CLINICAL VIGNETTE

Aggressive Systemic Mastocytosis in a 76-Year-Old Male

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A 76-year-old man was evaluated by his primary care doctor for moderate weight loss without changes in diet. He had also reported intermittent episodes of persistent non-bloody diarrhea over the previous eight months. He had loose bowel movements two to three times a day. He denied fever, chills, chest pain, shortness of breath abdominal pain, or blood, mucus, or fat in his stool. He had no new medications and no personal or family history of hematological disorders or malignancy. He reported a few night sweats over the last few months and denied skin rash, hives, or episodes of anaphylaxis. His previous medical history was significant for treated hepatitis C with ledipasvir/ sofosbuvir six years prior, Type 2 diabetes with neuropathy, and hyperlipidemia, He is a former 20 pack year smoker, but quit 20 years ago. He reported prior drug abuse including cocaine but denied any recent drug use and history of IV drug use. He previously worked as a waiter and bartender and reported no significant occupational exposures. There was no recent travel and no prior tuberculosis history or exposures. Current medications included amlodipine 5 mg/d, atorvastatin 40 mg/d, gabapentin 300 mg/d, lisinopril 40 mg/d and empagliflozin 10mg daily. One year earlier the patient was evaluated for recurrent low platelet counts. Peripheral blood smear revealed reduced red blood cells with mild anisocytosis, adequate numbers unremarkable white blood cells and decreased platelets with normal morphology. HIV, CRP and ANA were negative and the thrombocytopenia was ascribed to his prior history of hepatitis C presumed related to prior recreational drug use.

On physical exam the patient was afebrile with blood pressure of 117/71 mmHg, pulse 86/min and BMI of 25.6. He was well nourished. There was no scleral icterus and no rash and negative Darier sign (no inducible urticaria on rubbing the skin). His lungs were clear, with normal cardiac exam. Abdomen was soft and non-tender with normal bowel sounds with an enlarged spleen noted below the costal margin.

Labs included hemoglobin of 9.9 g/dl, Hct 32.4%, WBC 3.32 μL, and low platelets of 34K, decreased from 113K four years prior. PT was 17.8 and PTT 44.4. Chemistries were unremarkable. Imaging of his lung by Computed Tomography (CT) scan revealed bilateral lung traction bronchiectasis (lower greater than upper lung), linear opacities and ground glass opacities increased when compared to chest CT from three years earlier. This was most likely in keeping with bilateral lung fibrosis or nonspecific interstitial pneumonia (NSIP). Bilateral lung emphysema was also noted. A right lung non-calcified nodular opacity, measuring 4 millimeters in mean diameter was seen. His spleen was enlarged and increased in size compared to prior scans. Based on the constellation of pulmonary findings, thrombocytopenia, weight loss, night sweats, chronic diarrhea, splenomegaly, and abnormal coagulation tests a malignancy, or an autoimmune disease was high on the differential.

A fluorodeoxyglucose (FDG)-positron emission tomography (PET) CT scan revealed bilateral carinal and hilar adenopathy with intense FDG uptake and an enlarged spleen. Axial and appendicular bones revealed osteopenia and sclerosis also with high FDG uptake. These findings were suspicious for a myeloproliferative disorder and a bone marrow biopsy revealed ~6.8% mast cells, confirming the diagnosis of systemic mastocytosis with C-KIT D816V mutation on genetic analysis. There was no stainable iron detected and marrow aspirate revealed atypical mast cells with hypo-granulated cytoplasm and mild spindle shape. The patient's serum tryptase level was very elevated at 819 ng/mL. Given the diarrhea, colonoscopy and esophagogastroduodenoscopy identified significant esophagitis and ulceration in the duodenum. Duodenal biopsy revealed marked acute mucosal inflammation with ulceration without significant increase of mast cells. Esophageal biopsy revealed cardia type mucosa with chronic active inflammation and squamous mucosa with mild reactive epithelial changes negative for dysplasia or malignancy and no significant mast cells.

The patient was started on midostaurine 100mg twice daily. Unfortunately, his platelet count continued to decline and he received multiple transfusions before discontinuing midostaurine. He developed bilateral pleural effusions and his follow up FDG-PET CT revealed progressive disease. He and his family decided on end-of-life care, and he died in hospice care.

Discussion

Our case illustrates many of the key clinical features of systemic mastocytosis. There have been recent advances in diagnosis and therapy that are of interest. Based on the World Health Organization (WHO) criteria,[1] there are three major subtypes of mastocytosis. Skin confined or cutaneous type, which encompasses urticaria pigmentosa, the systemic variety which involves organs other than and or including the skin e.g., bone and bone marrow and lung as in our case, and finally the rare mast cell sarcoma which manifests as a single focal cancer without cutaneous or other areas of the body involved. The WHO diagnostic criteria can be summarized as: Major criteria, which are multifocal aggregates of mast cells (>15) in an

extracutaneous organ, typically the bone marrow as in this patient. The minor WHO criteria are: (1) basal serum tryptase of ≥20 ng/mL, (>800 ng/ml in our patient); (2) abnormal cell morphology (spindleoid cells) in >25% of mast cells in an infiltrate; (3) abnormal expression on mast cells of the markers CD2 or CD25 or (4) presence of the D816V mutation in KIT, the gene which encodes the CD117 cell surface receptor, also see in this case. Our patient had the classic presentation of major and three minor criteria.

