Journal Club

张丽英

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ORIGINAL ARTICLE

Rosai-Dorfman Disease of the Digestive System—Beware Vasculopathy

A Clinicopathologic Analysis

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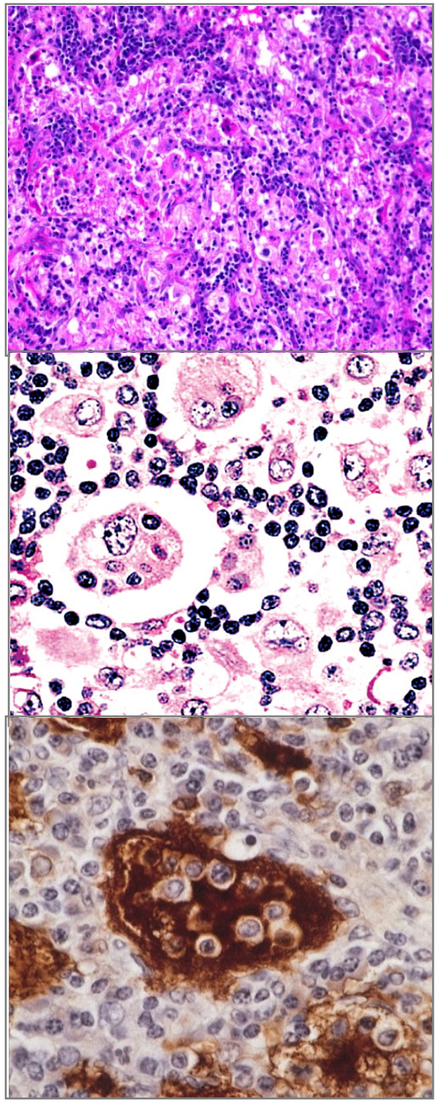
INTRODUCTION

- Sinus histiocytosis with massive lymphadenopathy, eponymously known as Rosai-Dorfman disease (RDD), is an idiopathic histiocytic disorder that is characterized by proliferation of S100-positive, CD1a-negative histiocytes characterized by zones of emperipolesis.
- Initially described in the lymph nodes, the disease can affect extranodal sites in 40% of the cases.
- Involvement of the gastrointestinal (GI) system is rare, accounting for <1% of the reported cases.
- Herein, we describe the clinicopathologic features of 11 patients with extranodal RDD in the digestive organs.



Pic. FROM www.pathologyoutlines.com/

MATERIALS AND METHODS

- An electronic search of the surgical pathology database at the Johns Hopkins Hospital was carried out for RDD involving the digestive organs, including the tubular GI tract, liver, and pancreas.
- For the purposes of this study, we diagnosed RDD based on the identification of histiocytes with the typical cytomorphology (namely slight nuclear atypia) of RDD with strong S100-protein expression and emperipolesis.
- CD1a and other immunohistochemical stains were added for some cases with atypical features/rare foci of RDD-histiocytes but were unnecessary in many cases because of wholly typical histologic features.

MATERIALS AND METHODS

- A total of 12 samples from 11 patients were identified (6 from the consultation files and 6 from the in house). These included 2 cases that had been previously published as case reports.
- Hematoxylin and eosin–stained sections and available immunohistochemical stains were reviewed by 2 pathologists (Z.I.A. and E.A.M.) to evaluate for the following features: margin status, architectural pattern, cytomorphology, emperipolesis, inflammatory pattern, the extent of fibrosis, necrosis, and the presence or absence of other associated pathology.
- Clinical and follow-up information was obtained from the patients' medical records.

RESULTS --- Clinical Findings

TABLE 1. Clinical Features of 11 Patients With RDD of the GI Tract

Case No.	Age (y)	Race	Sex	Location	Size (cm)	Presentation	Associated Conditions	Laboratory Features
1	70	U	F	Sigmoid	U	Diarrhea	U	U
2	65	B	F	Right colon	4.5	U	None	U
3	69	B	M	Rectum	3.3	Weight loss. Bleeding per rectum	MGUS (κ-restricted)	Anemia Increased neutrophils
4	54	U	F	Rectum	U	Incidental. Screening colonoscopy	U	U
5	46	B	F	Rectum	2	U	U	U
6	76	B	F	Appendix	6	Abdominal pain	CLL	Increased LDH, WBC (both neutrophils and lymphocytes), anemia
7	17	B	F	Rectum	6.5	Abdominal pain, gluteal mass	Juvenile idiopathic arthritis	Increased ESR, neutrophils. Anemia
8	61	W	M	Mesentery around the right colon	6.5	Abdominal pain	Asthma, Diabetes	Anemia Increased WBC
9	57	U	F	Pancreas	3.7	Abdominal pain	None	U
10	74	B	F	Pancreas	2	Abdominal pain	Rheumatoid arthritis	Anemia
11	68	W	M	Liver	Diffuse (nonmass forming)	Weight loss	IgA nephropathy	Increased ALT, AST, AP, neutrophils, CRP, ESR, ANA, and anemia

ALT indicates alanine aminotransferase; ANA, antinuclear antibodies; AP, acute pancreatitis; AST, aspartate aminotransferase; B, black; CLL, chronic lymphocytic leukemia; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; M, male; MGUS, monoclonal gammopathy of undetermined significance; U, unknown; W, white; WBC, white blood cell.

RESULTS *--- Clinical Findings*

- Subsequent investigations led to endoscopic identification of lesions in 2 cases. In the remaining instances, imaging revealed a mass.
- The clinical impressions included adenocarcinoma, lymphoma, and neuroendocrine tumor, and the mass lesions were surgically resected. Only 1 patient had the asymptomatic disease, which was discovered during routine endoscopy.
- Three patients had histologically confirmed (and reviewed for this study) multicentric disease, including 2 with nodal involvement and 1 with bone and soft-tissue lesions.
- Information regarding associated conditions was available for 8 patients; 6 had an associated immunologic or hematologic condition, 2 of the 6 had prior abdominal surgery.

RESULTS *--- Pathologic Findings*

- **Twelve specimens were available for pathologic examination; these included 7 resections (5 from the colon and 2 Whipple operations), 2 polypectomies, 2 colonic biopsies, and 1 liver wedge biopsy.**
- **Resected masses were firm, with white-tan cut surfaces and ill-defined-borders.**

RESULTS --- *Pathologic Findings*

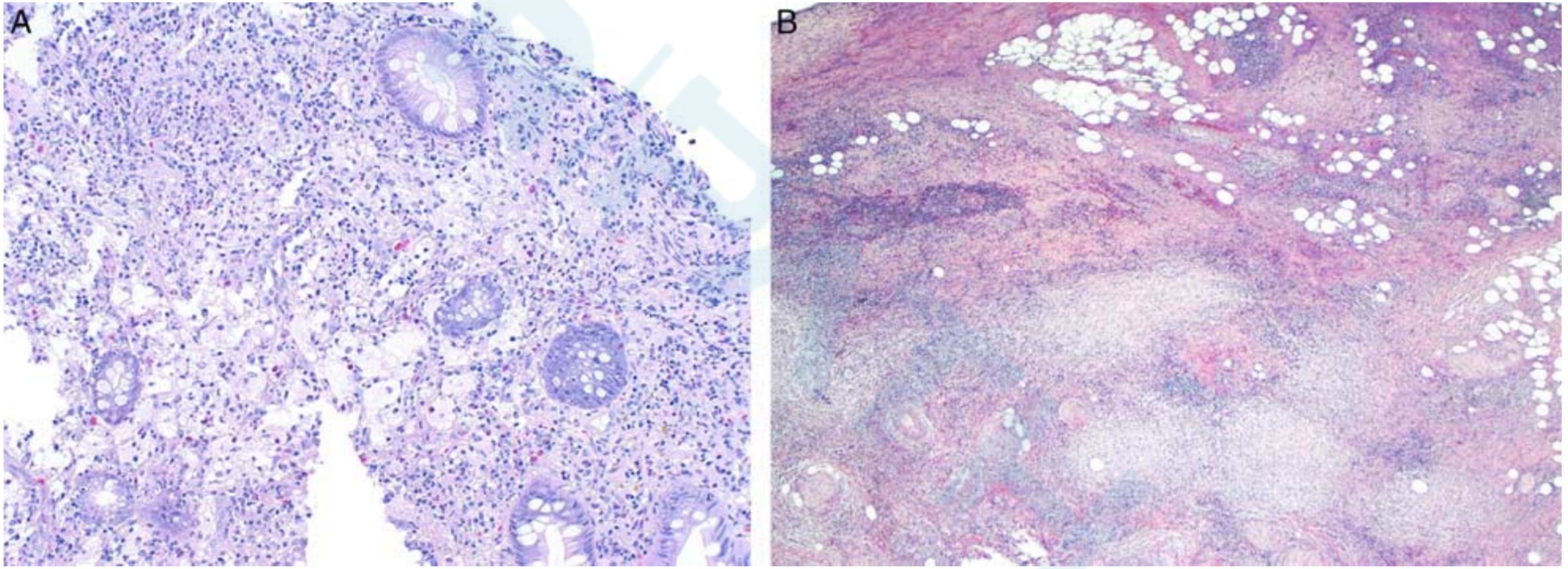


FIGURE 1. A, RDD of the colon (case 1) showing sheets of histiocytes with clear cytoplasm and scattered inflammatory cells infiltrating between the crypts. B, Nodular architecture and scattered lymphoid aggregate in a RDD of the rectum.

