A 61 year old woman presented for screening colonoscopy. A single 3 mm polyp was removed from the transverse colon.

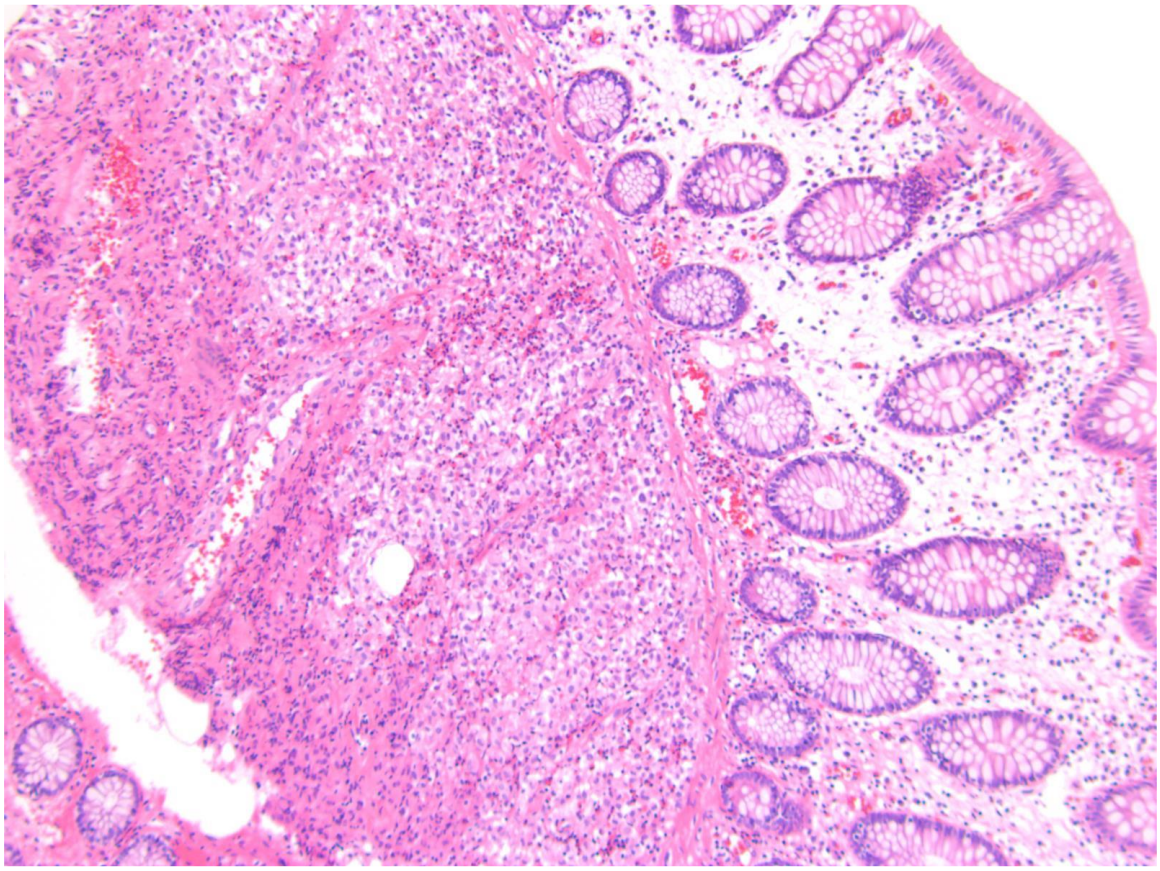

Figure 1. Colon polyp, H&E (10x magnification).

