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Spectrum of abdominal imaging findings in histiocytic disorders

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Abstract

Objectives: The present article provides an overview of the spectrum of abdominal findings of histiocytic disorders that may be observed in multimodality imaging illustrated by clinical cases from our Imaging Center.
Methods: We will review abdominal findings of Langerhans cell histiocytosis, Rosai–Dorfman disease, Erdheim–Chester disease, and hemophagocytic syndrome illustrated by clinical cases from our imaging department with histologic correlation.
Results: Abdominal involvement of histiocytic disorders is rare and may occur in the liver, biliary tract, kidney, retroperitoneum, kidney, gastrointestinal tract, and lymph nodes.
Conclusion: Histiocytic disorders encompass a group of rare diseases with a wide range of manifestations in which the abdominal involvement is quite infrequent. The role of the radiologist is to report the major imaging findings and the differential diagnosis; however, the imaging features are unspecific and biopsy usually is necessary to establish the definitive diagnosis.

Key words: Histiocytosis—Langerhans cell histiocytosis—Rosai–Dorfman disease—Erdheim–Chester disease—Hemophagocytic syndromes

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Histiocytosis is a complex and heterogeneous group of disorders of unknown etiology, more common among children and characterized by a proliferation of histiocytes. Differentiating each type of histiocytosis can be quite challenging and requires a combination of clinical, radiological, histological, and immunohistochemical features [1].

Histiocytes are a group of immune cells that include macrophages and dendritic cells. Although their origin is not completely understood, it is believed that these cells originate from the same bone marrow hematopoietic precursor. This progenitor cell develops monocytes that, after maturing in the bone marrow, are released in the peripheral blood and ultimately transferred to almost every organ as tissue macrophages. These cells are designated according to the tissue in which they are found, such as the Küpffer cells in the liver, the alveolar macrophages in the lung, and osteoclasts in the bone, and are responsible for the phagocytosis of elements that are strange to the organism. This same hematopoietic progenitor may originate dendritic cells, which have antigen-presenting functions, like the Langerhans cells and the interdigitating dendritic cells. Under specific circumstances, there is local induction toward the differentiation of these cells into the most suitable phenotype to meet the demands of the organism [1, 2].

Histiocytosis was first classified into three groups according to the type of histiocyte: (1) class I [Langerhans cell histiocytosis (LCH)]; (2) class II (histiocytosis of mononuclear phagocytes other than Langerhans cell); and (3) class III (malignant histiocytic disorders) [3].

As the knowledge on the biology of these disorders evolved, the necessity of a new classification that comprised those new information emerged. This novel classification was developed in 1997 by a joint of pathologists and pediatric hematologists/oncologists of the World Health Organization's Committee on Histiocytic/Reticulum Cell Proliferations and the Reclassification Working Group of the Histiocyte Society [1], and is summarized in Table 1. Histiocytosis is a multisystemic disorder and may produce a broad range of imaging manifestations. The present article provides an overview of the spectrum of abdominal findings of histiocytic disorders that may be observed on multimodality imaging.

Langerhans cell histiocytosis

LCH is the most common type of histiocytosis and is characterized by a clonal proliferation of histiocytes with Langerhans cell phenotype [2].

Clinical aspects

LCH is nearly twice as common in males as in females and have the peak age of diagnosis between 1 and 3 years of age, yet the disease can develop at any age [4–6]. The disorder has a broad spectrum of systemic involvement, ranging from unicentric to multicentric disease [7–10].

The most common manifestations of the LCH are bone lesions, but extraosseous disease has been reported in many organs [11, 12]. Extraosseous manifestations of LCH are less frequent and more difficult to be diagnosed than osseous LCH. Furthermore, the extraosseous manifestations usually appear as multicentric disease and may demonstrate a more aggressive behavior [13, 14].