RESULTS --- *Pathologic Findings*

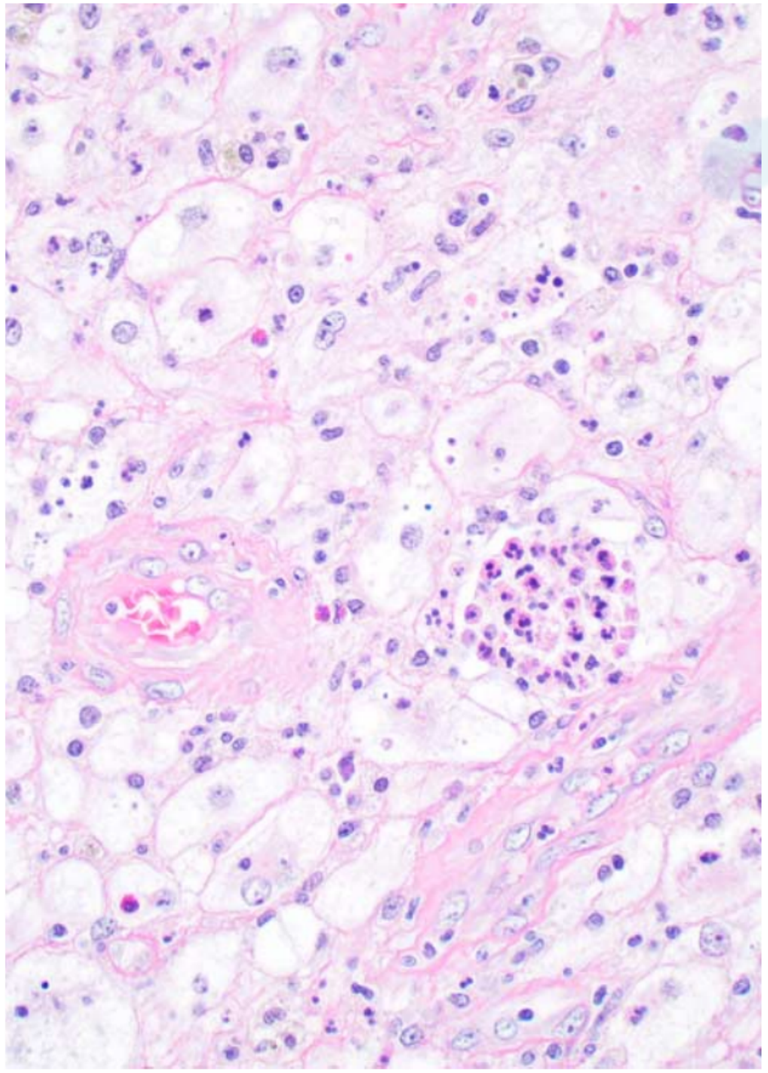


FIGURE 2. RDD. Some cases contain neutrophils forming microabscesses.

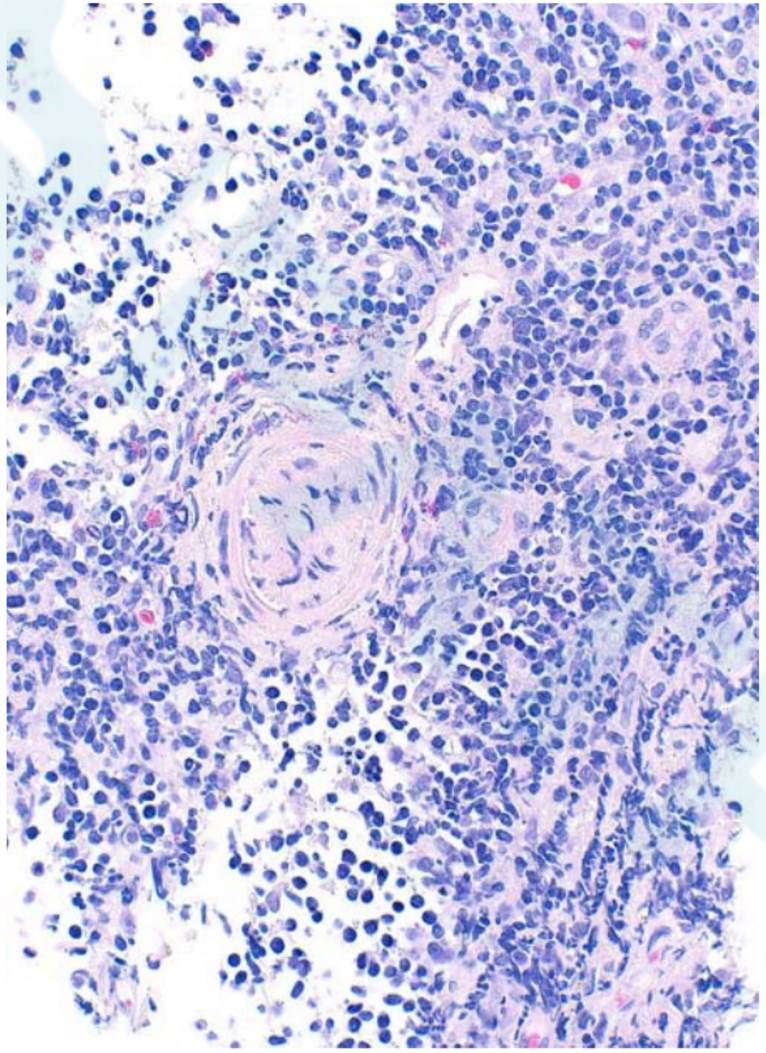


FIGURE 3. RDD. A small but thick-walled vessel is surrounded by lymphocytes.

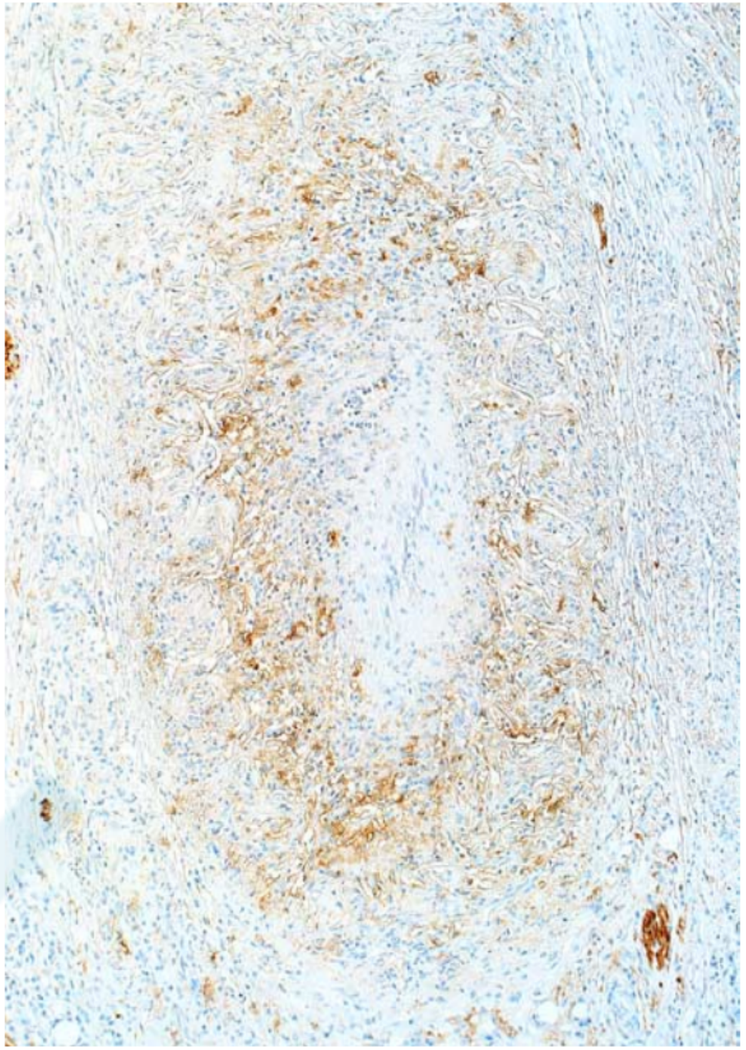


FIGURE 4. RDD. This damaged small thick-walled small artery is thickened in part by S100-protein–reactive lesional cells.

