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REVIEW ARTICLE

Abdominal manifestations of histiocytic disorders in adults: imaging perspective

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ABSTRACT

Histiocytic disorders (HDs) are a diverse group of diseases characterized by pathologic infiltration of normal tissues by cells of the mononuclear phagocyte system. The spectrum of these diseases ranges from treatable infectious diseases to rapidly progressive, life-threatening conditions. Although they are rare and difficult diagnoses, HDs can be diagnosed with the help of clinical and laboratory analyses, imaging features and tissue biopsy. The clinicopathology and imaging spectrum of select entities belonging to this disorder are presented in this review.

INTRODUCTION

Histiocytic proliferative diseases are disorders of the mononuclear phagocytic system (MPS) characterized by accumulation and infiltration of antigen-presenting cells, which include follicular dendritic reticular cells, interdigitating reticular cells and Langerhans cells (LC), or of phagocyte cells, which can affect any tissues or organs.¹ The heterogeneity of these disorders is due to the biologic variability of the cells of the MPS. Current research in immunology has enriched the understanding of their pathophysiology.² It is now accepted that a common haematopoietic progenitor is central to the development of histiocytosis. Molecular science has enabled classification of these disorders based on the cellular basis and the natural history of these disorders. The phagocytosis of foreign bodies and presentation to lymphocytes is the primary function and mechanism of action of the MPS. The central cell to this system, the mononuclear phagocyte or histiocyte, arises from a haematopoietic stem cell and represents an anatomically and functionally distinct cell. The histiocytes can be divided into two major classes, macrophages and dendritic cells. Macrophages process antigens by phagocytosis and produce cytokines, whereas dendritic cells present antigens to T-cells, leading to activation of the immune response to external stimuli.³ The development and differentiation of the cells of the MPS is regulated by specific growth factors which control the gene expression, resulting in cell proliferation and

differentiation. Dysregulation of this mechanism can lead to disease.³

Classification of histiocytic disorders (HDs) was proposed first in 1987. However, research performed after this classification showed several new findings regarding the cell origins, molecular pathogenesis and clinical presentations. Emile et al⁴ proposed a revision of the classification based on the current knowledge. They classified histiocytoses into five major groups: (1) Langerhans related (L group), (2) cutaneous and mucocutaneous histiocytoses (C group), (3) malignant histiocytoses (M group), (4) Rosai–Dorfman disease (RDD) (R group) and (5) haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (H group). These are summarized in Table 1. In addition to these conditions, there are several secondary, reactive and infectious conditions that may cause intestinal histiocytic proliferations. These are summarized in Table 2. Abdominal manifestations of some of these disorders can be primary/localized or part of widespread multisystem involvement. Some of these disorders can have specific imaging appearances, leading to its diagnosis. Imaging can also be helpful in staging and prognosis.

The “L” (Langerhans) group

In the new classification, Erdheim–Chester disease (ECD) and Langerhans cell histiocytosis (LCH) are classified under L group, as they share the same gene mutations and

Table 1. Classification of Histiocytic disorders.

HD type	Examples
L group	LCH Indeterminate cell histiocytosis ECD Mixed ECD and LCH
C group	Cutaneous non-LCH histiocytoses Cutaneous non-LCH histiocytoses with a major systemic component
M group	Primary malignant histiocytosis Secondary malignant histiocytosis
R group	Nodal RDD Extranodal RDD Neoplasia-associated RDD Immune disease-associated RDD
H group	Primary HLH Secondary HLH

ECD, Erdheim-Chester disease; HD, histiocytic disorder; HLH, haemophagocytic lymphohistiocytosis; LCH, Langerhans cell histiocytosis; RDD, Rosai-Dorfman disease.

both these conditions can have similar clinical complications such as diabetes insipidus and/or neurodegenerative disease.⁴