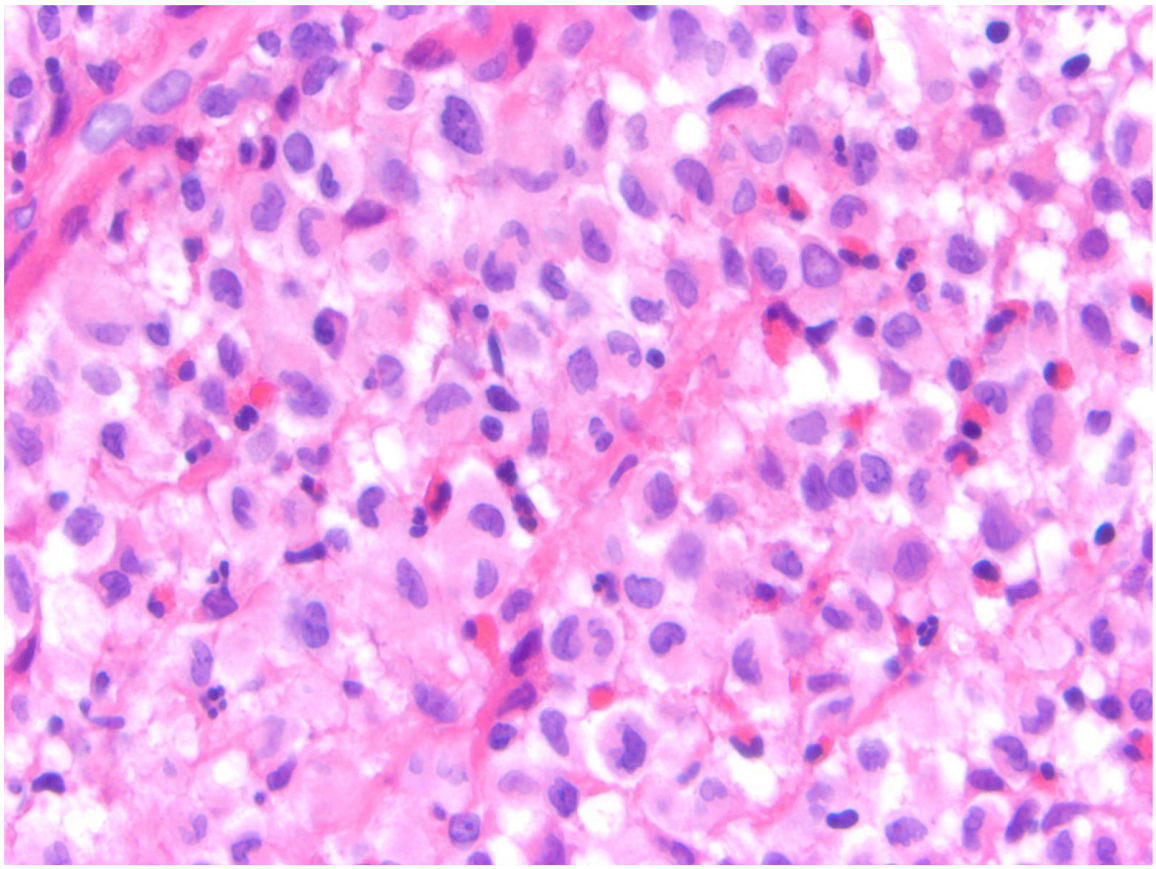

Figure 2. Submucosal cellular infiltrate, H&E (40x magnification).

What is your differential diagnosis?