RESULTS

--- *Pathologic Findings*

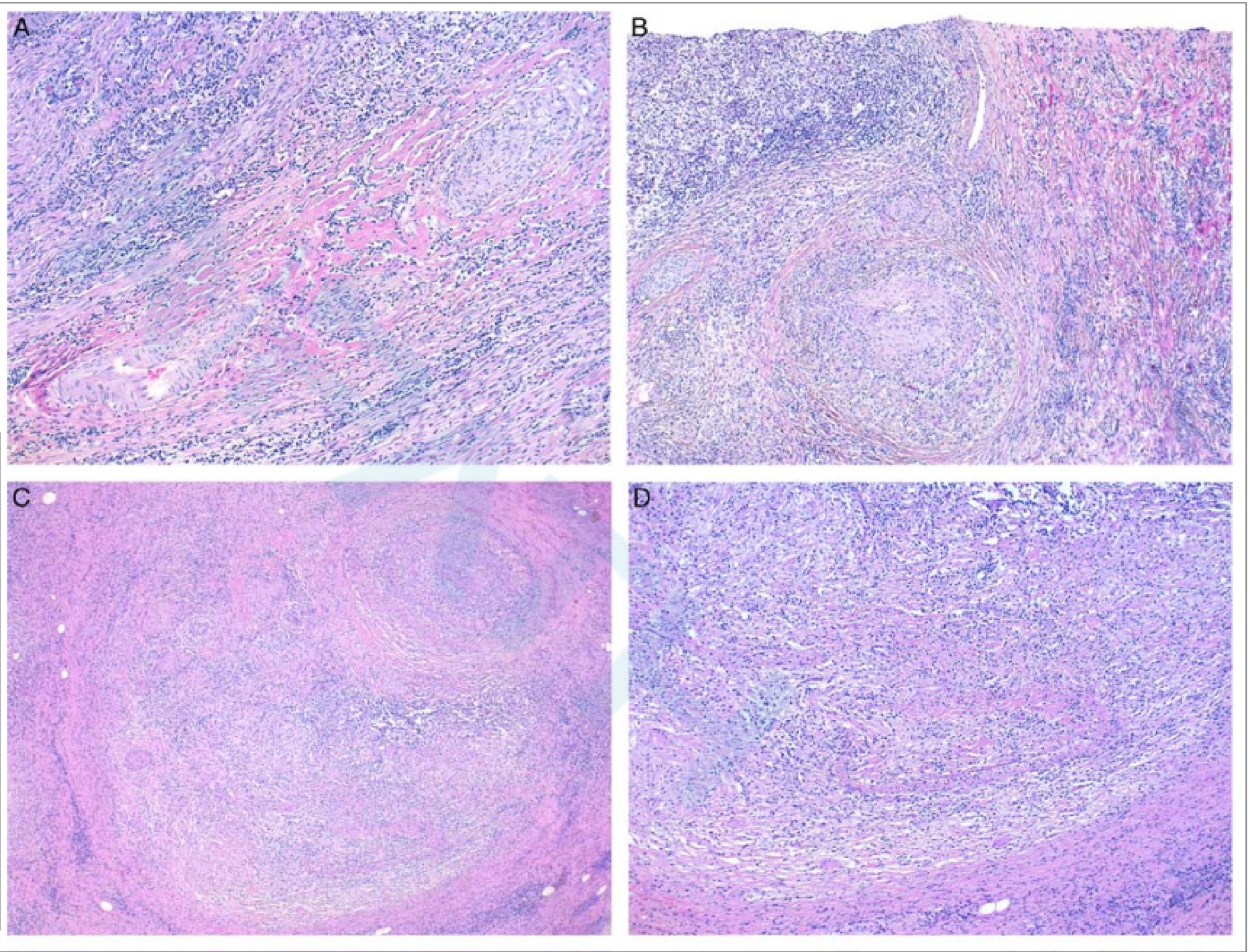
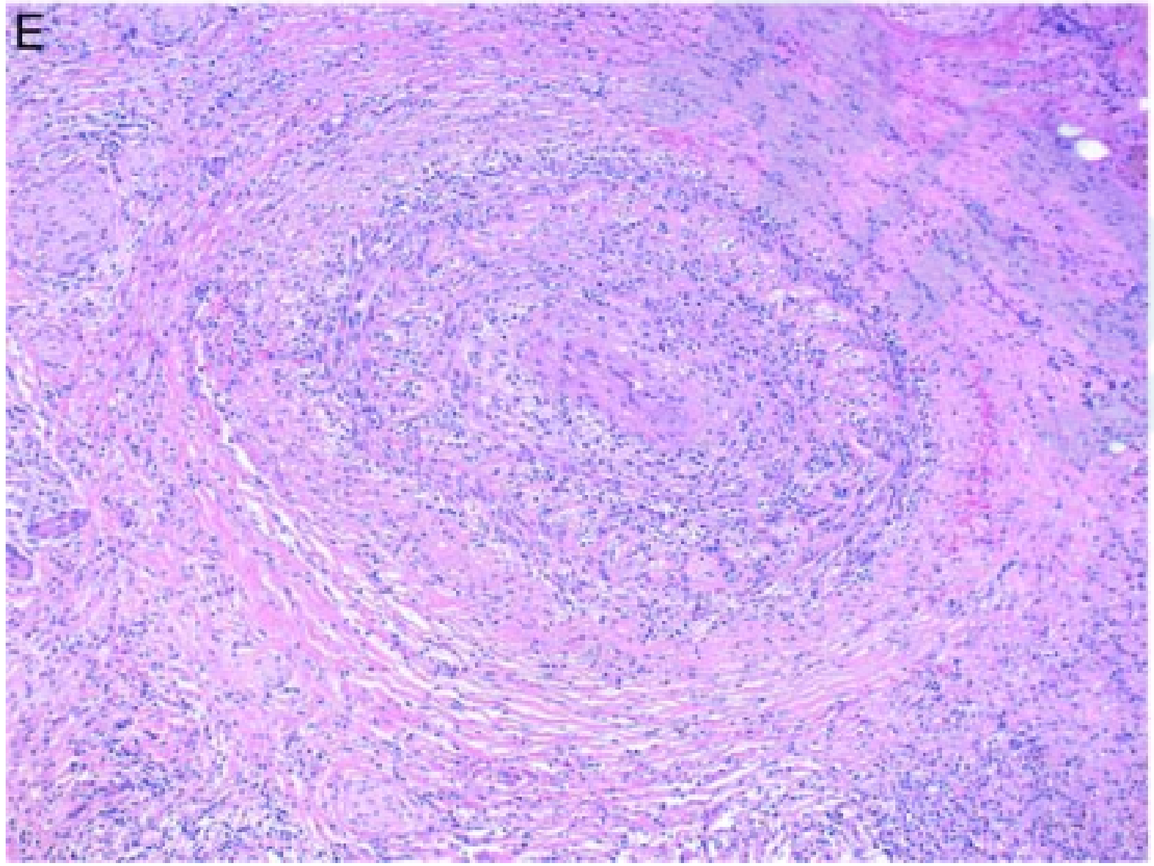


FIGURE5 Vasculopathy in RDD. **A,** The artery is involved by the inflammatory cell infiltrate; the adjacent vein is intact. **B**, Arteritis in RDD with focal phlebitis in the adjacent vein.

C and D, Arteritis and obliterative phlebitis.

