

Pathology of Extramedullary Mastocytosis

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KEYWORDS

• Mast cells • Mastocytosis • Urticaria pigmentosa • Mast cell sarcoma • KIT

KEY POINTS

- Histopathologic findings of mastocytosis have distinguishing features at different anatomic locations, but at all sites mast cell infiltrates may be subtle and easily overlooked.
- Useful immunohistochemical markers of mast cell lineage include KIT and tryptase; aberrant expression of CD25 is a marker of neoplasia in mast cell infiltrates.
- Gastrointestinal involvement by mastocytosis is increasingly recognized; endoscopic gastrointestinal biopsies can be used to establish a diagnosis of systemic mastocytosis in some patients with cutaneous mastocytosis and gastrointestinal symptoms.
- Mast cell sarcoma is an extremely rare clinically and pathologically distinct aggressive variant of mast cell disease.

ANCILLARY MARKERS IN SURGICAL PATHOLOGY FOR THE EVALUATION OF MASTOCYTOSIS

Nonneoplastic mast cells are round in shape, and contain a central nucleus and variable amounts of cytoplasm, which contains hundreds of membrane-bound modified lysosomes.¹ These lysosomes contain a variety of pharmacologically active substances, such as histamine, leukotrienes B₄, C₄, and D, and prostaglandin D₂, which are released in response to various stimuli. Mast cells also produce heparin and enzymes such as neutral proteases.² The wide range of substances produced by mast cells reflects the broad functions of these cells and their participation in diverse inflammatory disorders. Mast cells may also be increased in number in some neoplasms, such as neurofibroma and spindle cell lipoma. Mastocytosis includes a distinct group of clonal mast cell disorders that may be limited to the skin or may involve other sites.² Confirmation of mast cell lineage, and confirmation that a mast

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cell infiltrate is neoplastic, is afforded by the use of certain histochemical and, more reliably, immunohistochemical stains.

Mast cell granules, which are difficult to appreciate on a routine hematoxylin and eosin stain but may appear lightly basophilic, stain metachromatically with toluidine blue and Giemsa stains, and orange-red with chloroacetate esterase.³ Because these histochemical stains require the presence of mast cell granules, they may underestimate the number of mast cells in comparison with immunohistochemical staining for KIT or mast cell tryptase, as neoplastic mast cells often contain greatly reduced numbers of cytoplasmic granules.⁴ Consequently, these histochemical markers have largely been replaced by immunohistochemical markers in surgical pathology practice (Table 1).

KIT

KIT (also known as CD117), a type III receptor tyrosine kinase that plays a crucial role in mast cell development, is a highly sensitive marker of mast cells. In contrast to mast cell tryptase, expression is localized to the cell membrane rather than the cytoplasm. In addition to its role in mast cell development, KIT also functions in the development of melanocytes, germ cells, hematopoietic stem cells, and the interstitial cells of Cajal within the gastrointestinal (GI) tract.⁵ KIT is therefore expressed in some malignant melanomas, seminoma, some acute myeloid leukemias, and gastrointestinal stromal tumors (the latter reflecting differentiation toward the interstitial cell of Cajal lineage). However, although the overall specificity of KIT for mast cells is low, in the appropriate clinical context KIT is invaluable for the identification of mast cells, as relatively few normal cell types show expression of this marker.

Adult-onset mastocytosis is associated with somatic point mutations in exon 17 of *KIT* (codon 816) in most cases, which result in ligand-independent activation and autophosphorylation of KIT.⁶ *KIT* mutations can be detected in peripheral blood, bone marrow aspirates, or tissue samples, which can help support a diagnosis of mastocytosis; the presence of codon 816 mutations in *KIT* is one of the minor criteria for the diagnosis of systemic mastocytosis.⁷ The most common mutation, D816V (substitution of valine for aspartate), is detected in neoplastic mast cells of more than 95% of adult patients with systemic mastocytosis, and in approximately one-third of pediatric patients with cutaneous mastocytosis.^{8–10} Because this particular mutation results in a conformational change in the kinase domain of KIT that renders it resistant to the effects of imatinib, a tyrosine kinase inhibitor effective in the treatment of chronic

Table 1 Useful immunohistochemical markers in the evaluation of mastocytosis	
Antibody	Comments
KIT	Confirms mast cell lineage; highly sensitive for mast cells, but not entirely specific (melanocytes, interstitial cells of Cajal, hematopoietic stem cells also express KIT); stains both normal and neoplastic mast cells
Mast cell tryptase	Confirms mast cell lineage; highly specific for mast cells; may be less sensitive than KIT for neoplastic mast cells in the gastrointestinal tract; stains both normal and neoplastic mast cells
CD25	Stains only neoplastic mast cells; confirms neoplastic nature of mast cell infiltrate; also stains some T lymphocytes
CD30	Stains a subset of neoplastic mast cells; may be a marker of aggressive disease in bone marrow involved by mastocytosis; does not appear to be associated with aggressive disease in the gastrointestinal tract

myeloid leukemia and gastrointestinal stromal tumor, imatinib therapy is not effective treatment for most patients with mastocytosis.^{11,12} Less commonly, alternate activating point mutations are detected, such as D816Y, D816H, and D816F. Of note, a large subset of pediatric patients with urticaria pigmentosa (UP) has *KIT* mutations in the extracellular domain (exons 8 or 9), at approximately the same rate as exon 17 mutations.¹⁰

