Pathology of Extramedullary Mastocytosis

Leona A. Doyle, MD[a], Jason L. Hornick, MD, PhD[a,b,*]

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

The authors have no conflicts of interest to declare.

[a] Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115 USA; [b] Mastocytosis Center, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA
* Corresponding author.
E-mail address: jhornick@partners.org

Immunol Allergy Clin N Am 34 (2014) 323–339
http://dx.doi.org/10.1016/j.iac.2014.01.010 **immunology.theclinics.com**
0889-8561/14/$ – see front matter

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