RESULTS --- *Pathologic Findings*



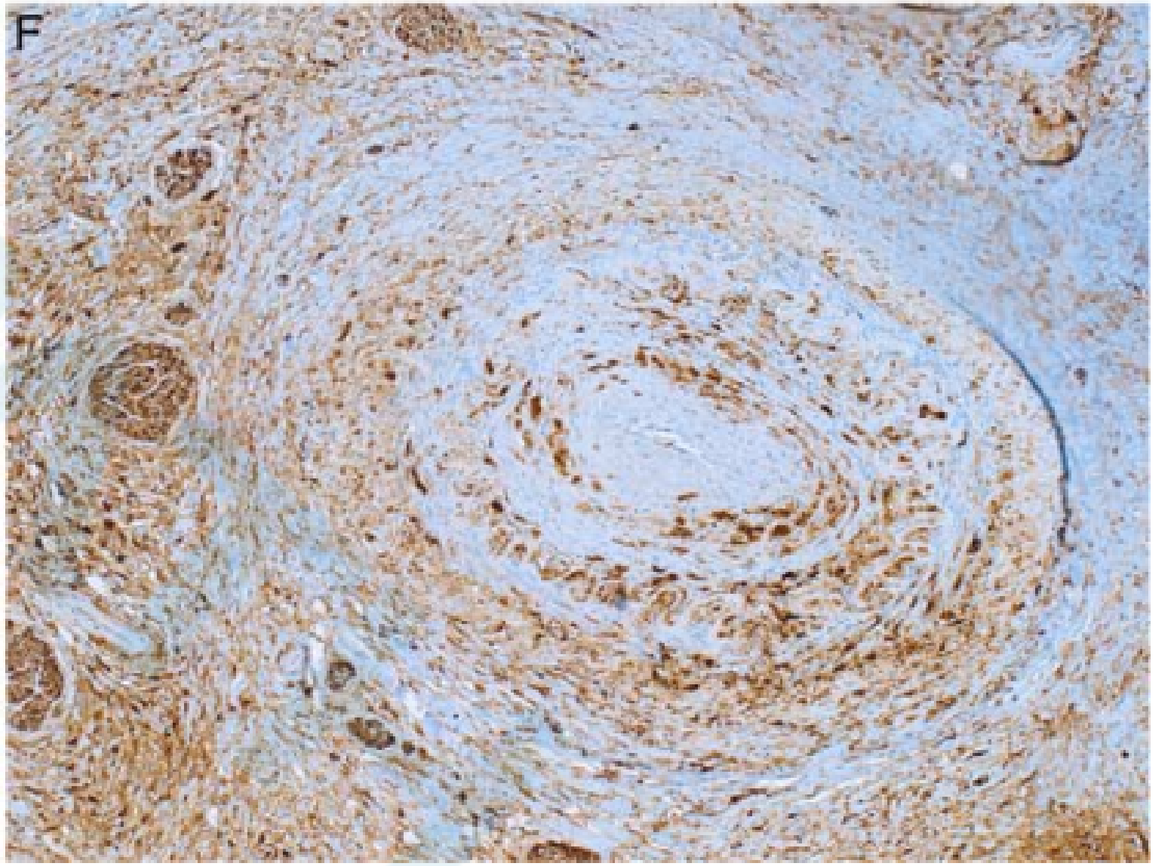


FIGURE 5. Vasculopathy in RDD. A, The artery is involved by the inflammatory cell infiltrate; the adjacent vein is intact. B, Arteritis in RDD with focal phlebitis in the adjacent vein. C and D, Arteritis and obliterative phlebitis. E and F, Higher magnification of phlebitis and arteritis in C with positivity for S100-protein.

RESULTS

--- *Pathologic Findings*

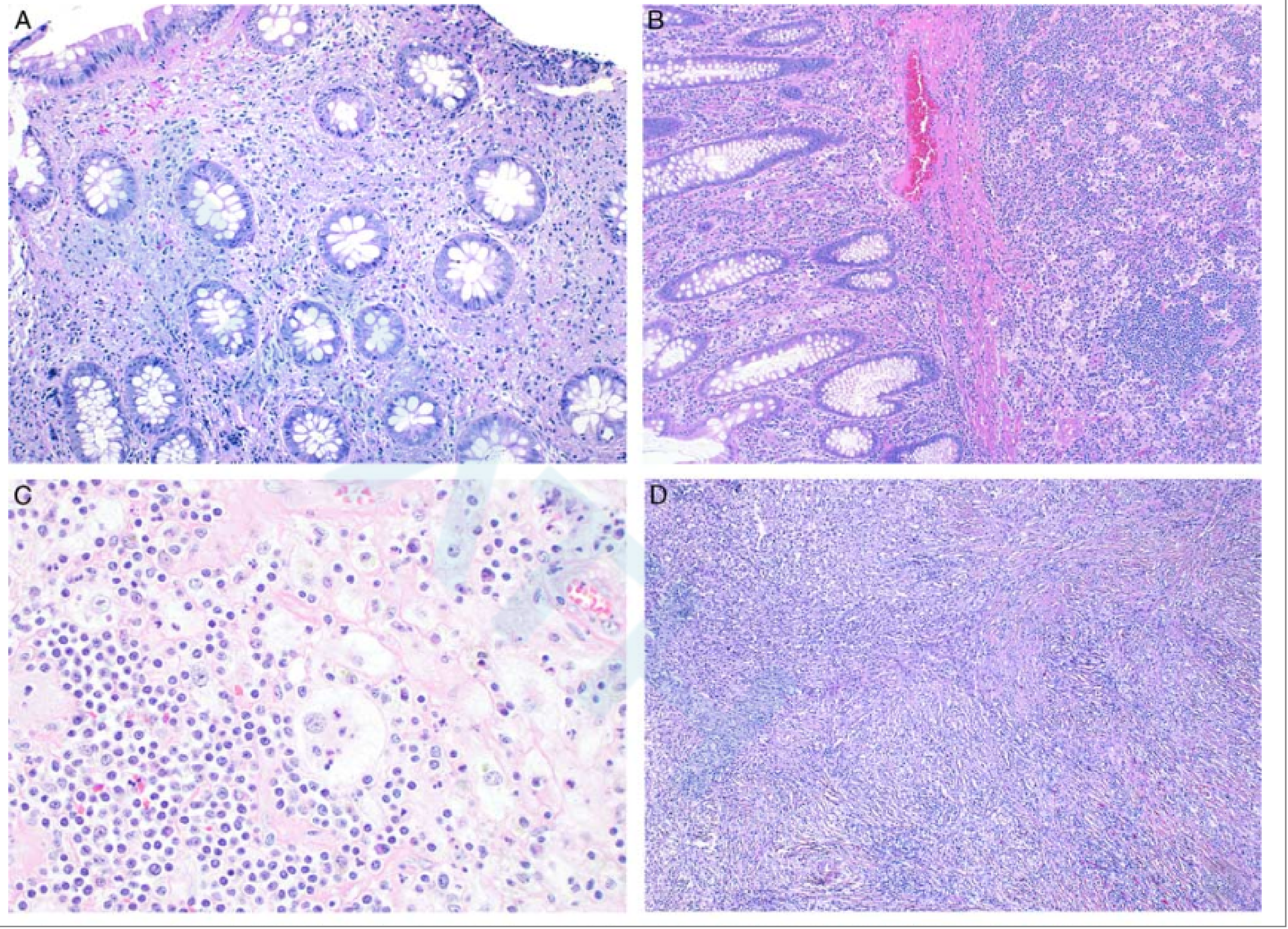


FIGURE 6. A, RDD with inconspicuous diagnostic features with infiltration between the colonic crypts. **A and B**, The disease exhibits minimal fibrosis when involving the mucosa and submucosa. **C**, Cells with emperipolesis are easily identified in the submucosa. **D**, Prominent fibrosis in RDD involving the subserosa of the colon

