Sirolimus as frontline therapy for *PTEN*-mutated histiocytic sarcoma

Histiocytic sarcoma (HS) is an extremely rare non-Langerhans histiocytic neoplasm that can present as unifocal or multifocal extranodal disease.[1] The limited reports available for this malignancy have estimated a median overall survival of 6 months, with an especially poor prognosis for multifocal disease.[2] Given the rarity and lack of prospective trials, there are no established standard-of-care therapies. In multifocal disease, previous reports have utilized regimens typically administered for aggressive lymphomas, such as ICE (ifosfamide, carboplatin, and etoposide) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).[3] However, these combination chemotherapy regimens have limited efficacy and are associated with significant hematologic toxicity. Herein, we present a case of HS complicated by severe cytopenias achieving objective disease response and prolonged survival with frontline sirolimus.

A 63-year-old woman presented with bilateral leg edema, fatigue, and weight loss. Laboratory workup demonstrated macrocytic anemia (hemoglobin [Hb]: 7.7 g/dL [normal, 11.6-15.0 g/dL], mean corpuscular volume [MCV]: 120.4 fL [normal, 78.2-97.9 fL]), severe thrombocytopenia (platelet count: $11x10^9$/L [normal, 157-$371x10^9$/L]), and borderline leukopenia (white blood cell [WBC] count: 3.5 $x10^9$/L [normal, 3.4-$9.6x10^9$/L]). The absolute neutrophil count (ANC) was $2.0x10^9$/L (normal, 1.56-6.45 $x10^9$/L), with some elevation in early myeloid progenitor cells (metamyelocytes 1% [normal, <1%]; myelocyte 2% [normal, <0.5%]). Folic acid: 9.7 mcg/L (normal, ≥4 mcg/L), vitamin B12: 218 ng/L (normal, 180-914 ng/L), and methylmalonic acid: 0.15 nmol/mL (normal, ≤0.40 nmol/mL) levels were determined to be within normal limits. Bone marrow (BM) biopsy initially revealed normal cytogenetics, with no features of myelodysplastic syndrome or neoplasia. Concurrently, during routine cardiac workup, the patient was noted to have lymphadenopathy on computed tomography (CT). This prompted positron emission tomography (PET)-CT which revealed multiple F^{-18} fluorodeoxyglucose (FDG) avid thoracic and abdominal lymph nodes, an enlarged spleen (largest diameter: 18.7 cm) with innumerable FDG-avid foci, and diffuse increased marrow FDG uptake (Figure 1A). In the weeks following presentation, the patient developed significant transfusion dependence requiring weekly packed red blood cells (pRBC) and platelets. Due to minimal improvement in the platelet count, pancytopenia of undetermined origin, and splenomegaly with hypersplenism, the patient underwent splenectomy with liver biopsy. Biopsies from the liver and spleen showed diffuse involvement by overtly malignant cells characterized by marked nuclear pleomorphism with occasional multinucleation, and abundant pale eosinophilic cytoplasm. Immunohistochemistry (IHC) showed the malignant cells had a histio-