Table 1. Contemporary classification of histiocytic disorders

Diseases of varied biological behavior
Dendritic cell-related
Langerhans cell histiocytosis
Secondary dendritic cell processes
Juvenile xanthogranuloma
Erdheim–Chester disease
Macrophage-related
Hemophagocytic syndromes
Primary hemophagocytic lymphohistiocytosis (familial and sporadic)
Secondary hemophagocytic syndromes
Infection-associated
Malignancy-associated
Other
Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy)
Malignant disorders
Monocyte-related
Leukemias
Monocytic leukemia M5A e B
Acute myelomonocytic leukemia M4
Chronic myelomonocytic leukemia
Extramedullary monocytic sarcoma (monocytic counterpart of granulocytic sarcoma)
Dendritic cell-related histiocytic sarcoma
Specific phenotype: follicular dendritic cell, interdigitating dendritic cell, etc.
Macrophage-related histiocytic sarcoma

Adapted from Refs. [1, 50]

Pathologic findings

The pathogenesis of LCH remains poorly understood and controversial despite various epidemiological studies [4–9]. The most likely theory is based on primarily reactive and immunologically mediated process [15] but the controversy on it being a clonal vs. a reactive immunologic response is still unsettled [16].

The diagnosis depends on the recognition of abnormal Langerhans cell, which has indistinct cytoplasmic borders, oval nuclei, nuclear grooves, pale and abundant cytoplasm with fine granules arranged in sheets or clusters. These Langerhans cells are frequently admixed with inflammatory cells, like eosinophils, neutrophils, lymphocytes, and plasma cells. Multinucleated osteoclast-like giant cells may be found. Necrosis is common and the cells may exhibit frequent mitosis. Atypical mitosis is not found [2, 15]. At ultrastructural studies, Birbeck granules in the cytoplasm are typical, which appear to be related with endosomal traffic. At immunohistochemistry, Langerhans cells have a characteristic CD68, S100 protein, CD1a, and langerin positivity [2] (Figs. 1, 2).

Abdominal imaging features

The most common manifestations of LCH are bone lesions. Extraosseous disease is less prevalent. Abdominal involvement corresponds to approximately 40% of overall extraosseous disease [11]. The main abdominal manifestations are hepatobiliary and gastrointestinal.

Hepatobiliary

The hepatobiliary involvement is observed usually in multicentric disease, but it is present in less than 20% of patients with LCH [17, 18].

The Langerhans cells infiltrate the periportal space of the liver and the bile ducts (Fig. 1). There are 4 histopathologic stages of hepatobiliary involvement: (1) proliferative; (2) granulomatous; (3) xanthomatous, and (4) fibrous. The main imaging findings in proliferative and granulomatous phases are periportal tissue with contrast enhancement on CT and MRI and periportal edema represented by periportal hyperintensity on T2-weighted MRI [19] (Fig. 2). Lipid-laden nodules in the liver appear on the xanthomatous phase. These nodules appear hyperechoic on US, hypoattenuating on CT, and hyperintense on unenhanced T1-weighted MRI without fat suppression [20, 21]. The final fibrous stage results in

