Systemic mastocytosis, in the context of a deleterious germline *SDHC* variant, treated with ripretinib

Sara Saheb Kashaf, MPhil,[a] Lucy A. Godley, MD, PhD,[b] Angad Chadha, MD,[c] and Jason B. Waldinger, MD[a,d]

Key words: alopecia; chronic myeloproliferative neoplasm; germline *SDHC* mutation; ripretinib; systemic mastocytosis.

INTRODUCTION

Mastocytosis results from mast cell proliferation, which can be limited to the skin (cutaneous mastocytosis) or can involve infiltration of other tissues (systemic mastocytosis [SM]). SM is commonly associated with a gain-of-function mutation in *KIT*, which encodes the receptor tyrosine kinase KIT (CD117), leading to its constitutive activation. A subset of patients with SM may also develop a hematologic malignancy. Various therapies are available for SM, including interferon-alfa, cladribine, and tyrosine kinase inhibitors (TKIs). Here, we describe a patient diagnosed with SM and an associated hematologic malignancy, found to have a deleterious germline succinate dehydrogenase complex subunit C (*SDHC*) variant, who was treated successfully with off-label ripretinib after intolerance to other TKIs.

Abbreviations used:

GIST: gastrointestinal stromal tumors
SM: systemic mastocytosis
TKI: tyrosine kinase inhibitor

CASE REPORT

A 57-year-old woman with a medical history significant for chronic bone pain, osteoporosis, and irritable bowel syndrome presented with a long-standing pruritic rash on her face, scalp, torso, and extremities for about 20 years. The rash consisted of multiple, 2-mm, monomorphic, reddish-brown macules (Fig 1). She also reported urticaria and flushing following hot showers, alcohol, or stress, and chronic bone pain in her knees, hip, and back, which was managed with opioids. Triamcinolone 0.1% cream and hydroxyzine 25 mg were ineffective. Narrowband UV-B phototherapy was beneficial, but the lesions and pruritus recurred shortly upon discontinuation of treatment.

Skin punch biopsy from the trunk showed a dense interstitial and perivascular infiltrate of mononuclear cells in the papillary and reticular dermis (Fig 2, *A, B*), positive by immunohistochemistry for KIT (Fig 2, *C*) and tryptase (Fig 2, *D*), thereby confirming mast cell infiltration as the etiology for her rash. The patient had an elevated serum tryptase level (44.7 ng/mL), leukocytosis (11,200/μL), and thrombocytosis (500,000/μL), with normal liver function tests.

Bone marrow biopsy revealed a diffusely fibrosed, hypercellular bone marrow with atypical mast cell aggregates (Fig 3, *A, B*) positive for tryptase (Fig 3, *C*) and CD25 (Fig 3, *D*), indicating clonal mast cell activation. The biopsy also revealed a chronic myeloproliferative disease. Molecular testing was negative for the *KIT* D816V mutation but identified *SDHC* mutation R72C, confirmed to be germline by its presence in cultured skin fibroblasts. The patient was screened for associated tumors, including paragangliomas and pheochromocytomas, using

From the Pritzker School of Medicine, the University of Chicago, Chicago, Illinois[a]; Section of Hematology/Oncology, Department of Medicine and Human Genetics, the University of Chicago, Chicago, Illinois[b]; Section of Dermatology, Department of Medicine, the University of Chicago, Chicago, Illinois[c]; and Division of Dermatology, Department of Medicine, NorthShore University & Health System, Evanston, Illinois.[d]

Funding sources: None.

IRB approval status: Not applicable.

Correspondence to: Jason B. Waldinger, MD, Clinical Assistant Professor of Dermatology, University of Chicago, Division Head, Division of Dermatology, Department of Medicine, NorthShore University & Health System, 71 Waukegan Rd., Suite 700, Lake Bluff, IL 60044. E-mail: JWaldinger@northshore.org.

JAAD Case Reports 2023;37:119-22.

2352-5126

https://doi.org/10.1016/j.jdcr.2023.04.007

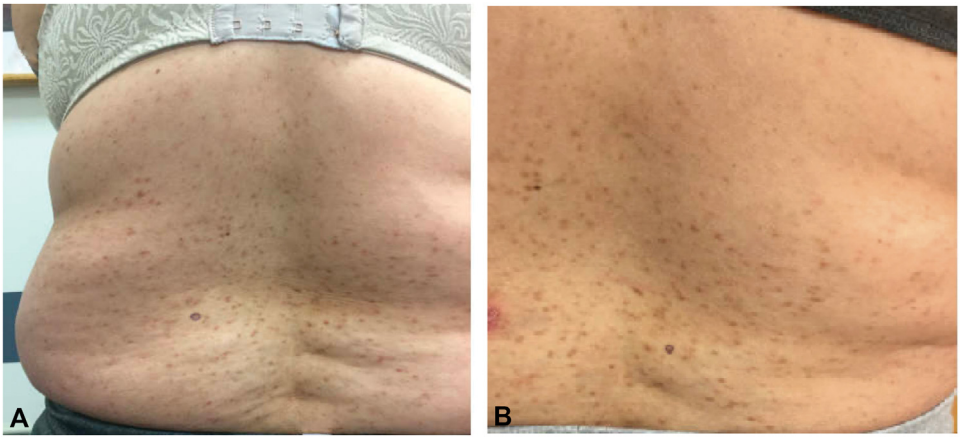

Fig 1. Cutaneous manifestations of systemic mastocytosis. **A**, **B** Characteristic small brown monomorphic lesions found on the trunk.