Langerhans cell histiocytosis

LCH is a rare proliferative disorder of Langerhans cells (LC) and can involve multiple organ systems with different clinical presentations. It can range from solitary bone lesions (formerly known as eosinophilic granuloma), which usually resolve without treatment, to a potentially life-threatening disorder with multisystem involvement (also referred to as Letterer-Siwe disease) requiring systemic chemotherapy.³ Pulmonary involvement is more common; typically, patients are in their second or third decade, have a history of smoking and present with multiple nodules in different stages of cavitation, predominantly in the upper lobes (Figure 1a). Hepatic involvement is relatively rare in adults.⁵ The natural history of liver LCH fits into two stages: (1) an early stage with infiltration by histiocytes, usually presenting with hepatomegaly and liver nodules and often responsive to immunosuppressive/chemotherapy agents; and (2) late stage of liver involvement, which is associated with chronic fibrosis centred on the bile ducts with little or no histiocytic infiltration, progressing to sclerosing cholangitis. This form is difficult to treat and often leads to cirrhosis requiring liver transplantation.⁵

The CT imaging features suggestive of hepatic LCH include hepatomegaly and periportal hypodensities (Figure 1b).⁶ Abnormal periportal signal on T_2 weighted MR images can also be seen with MR and may appear as hypoechoic on ultrasound.⁷ It is believed that infiltration by histiocytes accounts for the abnormal periportal abnormality. Hepatic nodules appear hyperechoic on sonography, show low attenuation on CT and may show signal loss on Gradient Recalled Echo (GRE) T_1 weighted out-of phase images, indicating the presence of microscopic fat (Figure 2a,b). This appearance is due to the lipid-rich LC.⁸

The histologic features of LCH consist of diffuse infiltrates of loosely dispersed LC with convoluted or grooved nuclei, a fine chromatin pattern and eosinophilic cytoplasm. They are often admixed with multinucleated giant cells and eosinophils. The LC typically express Cluster of Differentiation 1a (CD 1a) and S-100 on immunohistochemistry analysis (Figure 2c).

Erdheim-Chester disease

ECD is characterized by diffuse histiocytic infiltration, preferentially affecting the bones; however, involvement of the heart, vessels, pituitary gland, retroperitoneum and skin is also reported.⁹ It can be seen in children as well as in the elderly, but the mean age at diagnosis is 50 years. This disease is less common than LCH, with approximately 350 reported cases.¹⁰ The overall prognosis of ECD is poor, especially with pulmonary involvement. In the 2002 World Health Organization classification of soft-tissue tumours, ECD was classified under tumours of undefined neoplastic nature.³

The clinical spectrum of ECD is broad, ranging from asymptomatic tissue infiltration to fulminant multisystem organ failure.¹¹ Bone pain is the most common presenting symptom of ECD, mainly affecting the lower extremities.¹² ECD typically involves long bones causing osteosclerosis.¹³ Up to 50% of patients may present with extraskelatal manifestations including retroperitoneal fibrosis, orbital infiltration, interstitial lung disease, adrenal involvement and infiltration of the testis and/or cardiovascular system.¹⁴ The disease can be quite extensive and can span along the length of the thoracoabdominal aorta (up to the heart) and invade the retroperitoneum and mediastinum, with potentially life-threatening complications such as heart failure, tamponade and renal failure. Renal and perirenal involvement is relatively frequent, found in 29% of patients in a series reported by

Table 2. Secondary, reactive and infectious conditions causing intestinal histiocytic proliferations.

Reactive and infectious conditions	Examples
Infections	Xanthogranulomatous infections MAI Whipple disease
Histiocytic aggregates	Barium granuloma Melanosis coli

MAI, mycobacterium avium infection.

Figure 1. A 34-year-old male with history of cigarette smoking presenting with cough and diarrhoea: (a) the coronal CT image of the chest is demonstrating multiple cavities with varying and bizarre shapes with upper lobe predominance (arrow). (b) Contrast-enhanced CT of the abdomen is demonstrating periportal hypodense areas (arrow). Ultrasound-guided biopsy of this periportal lesion confirmed diagnosis of Langerhans cell histiocytosis.

