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Positive Quality Intervention: Advanced Systemic Mastocytosis Patient Diagnostic Algorithm

Description: The purpose of this PQI is to assist in the diagnosis of the advanced systemic mastocytosis (AdvSM) patient by providing a diagnostic algorithm.

Background: Systemic mastocytosis (SM) is a myeloid neoplasm driven in ~95% of cases by an activating mutation, D816V, affecting exon 17 of the *KIT* gene, and characterized by the accumulation of neoplastic mast cells in a variety of extra-cutaneous organs (as opposed to cutaneous mastocytosis, which generally affects children and is limited to the skin).[1] The bone marrow is almost always involved, and patients can exhibit an array of symptoms involving multiple organ systems, such as spots, itching, flushing, fatigue, headache, dizziness, brain fog, nausea, vomiting, diarrhea and abdominal pain, among many others. Osteopenia and osteoporosis are common. Patients may report a wide range of triggers, stress being the most common, for their symptoms, believed to be a result of mast cell degranulation and mediator release. Anaphylaxis can occur and it is essential that patients have an epinephrine auto-injector in hand. SM is rare, with an annual incidence of 0.89/100,000.[2] The diagnosis of SM is a pathologic one, typically based on examination of the bone marrow.[3] Serum tryptase testing and peripheral blood testing for the *KIT* D816V mutation using a sensitive technique such as digital droplet or allele-specific oligonucleotide polymerase chain reaction can provide extremely helpful clues to the diagnosis in the appropriate setting, and serve as the basis for referral to a hematologist for bone marrow biopsy. Importantly, myeloid mutation panels utilizing next-generation sequencing platforms, may miss low (ex. <2-5%) mutant allele frequency *KIT* mutations.[4] Well-differentiated SM, characterized by rounded, instead of spindled, mast cells is very rare but important to recognize because of the usual absence of *KIT* D816 mutations and hence, responsiveness to imatinib (imatinib is ineffective against the D816V and related mutations).[5] A recent, single-institution study estimated the annual incidence and prevalence of AdvSM to be 0.8 and 5.2 per million inhabitants in the region, respectively.[6] Survival in AdvSM has historically been poor; median survival was 5.7 years for patients with aggressive SM (ASM), 2.9 years for those with SM with an associated hematologic neoplasm (AHN), and 1.9 years for those with mast cell leukemia (MCL).[7]

PQI Process:

- Diagnosis of SM: major criterion and ≥1 minor criteria or ≥3 minor criteria required for diagnosis[8]
  - Major criterion
    - Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)
  - Minor criteria
    - >25% of all mast cells are immature or atypical on bone marrow aspirate smears or are spindle-shaped or atypical in mast cell infiltrates detected on biopsy sections of bone marrow or other extra-cutaneous organs
    - Activating c-KIT point mutation at codon 816 in bone marrow, blood or another extracutaneous organ
    - Mast cells in bone marrow or blood or another extracutaneous organ express CD25 and/or CD2, in addition to normal mast cell markers
    - Serum tryptase >20 ng/ml in the absence of an associated myeloid neoplasm
- SM Subclassification[8]
  - Indolent SM (ISM): 0-1 B finding and no C findings - life expectancy near-normal, with a 5-10% risk of progression to more advanced forms

- Smoldering SM (SSM): ≥2 B findings and no C findings - a condition with relatively high mast cell burden but without organ damage from infiltrating neoplastic mast cells
- AdvSM: ≥1 C findings - organ damage *attributable to* mast cell infiltration AdvSM Subtypes
  - ASM
  - SM-AHN *most common*
    - Usually myeloid, the most frequent being myelodysplastic/myeloproliferative overlap syndromes (chronic myelomonocytic leukemia)
    - Finding of *KIT* D816V with another myeloid neoplasm should prompt a search for an occult SM that may have been obscured on histopathology by the AHN[9]
  - MCL: presence of ≥20% mast cells on the bone marrow aspirate smear; in contrast, circulating mast cells are usually <10% ("aleukemic" MCL)
    - Rarely a "chronic" variant of MCL, without C findings, may be encountered[10]

- B and C Findings[8]
  - B findings (high mast cell burden but no organ damage)
    - >30% infiltration of bone marrow by mast cells and serum total tryptase >200 ng/mL
    - Signs of dysplasia/myeloproliferation in non-mast cell lineage, but criteria not met for diagnosis of AHN with normal/slightly abnormal counts
    - Hepatomegaly without impairment of liver function
    - Palpable splenomegaly without hypersplenism
    - Lymphadenopathy on palpation or imaging
  - C findings (organ damage caused by mast cell infiltration)
    - Bone marrow dysfunction caused by neoplastic mast cell infiltration manifested by ≥1 cytopenia: ANC $<1.0 \times 10^9$/L, Hgb level <10 g/dL, and/or platelet count $<100 \times 10^9$/L
    - Palpable hepatomegaly with impaired liver function, ascites, and/or portal hypertension
    - Skeletal involvement, with large osteolytic lesions with or without pathological fractures
    - Palpable splenomegaly with hypersplenism
    - Malabsorption with weight loss due to gastrointestinal mast cell infiltrates

Patient-Centered Activities:

- Discuss the importance of testing for *KIT* and other mutations in the context of other diagnostic criteria
- Ensure patient has prescription for epinephrine auto-injector and proper knowledge of how to use
- Ensure bone health is not ignored/overlooked and patients are treated for osteopenia/osteoporosis
- Discuss diagnostic findings and counsel patients regarding treatment options (symptom-directed therapies for non-advanced SM, KIT-targeted and other cytoreductive therapies for AdvSM)
- Patient Assistance: NCODA Financial Assistance Tool

References:

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