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Systemic mastocytosis associated with hematological neoplasm: a diagnostic challenge

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Case report

A 58-year-old male with a history of alcoholic liver cirrhosis, hypertension and peptic ulcer was admitted to the local hospital in August 2016. He complained of easy fatigue and significant weight loss (>10 kg within the previous six months). On physical examination, hepatosplenomegaly and ascites were observed. Complete blood count (CBC) showed moderate anemia [hemoglobin (Hb) = 10 g/dL] and thrombocytopenia [platelets (PLT) = 46 × 10^9/L]. Leukocyte count was elevated with monocytosis (1.76 × 10^9/L) and eosinophilia (6.5 × 10^9/L). Magnetic resonance imaging (MRI) confirmed the presence of ascites and hepatosplenomegaly (liver 175 mm, spleen 155 mm). The patient was referred to the Hematology Unit. On admission in September 2016, the blood film was in line with the previous findings. Bone marrow aspirate was normal except for eosinophilia. The *BCR-ABL* and *FIP1L1-PDGFRA* gene rearrangements were not detected, and karyotype was diploid on conventional cytogenetics. The patient was diagnosed with idiopathic hypereosinophilic syndrome and prescribed prednisone. As a result, blood eosinophilia normalized and platelet count increased to 140 × 10^9/L, but monocytosis persisted. He remained stable for four years. In April 2021, platelet count dropped to 60 × 10^9/L despite continued steroid treatment. Abdominal ultrasound and computed tomography (CT) scan detected splenomegaly, retroperitoneal lymphadenopathy, and fractures of the thoracic vertebrae. The patient was admitted to our Department in August 2021. He was thrombocytopenic (PLT = 52 × 10^9/L) and blood monocytosis was as high as 1.69 × 10^9/L. Eosinophilia was not present. On biochemistry, bilirubin concentration was slightly increased to 29.1 µmol/L (N: 3.42–20.6), while alkaline phosphatase (AP) was normal. Trephine biopsy showed the presence of spindle-shaped mast cells in 40% with 95% bone marrow cellularity. Flow cytometry on bone marrow aspirate demonstrated 5.1% of abnormal mast cells and 15.5% of monocytes. Serum tryptase level was elevated to 128 µg/L (N: 0–11.4). The *KIT D816V* mutation on bone marrow cells was detected with allelic load of 70%. A next generation sequencing (NGS) study demonstrated the mutations of *RUNX1* and *SRSF2*. The patient was diagnosed with systemic mastocytosis with chronic myelomonocytic leukemia (SM-CMML). Treatment with midostaurin (Rydapt®, Novartis) at 100 mg twice daily was started. Two weeks later he died of infectious complications.

Discussion

Mastocytosis is characterized by an accumulation of abnormal mast cells in various organs. The 2022 World Health Organization classification recognizes three main types of mastocytosis: cutaneous mastocytosis (CM), systemic mastocytosis (SM), and mast cell sarcoma (MCS) (Table I) [1]. Advanced SM (AdvSM) is an umbrella term encompassing the three variants of SM: 1) SM with an associated hematological neoplasm (SM-AHN); 2) aggressive SM (ASM); and 3) mast cell leukemia (MCL) [2]. Recent years have witnessed huge progress in the diagnosis and treatment of systemic mastocytosis. Based on our patient, we would like to draw attention to some important findings regarding patients with SM-AHN.

Firstly, one should keep an eye on blood eosinophilia, which is strongly associated with an unfavorable prognosis. In a study of 2,350 mastocytosis patients, the incidence of eosinophilia was 9.9% and it was mainly present in patients with AdvSM. Of note is that eosinophilia at diagnosis and at follow-up is a strong predictor of inferior progression-free survival (PFS) and overall survival (OS) [3].

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Table I. 2022 World Health Organization classification of mastocytosis [1]

Types of mastocytosis	Subvariants
Cutaneous mastocytosis (CM)	*Urticaria pigmentosa*/maculopapular cutaneous mastocytosis (UP/MCPM): • monomorphic • polymorphic
	Diffuse cutaneous mastocytosis (DCM)
	Cutaneous mastocytoma: • isolated • multilocalized
Systemic mastocytosis (SM)	Bone marrow mastocytosis (BMM)
	Indolent systemic mastocytosis (ISM)
	Smoldering systemic mastocytosis (SSM)
	Aggressive systemic mastocytosis (ASM)
	SM with an Associated Hematological Neoplasm (SM-AHN)
	Mast cell leukemia (MCL)
Mast cell sarcoma (MCS)	

Therefore, we suggest measuring serum tryptase level in those with elevated unexplained blood hypereosinophilia.

CMML remains the most common AHN associated with SM [4]. However, it is important to rule out the most common reactive causes of monocytosis. Of note is that *KIT D816V* can be detected both in mast cells and monocytes of patients with SM-CMML [5].

NGS is used to identify somatic mutations, including those prognostic for systemic mastocytosis (i.e. *SRSF2, ASXL1, RUNX1*). The presence of at least one from these mutations, thrombocytopenia (platelets <100 × 10^9/L), anemia (hemoglobin <10 g/dL), and age ≥60 years have been shown to adversely affect the outcome. Depending on the risk group, median OS was not reached for the low risk category, and was 3.9 years for the intermediate, and 1.9 years for the high risk [6].

Another method which should be used is droplet digital polymerase chain reaction (ddPCR) which serves as a tool for quantification of the *KIT D816V* variant allele fraction (VAF) [7]. It has been proven that in SM patients treated with midostaurin for at least six months, a significant reduction in *KIT D816V* allele burden of ≥25% was the strongest predictor of better survival [8].

In summary, the diagnosis of SM-AHN represents a major challenge for physicians. The physician's vigilance should be heightened already at the stage of blood differential analysis. An unexplained monocytosis and/or eosinophilia should serve as pointers towards mastocytosis. New molecular techniques should be implemented in order to better characterize patients' outcomes.

Authors' contributions

KC — manuscript preparation. KC, KB, MD — data collection. GH — supervision, final approval.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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