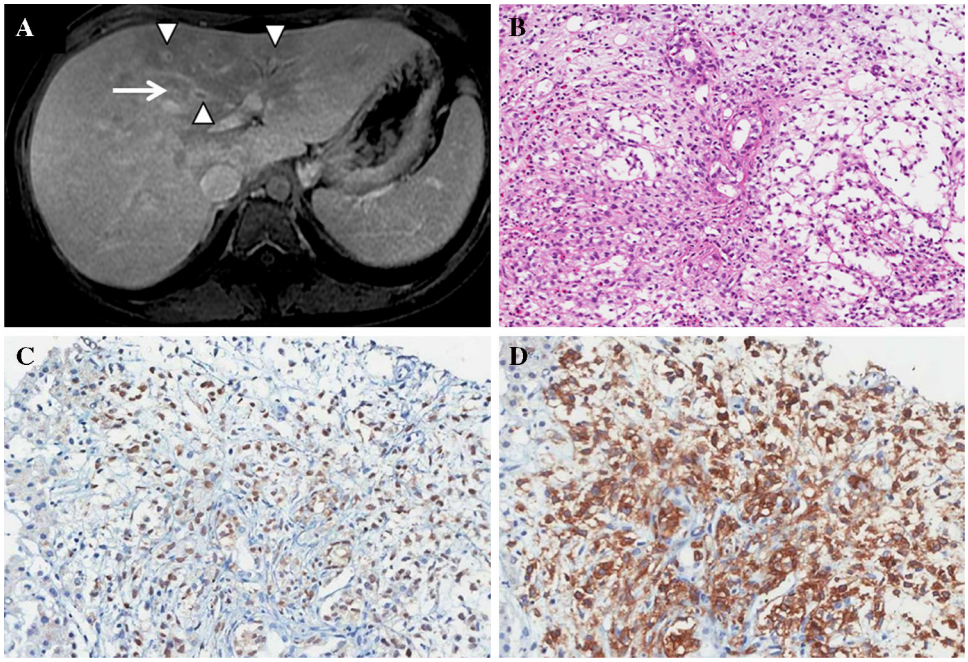

Fig. 1. Langerhans cell histiocytosis in an 18-year-old girl with abdominal pain and jaundice. **A** Axial contrast-enhanced T1WI GRE with fat saturation demonstrating hepatomegaly, infiltrative lesion in the left hepatic lobe (*arrow*), and focal mild intrahepatic biliary duct dilatation with wall thickening (*arrowheads*). **B** Histological examination of liver biopsy shows diffuse proliferation of histiocytes. **C** Immunochemistry positive for S100. **D** Immunochemistry positive for CD1a.

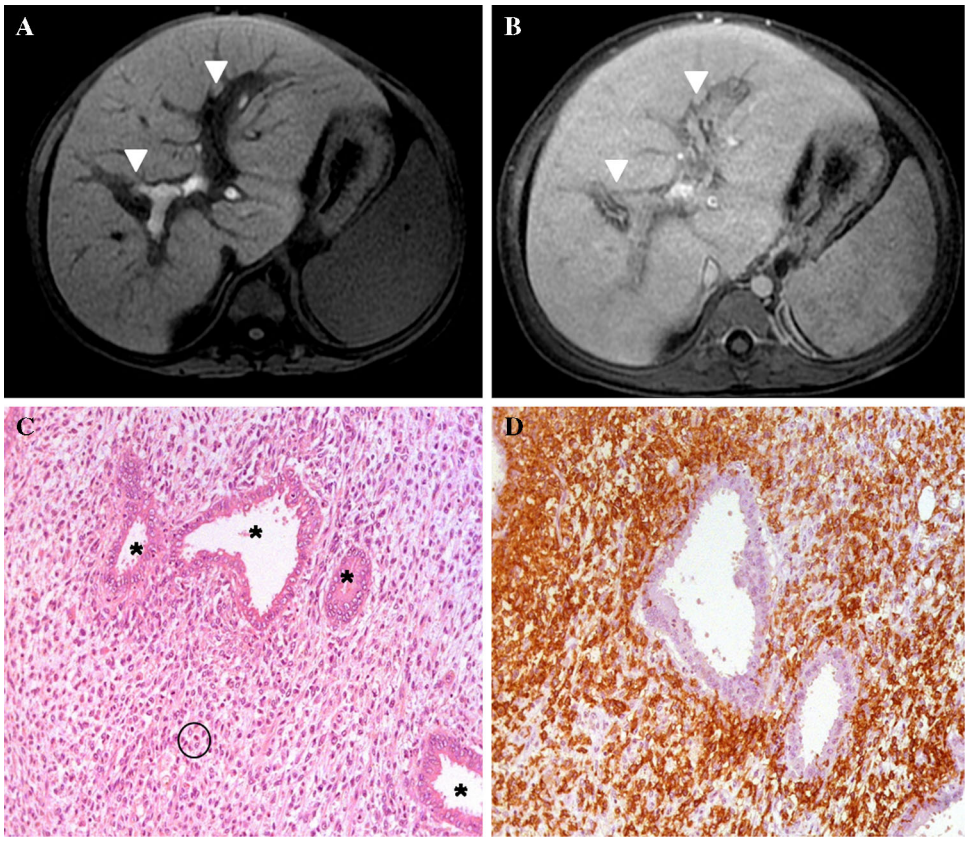

Fig. 2. Langerhans cell histiocytosis in a 3-year-old boy who underwent liver transplant. **A**, **B** Axial pre- and postcontrast T1WI GRE with fat saturation demonstrating hepatosplenomegaly and solid tissue in the hepatic hillum and periportal space (*arrowheads*). **C** Histological examination of liver explant shows sheets of cells with dark nuclei and pale cytoplasm aroud bile ducts (*asterix*), a few scattered eosinophils and macrophages (*black circle*) are also present. **D** Immunochemistry positive for CD1a.

diffuse liver disease, biliary cirrhosis, and secondary portal hypertension.

The direct histiocytic infiltration of bile ducts results in secondary sclerosing cholangitis with consequent intra- and extrahepatic biliary irregularities and areas of focal narrowing and dilatation [22].

