The flushing patient: Differential diagnosis, workup, and treatment

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Cutaneous flushing—a common presenting complaint to dermatologists, allergists, internists, and family practitioners—results from changes in cutaneous blood flow triggered by multiple conditions. Most cases are caused by very common, benign diseases, such as rosacea or climacterum, that are readily apparent after a thorough taking of history and physical examination. However, in some cases, accurate diagnosis requires further laboratory, radiologic, or histopathologic studies to differentiate several important clinicopathologic entities. In particular, the serious diagnoses of carcinoid syndrome, pheochromocytoma, mastocytosis, and anaphylaxis need to be excluded by laboratory studies. If this work-up is unrevealing, rare causes, such as medullary carcinoma of the thyroid, pancreatic cell tumor, renal carcinoma, and others, should be considered. (J Am Acad Dermatol 2006;55:193-208.)

Learning objective: At the completion of this learning activity, participants should be familiar with the mechanisms of flushing, its clinical differential diagnosis, the approach to establish a definitive diagnosis, and management of various conditions that produce flushing.

The phenomenon of cutaneous flushing has fascinated human beings since prehistoric times, as evidenced by numerous archaeologic artifacts that depict erythema in the classic blush area. The term *flush* itself was pioneered in 1882 by Dr. E. J. Tilt, who proposed a short and expressive word for this phenomenon. The conceptual framework for flushing reactions was developed over the past 2 centuries by many investigators, starting in 1829 with Burgess, but a more detailed mechanistic understanding came mainly in the latter part of the 20th century, owing to major advances in pharmacology and physiology.[1] The mechanisms of flushing reactions are pharmacologically and physiologically heterogeneous. Table I provides a list of pharmacologic mediators of flushing in various conditions. Flushing may result from agents that act directly on the vascular smooth muscle or may be mediated by vasomotor nerves. Vasomotor nerves may lead to flushing owing to events at both peripheral and central sites.[1-10]

Abbreviations used:

CS:	carcinoid syndrome
5-HIAA:	5-hydroxyindoleoacetic acid
5-HT:	5-hydroxytryptamine
MCT:	medullary carcinoma of the thyroid
NSAID:	nonsteroidal anti-inflammatory drug
TMEP:	telangiectasia macularis eruptiva perstans
VIP:	vasoactive intestinal polypeptide

Flushing may be defined as a sensation of warmth accompanied by visible reddening of the skin.[4] Normally, it is part of a coordinated physiologic thermoregulatory response to hyperthermia and results from increased cutaneous blood flow caused by transient vasodilation.[1,4] Flushing is usually most prominent in the classic "blush area," which includes the face, neck, upper portion of the chest, and upper limbs. Such predilection stems from the increased relative volume of visible superficial cutaneous vasculature in these regions, as well as qualitative differences in skin vascular response and vascular regulation compared with other body areas.[1,4,9]

Flushing can be episodic or constant. Episodic attacks are generally mediated by release of endogenous vasoactive mediators or by drugs.[4] Repetitive episodes over long periods (persistent flushing) may produce fixed facial erythema with telangiectases and a cyanotic tinge. This appearance is due to the development of large cutaneous blood vessels that contain slow-flowing deoxygenated blood.[4]

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Table I. Pharmacologic mediators of flushing

Foods, beverages, alcohol
Tyramine, histamine, sulfites, nitrites, alcohol, aldehyde, higher chain alcohols, monosodium glutamate, capsaicin, cigua toxin (fish)
Climacterium
Estrogen fluctuations
Carcinoid syndrome
5-HT (no flushing but diarrhea), substance P, histamine, catecholamines, prostaglandins, kallikrein, kinins, tachykinins, neurotensin, neuropeptide K, VIP, gastrin-related peptide, motilin
Pheochromocytoma
Catecholamines (epinephrine, norepinephrine, dopamine), VIP, calcitonin-gene-related peptide, adrenomedullin
Mastocytosis
Histamine, prostaglandin D2, leukotrienes, tumor necrosis factor α, vascular endothelial growth factor, interleukins, heparin, acid hydrolases
Anaphylaxis
Histamine, other mast cell and basophil mediators, as above for mastocytosis
Medullary carcinoma of the thyroid
Calcitonin, prostaglandins, histamine, substance P, levodopa, ketacalcin, adrenocorticotropic hormone, corticotropin-releasing hormone
Pancreatic cell carcinoma
VIP, prostaglandin, gastric inhibitory polypeptide
Renal cell carcinoma
Prostaglandins, pituitary down-regulation
Neurologic
Substance P, catecholamines

Table II. Differential diagnosis of flushing

Common causes
Benign cutaneous flushing
Emotion
Temperature
Food or beverage
Rosacea
Climacteric flushing
Fever
Alcohol
Uncommon, serious causes
Carcinoid
Pheochromocytoma
Mastocytosis
Anaphylaxis
Other causes
Medullary thyroid carcinoma
Pancreatic cell tumor (VIP tumor)
Renal cell carcinoma
Fish ingestion
Histamine
Ciguatera
Psychiatric or anxiety disorders
Idiopathic flushing
Neurologic
Parkinson's
Migraine
Multiple sclerosis
Trigeminal nerve damage
Horner syndrome
Frey syndrome
Autonomic epilepsy
Autonomic hyperreflexia
Orthostatic hypotension
Streeten syndrome
Medications (see Table IV)
Very rare causes
Sarcoid, mitral stenosis, dumping syndrome, male androgen deficiency, arsenic intoxication, POEMS syndrome, basophilic granulocytic leukemia, bronchogenic carcinoma, malignant histiocytoma, malignant neuroblastoma, malignant ganglioneuroma, peri-aortic surgery, Leigh syndrome, Rovsing syndrome

The differential diagnosis of flushing is extensive and comprises various benign and malignant entities (Tables II and III; Fig 1). Fever, hyperthermia, emotional blushing, menopause, and rosacea are by far the most common reasons for the flush reactions. With the exception of carcinoids, flushing due to tumors is rare and tends to occur in advanced stages. The following discussion focuses on the common and rare, benign and malignant causes of flushing, their diagnosis, differential diagnosis, and management.

FEVER

Fever is the most common cause of "hot flushes," particularly when associated with night sweats.[1] This elevation in body temperature can be easily diagnosed by taking the oral temperature during an attack and should prompt a fever workup, which may reveal an infectious or noninfectious cause.[11] Fevers generally are treated with antipyretics, including nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.

BENIGN CUTANEOUS FLUSHING

Benign cutaneous flushing is a large rubric that includes hyperthermia (from causes other than fever) and emotional flushing. It is triggered by emotion, exercise, temperature changes, and foods or beverages, especially spicy foods.[2] Associated findings may include a feeling of warmth and cognitive dysfunction. Benign cutaneous flushing affects women more often than men and, since it does not

Table III. Comparison of key history, physical, and laboratory findings in common and serious causes of flushing