Mast Cell Tryptase

Tryptase is a cytoplasmic serine protease that is expressed almost exclusively by mast cells.¹³ In contrast to other mast cell proteases, cytoplasmic tryptase expression appears to be present at all stages of mast cell maturation.¹⁴ Its superiority for the detection of mast cells over histochemical markers was established along with the observation that aggressive forms of mastocytosis, in which the neoplastic mast cells often have minimal cytoplasm, show less tryptase expression than mast cells of cutaneous mastocytosis.⁴ Similarly, it has been observed that in comparison with *KIT*, mast cell tryptase shows more variable levels of expression in the neoplastic cells of GI mastocytosis.¹⁵

CD25

CD25 is a low-affinity receptor for interleukin-2, which is normally expressed on a subset of T lymphocytes. Aberrant expression of CD25 is a consistent finding of neoplastic mast cells; CD25 is not expressed in normal mast cells.^{16–19} Expression of CD25 on mast cells therefore helps confirm that a mast cell infiltrate represents a neoplastic process rather than a reactive hyperplasia.²⁰ Prior studies have established the utility of CD25 in the evaluation of mast cell infiltrates at different anatomic sites, including bone marrow, skin, and GI tract.^{18,19,21} Coexpression of *KIT* on mast cells, more abundant cytoplasm in mast cells, and stronger CD25 staining on T lymphocytes all help distinguish between mast cells and T cells on a CD25 immunostain.²¹

CD2

Aberrant expression of CD2 is common in neoplastic mast cells.^{22,23} CD2, also known as LFA-2, is usually expressed in T cells and a subset of natural killer cells. However, not all cases of systemic mastocytosis show expression of CD2, and within individual cases expression may be highly variable. CD2 therefore has lower sensitivity than CD25 for the detection of neoplastic mast cells, and also has lower specificity, as CD2 stains nearly all T lymphocytes.²⁰ Although coexpression of CD2 is considered a minor diagnostic criterion for the diagnosis of systemic mastocytosis, its low sensitivity limits its clinical utility. Despite the role of CD2 expression in systemic mastocytosis being unknown, it has been hypothesized that because mast cells also express CD58 (LFA-3), a natural ligand of CD2, CD2-CD58 interactions may be involved in the accumulation of mast cells in patients with systemic mastocytosis.²³ Of note, mast cells may also express other less specific hematopoietic markers used in surgical pathology, such as CD45 and CD68, and other less specific diagnostic markers may be detected by flow cytometry (eg, CD9 and CD33).^{16,23}

CD30

CD30 is a member of the tumor necrosis factor receptor superfamily whose expression is normally limited to a subset of activated lymphocytes. Expression of CD30 in neoplastic mast cells in bone marrow biopsies has been found to be significantly associated with advanced disease.²⁴ By contrast, in the GI tract, the finding of CD30 expression does not seem to predict aggressive disease.¹⁵ Among other neoplasms,

CD30 is also expressed by tumor cells of Hodgkin lymphoma, anaplastic large cell lymphoma, and embryonal carcinoma.

CUTANEOUS MASTOCYTOSIS

Urticaria Pigmentosa

UP is the most common form of cutaneous mastocytosis (Table 2). UP typically presents as a generalized eruption of red-brown macules or sometimes papules, predominantly involving the trunk, and occasionally the extremities and head and neck region.^{25,26} It is named for the tendency for lesions to urticate when stroked (Darier sign) and the reactive basal hyperpigmentation of the epidermis. Most patients are younger than 4 years old at presentation, and in children with UP the clinical course is usually self-limited with resolution of disease by puberty.²⁷ However, when UP arises in adults, disease tends to be persistent and often reflects the presence of underlying systemic mastocytosis.^{28,29}

In normal skin, small numbers of dermal interstitial mast cells are observed, most prominent around blood vessels and skin adnexa.^{30,31} Histologically, UP in children is characterized by sheets of mast cells within the papillary dermis, often with extension into the reticular dermis, sometimes with a perivascular and periadnexal distribution (Fig. 1).³² The mast cells typically have a predominantly round morphology, with a subset of cells showing elongated cytoplasmic processes (spindle shaped). In adults with cutaneous mastocytosis, the density of mast cells is usually less than that seen in pediatric UP, and multiple biopsies may be needed to make a definitive diagnosis of mastocytosis; However, even in children the number of mast cells may be highly variable between patients, and in some cases consist of only sparse perivascular mast cells. Basal hyperpigmentation is a typical finding in UP, and scattered eosinophils may be present, particularly in adults; both of these features may be helpful clues to the diagnosis when the infiltrate is sparse (see Fig. 1). In children, subepidermal vesiculobullous changes may arise as a result of persistent superficial edema. The bullae may contain mast cells, eosinophils, and neutrophils, with an underlying typical dermal mast cell infiltrate.³³

Normal skin is reported to contain up to 15 mast cells per high-power field, although the range is in fact variable. A wide range of inflammatory dermatoses are

