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Red face revisited: Flushing

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Abstract The term *red face* is reserved for lesions located exclusively or very predominantly on the face that result from changes in cutaneous blood flow triggered by multiple different conditions. Facial erythema may not only present clinically as a distinct entity, but can also be a sign of other diseases. Patients with a red face challenge clinicians to consider a broad differential diagnosis. Diagnosis is based on date and mode of appearance, characteristics of the erythema, functional signs, and associated systemic manifestations. In most cases, the cause is a benign disease such as rosacea, contact dermatitis, photodermatosis, and climacterium, and a thorough history and physical examination is enough to make a diagnosis; facial erythema may also present as a symptom of drug allergies, cardiac disease, carcinoid syndrome, pheochromocytoma, mastocytosis, and anaphylaxis, as well as some rare causes such as medullary carcinoma of the thyroid, pancreatic cell tumor, and renal carcinoma where further laboratory, radiologic, or histopathologic studies are required. In this review, the mechanisms of flushing, its clinical differential diagnosis, and management of various conditions that cause flushing are discussed.

Introduction

Red is considered the color of emotion, and a red face or the phenomenon of cutaneous flushing has attracted attention for millennia. Balzac and Proust both described blotchy red faces admirably in their novels, and erythema in the blush area is detected in numerous archaeologic artifacts; however, the color red on the face remains ambivalent because a red face is a handicap in social relations and causes significant discomfort to the person who blushes.

The term *flush* was first used by E. J. Tilt in 1882 as a short and expressive word for this phenomenon.[1] With major advances in pharmacology and physiology, the mechanism of flushing was described in detail in the latter part of the 20th century. Heterogeneous pharmacologic and physiologic reactions are responsible for flushing reactions. Tyramine, histamine, sulfites, nitrites, alcohol, 5-hydroxytryptamine (5-HT), substance P, prostaglandins, and catecholamines are some of the proposed mediators of flushing.[1–4]

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Flushing may be defined as a sensation of warmth accompanied by visible reddening of the skin.[1] Flushing is a phenomenon of transient vasodilation, which is part of a coordinated physiologic thermoregulatory response to hyperthermia, resulting in increased cutaneous blood flow. The erythema is most prominent in the blush area, which includes face, ears, neck, and upper chest. The reason for this predilection is 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.[1,2,5]

Flushing can be episodic or constant. Generally, endogenous vasoactive mediators or drugs are responsible for episodic attacks, and repetitive episodes over long periods may result in a fixed facial erythema with telangiectases. Development of large cutaneous blood vessels that contain slow-flowing deoxygenated blood may cause a cyanotic hue.[1]

Various benign and malignant entities may cause flushing. The most common reasons for flushing are fever, hyperthermia, menopause, emotional blushing, and rosacea. Flushing caused by tumors (medullary carcinoma of the thyroid, pancreatic islet-cell tumors, and renal cell carcinoma [RCC])

is rare except for carcinoids and tends to occur in the advanced stages of the disease. Differential diagnosis of flushing is summarized in Table 1.

Common causes

Fever

Fever is the most common cause of hot flushes, particularly when associated with night sweat. If the temperature elevation is detected by taking the oral temperature during the attack, then the cause of the fever should be ascertained. Infectious and noninfectious causes may be revealed following a fever workup.[2]

Benign cutaneous flushing

Benign cutaneous flushing can be secondary to emotional status, foods, alcohol, or exercise. It is most commonly seen in women, and a feeling of warmth frequently accompanies cutaneous changes. Anxiety is the most common psychiatric cause of sweating and hot flashes. Although most people do not seek medical care for emotional flushing, it is one of the most common causes of flushing reactions. One must think of emotional flushing if episodes of flushing are triggered by emotional upset or feelings of embarrassment. Useful therapy for flushing accompanying normal emotional response includes biofeedback, hypnosis, or paradoxical intention. Nadolol, a nonselective beta-blocker that can attenuate the vascular response caused by anxiety in many patients, is considered to be another useful therapy, although the effectiveness of beta-blockers to treat emotional flushing is largely anecdotal.[1–3]

Foods or beverages, especially spicy foods that contain capsaicin, the active agent in red pepper, and alcohol may provoke flushing. Tyramine, histamine, monosodium glutamate, nitrites, sulfites, and higher chain alcohols are responsible in food-induced flushing reactions. In some cases, headache and wheezing can accompany flushing.[1,2,4] Eating could lead to flushing reactions through various mechanisms. Hot beverages cause flushing through countercurrent heat exchange mediated through the thermoregulating center of the anterior hypothalamus.[2]