Cause	Key history findings	Key physical findings	Key laboratory findings
Fever	Associated with sweating; elevated temperature; illness	None specific	None
Benign cutaneous flushing	Related to emotion; related to exercise; related to foods	None specific	None
Rosacea	Typical triggering factors; ocular symptoms	Papules, pustules, telangiectasia; flushing limited to face	None
Climacterium	Woman in 5th, 6th, or 7th decade; frequent brief episodes; profuse sweats	Flushing of head, neck, chest	Elevated FSH (usually not necessary to check)
Carcinoid	Hypotension, tachycardia; abdominal cramping, diarrhea; bronchoconstriction	Reddish brown or bright red flushing; may be widespread flush, including the palms; may develop permanent telangiectasia and bluish coloration of face	24-hour urine for 5-HIAA
Pheochromocytoma	Hypertension (sustained or episodic) Attacks: sweating, palpitations, chest pain; abdominal pain, nausea, vomiting; headache, sense of impending doom	None specific	24-hour urine for fractionated metanephrines, norepinephrine, epinephrine, dopamine, vanillylmandelic acid
Mastocytosis	Abdominal pain, nausea, vomiting, diarrhea; fatigue, malaise; weight loss, neuropsychiatric symptoms; hypotension	Cutaneous mastocytosis (urticaria pigmentosa, TMEP, etc.)	Serum tryptase persistently elevated; 24-hour urine for *n*-methylhistamine
Anaphylaxis	Hypotension; difficulty breathing, rhinitis; headache, chest pain	Urticaria, angioedema	Serum tryptase elevated during attacks only
Medullary carcinoma of the thyroid (MCT)	May be personal or family history of MCT, pheochromocytoma, hyperparathyroidism (i.e., multiple endocrine neoplasia)	Protracted flushing, persistent discoloration, telangiectasia of face and arms; thyroid nodule	Calcitonin level; radioimmunoassay for calcitonin after intravenous calcium and pentagastrin
Pancreatic cell tumor (VIPoma)	Prolonged watery diarrhea; abdominal pain, nausea, vomiting; lethargy, weakness	None specific	Elevated plasma VIP
Renal cell carcinoma	Hematuria; flank pain	Abdominal mass	Hematuria and Imaging studies

usually respond to medications, may be a source of frustration for patients.[2] Hyperthermia may result from overheating or exercise and is treated by means of cooling.[8] Emotional flushing can be an easy clinical diagnosis if episodes of flushing are correlated with emotional upset or feelings of embarrassment. Treatment options include biofeedback, hypnosis, and paradoxical intention to modify the behavioral pattern. Nadolol, a nonselective beta-blocker, may be tried in patients with benign cutaneous flushing, as it attenuates the vascular response due to anxiety,[1] but the effectiveness of beta-blockers in general to treat emotional flushing is largely anecdotal and has not been studied rigorously.

Foods, beverages, and alcohol may contain tyramine, histamine, higher chain alcohols, monosodium glutamate, aldehyde, nitrites, and sulfites, all of which may cause flushing. Ingestion of sulfites (potassium metabisulfite) is associated with wheezing, while ingestion of nitrites, commonly found in cured meats, is associated with headaches.[8] In

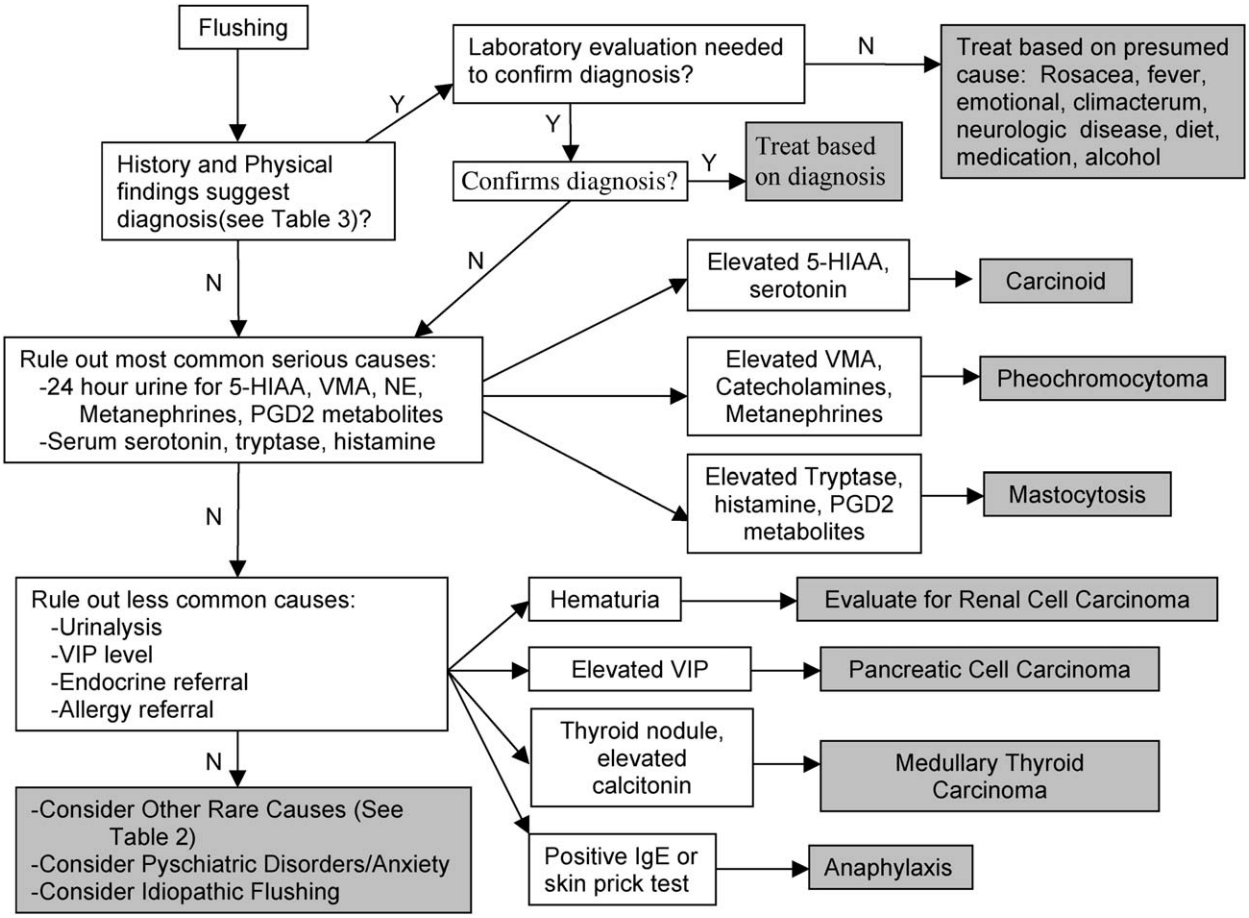

Fig 1. Algorithm for the evaluation of patients who present with flushing. *5-HIAA,* 5-Hydroxyindoleoacetic acid; *NE,* norepinephrine; *PGD2,* prostaglandin D2; *VIP,* vasoactive intestinal peptide; *VMA,* vanillylmandelic acid.

addition, spicy foods, especially those that contain the active agent in red pepper, capsaicin, may cause severe flushing and provoke headache and wheezing in sensitive persons.[1] Hot beverages may cause flushing via a mechanism of countercurrent heat exchange that involves the anterior portion of the hypothalamus.[1,8] Finally, gustatory flushing may present as bilateral flushing, accompanied by salivation, sweating, and nasal secretion.[1]

Histamine fish poisoning occurs particularly after ingestion of tuna or salmon. Its typical symptoms, such as flushing, urticaria, and palpitations, mimic those of allergy, so it may be easily misdiagnosed. This illness may be treated with antihistamines.[12-17] Flushing may also occur in ciguatera fish poisoning. Ingestion of fish that contains the cigua toxin produces, within hours after incubation, a characteristic syndrome that includes flushing, vomiting, diarrhea, abdominal pain, pruritus, diffuse tingling pain, dysesthesias (diffuse and of the tongue, teeth, and gingivae), myalgia, weakness, and ataxia. Cooking does not destroy the toxin. The syndrome is usually self-limited, but may last for years. The implicated fish are either herbivorous species that consume coral or carnivorous ones that consume the former group; they include sea bass, grouper, red snapper, barracuda, amberjack, and surgeonfish.[8]