RESULTS --- *Pathologic Findings*

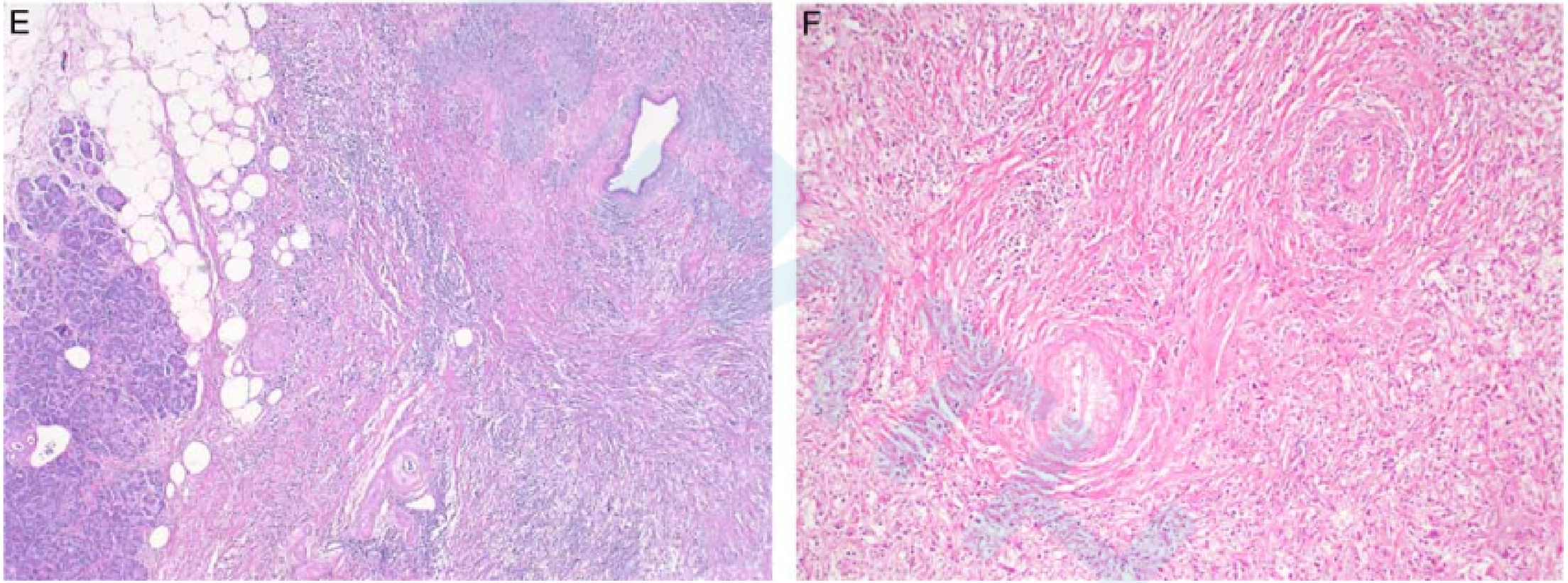


FIGURE 6. A, RDD with inconspicuous diagnostic features with infiltration between the colonic crypts. A and B, The disease exhibits minimal fibrosis when involving the mucosa and submucosa. C, Cells with emperipolesis are easily identified in the submucosa. D, Prominent fibrosis in RDD involving the subserosa of the colon. E and F, Storiform pattern of fibrosis and vascular injury in RDD of the pancreas, which has been initially diagnosed as type-1 autoimmune pancreatitis.

RESULTS --- *Pathologic Findings*

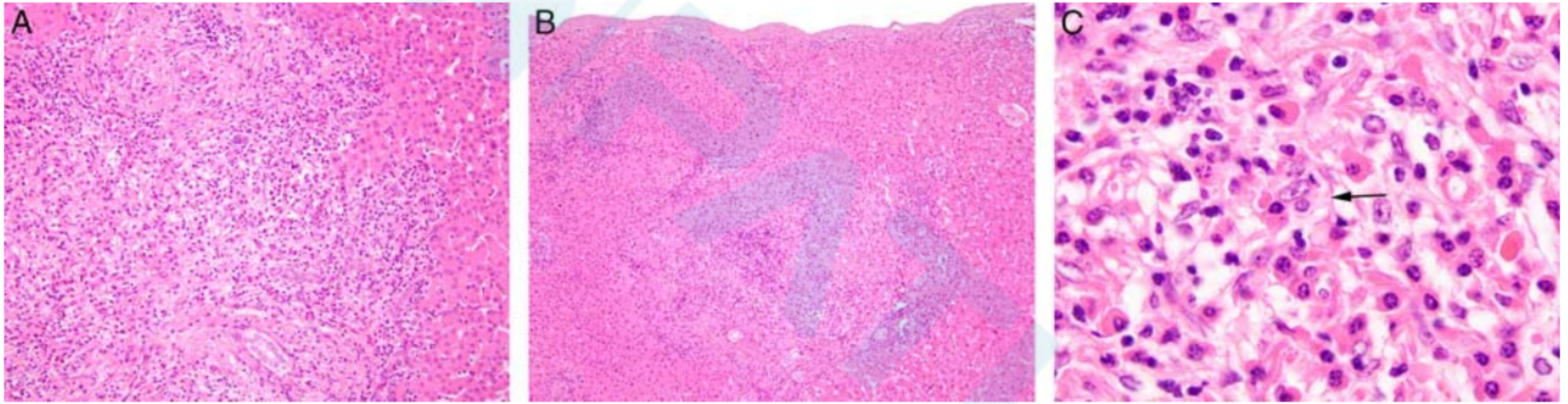


FIGURE 7. RDD involving the liver. A, At intermediate magnification, an infiltrate composed of clear to foamy spindle cells is present in a portal area. B, Note that the surrounding liver is minimally abnormal. C, Emperipolesis is indicated (arrow).

RESULTS *--- Pathologic Findings*

- On immunostaining, S100-protein showed strong staining in all cases (Fig. 8).
- CD68, performed in 8 of 12 lesions, was positive.
- CD1a staining performed in 6 lesions (5 in the colon and 1 in the liver) was negative.

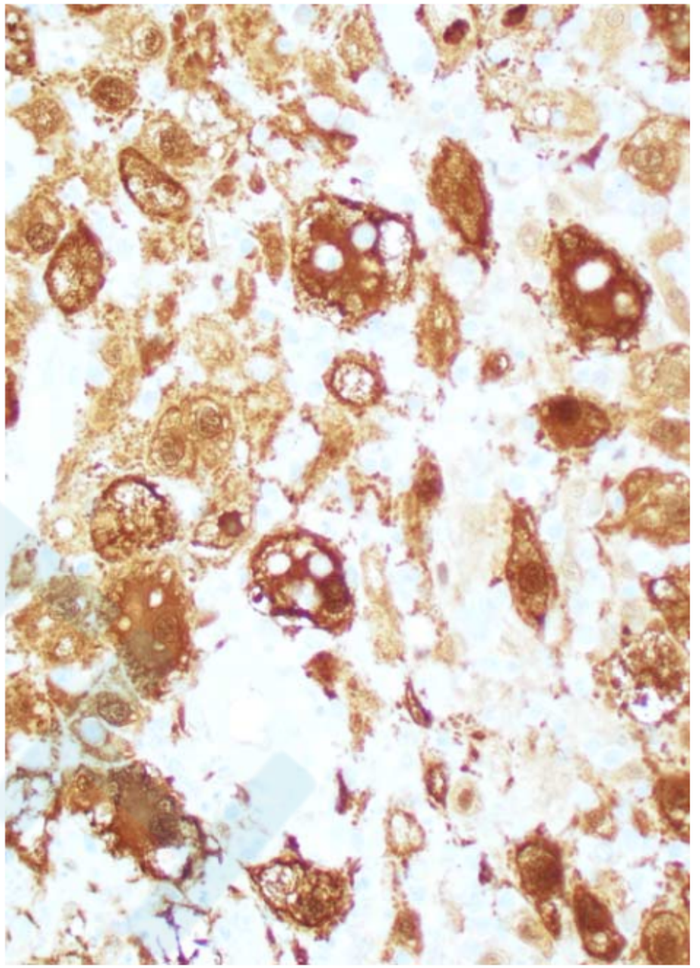


FIGURE 8. RDD. Strong reactivity to antibodies against S100-protein with prominent emperipolesis. The ingested lymphocytes appear pale within the stained cytoplasm of the lesional histiocytes. The nuclei of the RDD cells express S100-protein.

RESULTS

--- *Pathologic Findings*

- CD68, performed in 8 of 12 lesions, was positive.
- CD1a staining performed in 6 lesions (5 in the colon and 1 in the liver) was negative.
- Additional somewhat novel features include:
  - ➢ small vessel wall thickening (n=9)
  - ➢ arteritis of medium-sized arteries (n=5),
  - ➢ phlebitis (n=2)
- A subset of cases showed hemosiderin pigment deposition (n=4) and focal necrosis (n=1).