A usually transient facial flushing response may be observed, particularly with acute alcohol ingestion. The sensitivity to ethanol-induced flushing varies among people with different ethnic backgrounds. Increased sensitivity is frequently seen in a variety of Mongoloid populations, especially Chinese, Japanese, and a few Native American groups.[2,6] Flushing generally starts 3 to 10 minutes after alcohol ingestion and reaches maximal intensity within 15 minutes as a result of a temporary increase of blood supply to facial skin caused by vasodilation.[1,7] People with facial flushing response secondary to alcohol ingestion are reported to be more prone to metabolic syndrome.[7,8]

Flushing secondary to exercise is the result of hyperthermia, and cooling is usually enough to resolve the problem.

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

Table 1 Differential diagnosis of flushing

Common Causes
Fever
Benign cutaneous flushing
Rosacea
Climacteric flushing
Uncommon, Serious Causes
Carcinoid syndrome
Pheochromocytoma
Mastocytosis
Anaphylaxis
Other Causes
Medullary thyroid carcinoma
Pancreatic cell tumor (VIPoma)
Renal cell carcinoma
Neurologic flushing
Medications

Rosacea

Rosacea, a common cause of flushing, is a chronic inflammatory disorder of the facial skin characterized by periods of exacerbation, remission, and possible progression. Transient or persistent central facial flushing, erythema, visible blood vessels, and often papules and pustules are hallmarks of the disease. The principle subtypes include erythematotelangiectatic rosacea, which usually presents with flushing and redness, papulopustular rosacea, phymatous rosacea, and ocular rosacea. It is still not clear whether these subtypes represent a developmental march of different stages or are merely part of a syndrome that develops independently but overlaps clinically. Regarding the pathogenesis, several hypotheses have been proposed, including genetic and environmental factors, vascular abnormalities, dermal matrix degeneration, and microorganisms such as *Demodex folliculorum* and *Helicobacter pylori*. Innate immune mechanisms and dysregulation of the neurovascular system are involved in rosacea initiation and perpetuation, although the complex network of primary induction and secondary reaction of neuroimmune communication is still unclear. A recent study suggests a central role of the antimicrobial peptide cathelicidin and its activator kallikrein-5 by eliciting an exacerbated response of the innate immune system. Rosacea also may result in fibrotic facial changes, suggesting a strong connection between chronic inflammatory processes and skin fibrosis development.[9–13]

With the absence of specific histologic and serologic markers, the diagnosis of rosacea is based on clinical findings. For a diagnosis of rosacea, one or more of the following primary features concentrated on the convex areas of the face are required: flushing (transient erythema, which may last longer than 10 minutes); nontransient (persistent) erythema, which usually lasts longer than 3 months and tends to spare periocular skin; papules; pustules; and telangiectasia. Secondary features include burning or stinging, edema, plaques, a dry appearance, ocular manifestations, peripheral locations, and phymatous changes. A dramatic history of flushing in response to hot drinks, alcohol, spicy foods, temperature changes, hot baths or showers, emotional disturbance, exercise, and some topical products can be obtained.[9,14]

When evaluating patients with rosacea, it is important to exclude the diagnoses of acne vulgaris, steroid rosacea, seborrheic dermatitis, perioral dermatitis, contact dermatitis, photosensitive eruption, lupus erythematosus, mixed connective tissue disease, CS, systemic mastocytosis (SM), or polycythemia vera.[9,14]

A number of therapies are available to treat rosacea, some of which can be used in combination; however, the cure for rosacea remains elusive, and all currently used medications are for symptomatic control only. The nonpharmacologic approach to therapy is adequate skin care, trigger avoidance, and photoprotection. Topical medications include metronidazole, clindamycin, erythromycin, sulfa-based washes, benzoyl peroxide, azelaic acid, tretinoin, and tacrolimus. Among these, metronidazole, azelaic acid, and sodium sulfacetamide are FDA approved. 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; and isotretinoin for phymatous or treatment-resistant rosacea.[15] Light-based therapies with pulsed dye laser and intense pulsed light are effective in the treatment of erythema and telengiectasias.[16,17]