The signs and symptoms of benign cutaneous flushing may overlap with those of idiopathic anaphylaxis, carcinoid syndrome, and mastocytosis. All can present with abdominal complaints and flushing of the blush area.[2]

ROSACEA

Acne rosacea, another common cause of flushing, may present with transient or persistent central facial flushing, erythema, visible blood vessels, and often papules and pustules. There are 4 broad subtypes: erythematotelangiectatic (which usually presents with flushing and redness), papulopustular, phymatous, and ocular, with significant overlap possible in any individual patient.[18] Inflammatory acne

rosacea, marked by pustules and facial erythema, is a particularly serious entity, as it may also involve the conjunctiva and sclera. The cause of rosacea is unclear, but the pathogenesis may involve vascular abnormalities, dermal matrix degeneration, and microorganisms such as *Demodex folliculorum* and *Helicobacter pylori*.[18]

Since there is no laboratory benchmark test for rosacea, diagnosis is based on clinical findings. Patients may have persistent erythema on the cheeks and a dramatic history of flushing in response to various stimuli, complaints of burning and stinging, and intolerance to various topical products. Primary manifestations are (1) persistent erythema, which usually lasts longer than 3 months and tends to spare periocular skin, and (2) flushing episodes, which may last longer than 10 minutes. Stimuli for flushing in rosacea are multiple and include emotional stress, hot drinks, alcohol, spicy foods, exercise, cold or hot weather, and hot baths or showers. Secondary manifestations include burning, stinging, edema, plaques, dry appearance of affected skin, ocular manifestations, and phymatous changes.[18]

When evaluating patients with rosacea, it is important to exclude the diagnoses of polycythemia vera, photosensitive eruption, lupus erythematosus, mixed connective tissue disease, carcinoid syndrome, systemic mastocytosis, or side effects from long-term facial application of topical steroids. Since rosacea is typically limited to the face, extrafacial erythema is generally an exclusionary sign. Rosacea flushing is associated with burning or stinging but not sweating, lightheadedness, or palpitations.[18]

Erythematotelangiectatic rosacea, while considered by many to represent a separate entity, may in fact be difficult to distinguish from simple benign cutaneous flushing and sun-damaged skin. In attempting this distinction, it may be useful to assess the extent of baseline facial telangiectasia and the overall degree of poikiloderma. However, since these 3 conditions are all common, they may coexist in many patients. Also, since erythematotelangiectatic rosacea and benign cutaneous flushing may have common triggers for flushing, it may be reasonable to consider these 2 entities as different points on a single continuum, making distinction of academic value only.

There is no cure for rosacea, but a number of treatments are available, including topical antibiotics, oral antibiotics, laser therapy, light therapy, and sunscreen use or sun avoidance. Topical medications include metronidazole, clindamycin, erythromycin, sulfa-based washes, benzoyl peroxide, azelaic acid, tretinoin, and tacrolimus. Oral medications include tetracyclines, which are effective at subantimicrobial dosages and thus are used largely for an anti-inflammatory effect; macrolides such as erythromycin; metronidazole; isotretinoin; oral contraceptive pills; and spironolactone.[19] In the setting of inflammatory rosacea, standard rosacea treatments (including oral tetracyclines, topical antibiotics, other topical agents, and pulsed dye laser), while primarily aimed at improving inflammatory lesions and facial erythema, may also be effective at decreasing cutaneous flushing.

CLIMACTERIC FLUSHING

Climacterium is another common cause of flushing, affecting 50% to 85% of women who undergo natural menopause.[1,4] Perimenopausal flushing presents as transient episodes of intense heat sensation, flushing of the chest, head, and neck, and profuse drenching sweats.[1,4,5] These episodes are frequently followed by chills accompanied by palpitations and a sense of anxiety.[1] Episodes last 3 to 5 minutes and may occur as many as 20 times per day.[5] They may be provoked by warmth, hot drinks, alcohol, and mental stress.[5] Nocturnal flushes may cause insomnia, which leads to fatigue, irritation, and ensuing social, psychologic, and economic consequences.[1,4] Climacteric flushing normally subsides in months to several years but in rare instances can persist for up to 30 years.[1,5]

Although precise causes are not fully understood, hormonal changes of the climacterium are certainly implicated in the pathogenesis.[4,5] Estrogen fluctuations are particularly important triggers of flushing: for instance, flushing in isolated gonadotropin deficiency occurs only on withdrawal of previously administered estradiol, and perimenopausal flushing is successfully relieved with hormone replacement therapy but recurs upon withdrawal of that treatment.[4,20,21] Although hormone replacement therapy is an effective treatment of climacteric flushing, its current use is controversial and should be pursued with caution because of the potential risks.[22-24] In addition, the central adrenergic and opioid pathways may contribute to the pathogenesis, as the central acting α_2-adenergic agonist clonidine may reduce the frequency of hot flashes and the opioid antagonist naloxone may have an additive effect.[4,25,26]

CARCINOID SYNDROME

Carcinoid syndrome (CS) is one of the most important entities in the differential diagnosis of flushing because of the malignant nature of carcinoid tumors and the relatively high mortality. Therefore, CS must be suspected and ruled out in patients who present with flushing, even though flushing due to other disorders is more prevalent.[5]

Carcinoid tumors were first described by Lubarsch more than 100 years ago and in 1907 by Obendorfer, who first used the term *karzenoide*.[27] CS was first described by Biorck in the 19th century and classically presents with a triad of flushing, gastrointestinal hypermotility (abdominal cramping and diarrhea), and right-sided cardiac failure due to valvular disease, with significant but lesser incidence of bronchoconstriction.[1,5,28] Patients may also complain of fatigue.[2] Ninety-five percent of patients with CS have flushing at some point during disease, making it the most frequent clinical sign.[5]

CS occurs in approximately 10% of all patients with carcinoid tumors.[5] Tumors consist of malignant enterochromaffin or Kulchitsky cells that are derived from the neuroendocrine lineage.[28] It is estimated that CS develops in 40% to 50% of patients with small bowel or proximal colon tumors, occurs rarely in patients with bronchial and appendiceal tumors, and does not occur in patients with rectal tumors.[4] CS may also occur in patients with nongastrointestinal tumors, such as ovarian teratomas, glomus jugulare, and thyroid tumors.[1] While women have greater rates of lung and stomach carcinoids, men develop more carcinoids of the small intestine and rectum. From 1992 to 1999 the incidence increased about 3% annually; 13% of patients had metastasis at diagnosis, and 24% of carcinoid patients had more than 1 tumor.[29]

CS flush is distinctive. Flushes associated with gastric tumors are reddish-brown with variegated margination and occur as wheals over the entire body, including palms and soles, which may be intensely pruritic. Flushes associated with bronchoconstriction are bright red and confluent, cover most of the body, last hours to days, and are usually also associated with chemosis, facial edema, severe hypotension, and oliguria.[1] After several years, patients with CS flushing may develop thick skin changes with venous telangiectasia and bluish coloration of the chin, nose, and malar area.[1]

While patients occasionally present with hypertension, they are generally hypotensive and tachycardic during the flushing episode.[1,2] Flushing in CS may be provoked by (1) foods, via stimulation of gut hormone release, or via food-derived amines, such as those in sherry, beer, fermented foods, and chocolate[4]; (2) pharmacologic triggers, including norepinephrine, epinephrine, and dopamine (all of which are blocked by alpha-blockers but not beta-blockers), as well as pentagastrin and isoproterenol[2,4]; and (3) any stimuli that increase adrenergic activity, such as pain, anger, embarrassment, and exertion.[1,2] Flushing provoked by isoproterenol or pentagastrin also occurs in patients with mastocytosis and benign cutaneous flushing.[2]