The main differential diagnosis is adverse effects of chemotherapy, lymphoma, leukemia, hepatitis, and

cholangiopathies (infectious, ischemic, or mechanical) [12, 17].

Gastrointestinal

The involvement of the gastrointestinal tract is rare and may be primary or a part of a systemic disease [12, 23, 24]. It may affect any part of the gastrointestinal tract from the oral mucosa to the anal canal. The main clinical symptoms are abdominal pain, vomiting, diarrhea, malabsorption, intestinal obstruction, and bloody stools. Those symptoms may be preceded by or be associated with rash in most patients [25]. Considering that the gastrointestinal symptoms are nonspecific, its frequency is probably underestimated.

The histiocytic infiltration of the gastrointestinal wall may be continuous or discontinuous and results in mucosal erosion, wall thickening, mucosal atrophy, and glandular destruction.

The main imaging features in gastrointestinal LCH are loss of mucosal pattern, wall thickening, mucosal hyperenhancement, luminal narrowing with dilated segments, proliferation of mesenteric fat, mesenteric fat stranding, free fluid [12, 23–25], and rarely perforation [26].

The differential diagnosis includes inflammatory bowel disease, lymphoma, infection, and drug reaction [12, 23–25].

Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy)

Rosai–Dorfman disease (RDD) also known as sinus histiocytosis with massive lymphadenopathy is a rare benign disease and was established as a clinicopathologic entity by Rosai and Dorfman in 1969 [27]. It is much more frequent among children and young adults and the median age at diagnosis is 20 years. There is a slight predilection for males (58%), and for individuals of African descent [28].

Although the etiology remains unknown, the RDD is thought to be caused by an exaggerated response of the hematopoietic system to an immunological trigger probably caused by Epstein–Barr and herpesvirus 6 infections [29].

Clinical aspects

The most common initial presentation of RDD is massive painless cervical lymphadenopathy in children or young adults, but axillary, para-aortic, inguinal, and mediastinal lymph nodes may also be affected. Nonspecific systemic symptoms (fever, fatigue, and weight loss) are frequently observed [28, 29]. Immunological disorders (autoimmune hemolytic anemia, rheumatoid arthritis, glomerulonephritis, asthma, and diabetes mellitus) are common among these patients.

The RDD can also involve a large variety of extranodal sites [30]. The incidence of extranodal involvement of RDD in most recent series is approximately 40% [28, 30]. The most common extranodal involvement sites are bone, skin, soft tissue, central nervous system, eye, orbit, upper respiratory tract, including salivary glands. The most common abdominal organs involved are liver, pancreas, kidney, gastrointestinal tract, and retroperitoneum [30].

The clinical course of RDD is usually self-limited, with a tendency for total spontaneous regression [29]. However, involvement of the low respiratory tract, kidney, and liver is associated with worse prognosis, as well as the number of extranodal sites involved and the association of immunological disorders [30].

Pathologic findings

Lymph nodes involved by RDD have their normal architecture altered by dilatation of sinuses, leading to effacement of follicles and germinal centers, as well as capsular fibrosis and of pericapsular tissues. Lymph nodes sinuses are expanded by a mixed population of cells, composed mainly of histiocytes and plasma cells clustered around vessels (Fig. 3). Histiocytes have large vesiculous nuclei, prominent nucleoli, well-defined nuclear membranes, and abundant pale eosinophilic cytoplasm. Nuclear atypia, mitosis, and necrosis are rare. The most striking histological feature of RDD is emperipolesis, which is defined as the presence of intact lymphocytes inside intracytoplasmic vacuoles of histiocytes (Fig. 3). Plasma cells, neutrophils, and red blood cells may also be found inside these vacuoles [2, 31].

Extranodal RDD has similar morphologic features as nodal couterpart. However, extranodal RDD exhibits more fibrosis, less typical histiocytes, and less emperipolesis [2, 30–32].

At immunohistochemical studies, RDD histiocytes express S100 protein and pan-macrophage markers, like CD68 and CD14. They do not stain for CD1a nor for markers of dendritic differentiation, like CD21, CD23, and CD35 [2, 31].

Abdominal imaging features

Liver

The hepatic lesions usually occur in the form of multiple small hypovascular nodules on CT and MRI representing granuloma-like histiocytic infiltrates, which can be accompanied by clinically detectable hepatomegaly [33].