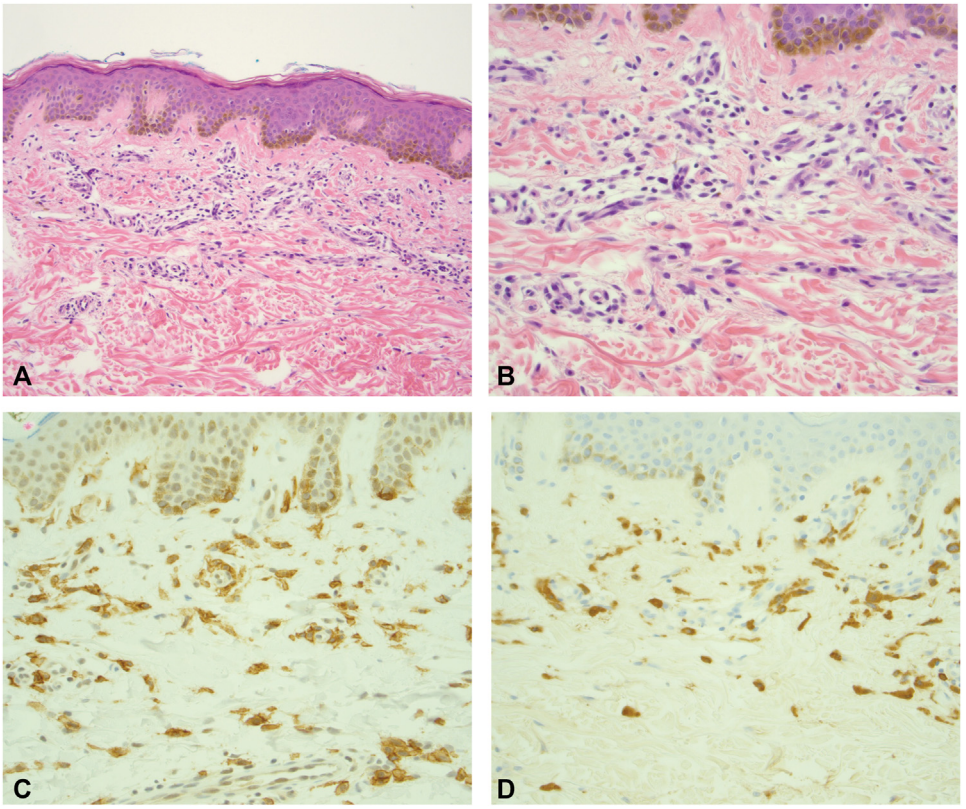

Fig 2. Punch biopsy demonstrating cutaneous mastocytosis. Hematoxylin and eosin stain showing a dense interstitial and perivascular infiltrate of mononuclear cells in the papillary and reticular dermis at low-power (20x) (**A**) and high-power (40x) (**B**) magnification. By immunohistochemistry, the mononuclear cells were positive for KIT (CD117) (**C**) and tryptase (**D**), which identify both normal and abnormal mast cells.

computed tomography imaging and urine metanephrine screening, which were both normal.

The patient began hydroxyurea (500 mg by mouth daily) for the chronic myeloproliferative disease. TKIs were initiated for the SM, the first midostaurin (25 mg orally twice a day for 1 month) followed by dasatinib (100 mg orally daily for 3 months), but were stopped because of adverse effects, including gastrointestinal side effects, headaches, and back pain. Next, the patient began

