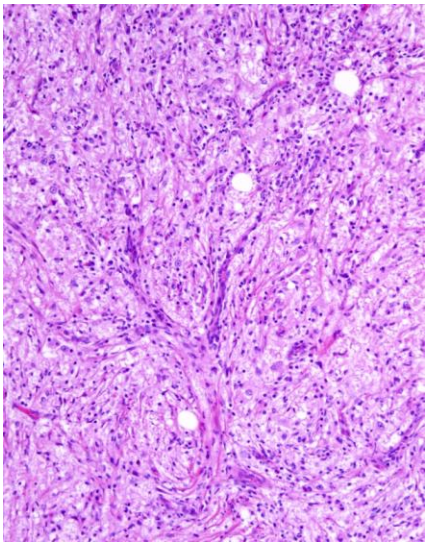

Figure 2. The mass is composed of spindle cells, intermixed with chronic inflammatory cells. (H&E, x100).

through the muscularis propria into the submucosa. Under low power microscopy, the nodules are well demarcated, and the colonic mucosa is not involved (**Figure 1**). The rest of the colon in the specimen shows no abnormalities. Three lymph nodes are identified in the specimen, which are not involved by the disease. Under higher magnification, each mass is composed of predominantly spindle cells, intermixed with chronic inflammatory cells, such as histiocytes and lymphocytes (**Figure 2** and **3**). The histiocytes show vesicular nuclei and single prominent nucleoli, and many of them contain lymphocytes and plasma cells, consistent with emperipolesis (**Figure 4**). Immunohistochemically, lesional cells are positive for S100 and CD68, negative for CD1a and CD117 (c-kit), supporting a diagnosis of RDD. The negative staining of CD1a and c-Kit do not support the differential diagnoses of Langerhans cells histiocytosis and gastroinstestinal stromal tumor (GIST).

Based on the presence of emperipolesis, distinctive histiocytic morphology, strongly positive S-100 and CD 68 staining, the final diagnosis is Rosai Dorfman disease, Extra-nodal type.

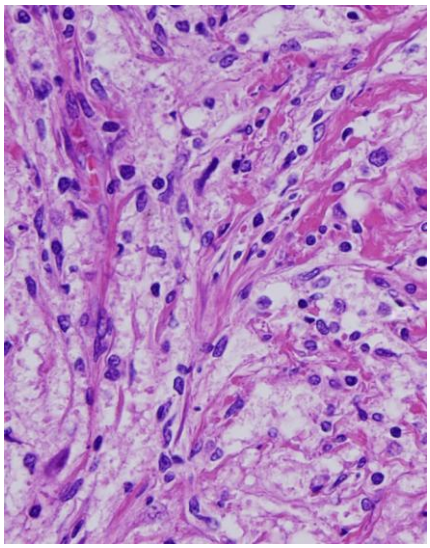

Figure 3. There are plenty of histiocytes, endothelial cells, and lymphocytes. (H&E, x400).

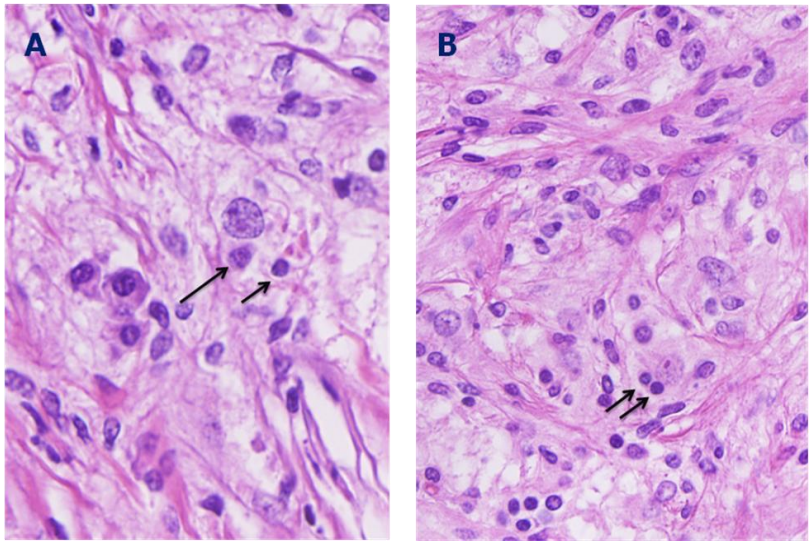

Figure 4. Emperipolesis. **A.** A lymphocyte (short arrow) and a plasma cell (long arrow) can be seen within a large histiocyte. **B.** Two lymphocytes (short arrows) can be seen within a histiocyte. (H&E, x400).

