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Flushing in (Neuro)endocrinology

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Abstract

Cutaneous flushing is a common presenting complaint in endocrine disorders. The pathophysiology of flushing involves changes in cutaneous blood flow triggered by multiple intrinsic factors that are either related to physiology or disease. Flushing can be divided into episodic or persistent causes. Episodic flushing is mediated by the release of endogenous vasoactive mediators or medications, while persistent flushing results in a fixed facial erythema with telangiectasia and a cyanotic tinge owing to the large cutaneous blood vessels that contain slow-flowing deoxygenated blood. The differential diagnosis of cutaneous flushing in neuroendocrine disorders is limited, yet encompasses a broad spectrum of benign and malignant entities, including carcinoid syndrome, pheochromocytoma, Cushing syndrome, medullary thyroid cancer, and pancreatic neuroendocrine tumors. In this review, we provide a concise and up-to-date discussion on the differential diagnosis and approach of flushing in neuroendocrinology.

Keywords

Flushing; Neuroendocrine tumor; Carcinoid; Pheochromocytoma; Histamine; Substance P

Introduction

Flushing is a subjective sensation of warmth that is accompanied by reddening of the skin anywhere on the body but favors the face, neck, and upper torso (1). This bodily predilection is primarily due to increased relative volume of visible superficial cutaneous vasculature, as well as qualitative differences in skin vascular response and vascular regulation, as compared with other body areas (1–3). Flushing can be broadly divided into episodic or persistent. Episodic flushing is mediated by the release of endogenous vasoactive mediators or medications, while persistent flushing results in a fixed facial erythema with

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telangiectasia's and a cyanotic tinge owing to the large cutaneous blood vessels that contain slow-flowing deoxygenated blood (2). Flushing should be differentiated from facial plethora, which is more chronic and develops insidiously, although the physiology of the two phenomena is similar.

The differential diagnosis of a patient with flushing is extensive and includes a broad range of benign and malignant conditions. Benign causes of flushing include rosacea, climacterium, fever, benign cutaneous flushing (as seen in emotional distress), and medication-induced. To the contrary, the following causes of flushing are associated with increased morbidity and mortality: carcinoid syndrome, pheochromocytoma, mastocytosis, neuroendocrine tumors, anaphylaxis, medullary thyroid cancer, renal cell carcinoma, inborn errors of metabolism such as Fabry disease, and autonomic dysfunction.

With the exception of carcinoids, flushing due to tumors is rare and tends to occur in advanced stages or as a manifestation of paraneoplastic syndrome. The signs and symptoms of benign cutaneous flushing include abdominal complaints and flushing of the blush area, which may overlap with those of carcinoid syndrome and pheochromocytoma (4,5). Thus, clinicians should obtain a careful history and perform a thorough physical examination in all cases of flushing as an early diagnosis of an endocrine tumor, such as a pheochromocytoma, may lead to decreased morbidity and mortality. In this review, we provide a concise and up-to-date discussion on the differential diagnosis and approach of flushing in neuroendocrinology (Table 1).

Initial evaluation

The initial evaluation of a patient with flushing includes a thorough history and physical examination. A directed history should focus on the type of a flush and its associated symptoms, including a detailed description of the type of flush and its distribution, associations (i.e.: lightheadedness, low blood pressure, bronchospasm, tachycardia) and triggers (i.e.: emotion, food, drugs, physical exertion, alcohol, stress). Vague complaints may be associated with a psychiatric comorbidity, such as anxiety, depression, or somatization disorder. Elevation of both arms can lead to marked facial plethora, indicative of compressed jugular veins, in patients with large sub/retrosternal goiter or mediastinal mass. This phenomenon is called Pemberton's sign (6,7).

Certain clinical characteristics may be elicited to assist in narrowing the differential diagnosis of flushing. Associated sweating ("wet flushes") indicates autonomic hyperactivation, while lack of ("dry flushes") is usually the result of a substance(s) that lead to vascular smooth muscle activation. Accompanying symptoms may further point to the cause; antidromic sensorineural-mediated flushing is accompanied by pain or burning sensation in the affected areas, while the presence of urticaria and pruritus is seen in histamine-mediated reactions, including mastocytosis, or as a side effect to vancomycin therapy. However, the majority of conditions that manifest with flushing do overlap in symptoms (Table 2).