Climacteric flushing

Climacteric flushing effects 50% to 85% of women who undergo menopause. The hot flush associated with menopause is a unique symptom and causes considerable distress and impairment of quality of life. Various situations such as stress, sudden temperature changes, alcohol, caffeine, or any warm drink can trigger hot flushes. Subjective features usually start with a sudden sensation of warmth especially in the upper body or back, often accompanied by sweating and reddening of the skin and sometimes palpitation. These episodes are frequently followed by chills and a sense of anxiety. The duration of the episodes ranges from 30 seconds to 60 minutes, with a mean between 3 and 5 minutes. The frequency of flushes varies between individuals, ranging from a few per month to several per hour. Nocturnal flushes may cause insomnia, which leads to fatigue and irritation. Climacteric flushing normally subsides in months to several years, but in rare instances can persist for up to 30 years. In 25% of patients, hot flushes will continue for more than 5 years.[1,2]

Although precise causes are not fully understood, hormonal changes and a disturbance of the temperature-regulating mechanism, which is situated in the hypothalamus, are implicated in the pathogenesis. Hormonal cause seems likely in view of the well-proven clinical value of estrogen therapy in eliminating hot flushes; however, the absence of hot flushes in prepubertal girls who have low circulating estrogen levels and hot flushes that occur in pregnancy when there is a high level of estrogen production leads to questions about the precise role of estrogens. There is no apparent difference in the estrogen levels of women who flush compared with those who do not.[18]

For women with mild hot flushes, keeping the core body temperature cool, avoiding alcohol, caffeine, and spicy foods, taking regular exercise, and using paced respiration may be useful in reducing the frequency and severity of the attacks. Phytoestrogens, black cohosh, and acupuncture are some of the alternative therapies that do not appear to have any significant benefit over placebo. In some clinical trials, gabapentin, oxybutynin ER, desvenlafaxine, soy-derived isoflavones, and black cohosh showed a clinically meaningful treatment effect. Among these five compounds, only gabapentin demonstrated consistent and statistically significant benefit over placebo in all of its well-designed, randomized clinical trials.[1,19]

Clonidine, an alpha-adrenergic agonist that may reduce peripheral vascular reactivity is an alternative licensed medication. Several randomized controlled studies have shown a reduction in the frequency and severity of hot flushes, but adverse effects such as dry mouth, visual disturbance, drowsiness, and insomnia are common. Patients with severe and frequent flushes usually need specific hormone replacement therapy. The use of the lowest effective estrogen dose and the shortest duration is recommended. When combined with a progestogen, the effects seem to be greater.[1,18]

Uncommon, serious causes

Carcinoid syndrome

Neuroendocrine tumors of the digestive system can cause diverse clinical symptoms. CS, which can be seen in 10% to 18% of patients with neuroendocrine tumors,[20] is one of the most important entities in the differential diagnosis of flushing because of the malignant nature of tumors and the relatively high mortality rate. Carcinoid tumors are most commonly encountered in the gastrointestinal tract, with the majority affecting the ileum,[21] but may also be found in the bronchus, pancreatic islets, and retroperitoneum.[22]

Lubarsch first described a patient with multiple ileal carcinoids in 1888, but regarded them as carcinomas. The classical symptomatology of the CS in a patient with an ileal carcinoid tumor and hepatic metastasis was described in 1890 by Ransom. The term *karzinoide* was first used by Obendorfer in 1907. Williams and Sandler classified carcinoids according to their embryologic site of origin in 1963.[23] CS, first described by Biorck in the 19th century, classically presents with a triad of flushing, gastrointestinal hypermotility (abdominal cramping and diarrhea), and right-sided cardiac failure caused by valvular disease.[1,2] Episodic cutaneous flushing is the most frequent clinical sign, appearing in 85% of patients at some time during the disease.[2,24,25]

The flushing of CS primarily involves the face, neck, and upper chest. Carcinoid tumors originating in the midgut (appendix, ileum, jejunum) produce what is known as the classical carcinoid flush, which is a rapid-onset cyanotic flush lasting approximately 20 to 30 seconds and associated with a mild burning sensation. Foregut carcinoids (stomach, lung, pancreas, biliary tract) produce a brighter pinkish red flush that may be pruritic and can be more difficult to differentiate from physiologic flushing.[24–26] As the disease progresses, the episodes may last longer, flushing may become diffuse and cyanotic, and the patients may develop thick skin changes with venous telangiectasia and bluish coloration of the chin, nose, and malar areas.[2] Prolonged vasodilation can cause purplish vascular lesions commonly seen on the nose, upper lip, and malar areas. Venous telangiectasia is a late feature of CS.[26]

Severe flushes are accompanied by a decline in blood pressure and increase in pulse rate. Flushing episodes in CS may occur spontaneously or may be provoked by food (fermented foods and chocolate), alcohol (especially sherry and beer), defecation, abdominal palpation, anesthetic agents, or emotional events. Carcinoid flushing is often associated with diarrhea and breathlessness or wheeze, and these associated symptoms are a method of differentiating the flushing of carcinoid from physiologic flushing.[24–26]