Veyssier-Belot et al,¹² and may be seen as an isolated presentation of the disease.¹⁵

A circumferential soft-tissue rind of the thoracic and abdominal aorta gives rise to the so-called “coated aorta” appearance on imaging.⁹ Bilateral adrenal involvement by the infiltrating soft tissue has also been reported (Figure 3a).¹⁶ CT classically shows bilateral perirenal hypodense homogeneous tissue infiltration with weak contrast enhancement. The perirenal infiltration may give rise to the “hairy kidney” appearance (Figure 3b) and is highly suggestive of the diagnosis.¹⁷

Pathologically, ECD is diffuse and infiltrative, involves multiple organs and shows tropism for connective, adipose and perivascular tissues.¹⁸

The “C” group: cutaneous and mucocutaneous histiocytoses

This group includes non-LCH localized to skin and/or mucosal surfaces. Systemic involvement is very uncommon.⁴

The “M” groups: malignant histiocytoses

This group includes malignant histiocytoses, histiocytic, interdigitating cell, LC or indeterminate cell sarcomas.⁴

The “R” group: Rosai-Dorfman disease

First described by Rosai and Dorfman,¹⁹ RDD is a benign disease predominantly affecting the cervical lymph nodes bilaterally, with spontaneous regression in most cases. This entity is also known as sinus histiocytosis with massive lymphadenopathy and is characterized by marked, painless lymph node enlargement. It is most commonly seen in young adult males. Some inherited conditions can have predisposition of RDD. The histopathological pattern of RDD was identified in the lymph nodes of 41% of patients with autoimmune lymphoproliferative syndrome and in 20% of patients with H syndrome.⁴

The clinical course is usually self-limiting and surgery or treatment with steroids is usually curative.²⁰ Extranodal manifestations of RDD are seen in up to 40% of cases and can be very challenging in terms of diagnosis.²¹ The most common reported sites of extranodal RDD are the skin and soft tissue, presenting as well-defined papules to palpable masses. There are several case reports that suggest that RDD can involve almost every organ.²¹

The nodal form of RDD has similar imaging features of lymphoma, with most frequent sites of involvement being the head and neck, paranasal sinuses, nasal cavity, soft tissue, skin, eye

Figure 2. A 39-year-old male with biopsy-proven Langerhans cell histiocytosis of the liver: (a) subtle hyperintense lesions can be seen on the GRE T_1 weighted (T1W) in-phase MR image (arrow) with signal drop on the GRE T1W opposed-phase MR image (arrow) (b) consistent with intracytoplasmic fat in these lesions. (c) Biopsy of the liver lesions showing diffuse infiltrates of loosely dispersed Langerhans cells (LC) with convoluted or grooved nuclei (arrowhead), fine chromatin pattern and eosinophilic cytoplasm. Admixed with the LC are many eosinophils (circles). The LC are positive for CD1a (right upper insert) and S-100 (right lower insert).

Figure 3. A 45-year-old male with Erdheim–Chester disease: (a) the contrast-enhanced coronal and (b) axial images are demonstrating a diffuse soft-tissue rind surrounding the thoracic and abdominal aorta, giving rise to a “coated aorta” appearance [arrows in (a)]. Left adrenal mass can also be seen (star). (b) Bilateral perinephric soft-tissue infiltration is seen with “hairy kidney” appearance (arrows).

and orbit. The retroperitoneum is an infrequent site with enlarged retroperitoneal nodes distorting the vessels and causing ureteral obstruction. The imaging appearance of this ureteral fibrosis can be similar to that seen with retroperitoneal fibrosis or lymphoma.²⁰

The imaging appearance of extranodal RDD is non-specific, but mimics soft tissue or mesenchymal sarcoma. Soft-tissue masses with uniform enhancement can be seen on CT or MR. These masses are typically hyperintense on T_2 weighted MR.²¹ In our biopsy-proven case of RDD, there was an intensely enhancing non-obstructive right renal hilar mass and enlarged pelvic lymph nodes (Figure 4a). On histopathology of the resected pelvic lymph node, large histiocytes were seen with oval vesicular nuclei and pale cytoplasm. The histiocytes show characteristic “emperipolesis”, in which lymphocytes penetrate the cytoplasm, which remains viable within the histiocytes.^{3,22} On immunohistochemistry, cells are positive for S-100 and stain

negative for CD1a (Figure 4b). These masses resolved after systemic steroid treatment.