Table 2 Subtypes of cutaneous mastocytosis		
Type	Clinical Features	Histologic Features
Urticaria pigmentosa	Most common in children; onset in adulthood is associated with systemic disease in nearly all patients; most common form of cutaneous disease	Aggregates and sheets of mast cells within dermis; often perivascular or periadnexal in distribution; cytology ranges from round to spindled cells; may be more subtle in adults
Telangiectasia macularis eruptiva perstans	Rare variant; occurs in adults; highly associated with systemic disease	Subtle increase in mast cells around slightly dilated superficial blood vessels
Solitary mastocytoma	Rare variant; virtually always in infants; predilection for trunk	Sheets of round to ovoid mast cells within the dermis, occasionally extending into subcutis
Diffuse cutaneous mastocytosis	Rare variant; virtually always in childhood; peau d'orange appearance	Sheets of mature-appearing mast cells or limited lichenoid infiltrate of mast cells in papillary dermis

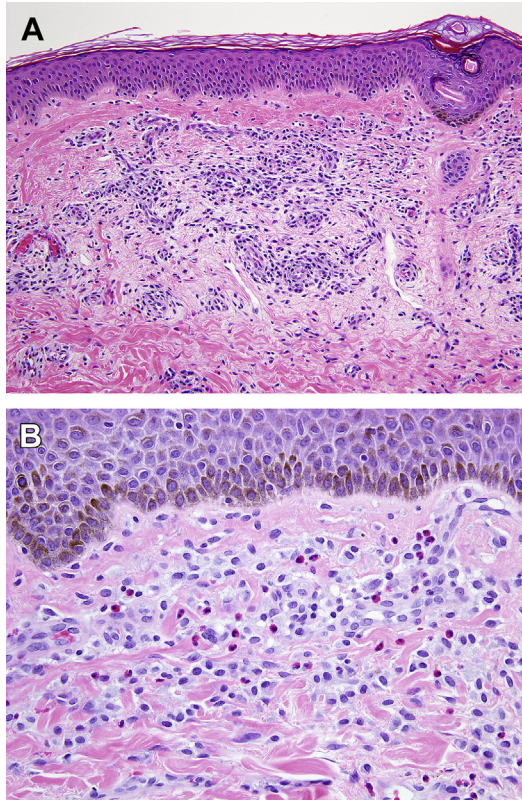


Fig. 1. Cutaneous mastocytosis. Urticaria pigmentosa is characterized by aggregates or sheets of mast cells within the dermis, sometimes showing a predominantly perivascular distribution (A) (H&E, original magnification $\times 100$). The mast cells are typically round with moderate amounts of eosinophilic, vaguely granular cytoplasm; admixed eosinophils may be present, particularly in adults (B) (H&E, original magnification $\times 400$). Note the characteristic hyperpigmentation of the basal layer of the epidermis.

accompanied by mast cell hyperplasia; therefore, mast cell density must be interpreted carefully in the context of the clinical presentation and other histologic findings. Given that some lesions, particularly those of telangiectasia macularis eruptiva perstans (TMEP), may be subtle, comparison with nonlesional skin in a given biopsy may be helpful.¹ As in other locations, mast cells express mast cell tryptase and KIT, both of which are invaluable in confirming a diagnosis of cutaneous mastocytosis. Expression of CD25 by mast cells in UP appears to be associated with systemic mastocytosis in adult patients.³⁴

Telangiectasia Macularis Eruptiva Perstans

TMEP is a rare variant of UP that occurs in adults and is highly associated with systemic disease.^{35–38} Clinically the skin lesions are lightly pigmented, telangiectatic and erythematous macules, usually few in number, which typically arise on the trunk and proximal extremities, and more rarely on the face. Histologically there is a subtle increase in mast cells, usually distributed around slightly dilated superficial dermal blood vessels.¹ The mast cells are predominantly spindle shaped, and an eosinophilic infiltrate is usually absent.

Solitary Mastocytoma of Skin

Cutaneous mastocytoma presents as a solitary skin lesion, virtually always in infants, over a wide anatomic distribution, with a predilection for the trunk and wrists.^{39–41} Lesions may measure up to 3 cm, and usually involute spontaneously. Histologically, mastocytoma is composed of sheets of round to ovoid mast cells with abundant pale eosinophilic cytoplasm within the dermis, occasionally extending into underlying subcutis.¹ Without correlation with clinical findings, small examples of solitary mastocytoma cannot be distinguished on histologic grounds from UP. In contrast to mast cell sarcoma, the lesional cells lack atypia and their mast cell lineage is usually easily recognizable. Localized necrobiosis and stromal fibrosis may be present.^{42,43}

Diffuse Cutaneous Mastocytosis

This clinical variant of cutaneous mastocytosis is uncommon and, similar to solitary mastocytoma, virtually always occurs in childhood.⁴⁴ Clinically the skin is diffusely thickened, erythematous or yellow-brown in color, and may have a peau d'orange appearance. Blistering, bullae, and nodule formation may occur.^{45–49} Histologically the skin findings may resemble mastocytoma, containing sheets of mature-appearing mast cells, or may consist of a more limited lichenoid infiltrate of mast cells in the papillary dermis. Fibrosis is occasionally present.