Discussion

RDD or SHML was first established as a clinicopathologic entity by Rosai and Dorfman in 1969,[1] although there had been cases described under other terms previously.[9] Most patients are young and present with massive painless lymphadenopathy (most often cervical), sometimes associated with fever, polyclonal hypergammaglobulinemia and elevated sedimentation rate. Extranodal involvement, either in association with the nodal disease or as primary prevention, occurs in approximately half of cases.[10] Extranodal RDD can affect practically every organ system, most commonly skin and soft tissue. Other less frequently involved extranodal sites include eye and orbit, upper respiratory tract including nasal cavity and paranasal sinuses, central nervous system, heart, bone and salivary gland. The GI tract is the least common site for extranodal RDD. To our knowledge, GI involvement of RDD is extremely rare with only 15 cases reported. Among them, only 8 cases involve the large intestine (including our case) in the English literature[2-8,11] (**Table 1**). The majority of patients with large intestinal involvement are older (median age 53 years) comparing to those with nodal disease. A female predilection is noted (M:F = 6:2) in the 8 cases reported in the literature. Although it was suggested that RDD has a definite predilection for the distal portions of the colon,[4] it can occur at any segment within the length of colorectal tract. In many RDD cases involving colon, nodal disease was also present in 4 out of 6 cases.

Table 1. Summary of the 8 RDD cases involving colon.

References	Patient Age/sex/race	Site of involvement	Nodal disease	Outcome
Anders3	51/F/NA	Sigmoid colon	Yes	AWD, 15 mo
Alatassi4	60/F/NA	Rectum, sigmoid mesentery, abdominal wall	No	AWD, 4.5 y
Lauwers5	53/F/W	Large intestine	Yes	AWD 17 mo
Long6	79/M/H	Ascending and left colon	Yes	NA
Nathwani7	50/F/B	Rectosigmoid colon, 5-25 cm from anal verge	NA	NA
Osborne8	53/M/NA	Ascending colon and terminal ileum	Yes	AWD
Shukla11	55/F/NA	Cecum	NA	NA
Chen (this case)	22/F/B	Colon	No	AWD

Note: W: White, B: Black, H: Hispanic; AWD: alive with persistent disease; NA: not available.

RDD has long been considered a reactive process; however, the etiology remains unclear. Immune deficiency4 and viral infection by Epstein-Barr virus,[12] human herpes virus 6[13,14] or parvovirus B19[15,16] have been implicated as potential players in pathogenesis. However, definitive evidence is lacking to prove any of these hypotheses.

Currently, the treatment for RDD is not well defined. Nodal RDD often resolves spontaneously, while RDD with GI involvement does not. These patients usually have a protracted clinical course, and may require surgical debulking, radiation therapy, or combination of both.[17] Chemotherapy is usually not used due to lack of response.[17] Morphologically, the major differential diagnosis in our case was Langerhans cell histiocytosis involving the colon, in which Langerhans cells with nuclear "grooves" proliferate and form sheets or large aggregates in a background of increased eosinophils. The Langerhans cells express surface antigen CD1a, langerin and are immunoreactive for S100. By electron microscopy, they contain characteristic Birbeck granules in the cytoplasm.

Other diagnostic considerations for this case include reactive histiocytosis, histiocytic sarcomas, GIST, and less likely, follicular dendritic cell neoplasms. Reactive histiocytosis is a self-limited process with no invasive behavior clinically or morphologically. The histiocytes usually do not show emperipolesis, and only rare cells are positive for S100.[18] Histiocytic sarcomas usually show sheets or large clusters of malignant histiocytes with marked nuclear atypia and frequent mitoses. The neoplastic cells are immunoreactive for CD4, CD68, CD163 and lysozyme, while CD1a, langerin and dendritic cell markers CD21, CD23 and CD35 are negative. S-100 can be expressed, but is usually weak and focal in histiocytic sarcomas.[19] GIST should always be included in the differential diagnoses for a spindle-cell tumor in the GI tract.

The histomorphology of GIST is heterogeneous, resembling tumors of smooth muscle or nerve sheath origin, or exhibiting epithelioid patterns. The expression of CD117 is therefore the single most characteristic feature for GIST. The tumor cells are usually also positive for CD34 (60-70%

cases) and smooth muscle acting (SMA).[20] The follicular dendritic cell sarcoma is a rare neoplasm, with only a few cases reported in the extranodal sites including the GI tract.[21] The neoplastic cells arrange in characteristic storiform arrays or fascicles, whorls, or diffuse sheets, with frequent nuclear pseudo-inclusions and indistinct cell borders. These cells are positive for CD21, CD23, and CD35, variably positive for CD68 and S-100, and negative for CD1a, CD34, CD117 and lysozyme.[19]

The most characteristic histological feature of RDD is emperipolesis (**Figure 4**), which is less commonly identified in extranodal cases. This makes diagnosis of RDD at an extranodal site particularly challenging. Immuno-histochemical stains for S100, CD68, and CD163 may aid the diagnosis. Coexpression of these 3 markers, as well as lack of CD1a and other dendritic cell markers, such as CD21, CD23, and CD35, would support a diagnosis of RDD.

In summary, we described a rare case of RDD involving colon in a young African-American woman, reviewed the major differential diagnoses, and summarized previously published colorectal RDD cases in this report. Due to its rarity at this location, it is crucial to include RDD in the differential diagnoses of an extranodal histiocytic lesion to avoid misdiagnosis.

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