Carcinoid tumors typically produce large amounts of serotonin. In addition, they may also secrete histamine, corticotropin, dopamine, substance P, neurotensin, prostaglandins, kallikrein, and tachykinins, which are inactivated by the liver. Patients with carcinoid tumors in the gastrointestinal tract develop CS only if they have hepatic metastases leading to secretion of the substances into the hepatic veins.[24,26] In contrast, bronchial and other extraintestinal carcinoids, the bioactive products of which are not immediately cleared by the liver, can cause CS in the absence of hepatic metastases because of their direct access to the systemic circulation.[25]

Midgut carcinoids contain enzyme dopa decarboxylase, which converts 5-hydroxytryptophan into serotonin (5-HT). Carcinoids of the foregut and hindgut do not secrete 5-HT and lack dopa decarboxylase. 5-HT is metabolized by the liver and excreted in urine as 5-hydroxyindolacetic acid (5-HIAA).[26] 5-HT is a potent vasodilator, but its administration in humans causes not flushing but diarrhea; substance P is secreted by most carcinoids, and systemic infusion causes flushing, hypotension, and tachycardia.[1,2]

Carcinoid tumors commonly present with obscure clinical features and require numerous investigations before an accurate diagnosis can be established. Symptom-based clinical diagnosis must be confirmed with biochemical tests. In the presence of classical clinical symptoms, specific peptides and amines should be measured.[26] The most specific test is a measurement of 24-hour urine levels of 5-HIAA. The test for urinary 5-HIAA has a sensitivity of 75% and a specificity of 88%; values of twice normal are highly suspicious of CS. Levels greater than 25 mg per 24 hours are indicative of the diagnosis[2]; however, ingestion of large amounts of tryptophan- and serotonin-rich foods such as bananas, avocados, and tomatoes can increase urinary 5-HIAA and lead to false-positive results.[1,24–26] Serum chromogranin A is another commonly used diagnostic test, with a sensitivity up to 99%. Plasma chromogranin A is a sensitive but not a specific marker for carcinoid tumors because it may be elevated for several other neuroendocrine tumors, as well as in patients with renal and liver failure, inflammatory bowel disease, or in patients on proton pump inhibitors.[24]

Once confirmed by biochemical testing, usually by an elevated 24-hour excretion of 5-HIAA, localization of the primary tumor and any metastasis must be done. Several different imaging modalities can be used, among which octreotide scintigraphy is the first choice, with an overall sensitivity of 80% to 90%. This technique allows imaging of the entire body in one session and identifies occult primary and metastatic deposits.[22,24]

The administration of long-acting analogs of somatostatin (octreotide and lanreotide) can control the symptoms of flushing and diarrhea in 70% to 80% of patients by reducing the secretion of vasoactive mediators. Somatostatin analogs are not only the most effective drugs for symptomatic treatment, but they can also stabilize tumor growth for many years and less frequently, may produce tumor regression. Other medical treatments used in metastatic carcinoid include interferon-alpha and chemotherapy agents, both with controversial and limited results. Surgery is the only curative treatment, but it is only possible with nonmetastatic disease or in resectable nodal or hepatic metastases.[24,26–28] The patient should be advised to avoid triggers of flushing episodes, such as alcohol ingestion, spicy foods, and specific forms of physical activity that involve pressure or trauma to the right upper quadrant.

Pheochromocytoma

According to Lenders et al,[29] "Pheochromocytomas are catecholamine-producing neuroendocrine tumors arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia." In 2004, the World Health Organization defined

a pheochromocytoma as an intra-adrenal paraganglioma, whereas closely related tumors of extra-adrenal sympathetic or parasympathetic paraganglia are classified as extra-adrenal paragangliomas. In general, about 80% of pheochromocytomas are located in the adrenal medulla.[30] Approximately 10% of pheochromocytomas are malignant.[31]

Main signs and symptoms of catecholamine excess include hypertension, palpitations, headache, sweating, and pallor. Less common signs and symptoms are fatigue, nausea, weight loss, constipation, flushing, and fever. According to the degree of catecholamine excess, patients may present with myocardial infarction, arrhythmia, stroke, or other vascular manifestations.[30] Hypertension occurring in patients with pheochromocytomas is sustained in about 50% and paroxysmal in the remainder; however, many patients remain normotensive. Hypertension attacks may be precipitated by physical activity, postural changes, anxiety, certain foods or wine, some drugs, and operative procedures.[32]