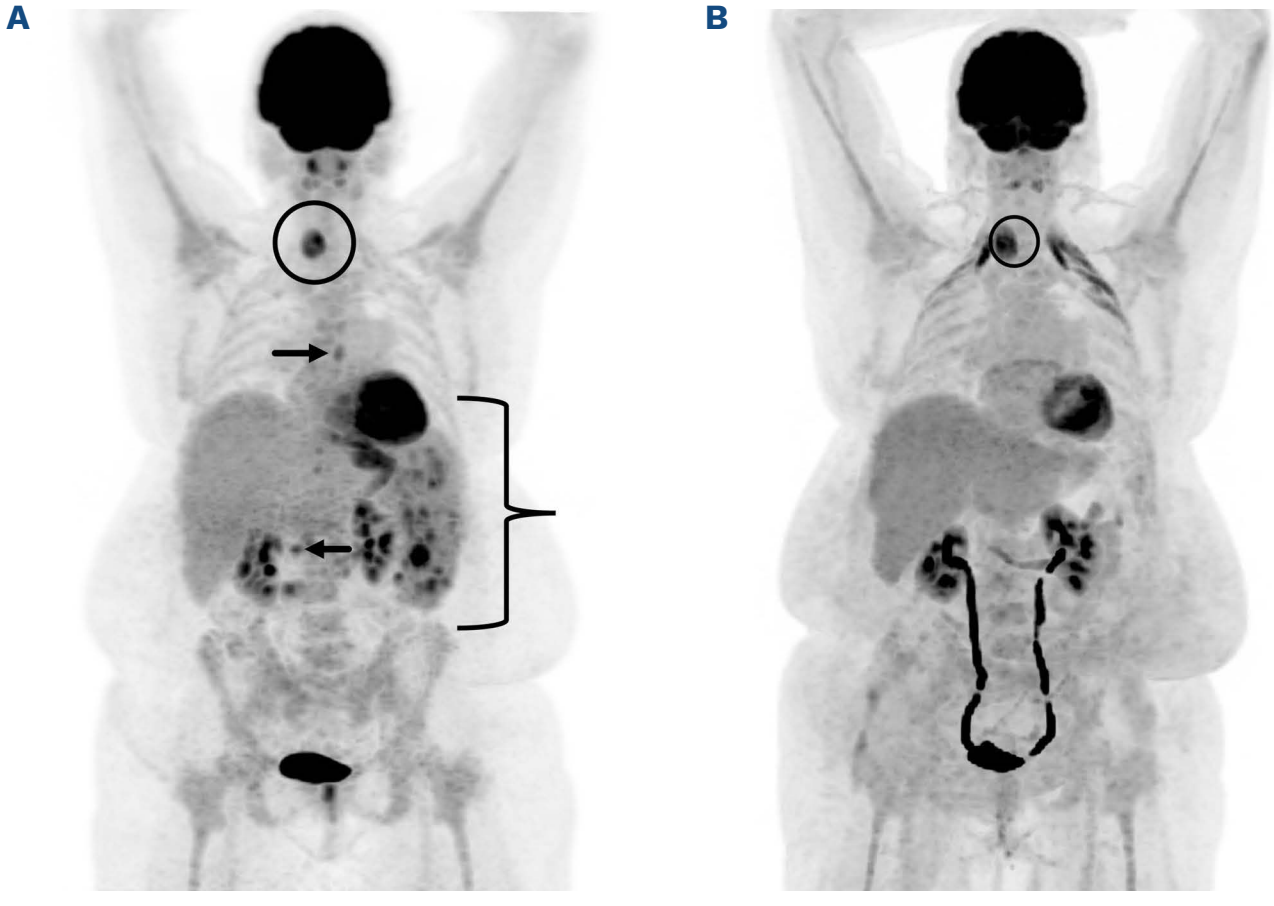

Figure 1. Maximum intensity projection images from F^{-18} fluorodeoxyglucose positron emission tomography. (A) Time of diagnosis and (B) 12 months after therapy demonstrating complete resolution of F^{-18} fluorodeoxyglucose avid lymph nodes (arrows) and splenic disease (bracket) post-splenectomy. Incidental biopsy-proven benign right thyroid nodule noted (circle).