MASTOCYTOSIS INVOLVING THE GASTROINTESTINAL TRACT

Involvement of the GI tract by mastocytosis is increasingly recognized, because of increasing awareness among pathologists and physicians involved in the care of patients with mastocytosis as well as the availability of sensitive and specific immunohistochemical markers to detect neoplastic mast cells. Key features of mastocytosis involving the GI tract are shown in **Box 1**.

GI symptoms are common in patients with mastocytosis, including patients without direct involvement of the GI tract, and include abdominal pain, nausea, and diarrhea. These symptoms are thought to be due to the release of mast cell mediators such as histamine and leukotrienes, and in patients with involvement of the GI tract may also be due to direct infiltration of the mucosa by mast cells, resulting in malabsorption or enhanced local effects of mediator release. The frequency of GI symptoms in patients with systemic mastocytosis is estimated at 70%,⁵⁰ diminishing in patients with UP (without known GI involvement) to 25%.²⁹ However, the true frequency of GI tract

Box 1

Key features: mastocytosis involving the gastrointestinal tract

- May be first presentation of systemic disease
- Colon and terminal ileum most commonly involved
- Endoscopically may be associated with mucosal erythema, granularity, or nodularity
- Lamina propria infiltrates of ovoid or spindle-shaped mast cells; superficial distribution underneath surface epithelium in colon is common
- Eosinophilic infiltrates may mask the mast cell infiltrate or lead to an erroneous diagnosis of eosinophilic gastroenteritis
- Disease is often focal; therefore multiple, systematic random biopsies are indicated
- Gastrointestinal involvement does not correlate with aggressive disease

involvement in patients with cutaneous mastocytosis or mastocytosis at other sites is not known, as many patients do not undergo endoscopic biopsy unless they have long-standing, persistent, or changing symptoms.

Detection of GI tract involvement by endoscopic biopsy is a useful method of confirming systemic disease in patients with GI symptoms; in a series of 24 patients with GI tract and liver mastocytosis, the first diagnosis of systemic disease was made based on GI/liver biopsy findings in 67% of patients.¹⁵ However, interestingly 2 patients in this study were asymptomatic, and disease was only detected during colonoscopic screening for colorectal cancer. The median interval from the time of diagnosis of skin disease to the time of documented GI involvement in that study was 10 years. Endoscopic abnormalities are seen in approximately 60% of patients with GI mastocytosis, and include mucosal erythema/congestion, granularity, or nodularity.^{51–53} GI mucosal involvement in the absence of malabsorption and weight loss does not appear to correlate with aggressive disease.¹⁵

Clinical and pathologic descriptions of mastocytosis in GI biopsies include case reports and small series,^{21,51,52,54–58} as well as 2 recent large series of 23 and 24 patients with GI tract and liver mastocytosis.^{15,59} When the GI tract is involved by mastocytosis, the most commonly involved sites are colon and ileum, followed by duodenum. The stomach is less often involved; only one-third of gastric biopsies from patients with other sites of GI tract involvement show involvement by mastocytosis.¹⁵ Mastocytosis typically does not involve the esophagus.

The diagnosis of mastocytosis in mucosal biopsies can be difficult for several reasons; involvement can be very focal and subtle, making recognition of the infiltrate challenging. Histologically, mucosal biopsies involved by mastocytosis show lamina propria infiltrates of ovoid to spindle-shaped mast cells in aggregates or sheets. The mast cell aggregates usually show a predominantly superficial distribution in the lamina propria, with greatest density directly under the surface epithelium, especially in the colon (**Fig. 2**). Occasionally, aggregates are scattered randomly throughout the lamina propria. The mast cell infiltrate may extend into the muscularis mucosae. Mast cell morphology is variable, ranging from rounded cells with moderate amounts of pale eosinophilic cytoplasm to, more commonly, ovoid or spindle cells with more limited cytoplasm. As at other sites, mast cell density is highly variable, and in itself is not a useful diagnostic feature. Mast cell count is variable in normal biopsies and may be increased in other inflammatory disorders such as parasitic infection^{15,21}; it is the presence of discrete aggregates or confluent sheets of mast cells, along with coexpression of CD25, that allow for a diagnosis of mastocytosis (see **Fig. 2**). Of importance is that involvement of the GI tract can be very focal in a given biopsy, consisting of a single discrete aggregate of mast cells. Heterogeneous, patchy involvement within biopsies taken from the same region can also be seen, with some biopsy fragments showing no or minimal involvement, and other fragments showing obvious sheets or aggregates of mast cells.¹⁵ This feature emphasizes the need for multiple, systematic random biopsies at the time of endoscopy.