The likelihood of flushing in CS is dependent on tumor-derived mediators and the extent of liver metastasis. Because the liver generally inactivates vasoactive substances that enter portal flow, vasoactive substances secreted by tumors distal to the portal vein or downstream of functioning hepatocytes may enter systemic circulation more readily to provoke flushing.[4,28] Several tumor-derived culprit vasodilators have been identified, none of which is the primary mediator: 5-hydroxytryptamine (5-HT) is a potent vasodilator, but its administration in human beings causes not flushing but diarrhea; substance P is secreted by most carcinoids, and systemic infusion causes flushing, hypotension, and tachycardia; gastric carcinoids secrete histamine; and other putative mediators are serotonin, catecholamines, prostaglandins, kallikrein, kinins, tachykinins, neurotensin, neuropeptide K, motilin, vasoactive intestinal peptide, and gastrin-related peptides.[1,3-5,27]

CS is diagnosed by measuring the 24-hour urine levels of 5-hydroxyindoleoacetic acid (5-HIAA), a major urinary metabolite of serotonin (5-HT): 5-HIAA values of twice normal are highly suspicious of CS, but false-positive findings may result from ingestion of bananas, caffeine, melphalan, or fluorouracil prior to testing.[4,27] Usually levels greater than 25 mg per 24 hours are indicative of the diagnosis.[1] Urinary 5-HIAA is not elevated in mastocytosis, because 5-HT is not made by human mast cells, nor in idiopathic anaphylaxis or idiopathic flushing.[2] Urinary 5-HIAA is the most useful and readily available screen for carcinoid tumors. While plasma 5-HT may be a useful laboratory value if elevated,[5] it is not readily available. Other additional tests may include serum chromogranin A and neuron-specific enolase,[30] which also are not readily available. Computed tomography, magnetic resonance imaging, and selective angiography of the abdomen and pelvis should be performed to identify and localize metastases, but a primary tumor may elude detection until laparotomy.[4,27] Recently, somatostatin receptor nuclear scintigraphy and whole-body positron emission tomography have proved to be more sensitive in localizing primary and metastatic tumors.[28] Surgical consultation should be sought after the initial medical investigations are completed.[27]

Flushing in CS can be blocked with somatostatin, its analog, octreotide, and the newly developed versions of octreotide (octreotide-long-acting release or lantreotide), which reduce the secretion of vasoactive mediators. These agents are administered subcutaneously or intravenously.[4,5,28] Somatostatin analogs also decrease tumor progression.[28] Treatment of flushing from histamine-secreting tumors

may be partially accomplished with a combined histamine$_1$ and histamine$_2$ receptor blockade.[2] In addition, the 5-HT antagonist ketanserin may abolish flushing in a proportion of patients, but its mode of action is uncertain.[4] Generally, there is minimal benefit from the administration of propranolol, chlorpromazine, 5-HT antagonists, or steroids.[3]

Because carcinoids are considered slow-growing tumors, survival for several years is common, even when the liver is largely replaced by metastases.[4] The overall 5-year survival rate was 82% in a series of patients from 1992 to 1999, when 24% of carcinoid patients had more than 1 tumor at presentation and 13% had metastases.[29] Occasionally primary carcinoid tumors may be resectable, but curative surgery is only rarely feasible if patients have hepatic metastases. Other options may include reduction of the tumor bulk by means of partial hepatectomy, embolization, or chemotherapy such as interferon-α.[2,4,27]

PHEOCHROMOCYTOMA

Pheochromocytoma, also known as chromaffin tumor, may present with flushing and hypertension. Chromaffin cells, derived most often from the adrenal medulla, produce, store, and release catecholamines; thus, the signs and symptoms are most likely related to catecholamine release. Hypertension is the most common finding: 60% of patients have sustained hypertension with significant blood pressure lability, and half of these patients experience distinct crises or paroxysms; 40% of the patients experience hypertension only during attacks.[1] Attacks are usually paroxysmal, last a few minutes to a few hours or longer, and may be associated with flushing or pallor if the attack is marked by alarmingly elevated blood pressure and tachycardia. Attacks commonly present with headaches, sweating, palpitations, a sense of apprehension and impending doom, and chest pain or abdominal pain associated with nausea and vomiting.[1] Such paroxysms may be precipitated by any activity that displaces abdominal contents, such as deep abdominal palpation.

The mechanism for flushing in pheochromocytoma probably involves the elevated production of catecholamines, well-described mediators of flushing when administered exogenously or when increased production is triggered after withdrawal of sympathetic suppression.[31-35] Since thermal vasodilation in the major portions of the face may be regulated by sympathetic vasodilator fibers and less predominantly by adrenergic vasoconstrictor fibers,[36] the predominant effect of elevated catecholamines might be vasodilation and flushing. Other basis for the catecholamine-induced flushing include general blood pressure lability and episodes of increased cardiac output in such patients. In addition, some pheochromocytomas may produce other flushing mediators, such as calcitonin gene-related peptide and vasoactive intestinal polypeptide (VIP)[37-40] and adrenomedullin, a recently described potent vasodilatory peptide with significant vasodilatory effects on skin.[41,42]

Pheochromocytoma may be diagnosed by measuring the 24-hour urine fractionated metanephrines (metanephrine and normetanephrine), metabolites of catecholamines. This highly sensitive test usually reveals the tumor, making it one of the most reliable and available screening tests for pheochromocytoma. Measurement of plasma-free metanephrines, which also is extremely sensitive in the detection of tumors when levels are elevated above 1.4 pmol/mL,[43] is a more technically challenging test. Measurement of total levels of urinary catecholamines (24-hour urinary norepinephrine, epinephrine, and dopamine) is another useful test in the diagnosis.[1,43] However, measurements of vanillylmandelic acid and urinary total metanephrines are less reliable tests and have little value in the initial screening.[44]

Computed tomography of the abdomen and pelvis is usually successful for the localization of an intra-adrenal pheochromocytoma.[1,43] Diagnosis of an extra-adrenal pheochromocytoma may require abdominal aortography or nuclear scintigraphy with radioactive iodine.[1,43] Surgical consultation should be obtained. The patient should be prepared for surgery with administration of alpha-receptor blockers. Beta-blockers may be given only after alpha-blockade is established, because an otherwise unopposed beta blockade may lead to a paradoxical increase in blood pressure by augmenting catecholamine effects at the alpha receptor.[43] Since pheochromocytoma is often benign, surgical resection by means of laparoscopic adrenalectomy is the definitive treatment and may be curative, with surgical mortality of 2% to 3% in experienced hands.[1,43]

MASTOCYTOSIS

Mastocytosis is an important cause of flushing reactions that must be suspected clinically in all patients with flushing, especially when it is associated with hypotension.[2,45,46] Mastocytosis, a rare disease caused by tissue infiltration with increased numbers of mast cells, was originally described by Nettership and Tay in 1869.[47,48] The disease is more common in childhood than in adulthood. Mastocytosis presents in the pediatric population with the characteristic skin eruption of urticaria pigmentosa in more than 90% of patients.[1] Urticaria pigmentosa consists of reddish-brown macular, papular, nodular, or plaquelike lesions that urticate, wheal, and

become pruritic on stroking, the latter maneuver known as the "Darier sign"; or lesions may appear as acneiform pustules or blisters on erythematous bases.[4,46] Occasionally, cutaneous mastocytosis may present with xanthelasmoid skin folds in babies with diffuse cutaneous mastocytosis (marked by a doughy consistency of skin), with bullous lesions in bullous mastocytosis, with reddish-brown oval or linear macules in a variant termed "telangiectasia macularis eruptiva perstans" (TMEP), or with a solitary papular mastocytoma.[46]

