Etiologies and management of cutaneous flushing

Malignant causes

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Learning Objectives
After completing this learning activity, participants should be able to describe the varied presentations of cutaneous flushing and list the potential etiologies of cutaneous flushing.

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The second article in this 2-part continuing medical education series reviews the following malignant causes of flushing: mastocytosis, medullary thyroid carcinoma, pheochromocytoma, carcinoid tumors, gastroenteropancreatic neuroendocrine tumors, bronchogenic carcinoma, vasointestinal polypeptide secreting tumors, and renal cell carcinoma. The information provided will allow physicians to better distinguish patients who have worrisome presentations that require a more thorough investigation. Appropriate diagnostic workup and treatment options for these malignancies are reviewed. (J Am Acad Dermatol 2017;77:405-14.)

Key words: bronchogenic carcinoma; carcinoid syndrome; carcinoid tumor; flushing; gastroenteropancreatic neuroendocrine tumor; mastocytosis; medullary thyroid carcinoma; pheochromocytoma; renal cell carcinoma; vasointestinal polypeptide–secreting tumor.

Flushing may be caused by the release of vasoactive intrinsic mediators produced by malignancies. It is important to consider malignancy in patients presenting with nonphysiologic causes of flushing. These include flushing episodes associated with concurrent systemic symptoms, those that involve extensive portions of the body, or episodes that do not resolve within minutes.

MASTOCYTOSIS

Mastocytosis is a clonal neoplastic proliferation of mast cells that can occur in various organs. The disease may range in severity from simple skin lesions to advanced mastocytosis, which can cause multiple organ failure. According to the World Health Organization's classification, there are 7 categories of mastocytosis: cutaneous, indolent systemic, systemic

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mastocytosis with associated clonal hematologic non−mast cell lineage disease, aggressive systemic mastocytosis, mast cell leukemia, mast cell sarcoma, and extracutaneous mastocytoma. Approximately 80% of patients with mastocytosis have skin involvement. In systemic mastocytosis, >50% of patients have skin lesions and almost all have bone marrow involvement. Clinical features of systemic mastocytosis include constitutional symptoms of fever, fatigue, weight loss, and diaphoresis; skin manifestations, such as pruritus, urticaria, and dermatographism; mast cell mediator symptoms, such as flushing, headache, syncope, hypotension, tachycardia, and gastrointestinal distress; and musculoskeletal complaints of myalgia, arthralgia, bone pain, and pathologic fractures.[1] Mast cell mediators responsible for these clinical features include histamine, prostaglandin D2, tryptase, and leukotriene C4.[2] Flushing is mediated by histamine and prostaglandin D2.[3,4]

Characteristic yellow-tan to reddish-brown macules and papules found mainly on the trunk and lower extremities[2] as well as Darier's sign, which is urtication of the lesion upon rubbing, may be evident on examination.[1,2] When obtaining a skin biopsy specimen from a patient with suspected mastocytosis, local anesthesia without epinephrine should be injected below the biopsy site to avoid degranulation.[3]

Laboratory evaluation is needed in cases of flushing or other systemic complaints. Serum total tryptase levels >20 ng/mL are suggestive of systemic mastocytosis and are used as a minor criterion for diagnosis.[1] Plasma and urinary histamine, urinary histamine metabolites (N-methylhistamine[3-5] and N-methylimidazoleacetic acid),[5] and urinary prostaglandin D2 metabolites[3,4,6] are elevated. Patients may have concurrent anemia, leukocytosis, eosinophilia, neutropenia, and thrombocytopenia.[1] Obtaining a biopsy specimen from bone marrow is strongly recommended in adults because there is almost always bone marrow involvement in patients with systemic disease.[1-4,7] The World Health Organization criteria for diagnosis of systemic mastocytosis can be found in Table I.[1]

More than 90% of adults and 80% of children with mastocytosis have a gain-of-function mutation in c-kit. It is most commonly a missense activating mutation at codon 816 causing substitution of Val for Asp,[1,2,7] which leads to augmented mast cell proliferation and survival.[2]

Patients should avoid triggers and mast cell degranulators, including temperature extremes, stress, pressure, friction, alcohol, opioids, dextran, iodinated radiocontrast dyes, aspirin, and nonsteroidal antiinflammatory drugs.[3,4,8]

The mainstay of treatment is oral H_1 and H_2 antihistamines.[3,8] Cutaneous blood vessels have H_1 and H_2 receptors, which are responsible for histamine-induced vasodilation and vascular permeability.[2] Because of this, combination H_1 antihistamine (ie, hydroxyzine, diphenhydramine, or nonsedating cetirizine) and H_2 antihistamine (ie, cimetidine, ranitidine, or famotidine) may be used to treat flushing associated with mastocytosis. These medications also provide relief of pruritus and gastric hypersecretion and act as prophylaxis for hypotensive and anaphylactic episodes.[2,3,9]

Aspirin and nonsteroidal antiinflammatory drugs, which decrease prostaglandin synthesis, can be an effective therapy for flushing in certain patients with mastocytosis. However, because these antiinflammatory agents can also provoke mast cell degranulation and vascular collapse, they should be started at low test doses under close monitoring in a hospital setting.[3,4,8]

Oral psoralen plus ultraviolet A light phototherapy has been shown to control flushing and pruritus. Leukotriene antagonists, cromolyn sodium, and corticosteroids may also be used in the treatment of mastocytosis. Patients with anaphylactoid episodes require a self-injectable epinephrine device (ie, EpiPen [Mylan NV, Canonsburg, PA]). Surgical excision may be considered for solitary lesions. Aggressive forms of systemic mastocytosis may necessitate chemotherapy with interferon-α or cladribine.[2,9] Imatinib is recommended in patients with systemic mastocytosis associated with chronic eosinophilic leukemia and Fip1-like1/platelet-derived growth factor receptor-α fusion.[2,10]

MEDULLARY THYROID CARCINOMA

Medullary thyroid carcinoma (MTC) represents a neuroendocrine malignancy of the parafollicular C cells of the thyroid.[11] Because the cells are of neural crest origin, they secrete a variety of active amines and peptides, including calcitonin, prostaglandins, histamine, corticotropin, corticotropin-releasing hormone,[11,12] serotonin, substance P, levodopa, katacalcin,[12] and vasoactive intestinal peptide.[13] Patients may complain of weight loss, fatigue, flushing, sweating, diarrhea, and a mass at the base of the neck producing subsequent dysphagia or hoarseness.[14] Flushing occurs as a result of secreted vasoactive mediators and involves the face and upper extremities.[11,12] Flushing is protracted and can occur with perspiration, discoloration, and telangiectasias.[12]

MTCs can be sporadic or caused by inherited mutations in protooncogenes, such as in multiple endocrine neoplasia (MEN) 2A and 2B. MEN 2A and

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