

Treatment of systemic mastocytosis in an infant with midostaurin

Mona M. Liu, MD^{a,*}, Lisa A. Kohn, MD, PhD^{a,*},
Gavin D. Roach, MD^b, Grace Sun, MD^c,
Maria I. Garcia-Lloret, MD^a, and
Manish J. Butte, MD, PhD^a



Clinical Implications

- We report a case of prenatal-onset systemic mastocytosis and the first reported treatment of the disorder in infants with the tyrosine-kinase inhibitor midostaurin.

TO THE EDITOR:

Systemic mastocytosis (SM) is a rare disorder entailing multiorgan accumulation of clonal mast cells that proliferate in a ligand-independent fashion due to somatic mutation of the growth factor receptor Kit. These activated mast cells cause symptoms including pruritus, flushing, and diarrhea depending on which organs are involved. We report here a severe, congenital case of SM and our success in treating the disorder with the tyrosine-kinase inhibitor midostaurin.

A full-term female had an uncomplicated prenatal course except for an ultrasound showing bullae on the face (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). At birth a few, scattered bullae on her scalp were noted. Over weeks, more bullae developed on the face and torso. A biopsy of the skin at 3 weeks demonstrated mast cell aggregates and led to an initial diagnosis of cutaneous mastocytosis. She was treated with daily antihistamines, cromolyn, and montelukast. At age 6 months, she developed many painful, hemorrhagic bullae on light touch or skin trauma. Regions of her back and legs showed thickened, leathery skin (Figure 1, A and B). Flushing and diarrheal episodes increased despite treatment. She also developed a fluctuant, axillary mass (~8 cm diameter) (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org), for which she was admitted for further workup.

Laboratory studies showed leukocytosis, mild microcytic anemia, thrombocytosis, and hypoalbuminemia. The serum tryptase level was 187 µg/L (normal, <13 µg/L). Intravenous antibiotics were given. The axillary fluid collection was proximal to a necrotic lymph node (LN). Aggregates of spindle mast cells were noted in the subcapsular space of the LN and in the soft tissue around the LN. The fluid collection was drained to reveal serosanguinous fluid with no mast cells and no growth on culture. Seromas are rare findings in patients with SM, and we speculate that it arose because of a combination of lymphatic injury due to destruction of the LN architecture (eg, seen after postsurgical LN dissection of the axilla), mast-cell-mediated capillary leakage, and the large capacity of the axillary space. The bone marrow was hypercellular and showed approximately 5% accumulation of mast cells that were CD25⁺, with nearby

aggregates of lymphocytes and slight megakaryocytosis (Figure 1, E and F). No hepatosplenomegaly was noted on imaging. Sequencing of the *KIT* gene from bone marrow tissue revealed the p.D816V pathogenic variant. In contrast, sequencing of whole blood for *KIT* revealed only the wild-type sequence. Given lack of hepatosplenomegaly, less than 30% mast cell burden in the bone marrow, no cytopenias, and no end-organ dysfunction, the patient was diagnosed with indolent SM.¹

One month later, she presented with worsening of the bullae, uncontrollable pruritus, irritability, and episodes of flushing despite continuation of therapy. The axillary fluid reaccumulated. She had worsening anemia, persistent thrombocytosis, low albumin, and low potassium. Her serum tryptase peaked at 267 µg/L. She received intravenous antibiotics and methylprednisolone (2 mg/kg/d) without improvement. The axillary fluid was drained again, with no mast cells seen. We decided to start midostaurin, a tyrosine-kinase inhibitor approved for use in adults with SM. After informed consent with an institutional review board—approved protocol, approval of the Food and Drug Administration in the form of an emergency investigational new drug application, and “compassionate use” approval by the manufacturer, we obtained a liquid formulation of midostaurin from the manufacturer. We gave 30 mg/m² twice daily, with prophylactic ondansetron given before each dose. She showed a modest response, with some decrease in skin blistering, decrease in flushing episodes, and down-trending tryptase levels. Over the next 2 months, because of persisting symptoms and still-elevated tryptase levels, we increased the dose of midostaurin to 45 mg/m² twice daily, and later 60 mg/m² twice daily, on the basis of recommendation of the manufacturer and a report of midostaurin use in children with relapsed acute leukemia.²

After 12 weeks, she showed significant clinical improvement with total resolution of bullae (Figure 1, B and C) and a decrease in serum tryptase levels down to nearly normal (Figure 2). She has had no reaccumulation of her axillary fluid. She remained on H₁ and H₂ blockers, cromolyn, and montelukast; corticosteroids were weaned and discontinued; and her hydroxyzine dose has been halved. She has continued to have mild anemia and thrombocytosis. The origin of her persistent thrombocytosis is still unclear, but may represent an early sign of abnormal myelopoiesis that has been reported when SM advances to a myeloproliferative neoplastic disorder.³ She also has occasional and unexplained bruising, which may represent platelet or capillary dysfunction.