THE “H” GROUP: HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Haemophagocytic lymphohistiocytosis

HLH is a rapidly progressive, life-threatening syndrome of excessive immune activation due to cytokine dysfunction, resulting in uncontrolled proliferation of inflammatory cells including macrophages and histiocytes. The diagnostic criteria include fever, splenomegaly, cytopenia affecting more than two cell lines, hypertriglyceridaemia, hyperferritinaemia ($>500 \mu\text{g l}^{-1}$), low fibrinogen level and haemophagocytosis in the reticuloendothelial system.²³ Early clinical signs associated with HLH include fever (90% of cases), hepatosplenomegaly (90%), lymphadenopathy (42%), rash and neurologic abnormalities (47%).²³ HLH can be primary (familial erythrophagocytic

Figure 4. A 22-year-old male with Rosai–Dorfman disease: (a) the contrast-enhanced axial coronal maximum intensity projection CT image is demonstrating multiple enhancing masses in the right pelvis (arrows). (b) Histologic section from the resected pelvic lymph node is showing large histiocytes (circles) with the characteristic “emperipolesis”, in which intact lymphocytes (arrows) are present in the cytoplasm of the histiocytes.

Figure 5. A 30-year-old female with haemophagocytic lymphohistiocytosis presenting with septic shock: the axial contrast-enhanced CT image is demonstrating hepatosplenomegaly and innumerable hypodense hepatic and splenic lesions (arrows). Periportal lymphadenopathy is also seen (arrowhead). Histopathology confirmed the diagnosis on transjugular liver biopsy.

lymphohistiocytosis) or secondary. The primary form presents in young infants with genetic abnormalities, leading to defects in the immune system. The secondary form is sporadic, typically associated with a pre-existing inflammatory condition, such as a malignancy or immunosuppressive state.^{23,24}

The presentation of these disorders is typically fulminant and consists of fever, pancytopenia, hepatosplenomegaly, hyperbilirubinaemia, hyperlipidaemia, hypofibrinogenaemia, coagulopathy, haemophagocytosis and central nervous system abnormalities such as seizures.²⁵ Two highly diagnostic parameters of HLH include an increased plasma concentration of the alpha chain of the soluble interleukin-2 receptor (sCD25) and impaired natural killer cell activity.²⁶

In the spleen, the red pulp is expanded and infiltrated with histiocytes; the white pulp is diminished and depleted of lymphocytes. In the liver, lymphocytes and histiocytes infiltrate the portal tracts and, to a much lesser extent, the hepatic lobules.²⁷ In lymph nodes, histiocytes accumulate in T-cell-rich areas and sinuses; the follicles become sparse and lymph nodes are depleted of lymphocytes in some patients. These findings can help explain the appearance of solid masses seen at imaging in the spleen, liver and lymph nodes (Figure 5).²⁸ A report of six children with HLH by Schmidt et al²⁸ (two children with primary HLH and four children with secondary HLH) highlighted the ultrasound findings of gallbladder wall thickening, increased periportal echogenicity and enlarged porta hepatis lymph nodes. Hepatosplenomegaly with innumerable nodules is commonly seen at both CT and ultrasound (Figure 5).

REACTIVE AND INFECTIOUS CONDITIONS

Xanthogranulomatous inflammation

Xanthogranulomatous inflammation (XGI) is a type of chronic inflammatory disease characterized by a focal or diffuse destructive inflammatory process, with accumulation of lipid-laden macrophages and acute/chronic inflammatory cells. It may involve any organ, but the most common sites are the gallbladder and kidney.^{30,31} Although the exact pathogenesis of XGI is not clear, several mechanisms are proposed, including chronic recurrent infection, obstruction and a defect in lipid transport.³² An obstructive hypothesis is suggested for xanthogranulomatous cholecystitis and xanthogranulomatous appendicitis. XGI of the gastrointestinal (GI) tract can progress to a chronic suppurative inflammatory process with tissue destruction and localized proliferation of lipid-rich macrophages.³³ It can mimic malignancy, as it can destroy normal soft tissues.³⁴ CT of XGI may show a mass-like infiltrating soft-tissue density lesion (Figure 6a). Surgical resection is necessary in most cases and histopathology shows xanthogranulomatous infiltrates with foamy histiocytes infiltrating into the bowel and surrounding fat (Figure 6b).