In contrast, adults do not usually present with the characteristic lesions of urticaria pigmentosa or other prominent skin signs, but present more often with systemic complaints or peripheral blood abnormalities. Cutaneous lesions in adults, if present, are usually 2- to 5-mm red-brown macules or papules. TMEP occurs mostly in adults, and occasionally, patients may present with xanthelasmoid mastocytosis.[47] Diffuse bone lesions are found in 57% of adult patients; bone marrow involvement, with bone marrow mast cells, in 90%; and splenomegaly in 48% to 61%.[47] The C-KIT 816 activating mutation can be identified in most adults with mastocytosis and rarely in children.[47] Patients with activating 816 mutations, whether adults or children, have life-long persistent disease that may be associated with systemic involvement; children without the activating mutation generally have mild disease that resolves by adulthood.[47] Mastocytosis should always be suspected in patients with unexplained flushing, and a high index of suspicion is necessary in the examination of patients without characteristic skin lesions of urticaria pigmentosa. Most frequently, such patients tend to be adults with more aggressive systemic disease and correspondingly increased potential for grave consequences.[45,46]

The mast cell was first described by Ehrlich in 1877. When stimulated, mast cells release several potent vasodilators, the most important of which are histamine and prostaglandin D_2, as well as tumor necrosis factor α, vascular endothelial growth factor, leukotrienes, interleukins, heparin, and acid hydrolases.[1,4,46] Episodic release of vasoactive mediators by the increased mast cell mass produces systemic symptoms as a consequence of induced vasodilation, notably flushing, hypotension, and tachycardia. Other symptoms include abdominal cramps and diarrhea, fatigue, malaise, fever, nausea, vomiting, neuropsychiatric symptoms, and weight loss.[1,4,49] Such symptoms may be grave and life-threatening, especially in patients who have a coexisting disease that predisposes for mediator secretion, such as allergies.[45] Osseous lesions in systemic mastocytosis may lead to osteoporosis.[1]

Flushing in mastocytosis may be provoked by narcotic analgesics and any agent capable of inducing anaphylaxis or an anaphylactoid reaction (including intravenous dextran or contrast dye).[2,4,46,47] Specifically, a number of systemic anesthetic agents have been directly or indirectly implicated in precipitating anaphylactic reactions in mastocytosis patients: lidocaine, morphine, codeine, D-tubocurarine, metocurine, etomidate, thiopental, succinylcholine, enflurane, and isoflurane.[48] Other precipitants include aspirin, NSAIDs, polymyxin B sulfate, anticholinergic medications, alcohol, and trauma, as well as physical and emotional factors.[2,4,46,47]

Diagnosis is usually straightforward if characteristic lesions of urticaria pigmentosa are present either during routine examination or concurrent with episodes of unexplained flushing or anaphylaxis.[2,4] In the absence of skin lesions, increased mast cell mass may be confirmed by means of histopathologic examination, as well as laboratory studies. Bone marrow biopsy performed to evaluate an abnormal peripheral blood finding is one way in which increased mast cell mass can be demonstrated.[2]

In addition, laboratory studies may reveal elevated plasma concentrations of mast cell mediators, such as histamine and tryptase, and elevated 24-hour urine excretion of histamine or prostaglandin D_2 metabolites. Serum tryptase is usually normal in patients with cutaneous mastocytosis (<20 ng/mL), but almost invariably greater than 20 ng/mL in those with systemic mastocytosis. If tryptase levels are greater than 30 ng/mL, the likelihood of systemic mastocytosis is 90%.[4,45,46] In addition, 24-hour measurement of urinary *n*-methylhistamine (i.e., 1-methylhistamine) and prostaglandin D2 metabolites are available and useful tests. Urinary 1,4-methylimidazole acetic acid, a major metabolite of histamine, is often elevated persistently,[47] but this test is not readily available.

Histopathologic analysis of cutaneous mastocytosis lesions reveals multifocal or diffuse mast cell aggregates in the papillary dermis and extending into reticular dermis.[46] Immunohistochemical staining for tryptase is more sensitive than staining for mast cells with Giemsa or toluidine blue.[46] However, histopathologic diagnoses are rarely rendered on the basis of a skin lesion biopsy that does not grossly resemble urticaria pigmentosa or TMEP.[2] Biopsy reports that state "consistent with mastocytosis because of increased mast cells" demand clinicopathologic correlation and some degree of caution, as increased mast cells may be observed in areas of skin inflammation or in association with idiopathic hives and anaphylaxis.[2] In the future, characteristic mutations in the C-KIT gene (CD117) may facilitate

molecular diagnosis, namely the common Asp-816-Val activating mutation.[2,45,50,51]

Once the diagnosis is made, it is important to ascertain whether a patient with indolent cutaneous or systemic mastocytosis has an associated hematologic disorder, which would require different management and portend a different prognosis.[2] Mastocytosis can be classified into 4 categories: *I,* indolent mastocytosis, cutaneous or systemic (*Ia*, indolent disease, or *Ib*, indolent disease with systemic disease); *II*, mastocytosis with an associated hematologic disorder (myeloproliferative disease or myelodysplasia); *III*, lymphadenopathic mastocytosis with eosinophilia; and *IV*, mast cell leukemia.[2,47] Disease associated with the activating 816 mutation, most common in adults and rare in children, tends to be systemic and persistent.[47] Patients with disease limited to the skin generally have a benign course.[49] In children, almost all cutaneous mastocytomas disappear with time. In adults, skin lesions are generally persistent, and only 10% of adult patients have spontaneous regression. However, in some of these people, disappearance of cutaneous lesions is accompanied by progression to visceral mastocytosis.[45,46] In addition, since adult-onset mastocytosis is almost always associated with bone marrow involvement (90% of patients),[47] hematologic consultation should be obtained. A complete blood count with platelets, liver function tests, and blood chemistries should be examined. If there are any peripheral blood abnormalities, a bone marrow biopsy may be recommended.[46,47]

Currently, there is no cure for mastocytosis. Treatment includes avoidance of precipitating factors, including heat, friction, and systemic anesthesia.[47] Flushing and hypotension from mastocytosis can be reversed with intravenous epinephrine; this treatment is in contrast to that for flushing in CS, which is usually exacerbated by epinephrine.[4] While treatment with H1 receptor antagonists is normally ineffective, combined blockade of H1 and H2 receptors prevents the vasodilatory effects of histamine.[4,45,49] Other modalities include cromolyn, oral steroids, topical steroids, traditional chemotherapies, psoralen and ultraviolet A therapy for urticaria pigmentosa, and laser therapy for TMEP.[45,47,49] Therapy with imatinib mesylate, an inhibitor of the c-kit tyrosine kinase, shows some promise for systemic disease associated with certain other c-kit mutations.[52] Treatment with acetylsalicylic acid or NSAIDs to block prostaglandin synthesis requires extreme caution and should be undertaken only after testing with very low doses, because any NSAID may provoke systemic mastocytosis and vascular collapse.[4,45] In those at risk for anaphylactoid shock, use of an autoinjector of epinephrine such as the EpiPen (Dey, LP, Napa, Calif) is recommended at the onset of symptoms.[45]

