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Proceedings of UCLA Health

Title

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Journal

Proceedings of UCLA Health, 20(1)

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Publication Date

2016-11-15

CLINICAL VIGNETTE

Mastocytosis - A Diagnosis with Varying Presentations

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A 75-year-old male initially presented with fatigue, malaise, and back pain seven years ago. Radiological evaluation showed multiple pathological fractures and bone abnormalities and moderate macrocytic anemia. Blood studies from time of diagnosis are not available.

Bone marrow biopsy showed multiple focal aggregates or nodules containing atypical spindle shaped mast cells staining for tryptase and CD 117 and aberrant staining for CD25 and CD2 (to lesser degree). Some of these nodules were present next to bony trabeculae. Flow cytometry showed aberrant population of mast cells that were positive for CD117, CD25, and CD2. FISH on bone marrow aspirate was positive for KIT D816V mutation.

Subsequent bone marrow biopsy 5 years later had similar findings with a small population of CD5 and lambda staining monoclonal B cell population. He was initially treated with cladribine with poor tolerance and no apparent response. He also had a trial of revlimid and was later treated with ibrutinib with no clinical benefit. Interferon and midostaurin were considered later.

He received primarily supportive care for anemia with erythropoietin products at increasing dose and blood transfusions. He developed iron overload with Ferritin >1700 (8-180ng/ml) and did not tolerate deferasirox. He was treated with zoledronic acid for bone lesions.

Seven years after diagnosis, he developed worsening anemia and thrombocytopenia. Follow-up bone marrow biopsy had similar findings of aberrant mast cells in nodules in the para trabecular areas. There was increased cellularity for age at 30-40% and diffuse mild reticulin deposit. Megakaryocytes were decreased, and erythroid precursors showed mild atypia. Increased iron stores were present. Flow had atypical mast cells CD117, CD25, and CD2 positive and smaller CD5 positive lymphocyte population. FISH studies were negative for MDS.

Peripheral blood smear showed increased reticulocytes, macrocytic anemia, thrombocytopenia, mild lymphopenia but no eosinophilia or increased schistocytes. Vitamin B12, folate, LDH, and haptoglobin levels were normal. Direct Coombs test was negative. Alkaline phosphatase was 220 (37-113u/l) and Total Bilirubin 2.2 (0.1-1.2mg/dl), but transaminases were normal.

Repeat bone scan showed multiple sites of abnormal tracer accumulation within bones. Long bones X-rays were normal. CT scans showed small 3-5 mm bilateral lung nodules, globular splenomegaly at 16 centimeters, and stable bone lesions.

He had history of hives from Erythromycin and Lisinopril. No other history of urticaria, angioedema, or anaphylaxis. Other problems included chronic diarrhea and worsening dyspnea on exertion with mild renal dysfunction but normal cardiac function. He developed ascites, pleural effusion, and anasarca. Therapeutic paracentesis and thoracentesis were performed and ascitic fluid showed albumin of 1.1gm/dl with Serum ascitic albumin gradient (SAAG) of 2.2.

He was admitted with significant upper gastrointestinal bleeding. Upper endoscopy showed moderate erosive esophagitis and a clean based ulcer at the gastroesophageal junction. Duodenal bulb had diffuse nodularity and erythema of mucosa. Biopsy showed infiltration with increased number of abnormal appearing mast cells. Gastric metaplasia and prominent Brunner cells were seen. A trial of prednisone for malabsorption was considered, but his performance status was rapidly declining, and he had significant confusion. He accepted hospice care; he died soon after, more than seven years after his initial presentation.

Mastocytosis is a disorder with abnormal mast cells accumulation in skin or other organs. Unlike children, skin involvement in adults is almost always (>95%) accompanied by systemic involvement. Cutaneous Mastocytosis (CM) usually appears as amaculopapular rash (urticaria pigmentosa), although it may have other presentations.¹ Skin biopsy is only helpful in the presence of typical rash.

Mast cell activation symptoms can occur without Systemic Mastocytosis. They usually affect at least two organ systems. These may include flushing, hypotension (dizziness), tachycardia, abdominal pain, diarrhea, nausea, and vomiting. Fatigue, anxiety, headache, depression, muscle and bone pain, and cachexia can develop. Symptoms may have variable frequency or be absent in patients with Mastocytosis. Many drugs, chemicals, and other stimuli like friction, temperature, or psychological stress may elicit these symptoms. Patients are prone to severe anaphylactic reactions with insect bites especially of Hymenoptera group.

Tissue infiltration by mast cells may cause enlargement of the liver, spleen, and lymph nodes. Bone involvement can lead to

osteoporosis, lytic, and sclerotic bone lesions, as well as pathological fractures and pain. Gastrointestinal tract involvement can lead to malabsorption.