Xanthogranulomatous cholecystitis is an unusual form of chronic cholecystitis that presents with gallbladder wall

Figure 6. A 52-year-old male with xanthogranulomatous inflammation of the transverse colon, mesocolon and omentum: (a) the axial contrast-enhanced CT image is demonstrating a large, heterogeneous, infiltrating mass in the omentum (arrow), also involving the transverse colon (asterisk) and its mesocolon. (b) Histopathology after surgical resection revealing xanthogranulomatous infiltrates in the omentum (area inside the square) with foamy histiocytes infiltrating into the adjacent bowel and mesentery.

Figure 7. A 46-year-old female with xanthogranulomatous cholecystitis: the right upper quadrant sonogram is showing marked thickening of the gall bladder wall (arrow) with hypoechoic areas within the thickened wall (open arrow) associated with gallstones.

thickening and can mimic malignancy on imaging. Gallbladder wall thickening may be focal or diffuse and has been reported to be up to 25 mm in wall thickness.³⁵ On ultrasound, hypoechoic nodules may be seen within the thickened gallbladder wall (Figure 7), and CT may demonstrate correlative hypodense foci in the gallbladder wall.³⁶

Xanthogranulomatous appendicitis is a very unusual type of appendicitis with around 10 cases reported in the literature³⁷ with a strong association with interval appendectomy.³⁸ On imaging, it may show features similar to an appendiceal mucocoele or tumour-like thickening with or without involvement of the caecum³⁹ (Figure 8a,b). Performing frozen section during surgery may suggest the diagnosis and radical surgery can be avoided.

Mycobacterium avium complex

Mycobacterium avium complex (MAC) consists of two species of acid-fast mycobacteria: (1) mycobacterium avium and (2) mycobacterium intracellulare. They are difficult to distinguish from each other and are therefore referred to collectively as MAC. These bacteria are obligate intracellular organisms that are found ubiquitously in the environment, including natural water

sources and soil.²⁹ Rates of MAC infections vary widely between developed and developing countries, as well as among different geographic locations.⁴⁰

Disseminated mycobacterium avium infection is one of the most commonly encountered opportunistic infections in patients with acquired immune deficiency. Presenting symptoms include severe abdominal pain, fever, night sweats and weight loss. Patients who are immunocompromised may also develop disseminated MAC infections with involvement of the liver, spleen, GI tract, LN and bone marrow. LN are typically necrotic and usually smaller compared with those associated with mycobacterium tuberculosis infections (Figure 9a).⁴⁰ Liver and splenic MAC present as numerous small hypodense lesions on CT (Figure 9b). Although the jejunum is the most common site of MAC in the luminal GI tract, any segment of the bowel can be affected. Imaging of GI MAC may present as an intestinal stricture with mass-like thickening (Figure 9c). Histology is diagnostic with foamy histiocytes containing mycobacterial organisms.⁴¹

Whipple disease

Whipple disease is a systemic bacterial infection caused by *Tropheryma whippeli* and is also known as intestinal lipodystrophy.⁴² It predominantly affects Caucasian males, with a male-to-female ratio of approximately 8:1 and a mean age of onset around 50 years. The disease can be fatal if not treated properly and relapse is common even with specific antibiotic treatment.⁴³

Whipple disease has traditionally been regarded as a GI disease, but in most cases, the disease begins insidiously with arthropathy. Patients with the classic form of Whipple disease present with diarrhoea and weight loss with abdominal pain, arthralgia and neurologic symptoms.⁴⁴ Whipple disease has two phases: (1) an early phase with fever, arthritis and/or arthralgia, followed by (2) a late phase characterized by diarrhoea and weight loss. The disease can progress and potentially involve almost every organ system, but commonly affects the eye, heart and central nervous system.⁴⁵