ANAPHYLAXIS

Anaphylaxis is a potentially life-threatening condition that may present with flushing and thus demands quick recognition and prompt treatment. It results from the release of mast cell and basophil vasoactive mediators into systemic circulation. Anaphylaxis most often presents with flushing, urticaria, and angioedema; other symptoms may include any or all of the following: hypotension, upper airway edema, pulmonary symptoms, gastrointestinal problems, rhinitis, headaches, and occasionally substernal chest pain.[2,53] Isolated flushing in the absence of other signs and symptoms usually excludes the diagnosis of anaphylaxis, but in rare cases, patients may report flushing with rare occurrence of hives or abdominal pain, or both, which may actually represent anaphylaxis.[2] Onset of flushing episodes with anaphylaxis is temporally related to substances that induce either an IgE-mediated form of anaphylaxis or reactions similar to anaphylaxis that are precipitated by physical factors, such as pressure, exercise, cold, and heat which trigger the release of mast cell and basophil vasoactive mediators.[2,53] Approximately one-third of all cases are idiopathic.[53]

Diagnosis is usually determined on the basis of clinical presentation and laboratory studies, including elevated plasma histamine and tryptase. Allergy and immunology specialists should be consulted. Identifiable allergic causes in anaphylactic reactions should be sought with radioallergosorbent testing and possibly prick testing, if indicated. Hereditary angioedema and acquired angioedema due to C1 esterase inhibitor should be eliminated by means of laboratory studies (check C4, C1, C1q levels and test for C1 esterase inhibitor deficiency).[2] Because of significant overlap among the signs and symptoms of idiopathic anaphylaxis, mastocytosis, CS, and idiopathic flushing, all of which may include flushing, abdominal pain, and tachycardia as a component, definitive clinical diagnosis may be difficult. Hives in mastocytosis occur at the site of urticaria pigmentosa lesions, and angioedema is rare. Furthermore, since carcinoid tumors may secrete histamine, differentiation among CS, mastocytosis, and anaphylactic reactions may become difficult. Finally, both anaphylaxis and mastocytosis may show elevated levels of histamine and serum tryptases, making clear laboratory distinction between these entities problematic.[2] One potential way to resolve this issue is to measure levels of tryptase between attacks; elevated levels would suggest the diagnosis of mastocytosis.

Anaphylaxis may be fatal if left untreated and thus demands immediate medical attention. During the anaphylactic episode, either intravenous or intramuscular epinephrine (the latter via EpiPen [0.3 mg] or 0.3-0.5 mL of 1:1,000 dilution) should be administered into either the anterolateral thigh muscles or the deltoid muscle every 5 minutes, as necessary, to control blood pressure and symptoms. Systemic glucocorticoids are usually not helpful in the acute setting, but may prevent prolonged reactions or relapses. Patients may require intensive care in cases of shock or compromised airway from angioedema.[53]

MEDULLARY CARCINOMA OF THE THYROID

Medullary carcinoma of the thyroid (MCT) is a malignant tumor of the parafollicular C cells that may present with protracted flushing of the face and upper extremities, discoloration, and telangiectasias.[5,54] Neoplastic cells of MCT are derived from the neural crest and secrete a variety of biologically-active peptides and amines, including calcitonin, prostaglandins, histamine, substance P, ketacalcin, levodopa, adrenocorticotropic hormone, and corticotropin-releasing hormone, that can cause flushing and sweating.[1,5] The inheritance pattern of MCT may be sporadic or may be autosomal dominant as part of multiple endocrine neoplasia (MCT, pheochromocytoma, hyperparathyroidism), which is due to mutations in the RET proto-oncogene.[1,54]

Most patients with sporadic disease present with an asymptomatic thyroid nodule. Some patients will have elevated calcitonin levels, but a radioimmunoassay for calcitonin after intravenous administration of calcium and pentagastrin is much more sensitive. This technique may be combined with thyroid nuclear scanning and thyroid fine-needle aspirate analysis for better diagnostic power.[1,54] Endocrinologic and surgical consultations should be obtained if MCT is suspected clinically. Hyperparathyroidism, pheochromocytoma, and other endocrine diseases must be excluded and treated. Finally, total thyroidectomy with lymph node dissection in the central zone of the neck is mandatory for this malignant entity.[1,54] If a concurrent pheochromocytoma is discovered, it should be removed prior to thyroidectomy, as its activity might make the patient's perioperative course unstable and difficult to manage.[54]

PANCREATIC CELL TUMOR

Patients with pancreatic cell tumor (vasoactive intestinal polypeptide [VIP] tumor) classically present with Verner-Morrison syndrome: watery diarrhea, hypokalemia, and achlorhydria. They may also rarely present with flushing during attacks. These non-beta islet-cell tumors are derived from cells of the neuroendocrine lineage and may be associated with multiple endocrine neoplasia.[30] They secrete VIP, gastric inhibitory polypeptide, prostaglandin, and pancreatic peptides.[1,55,56] Major signs and symptoms include prolonged massive watery diarrhea, as well as symptoms of dehydration and hypokalemia, such as lethargy, muscle weakness, nausea, vomiting, abdominal pain, and cramping. Fewer than 50% of the patients have hyperglycemia or impaired glucose tolerance.[1,55,56]

VIP tumor is diagnosed by demonstrating a high plasma VIP level in the setting of stool volume greater than 1 L per day.[1] Serum chromogranin A may also be elevated in such patients.[30] Abdominal and pancreatic ultrasound, as well as computed tomography and aortography, should be performed to localize the tumor and metastases. Surgical consultation should be obtained, as surgical removal is curative in 50% of eligible patients.[1] Medical management may include streptozocin and 5-fluorouracil to decrease diarrhea and tumor mass.[1]

RENAL CELL CARCINOMA

Renal cell carcinoma may cause flushing via secretion of prostaglandins or via pituitary down-regulation from release of gonadotropins.[1,57,58] Renal cell carcinoma presents with the classic triad of gross hematuria, flank pain, and abdominal mass in fewer than 10% of affected patients, presenting with hematuria alone in 60%.[1] Fifty percent of patients experience systemic symptoms of fatigue, weight loss, and cachexia.[1] Patients may also have anemia, intermittent fever, erythrocytosis, eosinophilia, and leukemoid reaction.[1] Diagnosis involves intravenous pyelography, renal ultrasound, computed tomography, or magnetic resonance imaging of the pelvis.[58] Surgical consultation should be obtained, as the treatment of choice is radical nephrectomy.[1] In metastatic disease, chemotherapy, immunotherapy, or hormonal therapy may be appropriate treatment modalities.[1,58]

NEUROLOGIC DISEASE

A number of neurologic diseases may present with flushing reactions. Flushing has been reported in patients with Parkinson's disease, dysautonomia and orthostatic hypotension, migraines, multiple sclerosis, brain tumors, epilepsy, and spinal cord lesions that produce autonomic hyperreflexia.[1,8,59-69] Flushing in patients with Parkinson's disease, migraines, and multiple sclerosis is due to vasodilation and autonomic dysfunction.[1]

Furthermore, flushing due to damaged trigeminal nerves or migraine may be examples of the so-called

antidromic sensorineural flushing. Trigeminal ganglia are connected to blood vessels by nerve fibers that contain substance P. Activation of such fibers, either via thermocoagulation of the trigeminal nerve branches or possibly as a mechanism in migraine, might release substance P and cause vasodilation and dysesthesias (pain, burning, analgesia). Some patients with migraine may also have associated facial flushing or even "facial migraine," which includes episodic flushing, facial neuralgia, and lacrimation.[8]

Unilateral flushing may result from contralateral sympathetic nerve lesions that produce Horner syndrome—the triad of ptosis, miosis, and anhidrosis—which leads to contralateral (unaffected side) facial reddening.[4,36,70,71] Since thermal vasodilation in the major portions of the face is regulated by sympathetic vasodilator fibers and less predominantly by adrenergic vasoconstrictor fibers, the asymmetry of facial flushing in unilateral Horner syndrome probably stems from impaired sympathetic vasodilation and may be further intensified by active vasoconstriction (due to supersensitivity to circulating catecholamines) on the affected side,[36] which leads to contralateral reddening.