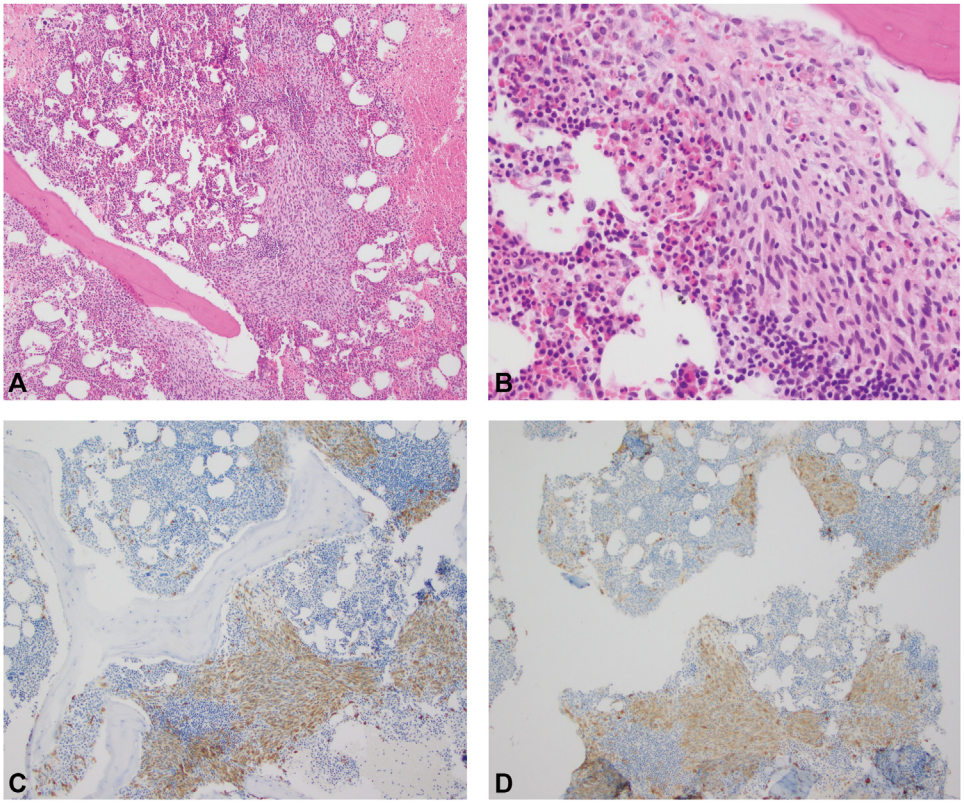

Fig 3. Bone marrow biopsy showing mastocytosis. Hematoxylin and eosin stain showing dense mast cell aggregates in the bone marrow at low-power (10x) (**A**) and high-power (40x) (**B**) magnification. The mast cells were intermediate in size with irregular nuclei, some with polygonal, spindle-shaped nuclei and moderate clear cytoplasm. By immunohistochemistry, the mononuclear cells were positive for tryptase (**C**), and CD25 (**D**).

ripretinib 50 mg by mouth daily, which was gradually increased to 150 mg by mouth daily, which was well tolerated. After 2 years of treatment with ripretinib, the patient's skin lesions had faded (Fig 4, *A*, *B*), and her tryptase had normalized (2.4 ng/mL). However, she also developed diffuse nonscarring alopecia (Fig 4, *C*). Scalp examination showed hair miniaturization superiorly greater than posteriorly/laterally and a slight widening of the midline part. Hair follicles were intact, but the interfollicular distance at the crown was increased.

DISCUSSION

Mastocytosis is a rare disorder, with an estimated prevalence of 1 per 10,000 people,[1] characterized by abnormal proliferation and accumulation of mast cells. Our patient presented with a papular eruption that had been present for 20 years prior to her diagnosis, along with symptoms suggestive of extracutaneous infiltration of mast cells, including bone pain, osteoporosis, and gastrointestinal symptoms, including diarrhea and abdominal pain.

Activating *KIT* mutations have been implicated in the pathogenesis of mastocytosis[2] and gastrointestinal stromal tumors (GISTs). *KIT* is expressed in hematopoietic stem cells and progenitor cells and drives hematopoiesis. It also promotes the growth and development of interstitial cells of Cajal, which have been implicated in GIST. Differentiated hematopoietic cells, except for mast cells, lose expression of *KIT* during maturation. Mutations in *KIT* have been associated with abnormalities in the growth, differentiation, apoptosis, and activation of mast cells. The *KIT* D816V mutation is the most common mutation in SM and a minor criterion according to the World Health Organization guidelines for the diagnosis of SM.[3]

Our patient did not have a detectable *KIT* D816V mutation, which may have been because of degree of fibrosis present in the marrow, complicating the sampling of mast cells in the aspirate. Instead, a novel *SDHC* germline mutation was identified. Mutations in the genes encoding subunits of succinate dehydrogenase have been identified in patients with *KIT*-wild-type GIST and are thought to promote pathogenesis via a different mechanism by