Generally, the patient is tolerating midostaurin well. Common side effects of midostaurin are nausea, vomiting, diarrhea, and thrombocytopenia. She has intermittent emesis, which is temporally unrelated to the administration of midostaurin; however, she has remained well hydrated and is growing along her growth curve. It is unclear whether her emesis is related to midostaurin or mastocytosis of her gastrointestinal tract, and an endoscopy is planned.

Mastocytosis in children takes on many forms but is mostly restricted to the skin. Localized collections of mast cells such as urticaria pigmentosa rarely require treatment. More extensive spread of mast cells such as diffuse cutaneous mastocytosis is

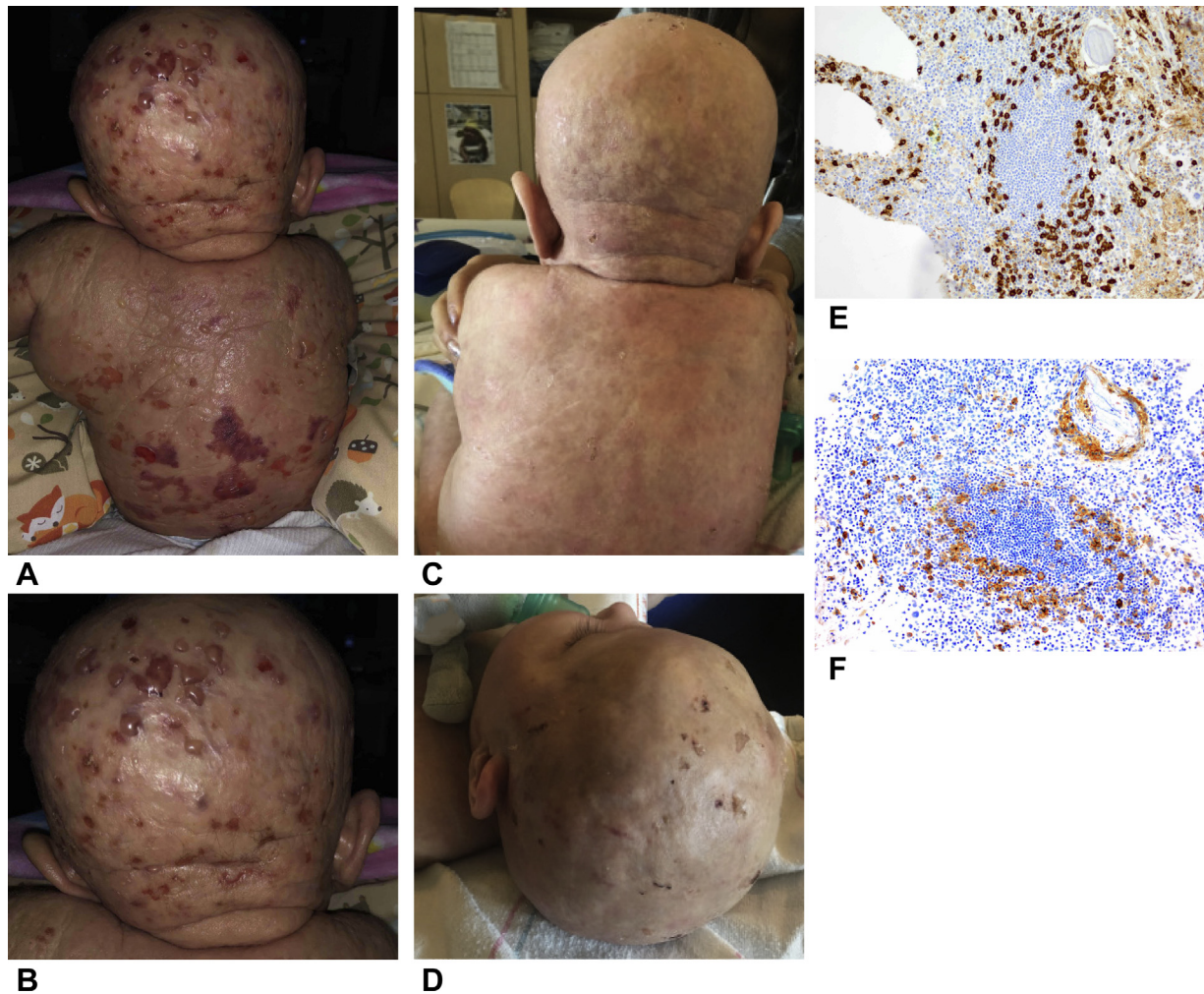


FIGURE 1. **A** and **B**, Skin findings at 7 months, showing hemorrhagic bullae before starting midostaurin. **C** and **D**, At 10 months, 12 weeks after starting midostaurin. **E** and **F**, Bone marrow histology showing CD25 staining (Figure 1, **E**, brown) and tryptase stain (Figure 1, **F**, brown).

confined to the skin,⁴ and given the generally good prognosis and response to standard therapy, evaluation of bone marrow or extracutaneous biopsies has not been suggested and is often not pursued.¹ There are only exceedingly rare reports of SM in newborns. A recent case series noted the presence of organomegaly in all cases of pediatric SM,³ but in contrast, our case had SM with no organomegaly. In adults with SM, the D816V mutation of Kit is common (>90%) but less so in children (34%),⁴ where other somatic mutations and even germline mutations are occasionally reported. This mutation allows ligand-independent, constitutive kinase activity, causing mast cell differentiation, activation, and proliferation.