Auriculotemporal flushing (Frey syndrome) also presents as unilateral flushing, accompanied by heat and sweating, and results most often from misdirected regenerated parasympathetic fibers after injury to the parotid gland in adults. It has also been shown to follow facial trauma in an 11-year-old and in infants after perinatal trauma with the introduction of solid foods. These latter entities are benign and resolve spontaneously.[1,72-74]

Autonomic epilepsy, also known as diencephalic epilepsy, is a rare syndrome of paroxysmal and transient autonomic discharges that may present with paroxysmal flushing, tachycardia, and hypertension from catecholamine release, in addition to generalized seizures or loss of consciousness. Other signs may include pilomotor activation, salivation, dilated pupils, and spasms of the sphincters. Seizures may be preceded by an olfactory or epigastric aura. This diagnosis should be considered in all patients with a history of flushing and unconscious episodes or other epileptiform behavior.[5,8,64-66] Diencephalic epilepsy probably results from acute distension of the third ventricle, which activates autonomic centers that reside within its wall. This activation may occur in glioblastoma multiforme of the preoptic area, colloid cyst of the third ventricle, or any encapsulated tumor that presses on the thalamus. Flushing and seizures may be treated with clonidine or carbamazepine, or both.[8]

Autonomic hyperreflexia, common in spinal cord disease, can present as a triad of flushing, headache, and sweating. Other associated symptoms and findings include systemic hypertension, painful flexor or lower extremity spasm, and postural hypotension. Autonomic hyperreflexia occurs in 85% of patients with transverse spinal cord lesions and in more than 50% of patients with severe spinal cord injuries above the midthoracic level as a consequence of injured or disconnected autonomic pathways. Spinal cord lesions that produce flushing are most often in the lower cervical region and at the thoracolumbar junction, and result from vertebral column fracture or dislocation more often than from deep penetrating wounds. Flushing is due to vasomotor reflexes activated by neurogenic hypertension via pressor receptors in the aortic arch, carotid sinus, and cerebral vessels.[1,8,61-63]

In addition, orthostatic hypotension by itself can present with flushing and sweating. Finally, Streeten syndrome, which is a combination of orthostatic hypotension and hyperbradykinism, can present with facial erythema, orthostatic lightheadedness, hypotension, tachycardia, flushing that is most prominent while patients are in the recumbent position, and purple discoloration of the legs of patients in the upright posture.[8]

MEDICATIONS

Multiple medications may cause flushing via different mechanisms.[1,4,6-8,75-82] A partial list of some known culprit medications is provided in Table IV, and a more comprehensive list of medications is provided by Litt.[82] Calcium channel blockers, such as diltiazem and nifedipine, are vasodilators that relax the vascular smooth muscle to induce flushing directly.[4] Nicotinic acid and its analog, acipimox, increase synthesis of prostacyclin, a potent vasodilator that is used therapeutically for severe Raynaud phenomenon with digital ischemia; this effect is antagonized by concomitant administration of acetylsalicylic acid.[4] Multiple chemotherapeutic medications may cause flushing, but generally patients can build up tolerance to this effect over time.[7,75] Any drugs that cause anaphylaxis or anaphylactoid reactions may also induce flushing via the release of mast cell and basophil mediators, leading to vasodilation associated with hypotension, dyspnea, wheezing, urticaria, and angioedema.[4] Finally, multiple drugs or drug metabolites may trigger the release of various mediators directly or indirectly.[1] Usually the temporal relationship between the medication and flushing is clear.[4]

ALCOHOL

Alcohol may cause flushing directly via its vasodilatory effects or via its metabolite, acetaldehyde, a potent trigger of flushing.[81] Acetaldehyde is

Table IV. Medications associated with flushing (partial list)

All vasodilators: nitroglycerin and nitric oxide releasers; sildenafil citrate; amyl nitrite, butyl nitrite (recreational drugs)
All calcium channel blockers: nifedipine, verapamil, diltiazem
Oral triamcinolone
Intrasynovial triamcinolone
High-dose pulse methylprednisolone
Beta-blockers
Angiotensin-converting enzyme inhibitors
Morphine and other opiates
Catecholamines
Prostaglandins D_2, E
NSAIDs
Enkephalin analogs
Nicotinic acid
Nicotine
Cholinergic drugs
Bromocriptine
Chemotherapeutics: tamoxifen, cyclosporine, doxorubicin, mithramycin, dacarbazine, cisplatin, interferon alfa-2, flutamide
Antiemetics: alizapride, metoclopramide
Contrast media
Leuprolide
Cyproterone acetate
Vancomycin
Rifampin
Calcitonin gene-related peptide
Thyrotropin-releasing hormone
Combination anesthesia of isoflurane and fentanyl
Caffeine withdrawal

Table V. Industrial solvents that, combined with alcohol, may cause flushing

Trichloroethylene vapor
n,n-Dimethylformamide
n-Butyraldoxime in the printing industry
Carbon disulfide
Xylene
Thiuram derivatives in the rubber industry

Data from Mooney.[6]

Table VI. Medications that, combined with alcohol, may cause flushing

Disulfiram
Disulfiram-like substance in fungus *Coprinus atramentarius*
Chlorpropamide
Metronidazole
Ketoconazole
Griseofulvin
Cephalosporins
Chloramphenicol
Antimalarials
Calcium carbamide
Phentolamine
Quinacrine
Benorylate
Tacrolimus (topical)

Data from Mooney.[6]

further metabolized by aldehyde dehydrogenase. Some people of Asian backgrounds may have a deficiency of aldehyde dehydrogenase-2 and develop severe flushing from the buildup of acetaldehyde after alcohol consumption.[4,83,84] An acquired enzyme deficiency may lead to flushing in Hodgkin's lymphoma and in hypereosinophilic syndrome.[81] Similarly, inhibition of aldehyde dehydrogenase by disulfuram may cause violent flushing, nausea, vomiting, hypotension, and, in rare cases, death.[4] Some Japanese patients deficient in aldehyde dehydrogenase may develop flushing in the absence of any other precipitants.[4] Flushing may also result from the combination of alcohol and various occupational exposures (Table V) and the combination of alcohol and other medications (Table VI).[1,6-8]

Coadministration of chlorpropamide with alcohol may cause flushing and should be considered in patients with flushing who also present with lightheadedness or dizziness and hypoglycemia.[5,76,85] The association between flushing and coadministration of sulfonylurea agents with alcohol is well described, and an estimated 10% to 30% of patients who use oral hypoglycemic agents may experience at least mild symptoms after alcohol ingestion.[5] Flushing generally starts 3 to 10 minutes after alcohol ingestion and reaches maximal intensity within 15 minutes. Episodes usually last for approximately 1 hour but may last longer. Chlorpropamide affects the intermediate metabolism of ethanol after it is converted to acetaldehyde. Chlorpropamide-alcohol flush is differentiated from flushing due to other causes by timing and duration of episodes and lack of hypotension, hypertension, syncope, and diarrhea.[5] Hypoglycemia itself may cause flushing.[86]