TABLE 2. Pathologic Features of the 12 Specimens of RDD With Involvement of the Digestive System

Case No.	Site (Specimen Type)	Features	Emperipolesis	Vasculopathy	Fibrosis	Immunostains
1	Sigmoid (biopsy)	Lamina propria expansion by polygonal to spindle cells with eosinophilic cytoplasm punctuated by lymphoid aggregates. Foci of histiocytes with clear cytoplasm. Entrapped crypts. Focal hemosiderin deposition. Fibrosis was focal	Focal	Small wall vessel thickening	Very focal	S100$^+$, CD68$^+$, CD163$^+$ CD1a$^-$
2	Right colon (right hemicolectomy)	Submucosal expansion by polygonal cells extending into the pericolic fat with spindle cells arranged in a nodular pattern	Easily identified in the submucosa	Arteritis phlebitis, vessel wall thickening	Extensive in the subserosa and pericolic fat, storiform	S100$^+$, CD68$^+$ CD163$^+$ CD1a$^-$
3	Perirectal mass (biopsy)	Polygonal to spindle cells with eosinophilic cytoplasm	Very rare	Not present	Moderate	S100$^+$, Keratin$^-$
4	Rectum (polypectomy)	Expansion of the lamina propria by round cells with lightly eosinophilic cytoplasm. Focal hemosiderin deposition	Focal	Not present	No/minimal	S100$^+$ CD68$^+$ CD1a$^-$
5	Rectum (polypectomy)	Submucosal infiltration by sheets of large polygonal cells with clear/foamy cytoplasm, some contained hemosiderin, mixed with lymphocytes and neutrophils. Focal extension into the mucosa	Easily identified	Small wall vessel thickening	Short and long bundles and around blood vessels	S100$^+$ CD68$^+$ CD1a$^-$
6	Appendix (right hemicolectomy)	Transmural involvement by spindle to polygonal cells with clear eosinophilic cytoplasm, and some foamy cells in sheets	Rare in appendix. Prominent in lymph nodes	Arteritis. vessel wall thickening	Extensive	S100$^+$ CD68$^+$ CD1a$^-$
7	Rectum (resection)*	Mostly spindle cells with eosinophilic cytoplasm masked by dense chronic inflammation in a nodular arrangement. Focal necrosis	Rare	Small wall vessel thickening	Extensive	S100$^+$ CD68$^+$, Lysozyme$^+$
8	Rectum (resection)*	Spindle-polygonal cells with eosinophilic to clear cytoplasm in a nodular arrangement	Rare	Arteritis, phlebitis, vessel wall thickening	Extensive	S100$^+$, CD68$^+$
9	Mesentery (right colon resection)	Mesenteric fat involvement by polygonal cells with abundant clear cytoplasm, some spindle cells. Focal nodular arrangement	Easily identified	Focal arteritis, vessel thickening	Extensive, focal storiform pattern	S100$^+$
10	Pancreas (Wipple)	Polygonal and spindle cells with eosinophilic cytoplasm. Focal nodularity. Few foci of histiocytes with clear cytoplasm and hemosiderin deposition	Few	Small wall vessel thickening	Extensive, storiform	S100$^+$, CD68$^+$, CD$^+$163, IgG4$^+$ plasma cells
11	Pancreas (Wipple)	Sheets of spindle cells with abundant eosinophilic to clear cytoplasm	Focal	Arteritis, vessel thickening	Extensive, focal storiform pattern	S100$^+$, CD68$^+$, IgG4 equivocal
12	Liver (Wedge biopsy)	Scattered fibrotic nodules in the portal tracts containing histiocytes, lymphocytes and plasma cells with Russell bodies	Focal in the liver. Rare in the lymph node	Not present	Portal tract fibrosis, sinusoidal storiform fibrosis of the lymph nodes	S100$^+$, CD1a$^-$

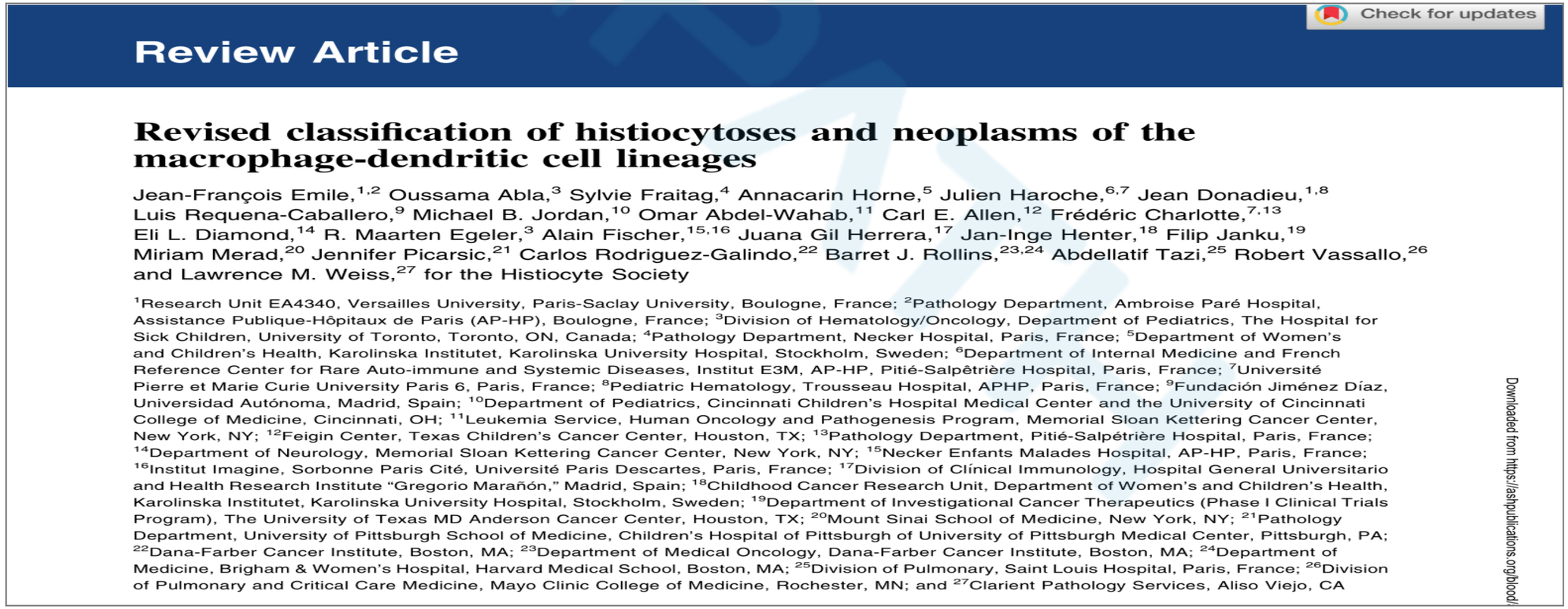
*Specimens 7and 8 were from the same patient.

RESULTS *--- Follow-up Data*

- **Treatment and follow-up information was available for 5 patients; 2 with the multicentric disease received prednisone. Chemotherapy was added for one of them.**
- **The patient with associated chronic lymphocytic leukemia was treated with rituximab; the other 2 patients were under observation.**

DISCUSSION

- **In its most recent revised classification in 2016, the writing group of the Histiocyte Society has classified RDD into the following subtypes: familial RDD, classical RDD, extranodal RDD, neoplasia-associated RDD, and immune disease-associated RDD.**



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Review Article

Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

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Blood. 2016;127:2672–2681.