The increased production of catecholamines is thought to be the reason for flushing in pheochromocytomas. Increased catecholamines may trigger vasodilation and flushing. A general blood pressure lability and episodes of increased cardiac output in these patients may also play a part in the flushing reaction, as well as some other flushing mediators that can be released from these tumors such as calcitonin gene–related peptide, vasoactive intestinal polypeptide, and adrenomedullin.[1]

The laboratory workup of patients with pheochromocytoma has traditionally focused on biochemical measurements of tumor secretory products or their metabolites, with ultimate diagnosis resting on routine histopathology and immunohistochemistry.[33] The diagnosis of pheochromocytomas depends mainly on the demonstration of catecholamine excess by 24-hour urinary catecholamines and metanephrines or plasma metanephrines.[34]

Once pheochromocytoma is diagnosed, localization should be undertaken. They are localized by a computed tomography scan and magnetic resonance imaging of the adrenal glands and abdomen; complementary ^{123}I-metaiodobenzylguanidine scintigraphy and ^{18}F-dihydroxyphenylalanine-positron emission tomography are available. Because approximately one of four pheochromocytomas turn out to be a hereditary entity, screening for genetic alterations is important. Laparoscopic and adrenal-sparing surgical intervention after preoperative alpha-blockade is the treatment of choice and is usually curative. In malignant pheochromocytomas, radiotherapy and chemotherapy are palliative treatment options.[2,34,35]

Although pheochromocytomas are an unusual cause of flushing, the dermatologist needs to consider this diagnosis in the appropriate circumstances, especially in the presence of hypertension and palpitation accompanying flushing.

Mastocytosis

Mastocytosis, an important cause of flushing reactions, is a group of rare disorders that affect adults and children, defined by abnormal growth and accumulation of clonal mast cells. Symptoms are typically related to mast cell mediator release. The mediators found within mast cells are classified as preformed mediators (histamine, serotonin, heparin, chondroitin sulfate, neutral proteases, major basic protein, acid hydrolases, peroxidase, and phospholipases), lipid mediators (LTB4, LTC4, LTE4, PGD2, and PAF), cytokines, chemokines, and growth factors.[36,37] 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.[1]

Mastocytosis can be limited to the skin, referred to as cutaneous mastocytosis (CM), or involve extracutaneous tissues, called SM. CM may present with skin lesions of urticaria pigmentosa, consisting of reddish brown macular, papular, nodular, or plaquelike lesions that urticate (Darier sign), diffuse CM, or mastocytomas.[25] In the pediatric population, urticaria pigmentosa is the most frequent type, whereas systemic complaints and peripheral blood abnormalities are more prominent in adults.[1,38] In most cases, CM in children appears in the first year of life and is typically not associated with systemic symptoms.[37]

Patients with mastocytosis tend to experience symptoms in discrete attacks when mast cell mediators are released. Clinical findings and course are highly variable interindividually and intraindividually. In CM, pruritus, erythema, and wheals after mechanical irritation of the skin is typical. Systemic complaints are the consequence of extensive skin infiltrates of mast cells, and they are the result of intensive histamine release.[36,37] If there is gastrointestinal involvement, patients may experience abdominal pain, diarrhea, nausea, vomiting, peptic ulcer disease, and gastrointestinal bleeding. Bone marrow involvement, commonly seen in adult cases of mastocytosis, can lead to anemia. Long bones and the spine are frequently affected, and osteopenic or osteolytic lesions with low bone density can be seen.[25]

Stimuli of mast cell release can lead to anaphylactic reactions with severe, prolonged hypotension. Anaphylactic reactions can be seen in all forms of mastocytosis.[36] Wasp or bee stings are the most common triggers of acute reactions. Other direct, nonimmunologically, pharmacologically mast cell–activating drugs, foodstuffs, radiologic contrast media containing ionic iodine, and substances administered during general anesthesia such as muscle relaxants, as well as massive physical stimuli, are further possible triggers of acute anaphylactic reaction in mastocytosis.[37]

The intensity of skin involvement is variable. Urticaria pigmentosa is the most common type of mastocytosis in children and adults.[25] Lesions of urticaria pigmentosa develop primarily on the upper and lower extremities, followed by the thorax and abdomen. The head, palms, and soles are usually spared; but in children, scalp and lateral face are typically involved. The lesions in children are usually larger than in adults.[37] Pruritus associated with urticaria pigmentosa is exacerbated by changes in temperature, local friction, ingestion of hot beverages, spicy food, ethanol, and

certain drugs such as narcotic analgesics and systemic anesthetic agents. Bullous eruptions with hemorrhage can also be seen.[25]

