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 organ-specific 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 99mTc-HYNIC-TATE SPECT/CT and 68Ga-DOTA-TATE PET/CT showed no areas of abnormal radiotracer uptake suggestive of NEN, while 18F-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
Systemic mastocytosis mimicking carcinoid syndrome

Dorota Brodowska-Kania et al.

CLINICAL VIGNETTE

Systemic mastocytosis (SM) is a rare, chronic disorder characterized by the accumulation of atypical mast cells in multiple organs. It can mimic other conditions due to the release of mediators that induce various clinical symptoms. In this case report, we describe a 68-year-old man with a long history of cutaneous flushing and other symptoms consistent with carcinoid syndrome (CS).

**Clinical Features:**
- **Symptoms:** The patient presented with episodic flushing, tachycardia, hypotension, and dyspnoea. These symptoms, combined with elevated concentrations 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.
- **Diagnosis:** The World Health Organization (WHO) criteria for diagnosing SM were met.
- **Genetic Testing:** 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.

**Differential Diagnosis:** 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. 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.

**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)

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**Conflict of interest**
Authors declare no conflict of interest.

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**References**