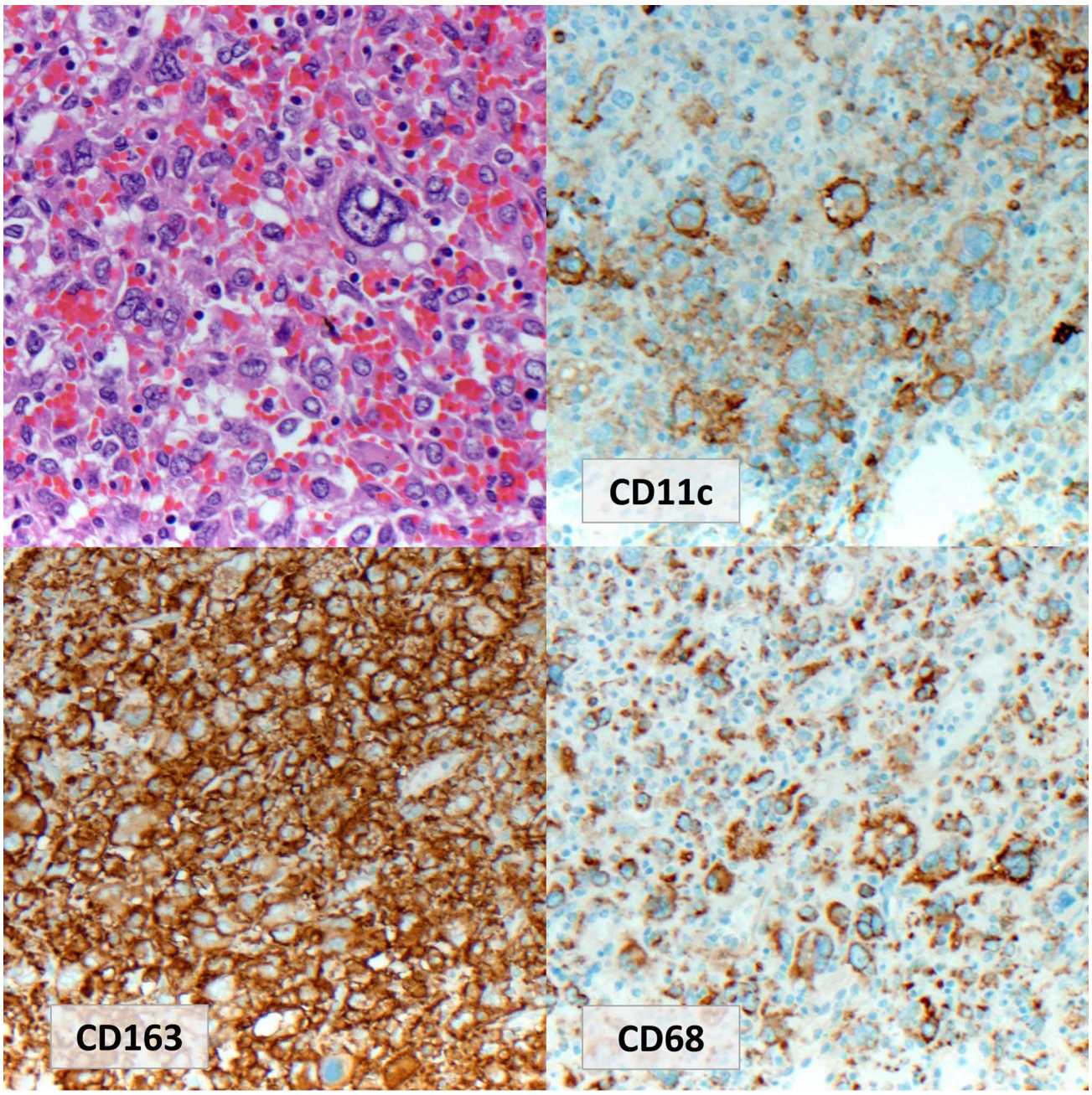

Figure 2. Light microscopy images. Spleen showing involvement by large pleomorphic cells (hematoxylin and eosin stain - top left) with positive staining for CD11c (partial), CD163, and CD68 (magnification, X400).

cyte/macrophage phenotype with expression of CD4, CD11c (partial, i.e., 50% of tumor cells positive), CD14 (partial), CD68, CD163 (partial), cyclin D1, lysozyme (partial), and S100 (focal) (Figure 2). Additional markers were negative including CD1a and langerin. Thus, a diagnosis of multifocal HS involving the spleen, liver, and lymph nodes was made. The initial BM biopsy was re-reviewed and revealed 5-10% involvement by HS without features of an underlying myelodysplastic/myeloproliferative neoplasm. Subsequently, tissue-based multigene next-generation sequencing (NGS) (Tempus xT assay) performed on the splenic specimen demonstrated the following mutations: *PTEN* p.K223fs frameshift-loss of function (LOF), variant allele frequency (VAF) 13.9%; *SETD2* p.V2108fs frameshift-LOF, VAF 14.7%; *FGFR3* c.2131C>T p.H711Y missense variant, VAF 13.5%. Given the mutation involving the *PTEN* gene, additional immunostains performed for phosphor-AKT (p-AKT) and phospho-ERK (p-ERK) revealed moderate (2+) p-AKT positivity and weak (1+) p-ERK expression in the tumor cells.

Due to underlying cardiac comorbidities and severe transfusion-dependent cytopenias, the patient was not a candidate for aggressive combination chemotherapy. Given the *PTEN* LOF and the role of this gene in the PI3k-AKT-mTOR pathway, the patient was initiated on sirolimus 2 mg with a goal trough of 8-12 ng/mL and prednisone 1 mg/kg with a tapering dose over 3 months.[4] During therapy, the patient had an objective clinical and radiological response. A repeat staging PET-CT demonstrated a favorable partial anatomic and metabolic response at 3 months with a complete anatomic and metabolic response after 12 months of therapy (Figure 1B). Interestingly, a repeat BM biopsy after 12 months of therapy demonstrated stable 5-10% involvement of HS. The patient experienced a drastic reduction in the requirement for both pRBC and platelet transfusions while on therapy (Figure 3). Unfortunately, despite the initial clinical improvement, she developed grade 3 anemia and thrombocytopenia after 13 months of therapy, requiring weekly transfusions (Figure 3). Out of concern for its potential myelosuppressive effect, sirolimus was stopped after 15 months of therapy. Shortly after, the patient presented with septic shock, anemia, and severe thrombocytopenia, which was transfusion refractory. Diagnostic imaging at the time revealed