Pancreas

Primary pancreatic RDD is a very rare entity. Only three cases have been previously reported in the literature [34–36]. Extranodal RDD simulates malignancy because it presents as an infiltrative mass lesion and can be multifocal [34–36].

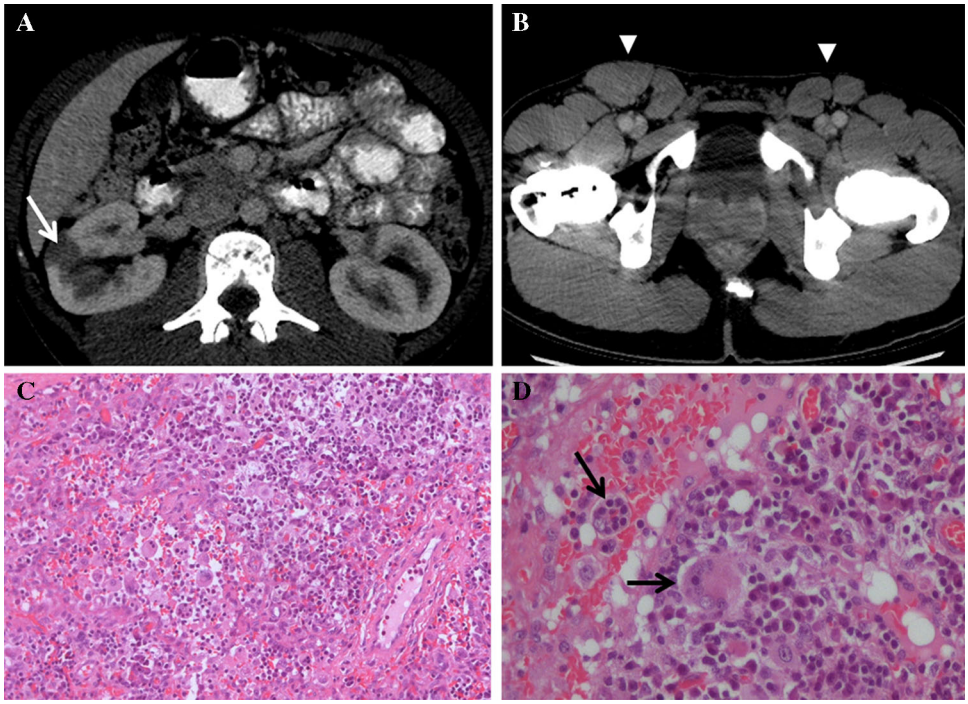

Fig. 3. Rosai–Dorfman disease in a 17-year-old boy with renal nodules on previous ultrasound. **A**, **B** Contrast-enhanced CT shows one of cortical kidney nodules (*arrow*) and bilateral inguinal lymphadenopathy (*arrowheads*). **C**, **D** Histological examination of right inguinal lymph node biopsy demonstrating expansion of sinuses by a mixed cellular infiltrate composed mainly of histiocytes and intact lymphocytes inside intracytoplasmic vacuoles of histiocytes, characterizing emperipolesis (*black arrows*).

Kidneys

The renal involvement by RDD should be included in the differential diagnosis of renal hilar masses, subcapsular hypodense infiltration, or renal cortical hypodense nodules on CT (Fig. 3). Renal involvement has been associated with a poorer prognosis, when compared with the overall disease mortality of less than 2% [28, 37, 38].

Gastrointestinal tract

The gastrointestinal tract is the least commonly involved site by RDD, accounting for less than 1% of all extranodal cases [16, 39]. It was described a predilection for the distal portion of the gastrointestinal tract with involvement of the colon and rectum in a majority of cases [39]. The involvement of gastrointestinal tract results in wall thickening or wall masses.

Retroperitoneum

The most frequent retroperitoneal involvement includes infiltrative mass or lymph nodes surrounding the kidneys, ureters, and retroperitoneal vessels, which may distort vessels and also produce ureteric or renal pelvis obstruction [28].

The main differential diagnoses of RDD are infectious or granulomatous conditions, primary malignancy, lymphoma, and metastatic disease.

Erdheim–Chester disease

Erdheim–chester disease (ECD) is a rare xanthogranulomatous histiocytosis of non-Langerhans cells most common in male adults between the fourth and seventh decades of life. It was first described by Erdheim and Chester in 1930 [40] and is characterized by multifocal osteosclerotic lesions of the long bones.