The diagnosis of Whipple disease is usually made by upper endoscopy and duodenal biopsy.²⁹ Endoscopic evaluation reveals the destruction of the normal mucosa of the small intestines and

Figure 8. A 24-year-old male with xanthogranulomatous appendicitis: (a) the axial contrast-enhanced CT image is demonstrating pericaecal fluid collection (arrow) not seen separate from the appendix. (b) The histopathology slide at low magnification demonstrating serosal xanthogranulomatous inflammation (arrow) in the serosa of the resected bowel wall.

Figure 9. Imaging spectrum of mycobacterium avium complex infection in three different patients: (a) contrast-enhanced axial CT image demonstrating small periaortic necrotic lymph nodes (white arrows); (b) multiple hypodense hepatic lesions (white arrows) and splenic lesions (black arrows) are seen in contrast-enhanced axial CT; and (c) diffuse mass-like wall thickening involving the duodenum causing partial obstruction (black arrows) is seen on the small bowel follow-through barium examination.

results in pale, yellow lesions with shaggy, erythematous and erosive mucosa.⁴⁶ Microscopically, there is crowding of large macrophages in the lamina propria with PAS-positive diastase-resistant rod- or sickle-shaped magenta-red bacterial inclusions.

Figure 10. A 52-year-old male with Whipple disease: the image from a small bowel follow-through fluoroscopic barium examination is showing diffuse nodular, thickened and irregular folds, predominantly involving the jejunum and, to a lesser degree, the ileum.

Immunohistochemistry with antibodies to *Tropheryma whipplei* is more sensitive and specific than Periodic acid–Schiff (PAS) stain.³

Extensive infiltration of the lamina propria with large macrophages infected with intracellular *Tropheryma whipplei* causes thickening of the intestinal villi and mucosal folds primarily in duodenum and proximal jejunum. When they become large enough, they may appear as irregularly thickened folds with sand-like nodules.⁴⁵ Barium studies reveal nodular, thickened and irregular folds, predominantly in the jejunum and, to a lesser degree, in the ileum (Figure 10).⁴⁷ Cross-sectional imaging demonstrates low-attenuation

Figure 11. An 82-year-old female with abdominal pain and barium granuloma: a fat density mass-like lesion is seen in the pelvis on the coronal CT image (arrowheads). High-density extraluminal barium is seen in the peritoneal cavity from prior perforation during a barium enema. Histopathology at resection showing a multinucleated giant cell with engulfed polarizing crystals.

mesenteric and retroperitoneal lymphadenopathy due to lymphatic obstruction and intranodal deposition of lipids.⁴⁸

Pigmented histiocytic aggregates

Barium granuloma

Barium granuloma is an uncommon complication of barium fluoroscopy of the colon.⁴⁹ Barium granuloma can result after barium leaks into adjacent tissues during or following a barium enema. The barium is subsequently engulfed and walled off by macrophages, resulting in a granuloma. The presence of barium particles in the interstitial tissues results in a foreign-body reaction, resulting in fibrosis and bowel strictures. This may lead to a tumour-like mass, fibrosis and stricture.⁵⁰ A barium granuloma may also develop within the bowel wall when the contrast material is forced through an ulceration in the mucosa (commonly in the rectum following barium enema).⁵¹

On imaging, a barium granuloma should be suspected when a very high-attenuation lesion is seen in the bowel wall or peritoneum on CT (Figure 11) and is associated with soft-tissue-like masses. Histopathology demonstrates a granuloma containing macrophages with the engulfed barium crystal.⁵¹

CONCLUSION

HDs are a diverse group of haematologic disorders defined by the pathologic infiltration of normal tissues by cells of the mononuclear phagocyte system. Although thought to be a difficult diagnosis owing to the rarity of these diseases, HDs can be diagnosed with the help of clinical history, imaging, histology and immunohistochemistry. Familiarity with the epidemiology, pathogenesis, imaging features and treatment of HDs can aid radiologic diagnoses and guide appropriate patient management.

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