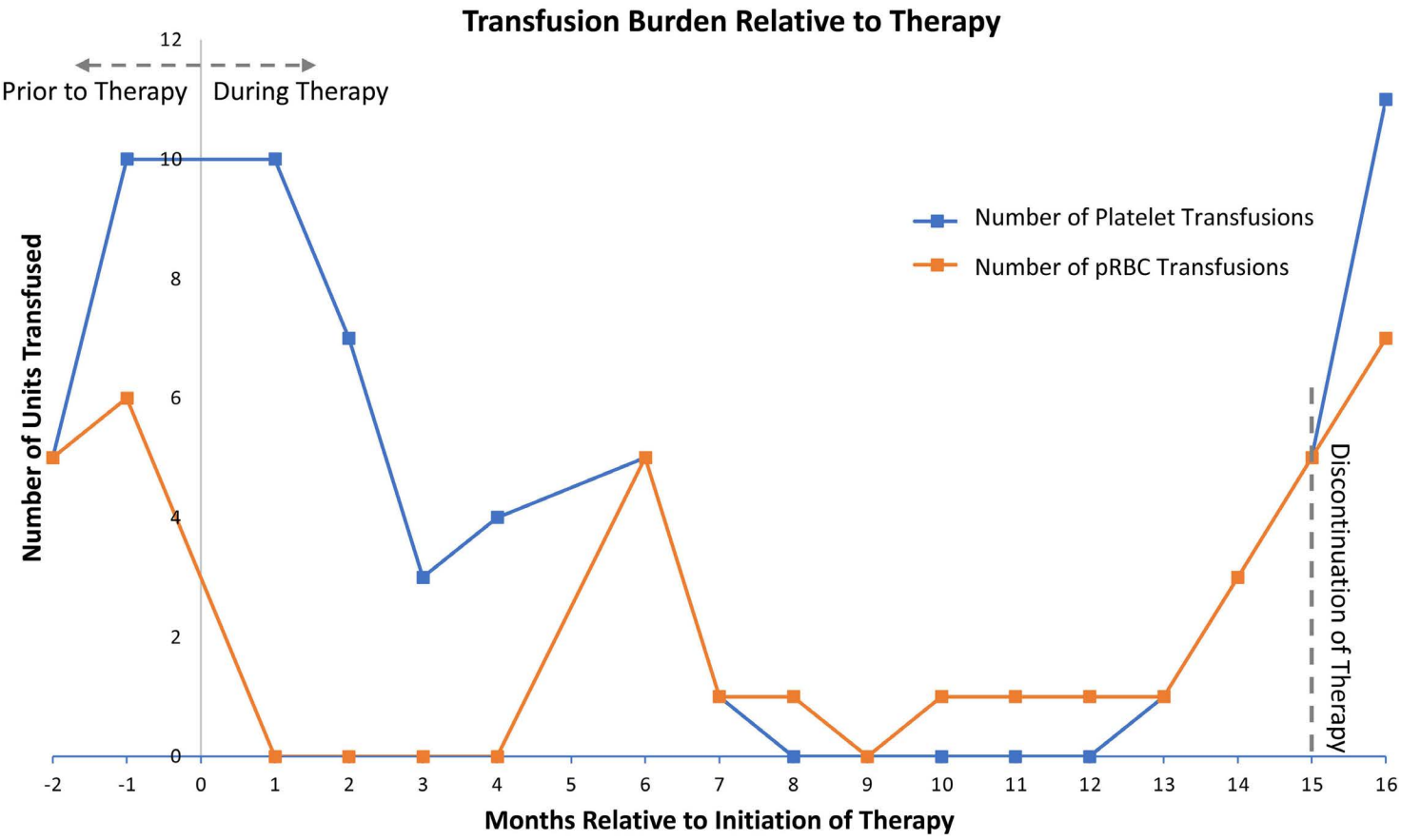

Figure 3. Transfusion requirement of packed red blood cells and platelets relative to the duration of therapy.

extensive fluid overload with diffuse anasarca. The patient's condition rapidly deteriorated, and she ultimately chose to pursue comfort care measures and died 1 month after discontinuation of sirolimus, surviving 19 months from initial diagnosis. A final autopsy was not done per the patient's preference.