Systemic Mastocytosis (SM) is diagnosed when a major criterion is accompanied by at least one minor criterion or three minor criteria are met without major criteria.¹ The major criterion is a bone marrow biopsy and or biopsy other non-skin organs showing multiple aggregates containing more than 15 mast cells. There are four possible minor criteria:

- 1) Elevated serum tryptase level of more than 20 ng/ml at baseline. (This is not valid if there is an associated clonal hematological non mast disease.)
- 2) Detection of a KIT D816V mutation in bone marrow, blood or organ other than skin.
- 3) Presence of at least 25% mast cells in a bone marrow biopsy, aspirate, or biopsy of extra cutaneous organs with atypical immature morphology.
- 4) Mast cells in bone marrow, extra cutaneous organs, or blood showing aberrant expression of CD25 or CD2 or both (along with normal expression of CD117 and tryptase).

Mast cells in bone marrow (and other organs) in SM have spindle or fusiform shape with cytoplasmic projections and eccentric oval nuclei with high nucleus to cytoplasm ratio. The nucleus appears immature (multi lobate). Cytoplasm may be hypo granular or with focal granule accumulation and granule fusion.² Para trabecular and perivascular localization of mast cells clusters are common, especially with thickened bony trabeculae. The burden of mast cells in the bone marrow does not always correlate with disease status.

Typically, these mast cells have positive staining CD117 (KIT), tryptase along with CD 25 and CD2 (usually weaker).³ Expression of CD25 and CD2 is not present in normal mast cells. Similarly, on flow CD25 or CD2 co-expression with CD117 also meets minor criteria.

Mast cells express stem cell Factor (SCF) also called KIT ligand (CD117). Many of molecular defects associated with mastocytosis involve gain of function mutation in KIT, so they are activated independent of SCF.⁴ Greater than 95% patients with SM have exon KIT mutation D816V. PCR detection of D816V is the most sensitive and is identified in bone marrow of 90% of patients with SM.⁴ This test can identify the mutation in blood of up to 40% of patients with SM.^{5,6} This activation mutation causes base substitution leading to codon 816 change. Some patients may have other KIT mutations and that only can be identified by whole cell sequencing methods, which are not routinely performed.⁴ In patients with SM associated other hematological neoplasms, additional molecular or cytogenetic abnormalities may be present.

Histological evaluation of other organs is usually not recommended as gastrointestinal biopsies can show abundant mast cells in absence of SM. Expression of CD25 with CD117 on mast cells in these biopsies can be helpful although they may stain negative for tryptase.⁷

Systemic Mastocytosis is further divided into five subtypes.^{1,8}

- 1) Indolent Systemic Mastocytosis (ISM) - stable or progressing slowly. Although a subtype Smoldering Systemic Mastocytosis (SSM) has higher mast cell burden in bone marrow (>30%) and organs (liver, spleen, lymph nodes) and higher tryptase level (>200 ng/ml) without overt evidence of organ dysfunction.
- 2) Aggressive Systemic Mastocytosis (ASS) have organ dysfunction due to aggressive tissue infiltration by mast cells (bone marrow, liver, spleen, bones, and GI tract).
- 3) Systemic Mastocytosis with associated hematological non mast cell lineage disorder (SM-AHNMD). These may be myeloproliferative, myelodysplastic, or lymphoproliferative.
- 4) Mast cell Leukemia (MCL) – This rare entity has >10% immature mast cells in peripheral blood or >20% Immature mast cells in bone marrow smears in non-specular areas.
- 5) Solid Mast cell tumor are rare and present as Mast cell Sarcoma or extra cutaneous mastocytoma.

Prostaglandins (PGD2 in particular), histamine, and other cytokines are thought to be responsible for many symptoms from mast cell activation, including duodenal ulcer as well as neuropsychiatric symptoms.^{9,10} Bone effects are attributed to a multitude of mast cell mediators including TNF, IL6, TGF beta, heparin, histamine, and tryptase.¹¹

Others symptoms are caused by organ infiltration, damage, and dysfunction. Patients may have concomitant allergic, bone marrow, or other diseases, confusing the diagnosis. There may also be increased reactive mastocytes in conditions other than SM.

Advanced SM carries a poor prognosis and has no curative treatment. Treatment can be directed towards chemical mediators of symptoms¹² including epinephrine at higher dosage, if needed, and anaphylaxis as well as trigger avoidance. Histamine 1 and histamine 2 receptor blockers and prednisone are used, along with leukotriene antagonists prior to procedures. Mast cell stabilizers (cromolyn sodium) are used for some refractory mediator symptoms of the GI tract. Aspirin may help flushing, if tolerated. Omalizumab (anti IgE) has been used to decrease anaphylaxis frequency.

Cytoreductive therapies to decrease mast cell population and organ dysfunction has limited success. Interferon alpha and cladribine and other Tyrosine Kinase inhibitors (TKI) have been tried. Imatinib is only effective in <5% of patients who do not have usual KIT D816V mutation. Many other TKI also have not been ineffective for Mastocytosis for the same reason.^{13,14}

Midostaurin (TKI) has been significantly more successful in recent trials against multiple subtypes of Mastocytosis.¹⁵ Trials are ongoing to use it in combination with other modalities including with myeloablative therapy and stem cell transplant.

Other treatments may be directed towards associated hematological non mast cell disorders in patients with SM-

AHNMD or SM-AHN as associated disorders may be causing symptoms and laboratory abnormalities beside SM.

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Submitted November 15, 2016