Finally, application of topical tacrolimus ointment to the face in patients with atopic dermatitis or steroid-exacerbated rosacea predisposes such patients to alcohol-induced facial flushing. The mechanism for this phenomenon is unclear,[87,88] but aspirin has been shown to inhibit this reaction.[89]

RARE CAUSES

Other rare causes of flushing include sarcoidosis, especially the lupus pernio variant, wherein the

diffuse granuloma underlies dilated blood vessels[1]; mitral stenosis, which may cause a malar flush with cyanosis due to an uncertain mechanism[4]; "dumping syndrome," a constellation of facial flushing with tachycardia, sweating, dizziness, weakness, and gastrointestinal disturbances that occurs in patients after gastric surgery upon ingestion of food or hot fluid or upon infusion of hypertonic glucose[1,8,90]; androgen deficiency in men after testicular injury, after orchiectomy, or due to pituitary tumor[91,92]; acute arsenic intoxication[93]; POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes)[94]; basophilic granulocytic leukemia, via increased histamine production and associated with symptoms of wheezing, urticaria, diarrhea, and pruritus[6,95]; bronchogenic carcinoma, possibly via overproduction of adrenocorticotropic hormone[96,97] or VIP[6]; malignant histiocytoma, neuroblastoma, and ganglioneuroma, wherein flushing also may be related to increased production of VIP[6]; postherpetic gustatory flushing and sweating in the distribution of the scarred trigeminal nerve[8]; surgeries in the periaortic region that involve traction on the mesentery and thus may provoke prostacyclin release[7,98]; Leigh syndrome, also known as subacute necrotizing encephalomyelopathy, which may have a prodrome of flushing that turns to pallor, sweating, drowsiness, lethargy, and restlessness, and is associated with increased levels of endorphins in the brain and spinal fluid[6]; and Rovsing syndrome in patients with horseshoe kidney that may present with flushing, abdominal pain, and nausea, all of which are relieved by the anteflexed position.[6,8] Flushing may also be a feature of homocystinuria,[99] which typically presents with malar flushing, and of hyperthyroidism.[100]

UNEXPLAINED FLUSHING AND PSYCHIATRIC DISEASE

Unexplained flushing has been studied by several groups and may be related to underlying psychologic or psychiatric disease. For example, anxiety may present with hot flashes and sweating. Anxiety is the most common symptom in psychiatric disease and occurs as part of most psychiatric syndromes, especially the depressive types.[1,101] Panic attacks may present with hot or cold flushes and discrete periods of apprehension or fear; other symptoms may include dyspnea, palpitations, chest pain, choking, paresthesias, feelings of unreality, faintness, trembling, and fear of dying or doing something uncontrollable during an attack.[5] Panic disorder is common, affecting 2% to 5% of the general population; occurs mainly in women (80%), with onset from 17 to 30 years of age; and follows a chronic and fluctuating course.[5]

Aldrich and colleagues have described the entity "idiopathic flushing," which may be related to undiagnosed psychologic disease because of its symptomatology and lack of an organic cause. Flushing occurred mainly in younger women and was marked by a longer duration of symptoms, as well as associated symptoms of palpitations, syncope, and hypotension, in comparison with flushing in CS patients. While the latter group had more wheezing and abdominal pain, both groups had diarrhea and increased plasma serotonin.[5]

In addition, Friedman and colleagues studied a series of patients with recurrent unexplained flushing. Patients had an exaggerated flush of the face and upper portion of the chest, occasionally associated with tachycardia, mild hypertension, and tachypnea. Flushing attacks lasted 15 minutes to 2 days, and other symptoms included anxiety, chest tightness, paresthesia, slurred speech, weakness, pruritus, abdominal cramps, and increased stool frequency.[3] These patients were predominantly women, with a mean age of 30 years, in whom mastocytosis or unexplained anaphylaxis had been previously diagnosed clinically. Administration of steroids, NSAIDs, or antihistamines provided minimal benefit.[3] At further investigation, somatization or mood disorder was diagnosed in 70% of these patients (86% with somatization). The authors postulated that the association of flushing with abdominal cramps and psychiatric complaints may represent a reaction to a released mediator, such as prostaglandin D_2, but no such laboratory proof had been obtained.[3]

Management of unexplained flushing should include elimination of the diagnosis of CS, mastocytosis, anaphylaxis, and other potentially life-threatening causes, and a reexamination in 6 to 12 months to determine whether symptoms are worsening and require further studies.[3] If symptoms are not progressive, no further studies may be necessary. For patients who present with unexplained flushing after organic causes have been eliminated, psychiatric consultation may establish an underlying cause, which may be treatable.

WORKUP

History and physical examination are critical in the proper evaluation and management of flushing and should be supplemented with other tests on the basis of patient presentation. The salient features of the most common and the most serious causes of flushing, as well as pertinent laboratory and diagnostic tests, are summarized in Table III and outlined in Figure 1. In the workup of flushing, it may be useful to divide reactions into "wet flushes," or those accompanied by sweating, and "dry flushes."[8] Wet

flushing indicates autonomic hyperactivation, while dry flushing usually results from agents that act directly on vascular smooth muscle. In cases of dry flushing, the presence of associated pain or burning sensation suggests antidromic sensorineural-mediated flushing such as that in migraine or that due to damaged trigeminal nerves. If there is no dysesthesia, then flushing is likely due to exogenous or endogenous mediators, such as those associated with foods, medications, or systemic diseases.[8]

One expert recommends that patients keep a diary for 2 weeks, documenting the timeline of flushing reactions, their qualitative aspects, associations (dyspnea, bronchospasm, lightheadedness, low blood pressure, tachycardia, abdominal cramps, diarrhea, headache, urticaria, pruritus), and all exogenous agents (food, drugs, physical exertion, alcohol, emotion, stress, occupational exposures). This practice may be especially helpful in cases in which the cause is particularly difficult to discern.[8] Vague complaints should arouse suspicion for anxiety, depression, and somatization disorders. If there is associated urticaria and pruritus, histamine-mediated reactions (mastocytosis, vancomycin, other mast cell–degranulating agents, etc.) should be considered.[8]

For further details of a proposed workup algorithm, please refer to Figure 1.

SUMMARY

The differential diagnosis of cutaneous flushing is extensive and encompasses a variety of benign and malignant entities (Table II). Most flushing reactions result from benign causes. However, since flushing may be the presenting sign or symptom of several life-threatening conditions, it should prompt a thorough investigation to exclude such possibilities as anaphylaxis, systemic mastocytosis, carcinoid syndrome and other malignant tumors, pheochromocytoma, and autonomic epilepsy after more common benign causes have been ruled out and if there is no response to treatment. In the absence of an identifiable benign organic cause of flushing, psychiatric illness must be suspected and the patient should undergo appropriate evaluation. History and physical examination are critical in the evaluation of the cause of flushing and should be supplemented with laboratory and other investigations based on the clinical suspicion of an underlying cause. The most common causes of flushing—fever, emotional flushing, climacterium, and rosacea—are obvious to most physicians and thus are likely to be promptly recognized and treated appropriately. Dermatologists have a unique role in the management of patients with flushing, as referred patients may be unresponsive to conventional therapy and are more likely to have a serious or life-threatening underlying cause. Accordingly, proper workup, recognition, and management of conditions that cause cutaneous flushing may have a significant impact on the patients' morbidity and mortality.

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