The clinical course of multifocal HS is typically highly aggressive. Due to its rarity, there is a lack of established therapies, and multiple chemotherapeutic agents have been utilized in case reports with limited efficacy. Moreover, the administration of combination chemotherapy can be challenging when significant cytopenias and comorbidities are present. In patients with targetable mutations, BRAF and mitogen-activated protein kinase (MEK) inhibitor therapies with agents such as dabrafenib, vemurafenib and trametinib have also been previously utilized.[5-7] Through genomic analysis, multiple genetic alterations have been implicated in HS. Previously, in a study of 21 patients with HS, whole-exome sequencing demonstrated a high prevalence of genetic alterations in the MAPK-ERK pathway.[8] Additionally, the authors found that 19% of patients had mutations in the PI3k-AKT-mTOR pathway. In another study of 28 patients with HS, targeted NGS revealed a MAPK-ERK pathway mutation in the majority of patients (57%), with a subset (21%) having mutations of the PI3k-AKT-mTOR signaling pathway.[9] These case series suggest possible distinct molecular subtypes of HS, allowing for potentially tailored targeted treatment strategies.

PTEN, the gene found to be implicated in our report, acts as a tumor suppressor and negatively regulates the PI3k-AKT-mTOR pathway. The positive p-AKT testing further indicated the *PTEN* LOF led to downstream activation of this pathway. The mammalian target of rapamycin (mTOR) pathway is involved in regulating cell growth, proliferation, apoptosis, and metabolic processes by integrating extracellular and intracellular signals.[10] Previously, somatic *PTEN* alterations have been shown to be implicated in HS and other hematological malignancies, where they have been hypothesized to contribute to tumor initiation and progression.[11,12] The *PTEN* LOF in our case indicated a potential benefit from mTOR inhibitor therapy.[13] Sirolimus is a potent macrocyclic lactone immunosuppressant inhibitor of the mTOR signaling pathway, with antiproliferative and immunosuppressive properties.[14] Previously, in a study of patients with Erdheim-Chester disease (ECD), another rare non-Langerhans histiocytic neoplasm, an open-label trial assessed sirolimus (target levels 8-12 ng/mL) in combination with prednisone.[4] Among the ten patients enrolled, eight had an objective response or disease stabilization. Upon comprehensive literature review, we did not find any reports of sirolimus used to treat primary HS; however, mTOR-directed therapy (1 dose of temsirolimus and daily oral sirolimus) led to symptomatic and radiological improvement in an 18-month-old boy with recurrent *mTOR*-mutated secondary HS and history of T-cell acute lymphoblastic leukemia.[6] We hypothesize that in our case, the objective response observed was likely secondary to targeted inhibition of the driver mutation with sirolimus, along with the immunosuppressive and anti-

proliferative properties of mTOR inhibition.

Despite the initial improvement in transfusion dependence in our case, the eventual worsening of cytopenias and transfusion burden led to the discontinuation of sirolimus due to concern for BM suppression. Sirolimus-related adverse events include thrombocytopenia, leukopenia, and hyperlipidemia, and previous cohorts have demonstrated these toxicities are generally self-limited.[15] In the trial of patients with ECD, mild toxicity was observed, with several patients having cushingoid changes, hypercholesterolemia and hypertriglyceridemia; however, the authors did not report significant cytopenias.[4] The cause of the worsening cytopenias in our case is unclear, as there was no significant improvement after sirolimus cessation. Given the initial improvement after sirolimus initiation, and then worsening of transfusion dependence, it raises the question of whether progressive malignancy contributed to BM suppression as opposed to sirolimus toxicity. It is possible that the disease ultimately progressed due to the contribution of other mutations like *SETD2* through an escape mechanism.

To the best of our knowledge, this is the first report of treatment of primary HS with sirolimus. HS is an exceedingly rare histiocytic neoplasm with a paucity of literature on optimal therapeutic management. Our case highlights that a patient with *PTEN*-mutated HS achieved an over 1-year objective response to the mTOR inhibitor sirolimus. With the PI3k-AKT-mTOR pathway being frequently implicated in patients with HS, further investigation is certainly needed to assess the role of these agents.

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https://doi.org/10.3324/haematol.2022.282207

Received: October 1, 2022.
Accepted: December 1, 2022.
Prepublished: December 7, 2022.

Disclosures

No conflicts of interest to disclose.

Contributions

KLC, GG and NNB conceived, wrote the first draft and modified the final draft; JPA, JRY, WOT, MJK, MVS, JHR, RV, KLR, AR and RSG critically appraised the manuscript and approved the final draft of the manuscript.

Funding

NNB gratefully recognizes support from the K12 Paul Calabresi Program in Clinical/Translational Research at Mayo Clinic (award N 2K12CA090628-21). NNB, JPA, and GG are supported in part by the University of Iowa/Mayo Clinic Lymphoma SPORE CA97422. KLR is supported by the Department of Laboratory Medicine and Pathology and GG is supported by the Walter B. Frommeyer, Jr., Fellowship Award in Investigative Medicine, University of Alabama at Birmingham.

Data-sharing statement

There is no relevant data to disclose.

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