⁵ *In vitro* studies demonstrated that midostaurin decreases phosphorylation and suppresses Kit-dependent mast cell growth.⁶ A recent trial showed favorable responses in D816V-mutation-positive adults with advanced SM,⁷ as well as in adults with indolent SM.⁸ In that study, adults showed a decrease in serum tryptase levels by 12 weeks of therapy; a similar tempo was seen in our case. In summary, we report the first use to our knowledge of midostaurin in an infant with SM.

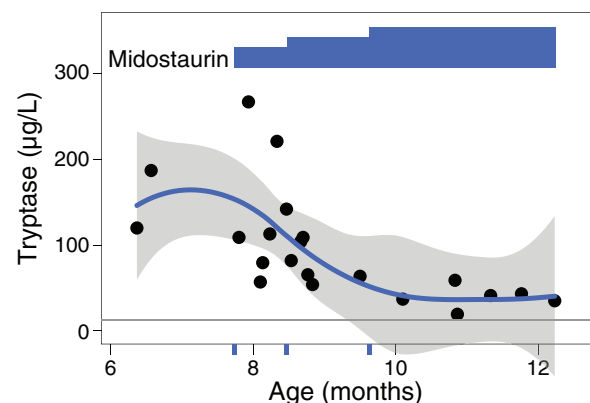


FIGURE 2. Serum tryptase levels (black), with locally weighted smoothing (blue) and 95% CI (gray). The adult upper limit of normal is 13 µg/L (horizontal line). Treatment with midostaurin at doses of 30, 45, and 60 mg/m² is indicated by the bars at the top and the ticks along the horizontal axis.

^aDepartment of Pediatrics, Division of Immunology, Allergy, and Rheumatology, University of California, Los Angeles, Los Angeles, Calif

^bDepartment of Pediatrics, Division of Hematology and Oncology, University of California, Los Angeles, Los Angeles, Calif

^cDermatology Medical Group of Oxnard and Camarillo, Oxnard, Calif

^{*}These authors contributed equally to this work.

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Corresponding author: Manish J. Butte, MD, PhD, Department of Pediatrics, Division of Immunology, Allergy, and Rheumatology, University of California, Los Angeles, Los Angeles, CA 90095. E-mail: mbutte@mednet.ucla.edu.

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ONLINE REPOSITORY



FIGURE E1. Fetal ultrasound at 35 weeks' gestation demonstrating 2 suspected bullae on the face (indicated by *arrows*).



FIGURE E2. Patient at 6 months with large axillary fluid collection before drainage.