Solitary mastocytomas occur almost exclusively in children and are found on the trunk and limbs, occur before 6 months of age, and are rarely associated with blistering.[37] Multiple lesions can occur as well. Lesions are similar in quality to those of urticaria pigmentosa, but can be larger. Flushing may be seen during the course. Spontaneous involution is frequently observed.[25]

Diffuse CM is the result of a diffuse mast cell infiltration in the dermis, sometimes involving the whole skin. This type presents before 3 years of age. The skin may be normal in color or yellowish brown, with an increased thickness. Discrete lesions are not seen.[25]

SM is a clonal and disseminated condition, most commonly seen in adults. SM can be divided in four subcategories: (1) indolent SM; (2) SM associated with another clonal, hematologic non–mast cell lineage disease; (3) aggressive SM; and (4) mast cell leukemia.[39] Symptoms of SM can be divided into skin symptoms, mast cell release symptoms, and symptoms caused by noncutaneous organ infiltration. Skin symptoms are predominant, and the most common picture is urticaria pigmentosa, occurring in 90% of patients with SM. Pruritus is the most common complaint provoked by the same triggers as in urticaria pigmentosa.[40]

The diagnosis of CM and a mastocytoma can usually be made based on history and careful clinical examination. Diagnostic hallmarks are biopsies from skin and bone marrow using tryptase antibodies for staining, as well as serum tryptase levels. Serum tryptase is usually normal in patients with CM (<20 ng/mL), but almost invariably greater than 20 ng/mL in those with SM. If tryptase levels are greater than 30 ng/mL, the likelihood of SM is 90%. When SM is suspected, abdominal sonography or computed tomography scan and a bone computed tomography scan can be performed.[1,37,41]

Skin biopsy typically reveals dense, often perivascular and periadnexal aggregates of mast cells within papillary dermis extending into reticular dermis. Mast cells within skin biopsies show a characteristic spindle shape with metachromatic granules. Special stains such as Giemsa or toluidine blue to identify the specific metachromatic granules should always be performed to differentiate mast cells from other spindle cells like fibroblasts. Immunohistochemical staining with antibodies toward tryptase is more sensitive.[36,37]

Patients with disease limited to the skin generally have a benign course. Childhood mastocytosis often resolves spontaneously before adolescence and has a good prognosis. Progression to SM with extracutaneous organ involvement is not common.[42] In contrast, skin lesions are generally persistent in adults, and spontaneous regression is seen in only 10% of patients. Because adult-onset mastocytosis is almost always associated with bone marrow involvement, hematologic consultation should be obtained.[1,43]

With the exception of excision of isolated mastocytomas, a curative treatment is not yet available for mastocytosis. Treatment can be divided into four stages: (1) comprehensive information of the patient or relatives concerning disease prognosis, risks, and avoidance of precipitating factors; (2) active and proactive treatment of acute mast cell mediator–induced symptoms; (3) therapy of chronic symptoms and disease sequela; and (4) attempt at mast cell reduction in progressive forms of mastocytosis.[37]

Treatment must be tailored to each patient's specific symptoms and organ involvement. Histamine receptor blockers (H1 and H2) along with cromolyn are effective for pruritus and for episodes of flushing, diarrhea, or abdominal pain.[36,37] Topical corticosteroids are effective at decreasing the number of skin mast cells, as well as psoralen ultraviolet radiation and ultraviolet A1 (UVA1) phototherapy.[25,36,37] Bone disease caused by marrow involvement can be treated similarly to osteoporosis of other causative factors, with calcium, vitamin D, and biphosphonates. Patients with anaphylactic reactions are treated with epinephrine.[36]

For patients with systemic disease, therapy is largely palliative. SM still remains incurable. Supportive therapy with oral H1 antihistamines, epinephrine, cromolyn sodium, short courses of prednisone, or psoralen ultraviolet radiation therapy have been used with different levels of success. Cytoreductive treatments such as interferon-alfa and cladribine are reserved for patients with more aggressive disease.[39]

Mastocytosis should always be suspected in patients who present with a constellation of symptoms, including flushing, abdominal pain, diarrhea, unexplained syncope, and classic urticaria pigmentosa lesions.