Prominent eosinophilic infiltrates frequently accompany GI involvement by mastocytosis, and may mask the mast cell infiltrate or lead to an erroneous diagnosis of eosinophilic gastroenteritis. Eosinophilic infiltrates appear to be more common in colonic biopsies than in upper GI tract biopsies involved by mastocytosis.¹⁵ Other histologic findings that may be seen include architectural distortion in colonic biopsies, villous blunting in small intestinal biopsies, chronic duodenitis, and chronic inactive gastritis. In the colon, these findings may mimic inflammatory bowel disease.⁵⁵

Neoplastic mast cells are highlighted by diffuse membranous staining for both KIT and CD25 (see **Fig. 2**). By contrast, expression of mast cell tryptase may be variable

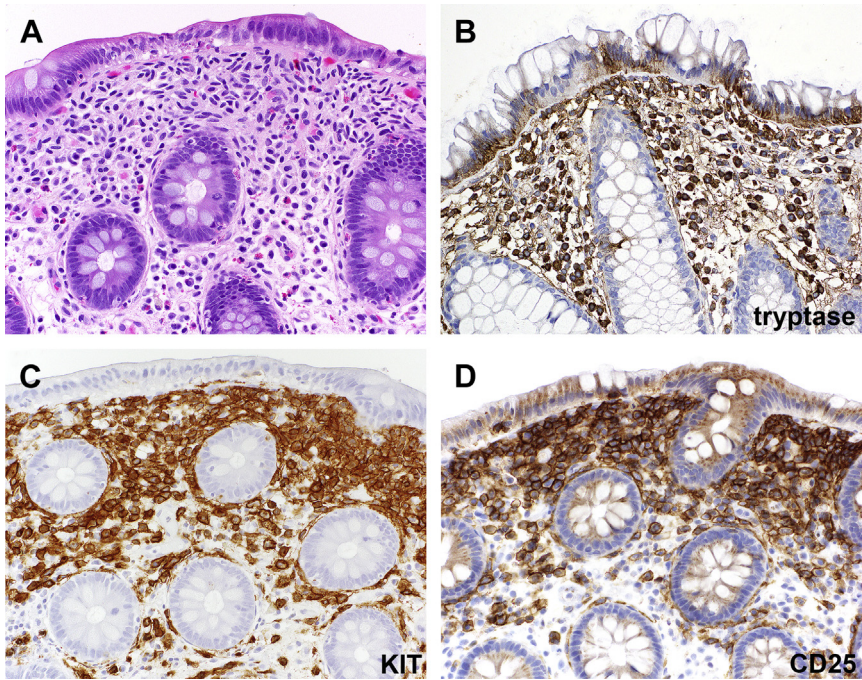


Fig. 2. Gastrointestinal mastocytosis. Mastocytosis involving the colon is typically characterized by aggregates of spindle-shaped mast cells with limited cytoplasm, localized underneath the surface epithelium (A) (H&E, original magnification $\times 400$). The mast cells are positive for tryptase (B) (original magnification $\times 400$) and KIT (C) (original magnification $\times 400$), and show aberrant membranous expression of CD25 (D) (original magnification $\times 400$), confirming their neoplastic nature.

and may show positive staining in only a subset of mast cells.¹⁵ In contrast to prior studies that have shown an association between CD30 expression and advanced disease in the bone marrow,²⁴ at least in the GI tract, the finding of reactivity for CD30 does not seem to predict aggressive disease: CD30 expression on GI mast cells has been reported in a subset of patients with an indolent clinical course, and was present in only 1 of 2 cases with aggressive features in a recent study, although the number of cases examined was small.¹⁵

In general, the histologic differential diagnosis of mastocytosis in the GI tract is limited; perhaps the most difficult differential diagnosis is with normal colonic mucosa for those cases whereby the mast cell infiltrate is focal and subtle, followed by eosinophil-rich disorders such as primary eosinophilic gastroenteritis, parasitic disease, and chronic inflammatory bowel disease.

MASTOCYTOSIS INVOLVING THE LIVER

In most cases, liver involvement by mastocytosis is associated with aggressive disease. Patients with mastocytosis involving the liver may present with hepatomegaly, ascites, and other signs of portal hypertension such as bleeding varices.^{15,60,61} Liver biopsies involved by mastocytosis typically show mast cell infiltrates in both a portal and sinusoidal distribution.^{60,61} The sinusoidal component may be subtle, but can be highlighted by KIT or tryptase immunostaining (Fig. 3). The mast cells usually have