Although there is a speculation that ECD and other histiocytic disorders may represent an aberrant response to infection, no infectious etiology has been identified. It remains controversial if ECD is a reactive polyclonal histiocyte proliferation or a monoclonal neoplastic process [41, 42].

Clinical aspects

ECD is a systemic disease with a wide spectrum of clinical manifestations. Bone tissue is the most frequently involved. Associated extraskeletal manifestations are observed in 50% of cases. The most common extraskeletal involvements are pituitary gland, skin, orbit, heart, lung, and retroperitoneum [43]. Spleen, lymph nodes, and liver are usually spared. However, a case of ECD with vertebral osteolytic lesions and involvement of liver has been reported [44].

The isolated bone involvement has a good prognosis while disseminated disease especially with involvement of heart or central nervous system has a worse prognosis [43].

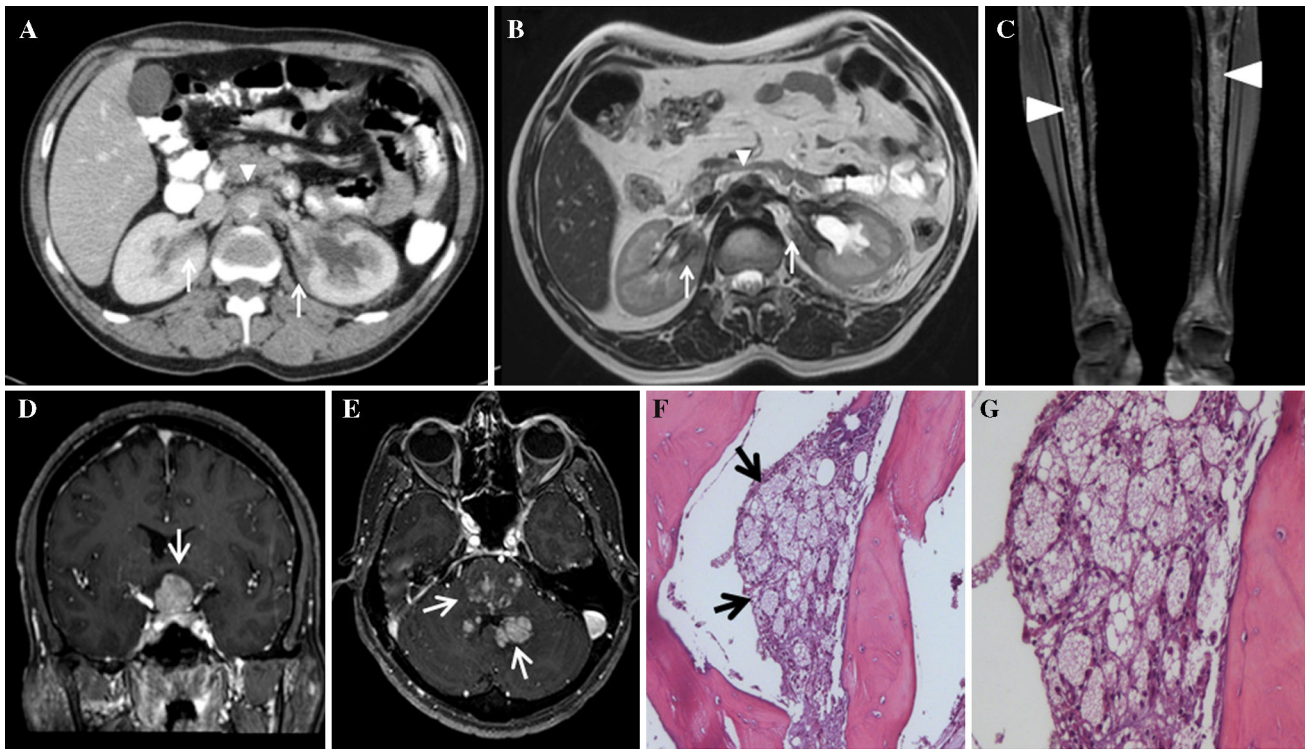

Fig. 4. Erdheim–Chester Disease in a 42-year-old man with weight loss. **A**, **B** Axial contrast-enhanced CT and T2WI shows a retroperitoneal infiltrative lesion surrounding the abdominal aorta (*arrowheads*) and the kidneys (*arrows*), causing moderate dilatation of the left calyceal system. **C**, **D** Contrast-enhanced T1WI demonstrating suprasellar, pontine, and cerebellar lesions with intense enhancement (*arrows*). **E** Postcontrast T1WI shows an intense and diffuse enhancement of the tibiae (*arrowheads*). **F**, **G** Histological examination of the right tibia biopsy showing infiltrate composed mainly of foamy histiocytes (*black arrows*) and a few scattered plasma cells and lymphocytes among sclerotic bone.