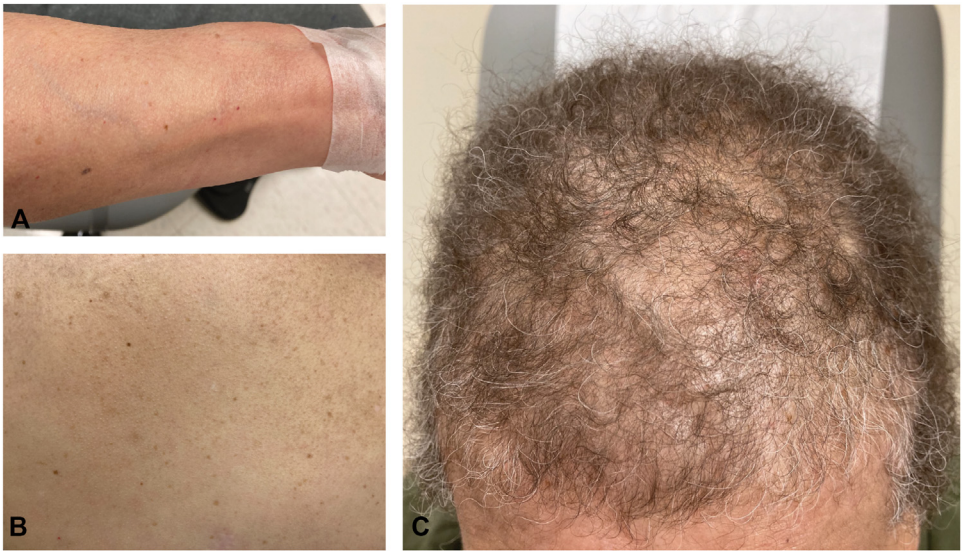

Fig 4. Successful treatment of SM with ripretinib, complicated by alopecia. Photographs of the patient's forearm (**A**) and trunk (**B**) illustrating an improvement in the patient's cutaneous lesions following treatment with ripretinib. **C** Treatment with ripretinib also led to diffuse nonscarring alopecia, with examination of the scalp revealing hair miniaturization and a slight widening of the midline part.

increasing the level of hypoxia-inducible factor-1 alpha and leading to the upregulation of its downstream molecules, such as insulin-like growth factor 1 and vascular endothelial growth factor receptor.[4] The role of germline *SDHC* mutations in SM is unknown and warrants further investigation.

The patient received off-label treatment with ripretinib, a small-molecule inhibitor of the KIT/PDGFRA kinases. Previous preclinical studies have shown that ripretinib has antineoplastic activity against both SM and GIST.[5,6] Ripretinib has now been studied in a phase II study with a dose of 150 mg twice a day for advanced SM (NCT02571036), with trial results pending. Targeting oncogenic kinase drivers in SM with small-molecule inhibitors is effective, but maximizing efficacy requires understanding disease-driving mutations and stratifying populations for treatments. The patient's clinical course was complicated by alopecia, which is the most common dermatologic adverse effect of ripretinib. Additional dermatologic side effects of ripretinib include palmar-plantar erythrodysesthesia and increased incidence of cutaneous malignancies, including squamous cell carcinoma and melanoma,[7,8] with the need for routine dermatology follow-up for patients treated with ripretinib.

In conclusion, we report a case of SM associated with a chronic myeloproliferative neoplasm and a germline *SDHC* variant, treated successfully via off-label use of ripretinib, with the patient's treatment being complicated by alopecia. Our work highlights the importance of future genomics and mechanistic studies in profiling disease-driving mutations, followed by additional large-scale studies that can further delineate the safety, efficacy, and tolerability of treatments.

Conflicts of interest

None disclosed.

REFERENCES

1. Brockow K. Epidemiology, prognosis, and risk factors in mastocytosis. *Immunol Allergy Clin North Am*. 2014;34(2):283-295.
2. Akin C. Molecular diagnosis of mast cell disorders: a paper from the 2005 William Beaumont Hospital Symposium on Molecular Pathology. *J Mol Diagn*. 2006;8(4):412-419.
3. Arock M, Soltar K, Akin C, et al. KIT mutation analysis in mast cell neoplasms: Recommendations of the European Competence Network on mastocytosis. *Leukemia*. 2015;29(6):1223-1232.
4. Rutkowski P, Seliga K, Dębiec-Rychter M. SDH-deficient gastrointestinal stromal tumours. *Nowotwory J Oncol*. 2022;72(5):326-333.
5. Evans EK, Gardino AK, Kim JL, et al. A precision therapy against cancers driven by KIT/PDGFRA mutations. *Sci Transl Med*. 2017;9(414). https://doi.org/10.1126/scitranslmed.aao1690
6. Schneeweiss M, Peter B, Bibi S, et al. The KIT and PDGFRA switch-control inhibitor DCC-2618 blocks growth and survival of multiple neoplastic cell types in advanced mastocytosis. *Haematologica*. 2018;103(5):799-809.
7. Janku F, Abdul Razak AR, Chi P, et al. Switch control inhibition of KIT and PDGFRA in patients with advanced gastrointestinal stromal tumor: a phase I study of ripretinib. *J Clin Oncol*. 2020;38(28):3294-3303. https://doi.org/10.1200/jco.20.00522
8. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(7):923-934.