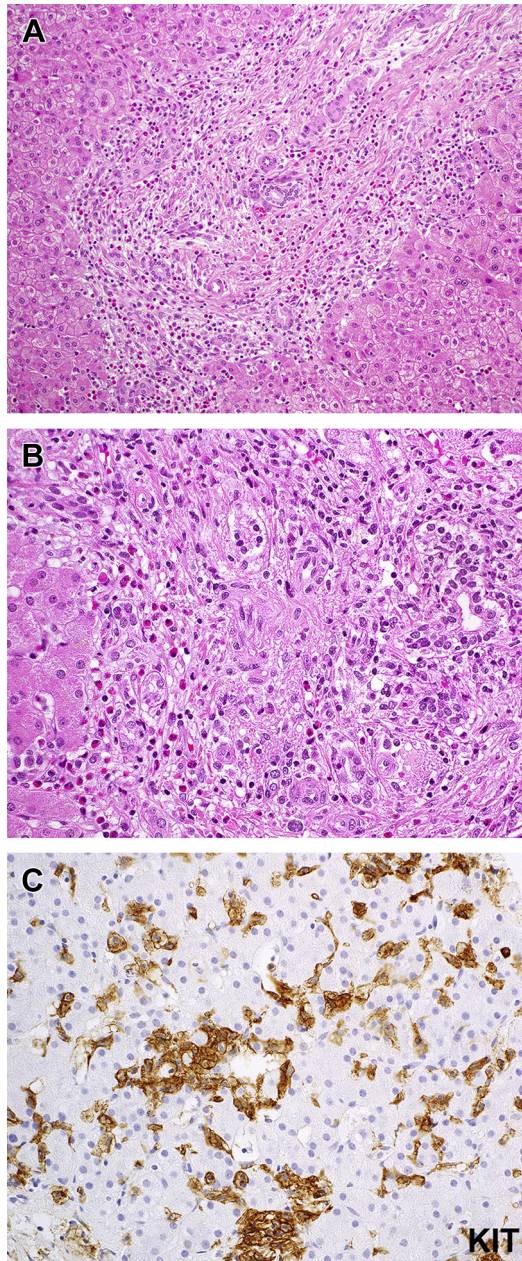


Fig. 3. Mastocytosis in the liver. Liver involvement by mastocytosis is often subtle, consisting of portal infiltrates (A) (H&E, original magnification $\times 100$) of spindle-shaped mast cells with admixed eosinophils (B) (H&E, original magnification $\times 400$). The mast cell infiltrate typically also involves sinusoidal spaces, which may be subtle and more readily appreciated with the aid of KIT immunohistochemical staining (C) (original magnification $\times 400$).

spindle cell morphology. Admixed eosinophils are common and may mask the mast cell infiltrate. Periportal fibrosis may be present, but development of cirrhosis is rare.

MASTOCYTOSIS INVOLVING THE SPLEEN AND LYMPH NODES

The prevalence of splenic involvement by mastocytosis is uncertain, as splenectomy is rarely performed in patients with mastocytosis, except in the past in some patients whose aggressive disease included hypersplenism. Mastocytosis in the spleen may present as focal mast cell infiltrates in parafollicular areas, aggregates within follicles, or diffuse infiltration of the red pulp.^{61,62} Similar to mastocytosis at other sites, an admixed eosinophilic infiltrate and fibrosis are common findings.

Involvement of lymph nodes by mastocytosis is rare, but can present as generalized lymphadenopathy. The paracortical region is most often involved (**Fig. 4**), either focally or diffusely, but any compartment can be infiltrated by mast cells. In addition to the presence of mast cells, which may be ovoid, round, or spindle in morphology, additional findings that may be seen include reactive follicular hyperplasia, eosinophilic infiltrates, fibrosis, and a plasma cell infiltrate (see **Fig. 4**).^{61,63} In a subset of patients with nodal infiltrates of mast cells who present with lymphadenopathy and peripheral eosinophilia, *PDGFRA* rearrangements are detected; these patients are classified in the category of “myeloid neoplasm with eosinophilia and rearrangement of *PDGFRA*” (rather than systemic mastocytosis).^{5,7}

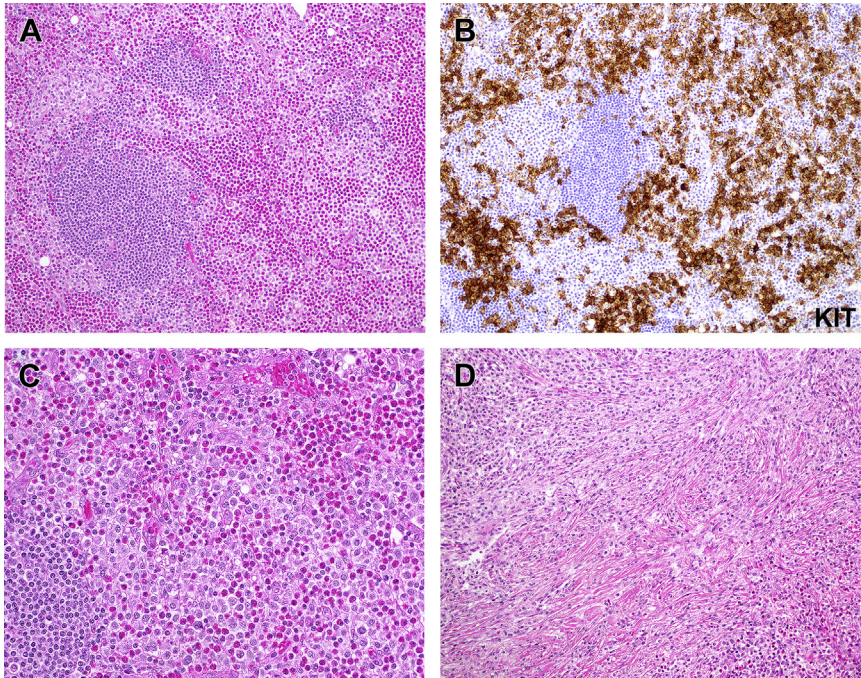


Fig. 4. Mastocytosis involving a retroperitoneal lymph node: the mast cell infiltrate shows a predominantly paracortical distribution (A) (H&E, original magnification $\times 100$). KIT immunostaining highlights mast cells, and demonstrates sparing of follicles in this case (B) (original magnification $\times 100$). The mast cells are variably ovoid to spindle-shaped; commonly associated features include a prominent eosinophilic infiltrate (C) (H&E, original magnification $\times 400$) and fibrosis (D) (H&E, original magnification $\times 200$).