Pathologic findings

ECD lesions are composed of an infiltrate of foamy histiocytes and Touton-type giant cells enmeshed in fibrous tissue and sclerotic bone (Fig. 4). Lymphocytes, plasma cells, and sparse eosinophils are also observed.

At immunohistochemical studies, ECD foamy histiocytes express CD68, CD14, CD163, factos XIIIa, and fascin. They are negative for S100 protein, CD1a, and langerin. Ultrastructural studies reveal that ECD histiocytes contain intracytoplasmic lipid vacuoles. Birbeck granules are absent [2].

Abdominal imaging features

Kidneys

Infiltration of the perirenal fat appears as an irregular renal border producing a "hairy kidney" appearance on CT and MRI. On CT, this manifests as a hypodense and homogeneous band with spiculated contours and mild contrast enhancement. On MRI, it is isointense to muscle on T1- and T2-weighted sequences, with a slight and homogeneous enhancement after contrast injection. Perirenal infiltration may progress to the renal sinuses and produce a post renal obstruction (Fig. 4). The ureteral segments which are most commonly affected by fibrosis are the middle and distal segments. The renal arteries may also be involved by tissue infiltration and fibrosis [43].

Retroperitoneum

Retroperitoneal involvement with ECD can manifest as a mass-like infiltrative surrounding the abdominal aorta with the same characteristics of the perirenal lesions (Figs. 4, 5). This can lead to acute or slowly progressive renal insufficiency. Retroperitoneal involvement frequently includes a bilateral, symmetric, and diffuse thickening of the adrenal glands associated with infiltration of the adjacent fat [43].

Others (rare)

There are few reports of involvement of the liver [44] and bile ducts [45]. Biliary hilar infiltration may produce Klatskin-like lesions.

The main differential diagnoses of RDD are retroperitoneal fibrosis, sclerosing mesenteritis, and

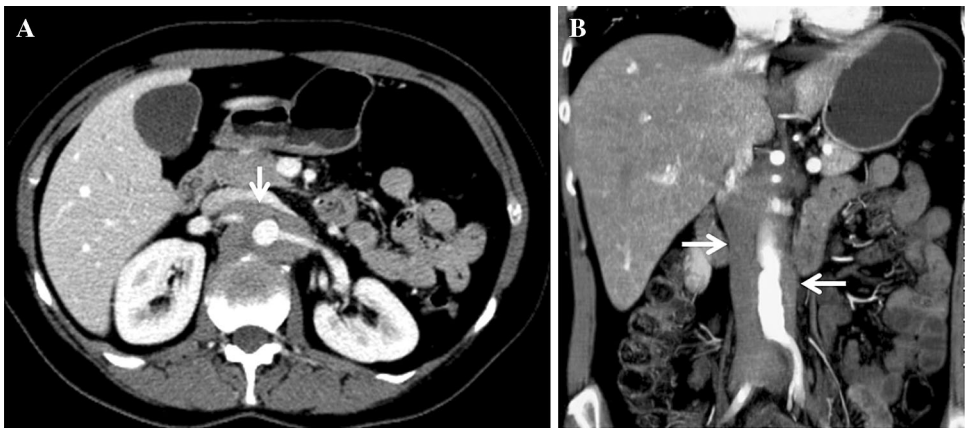

Fig. 5. Erdheim–Chester Disease in a 52-year-old woman with abdominal pain and fever. **A** Axial contrast-enhanced CT shows an infiltrative soft tissue lesion surrounding the abdominal aorta and the renal arteries (*arrow*). **B** Coronal contrast-enhanced CT demonstrating the longitudinal extension of the aorta encasement (*arrows*).

retroperitoneal neoplasms, mainly lymphoma and germ cell tumor.