The following ancillary stains were performed

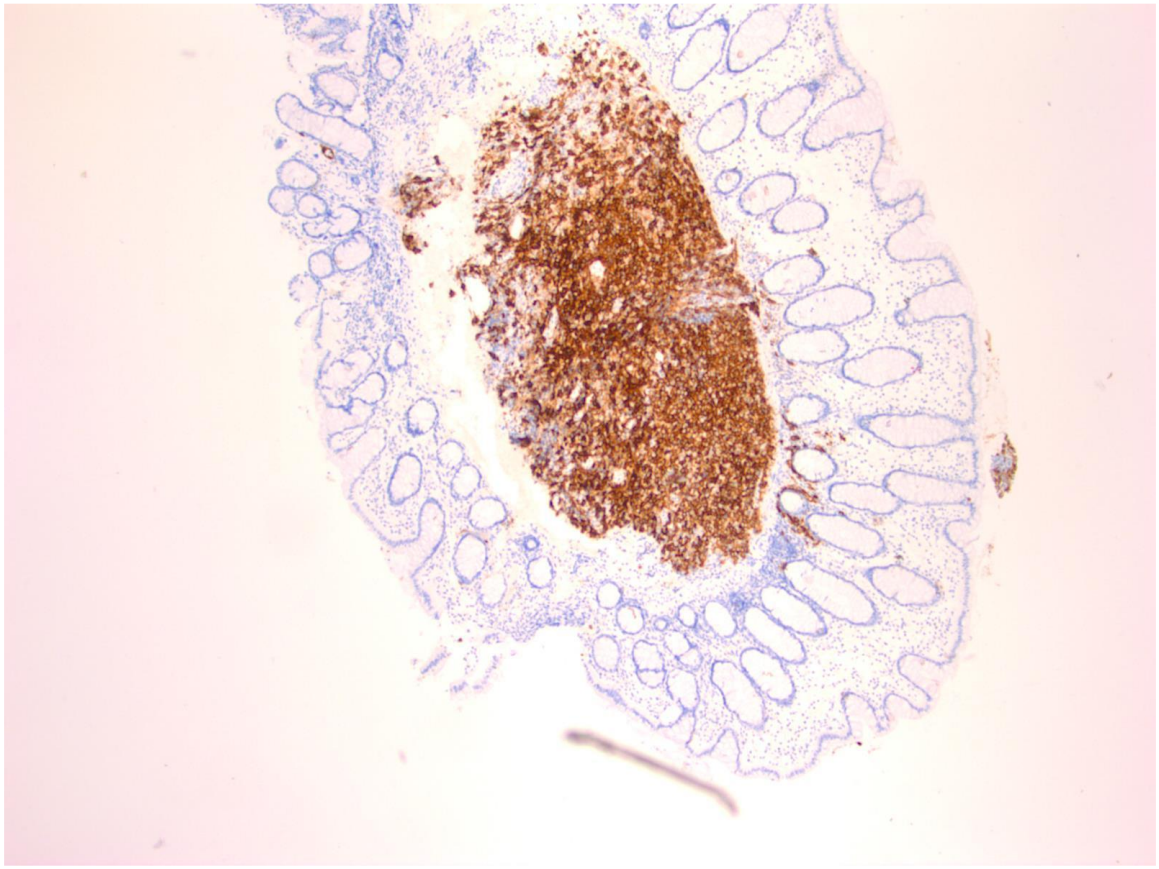

Figure 3. Colon polyp, CD1a immunostain. (4x)