Anaphylaxis

Anaphylaxis is a rare, potentially life-threatening systemic allergic reaction with symptoms ranging from mild flushing to upper respiratory obstruction with or without vascular collapse. Early recognition of symptoms with prompt institution of therapy is central to a successful outcome.[44] The clinical manifestations are the result of vasoactive mediators from mast calls and basophils, and include urticaria, angioedema, hypotension, tachycardia, wheezing, stridor, pruritus, nausea, vomiting, flushing, diarrhea, dysphagia, light-headedness, and loss of consciousness.[45] Onset of episodes may be triggered by physical factors, such as pressure, cold, heat, or exercise, or no precipitating agent or event can be detected. Approximately one third of all cases are idiopathic.[46]

Diagnosis is based on clinical and laboratory findings. Serum tryptase or urine histamine or its metabolite are found to be elevated. A detailed and focused history, examination, and follow-up will help to make a differential diagnosis between anaphylaxis and disorders that mimic anaphylaxis, such as indolent SM, CS, pheochromocytoma, hereditary angioedema, acquired C1 esterase inhibitor deficiency, or panic attacks.[3,45]

Anaphylactic episodes tend to decrease in frequency and severity with time. If left untreated, anaphylaxis may be fatal, so it demands immediate medical attention. During the anaphylactic episode, central to appropriate therapy is administration of either intravenous or intramuscular epinephrine every 5 minutes. Patients must carry and know when and how to self-administer epinephrine. With the advent of humanized anti-IgE monoclonal antibody, such reactions may be reduced in frequency and severity.[44] Although not usually helpful in the acute setting, systemic glucocorticoids may prevent prolonged reactions or relapses.[46]

Other causes

Medullary thyroid cancer

Medullary thyroid cancer (MTC) is an uncommon thyroid tumor representing 5% to 10% of all thyroid cancers. MTC originates from calcitonin-producing parafollicular C cells of the thyroid, believed to be derived from embryologic neural crest.[47] Thyroid C cells elaborate a number of peptides and hormones, such as calcitonin, prostaglandins, histamine, substance P, katacalcin, levodopa, adrenocorticotropic hormone, corticotropin-releasing hormone, carcino-embryonic antigen (CEA), and chromogranin A.[30] The inheritance pattern of MTC may be sporadic or may be autosomal dominant as part of multiple endocrine neoplasia.[1] Unlike hereditary MTC in which rearranged during transfection (RET) mutations are the most important precipitating events, in sporadic MTC, the genetic or molecular biomarkers are yet to be established.[48]

The clinical presentation is most often a thyroid nodule or cervical lymphadenopathy. Less common presentations include recognition during a search initiated after an associated disease, such as pheochromocytoma, or hyperparathyroidism becoming apparent, diarrhea caused by gastrointestinal secretion of fluid and electrolytes, and flushing caused by the secretion of other peptides by the tumor.[25]

Basal calcitonin testing for thyroid nodule patients with increased risk for MTC, including those with a family history of MTC, with a diagnosis of hyperparathyroidism or pheochromocytoma, or symptoms of flushing or diarrhea is recommended. If the basal calcitonin level is increased but less than 20 pg/mL and there is no hereditary disease, patients must be followed conservatively with ultrasound and basal calcitonin, considering surgery for progressive calcitonin increase or suspicious ultrasound or fine-needle aspiration (FNA) findings during follow-up.[49] A basal serum calcitonin level exceeding 20 pg/mL warrants further investigation to exclude MTC.[50] Thyroid nuclear scanning and thyroid fine-needle aspirate analysis can be performed for better diagnosis.[2]

Patients with hormonal symptoms may benefit from medical treatment with somatostatin analogs. These patients may also benefit from cytoreductive surgery of unresectable disease. Surgery has been demonstrated to effectively palliate patients with incurable MTC.[30]

RET is the most important target for recent systemic therapy trials of MTC, together with vascular endothelial growth factor receptors. Multikinase inhibitors including motesanib, vandetanib, sunitinib, sorafenib, and cabozantinib/XL give promising results in recent clinical trials. Across multiple studies reported to date, RET mutations, although prevalent in these subjects, have not proved so far to predict whether patients will respond to multikinase inhibitors. Available data for efficacy and toxicity of these agents, appropriate selection of patients with MTC for systemic treatment, and how best to integrate these therapies with established modalities of surgery and radiation therapy is yet to be investigated.[51]

The best chance of cure in familial MTC is still provided by complete surgical resection before malignant transformation or spread beyond the thyroid gland. Surgical approach should include a central nodal resection or even a more extensive resection if local lymph node dissemination is identified. Systemic chemotherapy in patients with locally advanced or metastatic MTC has so far produced modest clinical responses.[47]