Hemophagocytic syndromes

Clinical aspects

Among all types of histiocytosis, hemophagocytic syndromes are the most important in terms of morbidity and mortality. They may be primary (genetical) or secondary (acquired). These syndromes are characterized by a disseminated and uncontrolled proliferation and activation of macrophages and T lymphocytes, with upregulation of inflammatory cytokines, mediated mainly by TNF-α, in response to varied stimuli. The excessive activation of inflammatory cytokines may lead to a potentially fatal systemic inflammatory syndrome, characterized by bone marrow depression, hepatosplenomegaly, alteration of liver function, and coagulation cascade disturbances [46, 47].

Primary forms are motivated by mutations of genes related to NK cells and T lymphocytes function, which prompt disturbances in these cells activities. However, many of the genes involved are yet to be detected and the pathogenesis of these conditions remains to be clarified [46]. On the other hand, secondary forms are triggered by a varied number of stimuli, like viral infections, especially EBV, lymphoproliferative diseases and other neoplasms, parenteral nutrition, multiple organic failure, and rheumatologic disorders.

Pathologic findings

Hemophagocytosis is a common finding in bone marrow biopsies and is not a sufficient criterion for the diagnosis of hemophagocytic syndrome. It is necessary to consider clinical aspects and laboratory data as well. Histiocyte Society has defined criteria for the diagnosis of he-

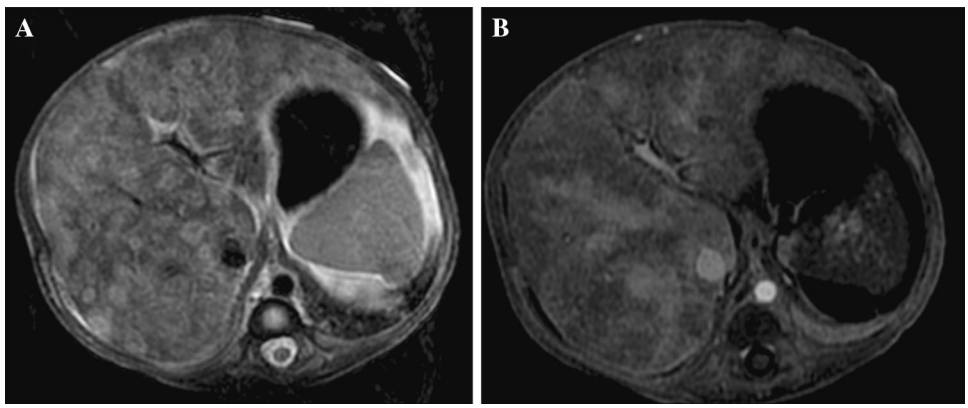

Fig. 6. Hemophagocytic syndrome (HS) in a 1-year-old girl with fever, hepatosplenomegaly, and biochemical markers of HS. **A** Axial T2WI shows hepatomegaly, heterogeneous liver signal, splenomegaly, and ascites. **B** Axial contrast-enhanced T1WI GRE with fat saturated demonstrating diffuse transient hepatic parenchymal enhancement. Liver biopsy confirmed HS associated with veno-occlusive disease.

Table 2. Diagnostic criteria of hemophagocytic lymphohistiocytosis

At least 5 of the 8 following criteria
Fever
Splenomegaly
Cytopenias (affecting ≥2 lineagens in the peripheral blood)
Hypertriglyceridemia and/or hypofibrinogenemia
Hemophagocytosis in bone marrow, spleen, or lymph nodes
Low or absent NK-cell activity
Ferritin ≥500 μg/L
Soluble CD25 ≥2400 U/mL

Adapted from Ref. [46]

mophagocytic lymphohistiocytosis, which are summarized in Table 2.

Abdominal imaging features

The main abdominal radiological findings are hepatosplenomegaly, increased periportal echogenicity at ultrasound, gallbladder wall thickening, nephromegaly with increased cortical echogenicity, lymphadenopathy and free fluid [48] (Fig. 6).

Veno-occlusive disease is a rare complication of hemophagocytic syndrome [49] (Fig. 6).

Conclusion

Histiocytic disorders encompass a group of rare diseases with a wide range of manifestations, in which the abdominal involvement is quite infrequent. The role of the radiologist is to report the major imaging findings and the differential diagnosis; however, the imaging features are unspecific and biopsy usually is necessary to establish the definitive diagnosis.

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