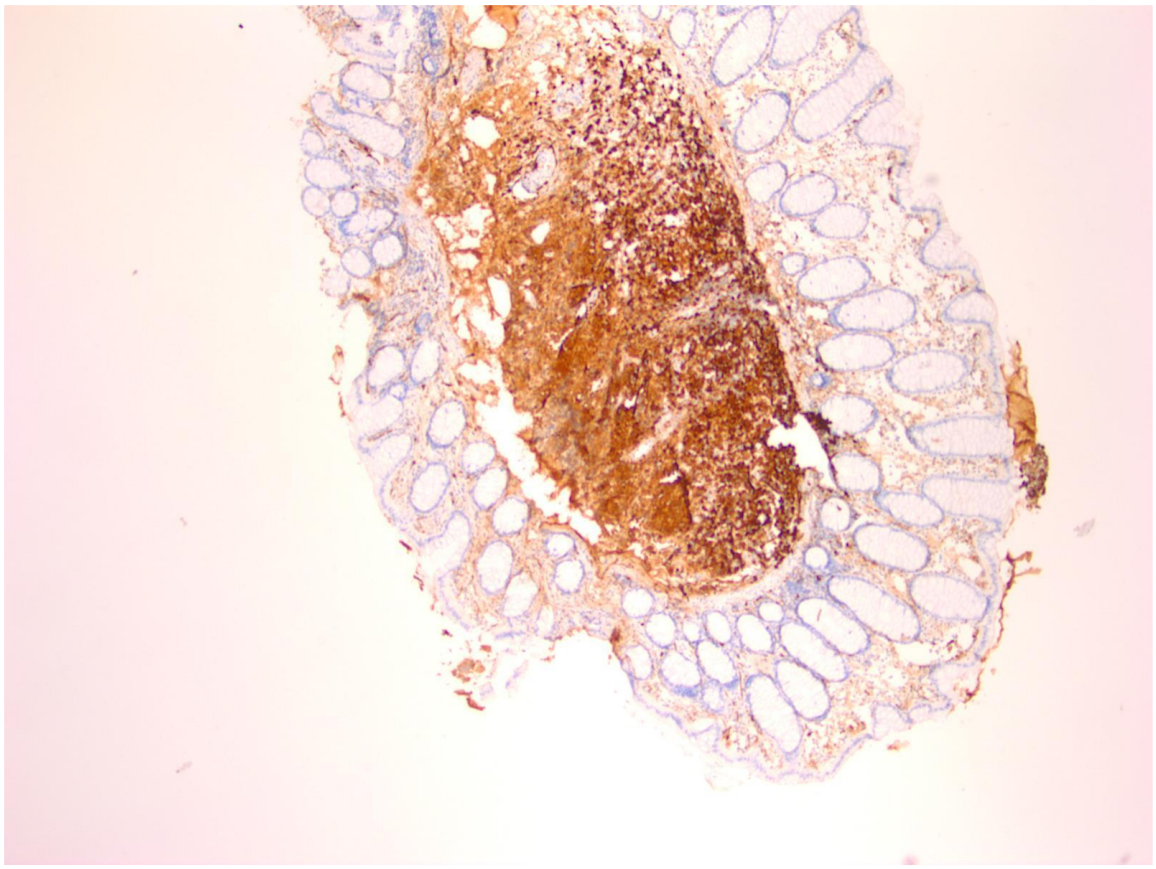

Figure 4. Colon polyp, S100 protein immunostain. (4x)

What is your diagnosis?

A. Rosai-Dorfman disease
B. Histiocytic sarcoma
C. Erdheim-Chester disease
D. Langerhans cell histiocytosis
E. Langerhans cell sarcoma

Correct answer:

D. Langerhans cell histiocytosis

Histologic sections showed a submucosal infiltrate with normal overlying colonic mucosa. High power magnification showed sheets of medium-sized cells with grooved or folded nuclei with abundant eosinophilic cytoplasm. No nuclear atypia or mitotic figures were seen. Admixed amongst these cells were scattered eosinophils, as well as fewer neutrophils and small lymphocytes. The lesional cells were strongly and diffusely immunoreactive for CD1a and S100. A diagnosis of Langerhans cell histiocytosis was rendered.

Langerhans cell histiocytosis (LCH) is a neoplastic proliferation of Langerhans cells with expression of CD1a, S100 proteins and the presence of Birbeck granules by ultrastructural examination. LCH comprises a clinical spectrum ranging from solitary indolent lesions to fulminant disseminated disease. The incidence is about 5 per million with most cases occurring in children. There is an association of the disseminated form of LCH with acute lymphoblastic leukemia. LCH is also associated with malignant lymphoma, either non-Hodgkin or Hodgkin lymphoma. In adults, LCH of the lung is nearly always associated with tobacco or marijuana use. Patients with multifocal, multisystem disease are usually infants who present with fever, skin lesions, hepatosplenomegaly, lymphadenopathy, bone lesions and pancytopenia. Patients with unifocal disease are usually older children or adults who present with a lytic bone lesion or a lesion in other extranodal sites, such as the skin.

