Mast cell sarcoma (MCS) is an exceedingly rare clinicopathologic entity characterized by a unifocal accumulation of neoplastic mast cells that grow in a locally destructive manner. We report a case in a 2-year-old boy who was initially diagnosed at 8 months of age with atypical cutaneous mastocytoma of the right ear with subsequent aggressive, destructive growth pattern; features that were most consistent with MCS. So far, MCS has been documented in the literature in at least 6 human cases. To the best of our knowledge, our case represents the first MCS in an infant. Thorough multimodal approach with strict follow-up is relevant in appropriately diagnosing this rare entity, particularly in differentiating this lesion from other neoplasms that are more likely to occur in infancy.

Key Words: mast cell sarcoma, mastocytosis, temporal bone

(J Pediatr Hematol Oncol 2013;35:315–320)

Mast cell disease (MCD) is a group of lesions that encompasses cutaneous mastocytosis (CM), systemic variants, and unifocal tumor formation including extracutaneous mastocytoma and mast cell sarcoma (MCS). MCS is an extremely rare entity with only 6 documented human cases in the literature. We report a case in a 2-year-old boy who, at 8 months of age, was found to have a unifocal right ear mass that was initially diagnosed as atypical CM, and subsequently was demonstrated to actually be MCS due to the aggressive and destructive tumor growth pattern. This represents the first case of MCS documented in an infant.

CASE REPORT

This male infant first presented with foul-smelling, purulent otorrhea of the right ear beginning at about 4 months of age. He was treated with antibiotics and ear drops for otitis and the otorrhea resolved, but he continued to behave as if the ear irritated him. Imaging performed at that time, from an outside institution, showed a 5-mm soft tissue mass involving the right distal auditory canal adjacent to the tympanic membrane. No evidence of soft tissue invasion or bone erosion was seen. Follow-up physical examination at 8 months of age showed a large, polypoid, soft tissue mass causing near complete obstruction of the right external auditory canal. A biopsy of this mass revealed a subcutaneous infiltrate of mildly atypical mononuclear-like or histiocytic-like cells with folded or polypolated nuclei admixed with significant numbers of eosinophils (Figs. 1A, B). No Touton-type giant cells were identified. At that time, this was interpreted as an “atypical” CM based on the clinically localized growth without definite evidence of destructive growth pattern as per outside imaging impression, positive staining for tryptase (Fig. 1C), CD68, and CD117 (Fig. 1D), and expression of CD43. Of additional concern was the lack of classic metachromatic granules on Giemsa stain. Immunohistochemical (IHC) stains for CD2 and CD25 from the initial biopsy were both negative. Langerhans cell histiocytosis (LCH), granulocytic sarcoma, and histiocytic sarcoma were considered, but were excluded or considered highly unlikely based on negative staining for CD1a protein (Fig. 1E), S100 (Fig. 1F), myeloperoxidase (MPO), CD34, CD45, and CD163, respectively.

At the age of 11 months, 3 months after initial diagnosis, follow-up imaging (Fig. 2) revealed rapid disease progression manifested by a destructive, 3.3 x 3.8 x 3.6 cm, lesion arising from the right petrous temporal bone and extending through the skull base, involving the carotid sheath, and effacing or occluding the right jugular vein. The initial mass had been biopsied but not resected, and no treatment had been given during this interval. Serum tryptase level was elevated at 34.1 ng/mL (reference range, <11.5 ng/mL).

Subsequent biopsies showed a lesion histologically identical to the initial biopsy with the exception of a small, previously unsampled population of cells (2% to 5%) showing mild to moderate atypia (Fig. 3A). The tumor cells had a low Ki-67 proliferation index (1% to 2% overall; Fig. 3B) and were positive for CD33, CD68, CD117, and CD25 (Fig. 3A). The tumor cells had a low Ki-67 proliferation index (1% to 2% overall; Fig. 3B) and were positive for CD33, CD68, CD117, and CD25 (Fig. 3A).

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A stain for langerin was negative. Electron microscopy showed non-specific cytoplasmic features, with neither typical mast cell nor Birbeck granules. Chromosomal studies of the tumor cells showed a normal 46, XY karyotype. Polymerase chain reaction analysis on fresh tumor tissue was performed at Stanford University Medical Center (Palo Alto, CA). This polymerase chain reaction test included specific evaluation of c-KIT exons 8 and 17, and no mutations were detected.