MAST CELL SARCOMA

Mast cell sarcoma is characterized by cytologically malignant mast cells presenting as a destructive mass. Mast cell sarcoma may arise *de novo* (ie, in a patient with no history of mastocytosis) or, much more rarely, as a secondary (transformation) event in patients with cutaneous mastocytosis (see later discussion). Mast cell sarcoma is exceedingly rare in humans. Only 14 human cases of mast cell sarcoma have been reported to date in the English-language literature, either as single case reports or small series. Unlike cutaneous mastocytosis, which typically presents in infancy, mast cell sarcoma can arise at any age, with a reported range of 4 to 77 years. Mast cell sarcoma can also occur at a wide range of anatomic sites; tumors have been reported in oral/laryngeal mucosa,^{64,65} gastrointestinal tract,^{66,67} cranial bones and meninges,⁶⁸ extracranial skeleton,^{69,70} somatic soft tissue,⁷⁰ uterus,⁷¹ and skin.^{55,72,73} Key features of mast cell sarcoma are listed in **Box 2**.

Histologically, mast cell sarcoma is composed of sheets of medium-sized to large pleomorphic epithelioid cells, usually with an infiltrative growth pattern. Tumor cells have abundant cytoplasm and well-defined cell borders. Nuclei often have prominent nuclear membrane irregularities and may be bilobed (**Fig. 5**). Bizarre multinucleated tumor giant cells are frequently present. Characteristically an eosinophilic infiltrate is present, and may be a helpful clue to the diagnosis. Similar to systemic mastocytosis, tumor cells are positive for KIT, CD25, and mast cell tryptase, but expression of histiocytic or myeloid lineage markers (CD68, CD4, CD43, lysozyme) has also been reported, which can lead to diagnostic confusion.⁶⁵ The cells of mast cell sarcoma do not closely resemble either normal tissue mast cells or the spindle mast cells typical of systemic mastocytosis, but show some similarity to the cytologically defined “atypical type II mast cells” or “promastocytes” reported in some cases of aggressive systemic mastocytosis, although the degree of nuclear atypia and pleomorphism are much more striking.⁷⁴ To date, the D816V mutation of the *KIT* kinase domain characteristic of systemic mastocytosis has not been detected in any case of mast cell sarcoma. However, 2 cases have shown other *KIT* mutations: a deletion mutation in exon 8 (D419del), similar to a common mutation in pediatric UP,⁶⁵ and an alternative exon 17 mutation (N822K).⁶⁶ Because the D816V mutation confers resistance to imatinib, the absence of this mutation in mast cell sarcoma has allowed treatment with imatinib to produce at least a temporary clinical response in a subset of patients.^{65,71}

The histologic differential diagnoses of mast cell sarcoma include poorly differentiated carcinoma, melanoma, anaplastic large cell lymphoma (ALCL), Langerhans cell histiocytosis (or the exceptionally rare Langerhans cell sarcoma), and other myeloid or histiocytic neoplasms. Poorly differentiated carcinoma can usually be readily

Box 2

Key features: mast cell sarcoma

- Extremely rare malignant neoplasm composed of mast cells presenting as an isolated destructive mass
- Sheets of medium-sized to large pleomorphic epithelioid cells
- Tumor cells have abundant cytoplasm and well-defined cell borders
- Multinucleated tumor giant cells and eosinophilic infiltrates often present
- May mimic poorly differentiated carcinoma, melanoma, or anaplastic large cell lymphoma
- Lack D816V *KIT* mutations and may respond to imatinib in some cases