Crucial to the diagnosis is recognition of the Langerhans cell. Langerhans cells have characteristic grooved, folded, indented, or lobulated nuclei that contain fine chromatin and inconspicuous nucleoli. The cytoplasm is moderately abundant and eosinophilic. If frankly malignant cytologic features are seen, then consideration of Langerhans cell sarcoma should be made (see below). The appropriate cellular milieu is also important to recognize: variable numbers of eosinophils, histiocytes, neutrophils, and small lymphocytes. Occasionally, eosinophilic abscesses may be found.

Recent studies have shown that a *BRAF* V600E mutation occurs frequently in LCH and these patients manifest with more severe disease. The presence of *BRAF* mutations in LCH indicates that it may potentially respond to RAF pathway inhibitors. (3-4)

Gastrointestinal tract involvement is rare with only a handful of cases in the stomach, small intestine, colon, and perianal skin reported in the English literature. In the stomach, some reported cases revealed malignant features, including high mitotic rates, cytologic atypia, and pancreatic invasion. In the small bowel, LCH has presented in infants with failure to thrive, diarrhea, and weight loss. In one adult, LCH of the small bowel was seen in a patient with Crohn's disease and chronic myelomonocytic leukemia (5). In children, LCH involvement of the colon was related to widespread multisystem disease (6).

There have been 3 reported cases, in the English language literature, of LCH presenting as isolated polyps in adults. All of these patients were asymptomatic and the polyps were detected during screening colonoscopy. Extensive work up in these cases did not reveal involvement in other organs. (2)

In this case, the patient was referred to a hematologist/oncologist and *BRAF* V600E mutation testing performed on the tissue block of the colon polyp was positive.

A. Patients with Rosai-Dorfman disease typically present with lymphadenopathy; the gastrointestinal tract is the least commonly affected organ. The diagnosis requires the presence of large histiocytic cells which are positive for S100, CD68 and negative for CD1a. Emperipolesis of intact leukocytes is typical. (7,8)

B. Histiocytic sarcoma is a rare neoplasm most commonly found in extranodal sites including the intestinal tract, skin and soft tissue. Typically, the cells are non-cohesive, large and round to oval in shape but may have spindling/sarcomatous features. Nuclear pleomorphism can be seen. Expression of histiocytic markers (CD163 or CD68) is required for the diagnosis and CD1a is absent. S100 may be sometimes expressed but is usually weak and focal. Follicular dendritic cell markers (CD21, CD35) and myeloid markers (CD13, MPO) should be also negative. (1)

C. Erdheim-Chester disease is a rare inflammatory disease characterized by systemic infiltration of non-Langerhans cell histiocytes. It most commonly affects the long bones, heart, retroperitoneum and CNS. Involvement of the gastrointestinal tract is very rare. (9) Microscopic examination shows infiltration of foamy mononucleated histiocytes with a small nucleus. Few multinucleated histiocytes are also commonly seen. The histiocytes are positive for CD14, CD68, CD163, and typically negative for CD1a and S100, however S100 may be focally positive in some cases. (7)

E. Langerhans cell sarcoma is a rare neoplasm with high-grade malignant cytologic features and expression of CD1a and S100 (both of which may be focal). Electron microscopy will show Birbeck granules. Langerhans cell sarcoma most commonly involves the skin and underlying soft tissue. (1)

Key Points

- **Langerhans cell histiocytosis (LCH) is rarely seen in the gastrointestinal tract and the diagnosis can be confirmed by CD1a and S100 immunohistochemical stains.**

- **LCH has been recently associated with *BRAF* V600E mutation in a subset of patients and may potentially be responsive to RAF pathway inhibitor treatment.**

- **LCH can be associated with lymphoma and leukemia.**

- **LCH presenting as an isolated colon polyp in adults is very rare and, as of yet, has not been associated with disseminated LCH or a concurrent malignancy.**

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Author:

Saryn Doucette, MD

Staff Pathologist
Poplar Healthcare
3495 Hacks Cross Road
Memphis, TN 38125
Phone: 901-526-7444 Ext.128