Summary: Mast cell diseases comprise a spectrum of disorders including cutaneous mastocytosis, indolent or aggressive systemic variants including leukemia, and unifocal tumor formations such as benign extracutaneous mastocytoma or aggressive mast cell sarcoma (MCS). Many mast cell diseases are associated with aberrancy of c-KIT proto-oncogene resulting in tyrosine kinase activity, typically exhibiting point mutation in codon 816. MCS is an exceedingly rare clinicopathologic entity characterized by a unifocal accumulation of neoplastic mast cells that grow in a locally destructive manner. We report a case in a 2-year-old boy who was initially diagnosed at 8 months of age with atypical cutaneous mastocytoma of the right ear with subsequent aggressive, destructive growth pattern; features that were most consistent with MCS. So far, MCS has been documented in the literature in at least 6 human cases. To the best of our knowledge, our case represents the first MCS in an infant. Thorough multimodal approach with strict follow-up is relevant in appropriately diagnosing this rare entity, particularly in differentiating this lesion from other neoplasms that are more likely to occur in infancy.

Key Words: mast cell sarcoma, mastocytosis, temporal bone

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FIGURE 1. A and B, Hematoxylin and eosin stain of the initial biopsy of the auditory canal mass showing a subcutaneous infiltrate of monocytoid or histiocytoid cells with folded or polylobated nuclei admixed with significant numbers of eosinophils (A: ×100, B: ×400). Immunohistochemistry showing expression of tryptase (C, ×200) and CD117 (D, ×400). CD1a (E, ×400) and S100 (F, ×400) were negative, essentially ruling out Langerhans cell histiocytosis.

FIGURE 2. Magnetic resonance imaging of the head showing a destructive 3.3 × 3.8 cm lesion arising from the right petrous temporal bone and extending through the skull base (sagittal view).

FIGURE 3. A, Hematoxylin and eosin stain of the second biopsy of the destructive mass showing mild to moderate nuclear atypia (×400). B, The neoplastic cells demonstrate a low proliferation index, with Ki-67 nuclear positivity in only about 1% to 2% of tumor cells (×200).
Despite a milder degree of cellular atypia than described in previous cases, and the absence of the most common \( c-KIT \) mutations in MCD, the clinical, radiologic, histologic, and immunophenotypic characteristics were most consistent with MCS. Complete staging work-up showed no evidence of bone marrow or peripheral blood involvement. He underwent tumor debulking surgery followed by a month-long trial of imatinib (150 mg/d) with no clinical or radiographic evidence of tumor response. He was subsequently placed on an investigational oral regimen, protein kinase C-412 (PKC412; 40 mg, tid) and has recently completed 12 months of therapy with no significant adverse effects. Minimal decrease in residual tumor size, evident from subsequent radiographic impressions, from 2.1/2.7 to 2.1/2.4 cm was noted after the first 6 months of treatment with the aforementioned agent. This decrease in tumor size has allowed possibility for further debulking surgery. Subsequent histology showed residual tumor cells limited to the right middle ear in a background of moderate fibrosis and mixed inflammatory cells. The patient is now 2 years old, and has experienced mild right-sided cranial nerve VII palsy and possible right-sided hearing deficit since the initial subtotal resection, but no worsening of these deficits or new clinical symptoms have emerged.

**DISCUSSION**

Mastocytosis is a diverse group of diseases exhibiting unifocal or multifocal proliferation of clonal mast cells. Different subtypes are characterized by differing clinical symptoms and distribution of abnormal mast cell clusters. Isolated CM often occurs in children, whereas systemic forms such as indolent systemic mastocytosis, systemic mastocytosis with associated clonal hematological nonmast cell lineage disease, aggressive systemic mastocytosis, and mast cell leukemia (MCL) are more commonly observed in adults. Other variants consist of a unifocal infiltrate of neoplastic mast cells without evidence of systemic involvement. Examples of the latter include MCS and extracutaneous mastocytoma (ECM), with the former characterized by a destructive pattern of growth, typically showing high-grade cytology, whereas ECM demonstrates a nondestructive growth pattern and low-grade cytology. Mutations of \( c-KIT \) oncogene in the tyrosine kinase domain, expressing substitution from aspartate to valine at codon 816 (D816V) have been detected in most cases of systemic mastocytosis (SM).