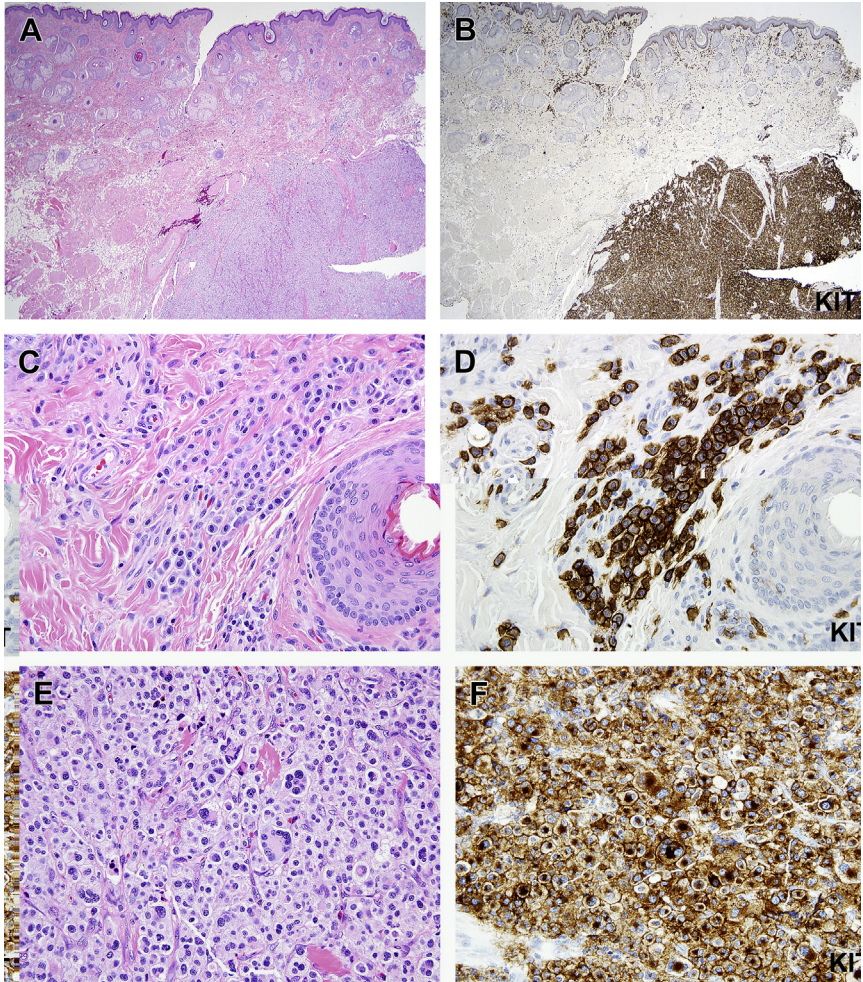


Fig. 5. Mast cell sarcoma. Mast cell sarcoma arising as a discrete nodule in the deep dermis (*lower right*) of the lip in a patient with a long-standing history of urticaria pigmentosa (A) (H&E, original magnification $\times 400$). The tumor cells in mast cell sarcoma show strong staining for KIT (B) (original magnification $\times 40$). Conventional cutaneous mastocytosis is seen in the adjacent dermis and is composed of numerous uniform, round mast cells (C) (H&E, original magnification $\times 400$), highlighted by a KIT immunostain (D) (original magnification $\times 400$). By contrast, the tumor cells of the mast cell sarcoma do not resemble normal mast cells and instead show marked cytologic atypia, nuclear pleomorphism, and frequent multinucleated cells (E) (H&E, original magnification $\times 400$). Mast cell lineage is supported by expression of KIT (F) (original magnification $\times 400$), as well as tryptase and chymase (not shown).

distinguished from mast cell sarcoma by demonstrating keratin expression; similarly, melanoma typically expresses S100 protein, and often HMB-45 or MART-1. Similar to mast cell sarcoma, a dense infiltrate of eosinophils is usually present in Langerhans cell histiocytosis. However, Langerhans cell histiocytosis is composed of tumor cells with characteristic longitudinal nuclear grooves, which are not seen in mast cell

sarcoma, as well as abundant pink cytoplasm and indistinct cell borders. Langerhans cell sarcoma shows considerable cytologic pleomorphism and features that may overlap with mast cell sarcoma. Tumor cells of Langerhans cell histiocytosis and Langerhans cell sarcoma express S100 protein, CD1a, and langerin. ALCL is composed of large epithelioid cells, often with bilobed or multilobed nuclei, similar to mast cell sarcoma. Eosinophilic infiltrates are uncommon in ALCL. ALCL consistently expresses CD30, as well as CD3, CD5, EMA, or cytotoxic granule markers in most cases. ALK expression is present in around half of ALCL cases. Detection of a clonal T-cell receptor gene rearrangement by polymerase chain reaction studies may be helpful in some cases. Variable KIT expression may occasionally be seen in T-cell lymphomas, but the uniformly strong expression seen in mast cell sarcoma is not a feature of lymphomas.

Two cases of mast cell sarcoma arising in association with long-standing cutaneous mastocytosis have been described. One occurred in a patient who had a history of infantile cutaneous mastocytosis 17 years before presenting with a mass on the lip (see [Fig. 5](#)). A residual lesion of UP was identified adjacent to the mast cell sarcoma.⁶⁵ Similarly, the development of mast cell sarcoma has been described in an adult patient with persistent localized cutaneous mastocytosis.⁷² These 2 cases appear to represent malignant transformation of a previously indolent form of mastocytosis, implying that at least some cases of mast cell sarcoma may be biologically closely related to pediatric cutaneous mastocytosis.

SUMMARY

The histopathologic findings of mastocytosis have distinguishing features at different anatomic locations, but mast cell infiltrates may be subtle, because of either their sparse nature (eg, in some cases of cutaneous mastocytosis) or focality of involvement (eg, in gastrointestinal mucosa). Advances in immunohistochemical detection of mast cell lineage, along with the identification of aberrant CD25 expression as a marker of neoplasia in mast cell infiltrates, have been extremely useful in the evaluation of mast cell disorders, and broader application of these markers in surgical pathology practice will likely improve the recognition of mastocytosis. Finally, endoscopic GI biopsies are emerging as a useful method of detecting systemic disease in some patients with cutaneous mastocytosis and GI symptoms.

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