Once the diagnosis is made, the severity of disease should be determined. This depends on the presence or absence of key clinical features: known as B or C.[2] B findings include >30% infiltration of bone marrow by mast cells and a serum tryptase level >200 ng/mL; dysplasia or myeloproliferation in non-mast cell lineages with normal or slightly abnormal blood counts; hepatomegaly without impaired liver function; palpable splenomegaly without hypersplenism and/or lymphadenopathy. C findings include bone marrow dysfunction with associated cytopenias; (low hemoglobin and thrombocytopenia as in our case) palpable hepatomegaly with impaired liver function; ascites and/or portal hypertension; skeletal involvement with osteolytic lesions and/or pathological fractures; palpable splenomegaly with hypersplenism (our patient) or malabsorption with weight loss due to gastrointestinal mast cell infiltrates.

Positive B and C findings are then tallied, and condition of the disease can then be defined as Indolent, when a patient has general criteria for systemic mastocytosis with one B finding and no C findings. The condition is defined as smoldering when two or more B findings are present but no C findings. If there is one or more C finding present, it is considered aggressive. Our patient presented with two C criteria (bone marrow dysfunction leading to thrombocytopenia/anemia as well as splenomegaly.

The medical management depends on the severity of disease. Both indolent and smoldering systemic mastocytosis are usually treated symptomatically. Symptoms usually result from the effects of excessive mast cell degranulation. Drugs that have efficacy include mast cell stabilizers (cromolyn), antihistamines, proton pump inhibitors, leukotriene receptor antagonists (montelukast), steroids and rarely monoclonal antibody therapies.[3] Our patient presented with aggressive disease. The goal of treatment was control of the disease and specifically target the C-KIT mutation. In particular, tyrosine kinase inhibitors (TKIs) which target the mutated KIT receptor were started. Midostaurin is a multi-kinase/KIT inhibitor which blocks the protein produced by the *KIT gene* as well as the kinase encoded by D816V-mutated *KIT*.[4] Usually, most subtypes of systemic mastocytosis respond well to midostaurin and about sixty percent of patients with advanced disease have a positive response.[5] Unfortunately our patient's platelets did not demonstrate a sustained increase above 25, 000 after three weeks of therapy and the drug was discontinued.[6,7]

REFERENCES

1. **Swerdlow SH, Campo E, Harris NL, et al**. (Eds). *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th revised edition*. Lyon, France: International Agency for Research on Cancer (IARC); 2017.
2. **Swerdlow SH, Campo E, Harris NL, et al**. (Eds). *World Health Organization (WHO) Classification of Tumours. Pathology & Genetics. Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2016.
3. **Nallamilli S, O'Neill A, Wilson A, Sekhar M, Lambert J**. Systemic mastocytosis: variable manifestations can lead to a challenging diagnostic process. *BMJ Case Rep*. 2019 Aug 30;12(8):e229967. doi: 10.1136/bcr-2019-229967. PMID: 31471359; PMCID: PMC6721155.
4. **Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, Awan FT, Hexner E, Mauro MJ, Sternberg DW, Villeneuve M, Huntsman Labed A, Stanek EJ, Hartmann K, Horny HP, Valent P, Reiter A**. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. *N Engl J Med*. 2016 Jun 30; 374(26):2530-41. doi: 10.1056/NEJMoa1513098. PMID: 27355533.
5. **Chandesris MO, Damaj G, Canioni D, Brouzes C, Lhermitte L, Hanssens K, Frenzel L, Cherquaoui Z, Durieu I, Durupt S, Gyan E, Beyne-Rauzy O, Launay D, Faure C, Hamidou M, Besnard S, Diouf M, Schiffmann A, Niault M, Jeandel PY, Ranta D, Gressin R, Chantepie S, Barete S, Dubreuil P, Bourget P, Lortholary O, Hermine O; CEREMAST Study Group**. Midostaurin in Advanced Systemic Mastocytosis. *N Engl J Med*. 2016 Jun 30;374(26):2605-7. doi: 10.1056/ NEJMc1515403. PMID: 27355555.
6. **DeAngelo DJ, George TI, Linder A, Langford C, Perkins C, Ma J, Westervelt P, Merker JD, Berube C, Coutre S, Liedtke M, Medeiros B, Sternberg D, Dutreix C, Ruffie PA, Corless C, Graubert TJ, Gotlib J**. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. *Leukemia*. 2018 Feb;32(2):470-478. doi: 10. 1038/leu.2017.234. Epub 2017 Jul 24. PMID: 28744009.
7. Prescribing Information: RYDAPT (midostaurin). Available at: https://www.accessdata.fda.gov/ drugsatfda_docs/label/2017/207997s000lbl.pdf. (Accessed on August 27, 2023).