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Clinical Symptoms</th>
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<tbody>
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<td>Isolated CM</td>
<td>Often occurs in children, whereas systemic forms such as indolent systemic mastocytosis, systemic mastocytosis with associated clonal hematological nonmast cell lineage disease, aggressive systemic mastocytosis, and mast cell leukemia (MCL) are more commonly observed in adults. Other variants consist of a unifocal infiltrate of neoplastic mast cells without evidence of systemic involvement. Examples of the latter include MCS and extracutaneous mastocytoma (ECM), with the former characterized by a destructive pattern of growth, typically showing high-grade cytology, whereas ECM demonstrates a nondestructive growth pattern and low-grade cytology. Mutations of ( c-KIT ) oncogene in the tyrosine kinase domain, expressing substitution from aspartate to valine at codon 816 (D816V) have been detected in most cases of systemic mastocytosis (SM).</td>
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|    | FIGURE 4. Gating is applied on the granulocyte region as depicted on the flow cytometry scattergram of side scatter versus CD45 (A). A population of cells (~40% of the total events) expresses CD11b and CD13 (B and C, respectively), CD9, CD33 and CD117 (D and E, respectively), but the population of interest do not express CD15, CD36, CD25, and 56 (C, B, E, and F, respectively). CD2 expression was equivocal (F). |
Serum tryptase Normal to c-KIT gene in several MCL cases. It is probable that MCL does not always show the D816V mutation, IHC (+) tryptase. We report a case in a 2-year-old boy with a unifocal right ear mass, initially diagnosed as CM with atypical features, showing rapid increase in tumor size and subsequently exhibiting destructive growth pattern; findings that are most consistent with MCS. It is likely that the initial diagnosis of “atypical” CM corresponded to early phase of MCS. Our case showed rapid disease progression initially with no evident tumor response with imatinib. However, minimal decrease in tumor size with disease stabilization was achieved after the first 6 months of treatment with the experimental agent PKC412, allowing for further debulking surgery. Histologic findings from the most recent surgery mainly demonstrated fibrosis and mixed inflammation, with evidence of residual tumor limited to the right middle ear. To the best of our knowledge, this represents the first reported occurrence of MCS diagnosed in an infant.

Several IHC stains are helpful in identifying mast cells and differentiating them from other cell lineages. In addition to positivity for CD68, reactivity with c-KIT or CD117 and tryptase are frequently observed, and are required for the diagnosis of mast cell lesions. In fact, among hematolymphoid neoplasms, these 3 markers (tryptase, CD117, and CD25) are distinctive of MCD. Neoplastic mast cells typically coexpress CD2 and/or CD25 in addition to CD117 and tryptase. Bel-2 expression has been reported in some MCL cases. Mast cells are typically negative for MPO, most myelomonocytic, and lymphoid antigens.

### TABLE 1. Typical Features* of Mast Cell Diseases\(^1,11\)

<table>
<thead>
<tr>
<th>Location</th>
<th>CM</th>
<th>ECM</th>
<th>ISM</th>
<th>SM-AHNMD</th>
<th>ASM</th>
<th>MCL</th>
<th>MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Skin + 1 or more organs (usually bone marrow)</td>
<td>Multifocal disseminated</td>
<td>Bone marrow and blood; skin uncommon</td>
<td>Variable, hematolymphoid uncommon</td>
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<tr>
<td>Lung</td>
<td>1 or more organs (usually hematolymphoid); skin uncommon</td>
<td>Multifocal disseminated</td>
<td>Disseminated</td>
<td>Unifocal with frequent secondary dissemination/leukemic transformation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults &gt; children</td>
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#### Extent
- Usually multifocal, can be unifocal
- Multifocal
- Multifocal/disseminated
- Disseminated
- Unifocal with frequent secondary dissemination/leukemic transformation

#### Population
- Children > adults
- Adults
- Adults > children
- Adults > children
- Adults > children

#### Histology
- Aggregates of rounded mast cells surrounding dermal blood vessels and adnexal structures
- Monomorphic, rounded mast cells; nondestructive growth
- Skin lesions similar to those of CM plus compact infiltrates of round to spindle mast cells with reactive bone marrow changes
- Variable; must show multifocal mast cell infiltrates and morphologic features of AHNMD
- Focal and diffuse infiltration by atypical, spindled mast cells
- Dense, diffuse-compact infiltrate of atypical, round mast cells. Often blast-like morphology with monocytoid or lobulated nuclei

#### Metachromatric granules
- Strong
- Strong
- Present
- Present (mast cells)
- Absent
- Absent

#### IHC
- (+) tryptase, CD117
- (+) tryptase, CD117, CD25
- Variable CD2
- (+) tryptase, CD117, CD25
- Usually (+) CD2
- Variable CD2
- Variable CD25 and CD2

#### Serum tryptase
- Normal to slightly elevated
- Persistent elevation (> 20 ng/mL), often marked (> 200 ng/mL)
- Persistent elevation (> 200 ng/mL)
- Often marked (> 200 ng/mL)

*The most common features of each disease are included; however, mast cell disorders are highly variable in their presentation and not all potential presentations are described.

