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The challenging differential diagnosis of recurrent flushing episodes: systemic mastocytosis mimicking carcinoid syndrome

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Systemic mastocytosis (SM) is a rare disorder characterised by abnormal proliferation and activation of clonal mast cells (MCs). Clinical manifestations of SM are fever, fatigue, weight loss, skin lesions, and musculoskeletal complaints, as well as MC-mediated symptoms like flushing, headache, syncope, hypotension, tachycardia, and gastrointestinal distress [1]. Differential diagnosis is crucial due to overlapping clinical features with other conditions. This paper presents a case of SM mimicking carcinoid syndrome (CS).

A 44-year-old woman was admitted to the Endocrinology Department due to suspected CS. Two months prior, she suffered a significant local reaction after a hornet sting, followed by recurring episodes of facial flushing and headaches. Subsequently, she experienced sudden cardiac arrest (SCA), requiring brief cardiopulmonary resuscitation. Extensive diagnostics ruled out cardiac and neurological causes of SCA, as well as organic pathologies and infections. The evaluation revealed only slightly elevated serum chromogranin A (CgA) and methoxy-catecholamines (MCA) concentrations in the 24-hour urine collection, without any other significant abnormalities. A suspicion of a neuroendocrine neoplasm (NEN), potentially causing CS, prompted referral for further endocrinological assessment.

After admission to the Endocrinology Department, the patient's condition remained serious, with daily morning episodes of sudden headaches, facial flushing, nasal congestions, and conjunctival redness, followed by hypotension, desaturation, and drowsiness. Treatment with short-acting somatostatin analogue (octreotide) and glucocorticoid infusions resulted in slight improvement. Comprehensive diagnostic assessments were performed, including repeated measurements of serum CgA, as well as MCA and 5-hydroxyindoleacetic acid (5-HIAA) concentration in the 24-hour urine collection, all within normal limits. Somatostatin receptor imaging using ^{99}Tc-HYNIC-TATE SPECT/CT and ^{68}Ga-DOTA-TATE PET/CT showed no areas of abnormal radiotracer uptake suggestive of NEN, while ^{18}F-FDG PET/CT scans demonstrated no focal lesions indicative of proliferative disease (Fig. 1), largely ruling out CS. Interestingly, imaging tests demonstrated heterogeneous spine bone remodeling with sclerotic areas (maximum SUV up to 5.2).

Due to the nature of the attacks, particularly episodes of nasal stuffiness and conjunctival redness, suspicion arose regarding excessive histamine release and mast cell activation disorders (MCAD). The tryptase concentration was significantly elevated in multiple tests (59.2 ng/mL, 65.8 ng/ml, 90.8 ng/ml), and bone marrow samples

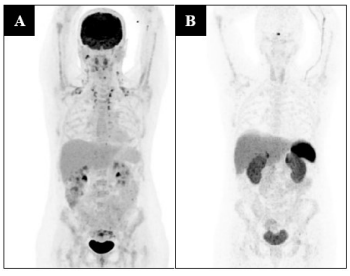

Figure 1. *Imaging studies.* **A**. *^{18}F-FDG PET/CT scans demonstrating no focal lesions indicative of proliferative disease.* **B**. *^{68}Ga-DOTA-TATE PET/CT showing no areas of abnormal radiotracer uptake suggestive of neuroendocrine tumour (NET)*

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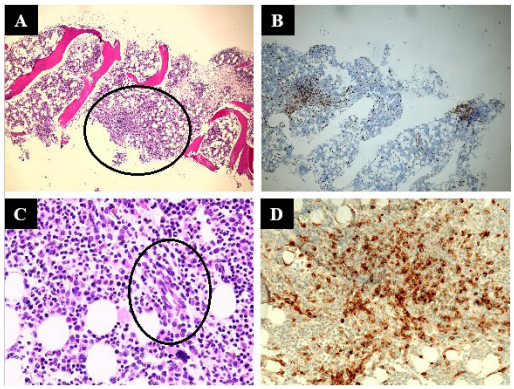

Figure 2. *Microscopic pictures of bone marrow smear.* **A**. *Mast cells (MCs) aggregate (haematoxylin and eosin (H + E) staining, magnification ×40).* **B**. *Multifocal infiltrates ≥ 15 MCs (CD117 immunostaining, magnification ×40).* **C.** *Atypical, spindle-shaped MCs (H + E staining, magnification ×400).* **D**. *Abnormal expression CD25 on MCs (CD25 immunostaining, magnification ×400)*

revealed atypical, spindle-shaped mast cells with abnormal immunophenotype (CD25+, MCT+ CD117+) comprising approximately 4% of marrow cells (Fig. 2). Genetic testing showed an activating point mutation in the KIT gene at codon 816 (D816V). Ultimately, SM was confirmed, and treatment with antihistamines, glucocorticoids, and a tyrosine kinase inhibitor (midostaurin) was initiated, resulting in clinical improvement.

CS refers to symptoms arising from the uncontrolled release of biogenic amines, mainly serotonin (5-hydroxytryptamine) by NET [2]. The described patient exhibited several typical clinical manifestations of CS, including episodic flushing, tachycardia, hypotension, and dyspnoea. These symptoms, combined with elevated concentration of CgA and MCA, initially strongly suggested the presence of NET. However, negative test results for NET largely ruled out primary suspicion and prompted consideration of alternative diagnoses. During the further diagnostic procedure, the World Health Organisation (WHO) criteria for diagnosing SM were met.

MCs release mediators, notably histamine, tryptases, proteases, prostaglandins, and leukotrienes, inducing symptoms resembling CS, such as flushing, hypotension, and tachycardia, which can lead to life-threatening consequences [1]. Moreover, individuals with SM are susceptible to severe allergic reactions, especially following Hymenoptera stings, as was probably experienced by our patient early in her medical history when stung by a hornet.

The bone changes observed in imaging studies were consistent with increased bone turnover characteristic of SM. MCs express RANK ligand, stimulating osteoclasts via the RANK-RANKL signalling pathway, leading to increased bone resorption. Cytokines released by MCs further influence osteoblasts and osteoclasts, contributing to bone remodeling. For example, heparin, tumour necrosis factor alpha (TNF-α), interleukins (IL): IL-1, and IL-6 promote osteoclast activity, causing bone loss, while histamine promotes bone formation, contributing to osteosclerosis [3].

The differential diagnosis of flushing episodes can be challenging due to a wide spectrum of potential causes, ranging from benign emotional reactions, thermoregulatory problems, and menopausal symptoms to malignant diseases such as carcinoid syndrome, pheochromocytoma, medullary thyroid carcinoma, renal cell carcinoma, systemic vasculitis, and mastocytosis [3, 4]. While the clinical features of these conditions may overlap, accurate diagnosis and early treatment are crucial. Considering SM in the differential diagnosis of flushing episodes is essential, positioning it at the intersection of endocrinology due to the hormonal nature of the released mediators. Early diagnosis of SM offers the opportunity for targeted treatment with midostaurin, a tyrosine kinase inhibitor, leading to the improved prognosis.

Ethics statement

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Data were collected retrospectively.

Author contributions

The authors' contributions to the work were as follows: conception of the article — D.B-K, M.S; design of the article, acquisition of data, analysis and interpretation of data — D.B-K, N.O, D.B, A.M, W.Ż, D.L, writing of the manuscript — D.B-K, N.O; revising the article critically for important intellectual content — A.M, W.Ż, final approval of the version to be published — G.K, M.S.

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Conflict of interest

Authors declare no conflict of interest.

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