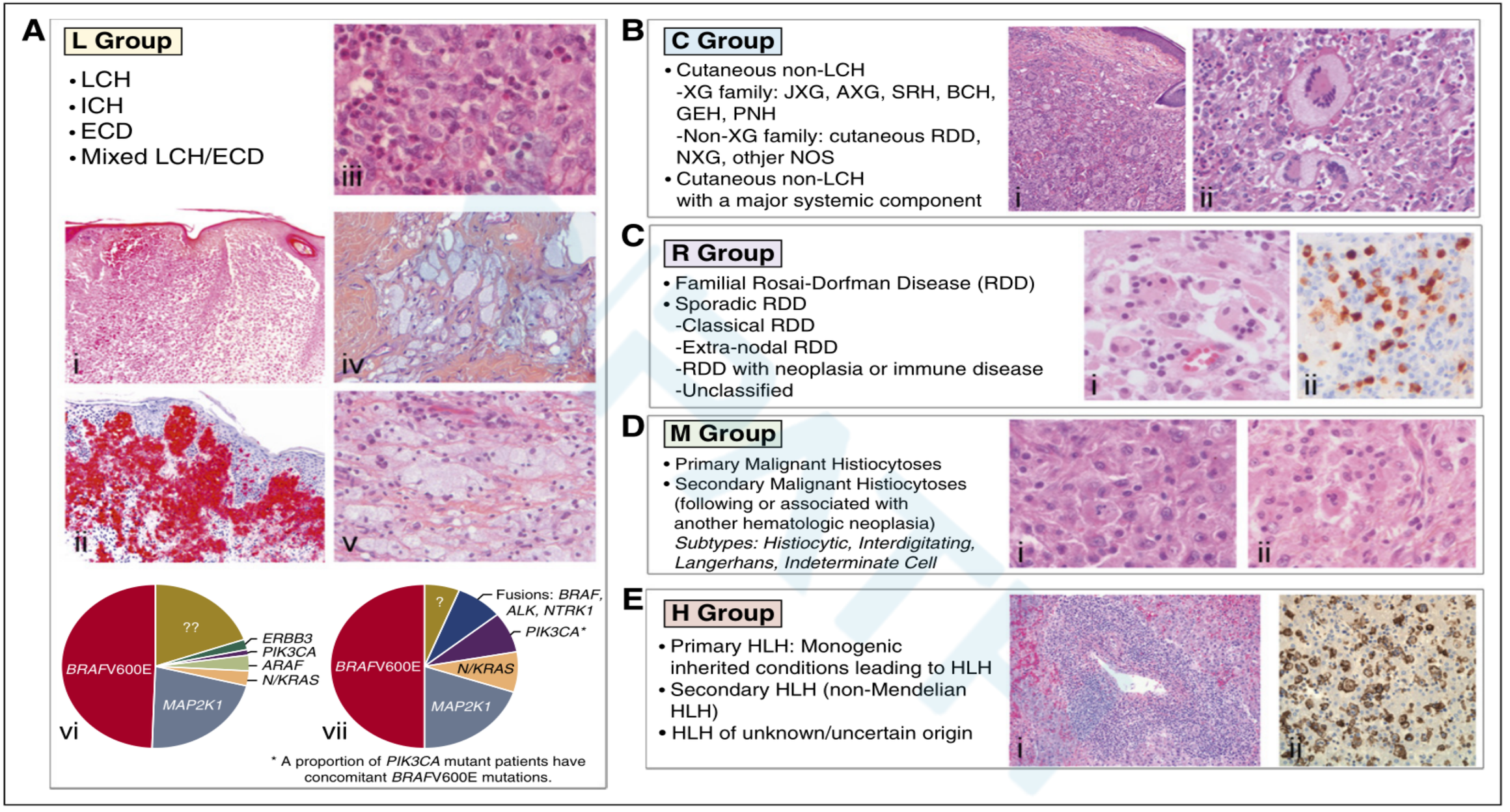


Figure 1. Histology and somatic mutations of histiocytoses of group L, C, R, M, and H. (A) L group: Histology of LCH (skin [i-ii] and bone [iii]) and of ECD (perirenal [iv-v]). Pie chart of relative frequencies of activating kinase mutations in LCH (vi) and ECD (vii). (B) C group: Histology of JXG (i-ii). (C) R group: Histology of RDD (meningeal with high IgG4^{+} plasma cell infiltration [i-ii]). (D) M group: Histology of MH (i-ii). (E) H group: Histology of inherited HLH (liver [i-ii]). Staining with CD1a (Lii in red), IgG4 (Rii in brown), CD163 (Hii in brown), or hematoxylin and eosin (all others). NOS, not otherwise specified.

DISCUSSION---关于发生部位

- The extranodal form has been described in virtually every organ in the body, including skin, nasal cavity, nervous system, bone, and soft tissue.
- The GI system is one of the least commonly affected sites; we are aware of only 29 examples reported in the English literature.
- On the basis of the published cases and the cases in this series, the disease mostly affects middle-aged females. Most digestive system cases arise in the tubular GI tract with a marked preference for the colon. Isolated gastroesophageal lesions have not been described to date; the only 2 reported gastroesophageal cases were part of multicentric RDD affecting the colon as well.

DISCUSSION---关于临床特点

- Presenting symptoms of digestive system RDD include abdominal pain, diarrhea, rectal bleeding, and weight loss. A few cases have been incidentally colonoscopy.
- Hepatic lesions tend to present in younger patients; all but the 1 reported patient has had systemic disease.
- The pancreas is a rare site with only 7 reported cases, including the 2 in this series (1 previously reported 4). All were in females. The lesions were equally distributed in the proximal and distal pancreas.
- Although the association with neoplastic or immunologic diseases was described in 5 of the 29 previously reported cases, more than half of patients in our cohort showed this association. Therefore, the digestive system RDD seems to preferentially occur in the clinical context of an immunologic or neoplastic condition.

DISCUSSION---关于组织学特点

- Histologically, RDD comprises sheets of histiocytes with abundant eosinophilic to clear cytoplasm that is accompanied by a lymphoplasmacytic infiltrate and a variable amount of fibrosis.
- Finding histiocytes in the act of emperipolesis—albeit nonspecific—is a helpful diagnostic feature. However, reaching the diagnosis may be challenging, particularly in the setting of small biopsies or lesions with extensive fibrosis as might be seen in subserosal, mesenteric, and pancreatic lesions.
- Moreover, the presence of vascular injury, newly described for the digestive organs in 5 cases in this series, can complicate the histologic picture and lead to a diagnosis of immunoglobulin G4–related fibrosclerosing disease (IgG4-RD). This phenomenon of vasculopathy has been noted by others in, for example, the breast.

DISCUSSION---关于组织学特点

- However, in general, whereas obliterative phlebitis is a key component of IgG4-RD, arteries were more likely to be affected in our RDD cases.
- Compounding the issue, increased numbers of IgG4-positive plasma cells have been reported in RDD in some but not all studies. In such cases, immunostaining with S100-protein is useful in confirming the diagnosis.
- Because the significance of increased IgG4-positive plasma cells in RDD remains unknown, the 2016 classification of histiocytosis recommends evaluating the IgG4-plasma cell infiltration in all cases of RDD.

DISCUSSION---关于鉴别诊断

- The differential diagnosis also includes other histiocytic lesions, such as Langerhans cell histiocytosis (LCH) and histiocytic sarcoma.
- GI-LCH presents in children as a multifocal disease with poor prognosis, whereas in adults the disease usually presents as an incidental lesion, centered in the mucosa.
- The proliferating histiocytes in LCH exhibit nuclear grooves and nuclear membrane irregularity. The accompanying inflammatory infiltrates consists primarily of eosinophils, and immunohistochemical studies are positive for S100-protein and CD1a, features not found in RDD.

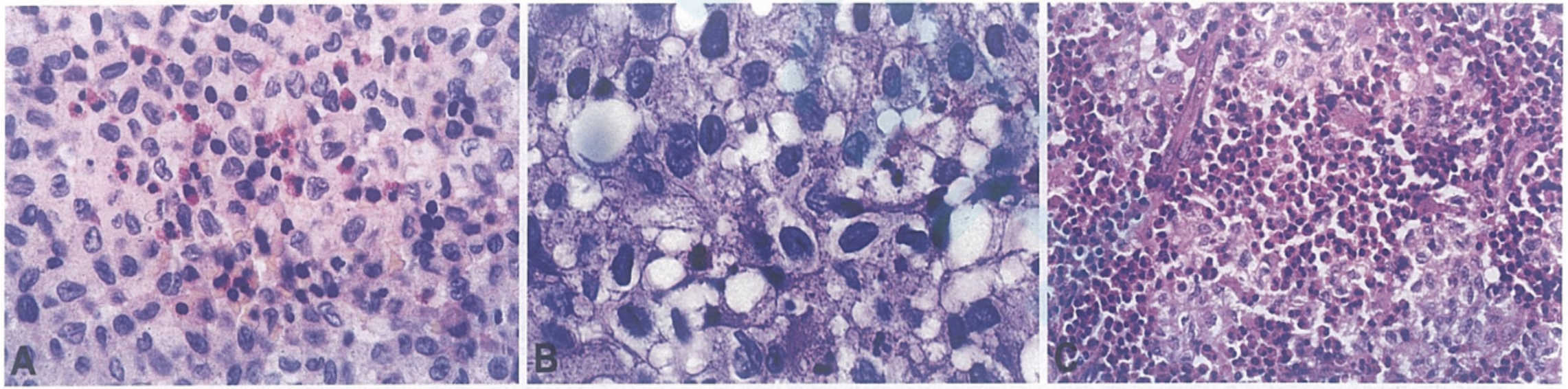
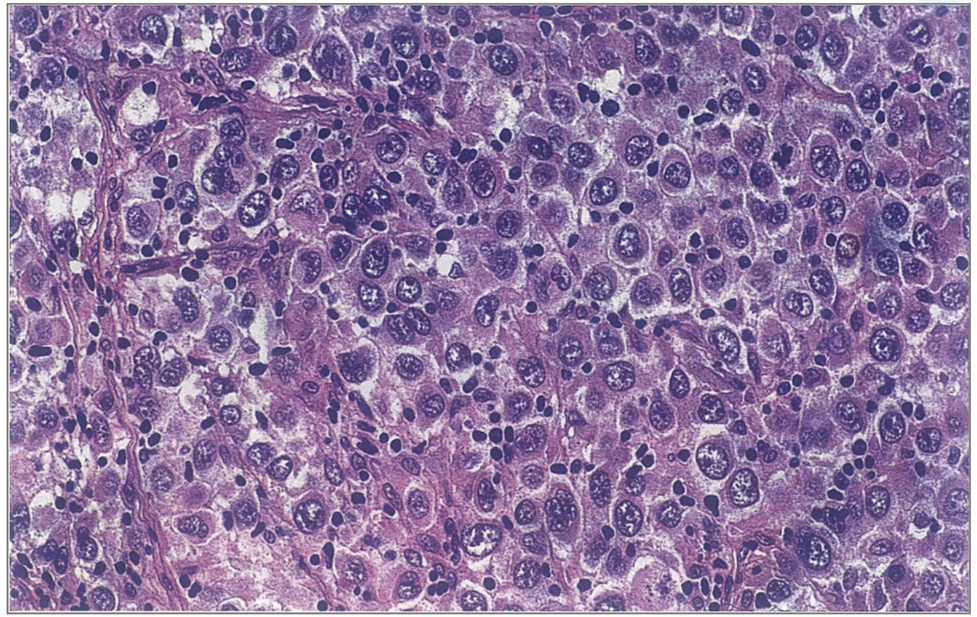