ASM indicates aggressive systemic mastocytosis; CM, cutaneous mastocytosis; ECM, extracutaneous mastocytoma; IHC, immunohistochemistry; ISM, indolent systemic mastocytosis; MCL, mast cell leukemia; MCS, mast cell sarcoma; NA, data not available; SM-AHNMD, systemic mastocytosis with an associated clonal hematologic nonmast cell lineage disorder.

of the 6 patients succumbed to the disease.\(^3,5\) As with MCS, MCL does not always show the D816V mutation, however, recent studies revealed alternate mutations of the c-KIT gene in several MCL cases.\(^12-15\) It is probable that full sequencing of the c-KIT gene in cases of aggressive MCDs such as MCS or MCL that lack the commonly tested mutations will show alternate or new abnormalities. Table 2 shows a brief summary of MCS reported in tested mutations will show alternate or new abnormalities. MCDs such as MCS or MCL that lack the commonly tested mutations will show alternate or new abnormalities.
Hence, granulocytic sarcoma may be distinguished from MCD by MPO staining. Nevertheless, a prior study demonstrated a subset of atypical mast cells in CM that showed positivity for MPO,17 further imposing challenge in differentiating MCD from other myeloid tumors. LCH is one of the more common histiocytic disorders of childhood and may morphologically mimic MCD. CD1a, S100 protein, and langerin are characteristically positive in LCH but may morphologically mimic MCD. CD1a, S100 protein, and langerin are characteristically positive in LCH but may morphologically mimic MCD. Hence, granulocytic sarcoma may be distinguished from MCD by MPO staining. Nevertheless, a prior study demonstrated a subset of atypical mast cells in CM that showed positivity for MPO,17 further imposing challenge in differentiating MCD from other myeloid tumors. LCH is one of the more common histiocytic disorders of childhood and may morphologically mimic MCD. CD1a, S100 protein, and langerin are characteristically positive in LCH but may morphologically mimic MCD. CD1a, S100 protein, and langerin are characteristically positive in LCH but may morphologically mimic MCD. CD1a, S100 protein, and langerin are characteristically positive in LCH but may morphologically mimic MCD. CD1a, S100 protein, and langerin are characteristically positive in LCH23 but negative in MCD.

Available cytoreductive treatment for SM and its subtypes includes interferon-α (IFN-α) with or without corticosteroids, hydroxyurea, imatinib mesylate,24 or 2-chlorodeoxyadenosine (2-CdA or cladribine).24,25 Of these agents, IFN-α and 2-CdA or cladribine have shown modest response rates; thus, both have been recommended as first line agents in SM.24 SM with c-KIT tyrosine kinase D816V activating mutation has demonstrated resistance to imatinib;26 however, this drug was recently reported to show a reasonable disease response in 1 MCS case.5 Although our patient lacked the D816V mutation, a trial of imatinib was pursued. However, no appreciable decrease in tumor size was noted with imatinib treatment. A clinical trial of a protein kinase inhibitor, PKC412 (midostaurin) is in progress, and has revealed some promise in the treatment of aggressive forms of SM such as aggressive systemic mastocytosis and MCL.16 Moreover, PKC412 has been discovered to inhibit activation and subsequent release of chemical mediators by binding of immunoglobulin-E in basophils and mast cells, thus minimizing adverse effects from these mediators during treatment.27 Although minimal decrease in tumor size, based on subsequent radiographic impressions, was observed in our patient after the first 6 months of treatment with PKC412, this has permitted feasibility of performing further resection, which showed histologic evidence of limited residual disease. Nonetheless, insufficient data are available at present on long-term response to PKC412.

**CONCLUSIONS**

MCS in infants is extremely rare, and must be histopathologically distinguished from a number of the more common tumors of infancy, including LCH, benign localized mastocytoma, juvenile xanthgranuloma, neuroblastoma, rhabdomyosarcoma, central nervous system neoplasms, and acute leukemia, or granulocytic sarcoma. A multimodal approach, including clinical, radiographic, and immunophenotypic correlation is necessary to make these distinctions. Although most systemic MCDs demonstrate activating mutations of the c-KIT tyrosine kinase domain,
particularly substitutions in exons 8 and/or 17; a c-KIT abnormality has been documented in only 1 case of MCS in humans.8 MCS may harbor mutations in the c-KIT gene other than the usually tested aforementioned abnormalities. Hence, a full c-KIT gene sequence analysis may be helpful, and perhaps may lead to the investigation of other treatments for MCS, including targeted gene therapy.

ACKNOWLEDGMENT

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REFERENCES