Pancreatic endocrine tumors

Functional pancreatic endocrine tumors other than gastrinoma and insulinoma are rare. Vasoactive intestinal peptide–producing tumor (VIPoma) or Verner–Morrison syndrome is a rare neuroendocrine tumor, 70% to 80% originating from pancreas.[52,53] Also known as WDHA (watery diarrhea, hypokalemia, achlorhydria syndrome), these tumors secrete excessive amounts of vasoactive intestinal peptide (VIP), a hormone that stimulates adenosine 3′5′-cyclic phosphate production by the intestinal tract, resulting in profuse diarrhea manifesting as water and electrolyte loss, especially potassium.[52] They also secrete gastric inhibitory polypeptide, prostaglandin, and pancreatic peptides.[1] During attacks of diarrhea, flushing similar to that observed in CS can rarely occur.[52]

VIP level is increased in almost all cases of VIPoma but can also be normal between diarrheal episodes. Assessment of VIP offers high sensitivity in establishing the diagnosis. A high plasma VIP level in the setting of stool volume greater than 1 L/day is highly diagnostic. Imaging modalities include endoscopic ultrasonography, computed tomography and magnetic resonance imaging, and particularly, scintigraphy with somatostatin analogues.[54]

Treatment options include resection of the tumor, chemotherapy, or somatostatin analogues to improve hormone-mediated symptoms.[52,54]

Renal cell carcinoma

RCC has the highest mortality rate of the genitourinary cancers. It may cause flushing via secretion of prostaglandins

or via pituitary downregulation from release of gonadotropins.[1,2] Early clinical manifestations of RCC are diverse and may cause a range of nonspecific and often misattributed symptoms. Only 10% of individuals with RCC present with the classic triad of hematuria, pain, and a flank mass, and these individuals most often have advanced disease.

Diagnosis involves intravenous pyelography, renal ultrasound, computed tomography, or magnetic resonance imaging of the pelvis.[1] Treatment of choice is radical nephrectomy. In case of metastatic disease, chemotherapy, immunotherapy, or hormonal therapy may be appropppriate.[1]

Until recently, there were few therapeutic options other than the cytokines interferon or interleukin-2 for RCC. Two small-molecule kinase inhibitors, sunitinib and sorafenib, are becoming standard of care for metastatic RCC as studies support improvements in progression-free and overall survival. The mammalian target of rapamycin inhibitors, temsirolimus and everolimus, as well as the monoclonal antibody, bevacizumab, and the angiogenesis inhibitor, pazopanib, are also in clinical trials.[55–57]

Neurologic flushing

A wide variety of neurologic diseases may present with flushing reactions. Flushing has been reported in patients with Parkinson disease, dysautonomia and orthostatic hypotension, migraines, multiple sclerosis, brain tumors, epilepsy, and spinal cord lesions that produce autonomic hyperreflexia; moreover, trigeminal nerve damage, Horner syndrome, Frey syndrome, autonomic epilepsy, and autonomic hyperreflexia are some other rare causes of flushing.[1,2]

Medications

Some drugs may induce flushing reactions with different mechanisms. All vasodilators, all calcium channel blockers, nicotinic acid, morphine and other opiates, amyl nitrite and butyl nitrite (recreational drugs), cholinergic drugs, bromocriptine, thyrotropin-releasing hormone, tamoxifen, cyproterone acetate, cyclosporine, vancomycin, rifampin, beta-blockers, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs are among drugs that may provoke flushing.[1,2]

Some drugs may cause flushing when combined with alcohol. Coadministration of alcohol with disulfiram, chlorpropamide, metronidazole, ketoconazole, griseofulvin, cephalosporins, chloramphenicol, antimalarials, and topical tacrolimus and pimecrolimus to the face may trigger flushing reaction.[1,58]

Conclusions

The differential diagnosis of cutaneous flushing is extensive and encompasses a broad spectrum of benign and malignant entities. Although the most common causes of flushing (fever, emotional flushing, climacterium, and rosacea) are benign and easy to recognize, a thorough history and physical examination, and laboratory investigations are mandatory to reveal a possible underlying disease such as mastocytosis, CS, pheochromocytoma, or malignant tumors of pancreas, kidney, and thyroid. Because dermatologists are usually the first doctors to refer, they have a unique role in the diagnosis and management of patients with flushing. The goal of the dermatologist is to separate benign from potentially life-threatening conditions, make an accurate differential diagnosis, and offer effective treatment options.

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