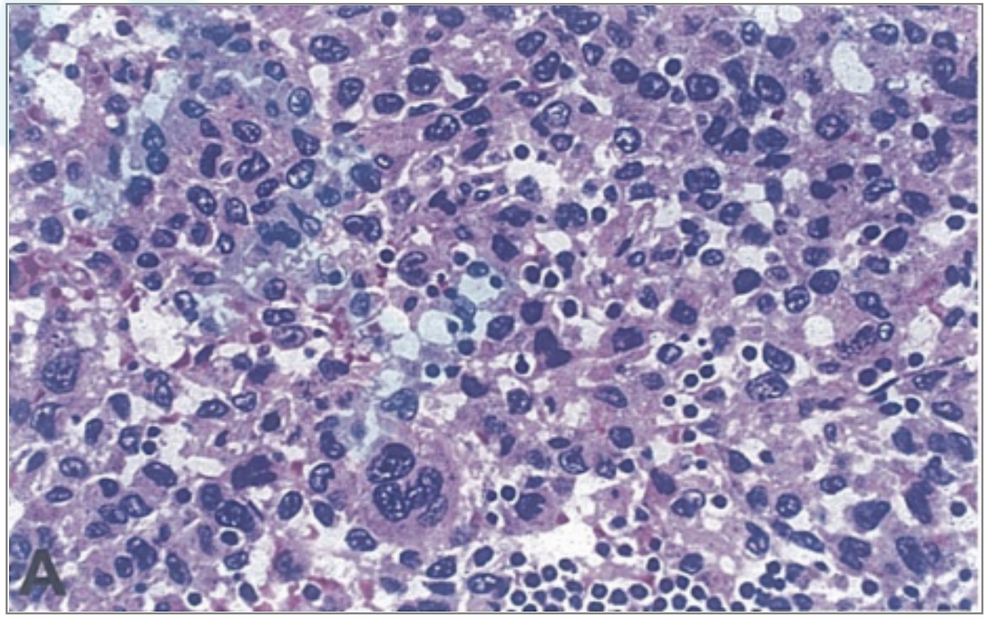
Fig. 17.07 Langerhans cell (LC) histiocytosis. **A** Numerous LCs are seen, with scattered eosinophils and small lymphocytes. **B** Note the typical cytological features of LCs, with many nuclei containing linear grooves. **C** Eosinophilic microabscess.

Pic. from WHO

DISCUSSION---关于鉴别诊断

- Histiocytic sarcoma is an aggressive malignant neoplasm that can involve the GI tract. The neoplastic cells exhibit abundant eosinophilic cytoplasm or focal clear or foamy cytoplasm and occasional cytophagocytosis within a background of a mixed inflammatory cell infiltrate. However, the nuclei are irregular, and S100-protein immunostaining is usually weak and focal.





Pic. from WHO

DISCUSSION---关于病因学及分子改变

- The etiology of RDD remains unclear. Earlier reports linked RDD with viral infections including, but not limited to, human herpesvirus 6 and Epstein-Barr virus. However, that link has not been confirmed with subsequent studies.
- Recently, several reports have identified KRAS,NRAS, NRAF and MAP2K1 mutations in a subset of cases.
- In a study by Garces et al, KRAS mutations were detected in one third of extranodal/nodal RDD. However, another study by the same group on lymphoma-associated RDD involving the same lymph nodes has demonstrated over-expression of MAPK in the absence of detectable mutations, suggesting that the lesion is reactive.
- These data suggest that the disease has different pathogenesis among its subtypes. Whether it is neoplastic or reactive, recent evidence highlights the role of MAPK/ERK pathway activation, a potential target for therapy.

DISCUSSION---关于治疗

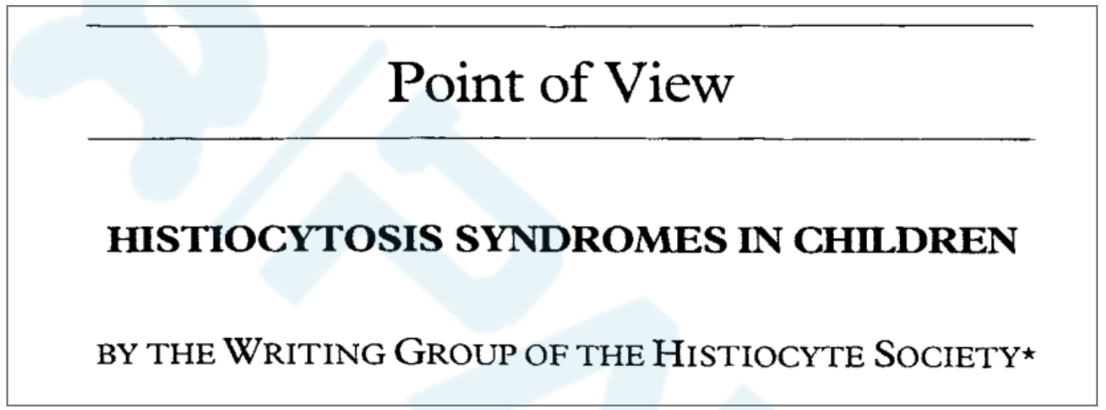
- Unfortunately, there is no unified approach to evaluation and treatment of RDD.
- The management depends mainly on the clinical picture.
- Most asymptomatic and nodal cases regress spontaneously and can be managed by observation, while surgical resection can be beneficial in isolated or bulky lesions.
- Other treatment modalities such as corticosteroids, chemotherapy, and nucleoside analogs have shown a variable response in patients with disseminated disease.

CONCLUSION

- In conclusion, RDD involving the digestive organs is rare.
- In this series, the disease mostly affected middle-age females in association with immunologic or hematologic conditions.
- The diagnosis can be challenging in the absence of typical morphology.
- Vasculopathy, usually affecting arteries rather than veins, can complicate the histologic picture and lead to the diagnosis of IgG4-RD.
- In such cases, S100-protein staining is useful in reaching the correct diagnosis.


Thanks for your attention!

Classification of histiocytosis



Point of View

HISTIOCYTOSIS SYNDROMES IN CHILDREN

BY THE WRITING GROUP OF THE HISTIOCYTE SOCIETY*

- **The first classification of histiocytosis, published in 1987 by the Working Group of the Histiocyte Society (HS), consisted of 3 categories: Langerhans cell (LC) or non-LC-related, and malignant histiocytoses (MH).**

Writing Group of the Histiocyte Society. Histiocytosis syndromes in children. L ancet. 1987;1(8526):208-209.