Neuroendocrine causes of flushing

1. Carcinoid syndrome

Carcinoid syndrome (CS) is a life-threatening medical condition that affects approximately 10% of patients with carcinoid tumors (8,9). Carcinoid tumors are slow-growing benign lesions of enterochromaffin or Kulchitsky cells that are derived from the neuroendocrine lineage and have a low incidence rate of 1.9 per 100,000 (10–16). Patients with carcinoid tumors are usually asymptomatic or may have vague gastrointestinal complaints. However, patients with CS typically present with flushing that is often times accompanied by diarrhea, abdominal cramping, and fatigue. In the majority of patients (approximately 50%), particularly males, tumors are located in the small bowel or proximal colon, and rarely in the stomach, bronchus or appendix (3,8,17). CS may rarely arise from ovarian teratomas, tumors of the uterine cervix, glomus jugulare, and thyroid gland or present with right-sided cardiac failure from valvular disease or severe bronchoconstriction (8,17,18).

Aggressive carcinoid tumors tend to be functional and secrete several biologically active substances. The clinical hallmark of functional carcinoids in over 90% of cases is flushing, which is often episodic (3,10). Generally, vasoactive substances, such as serotonin (5-HT), substance P, histamine, catecholamines, prostaglandins, among others, that escape hepatocyte inactivation, provoke flushing (12,19,20). These substances are usually secreted by carcinoid tumors that are located distal to the portal vein or downstream of functioning hepatocytes. The release of these substances is triggered by amine-rich foods, such as sherry, beer, fermented foods, and chocolate, pharmacologic triggers such as catecholamines, dopamine, pentagastrin and isoproterenol (also seen in patients with mastocytosis and benign cutaneous flushing), and increase in adrenergic activity, as seen in pain, anger, embarrassment, or exertion. Niacin-induced flushing, which can only be reduced by ~ 30% by taking aspirin, is influenced by 9alpha, 11beta-prostaglandin F (2) combined with an imbalance of the sympathetic and parasympathetic nervous system (21). Facial flushing, sometimes seen when 1-desamino-8-D-arginine vasopressin (DDAVP) is administered intravenously, appears to be mediated by prostacyclin production (22).

The flush in CS may be distinguished from other causes and can help point out the location of the tumor. Midgut tumors cause a rapid cyanotic flush that last for less than a minute and commonly associated with a mild burning sensation, while foregut tumors produce pruritic wheals that are reddish-brown and occur over the entire body (Image 1), and those with bronchoconstriction are usually bright red and confluent, and associated with chemosis, facial edema, or hypotension. Accompanying symptoms are common, including diarrhea, dyspnea, abdominal pain or wheezing. The chronicity of symptoms will dictate the length of episodes, development of bluish coloration of bodily areas, such as the malar area or nose, or thick skin changes with venous telangiectasia.

The diagnosis of CS is established by measuring the 24-hour urine levels of 5-hydroxyindolacetic acid (5-HIAA) or chromogranin A (CgA). 5-HIAA is a major urinary metabolite of 5-HT, with a sensitivity of 73% and a specificity of 100% for diagnosing carcinoids (23). Urinary 5-HIAA is not elevated in mastocytosis, because 5-HT is not made by human mast cells or in idiopathic anaphylaxis or idiopathic flushing. Moreover, some

patients with carcinoid tumors have symptoms of flushing with low or normal levels of 5-HIAA (24). Unlike 5-HIAA, CgA levels are independent of symptoms and are elevated to 100–1000 times normal in 85%–100% of patients with a carcinoid tumor regardless of whether the tumor is functional or nonfunctional. The specificity and sensitivity of CgA is 98.4% and 62.9%, respectively (25).

The main goals of CS management are symptom control. This is best achieved with somatostatin analogs (e.g.: octreotide or lanreotide) by reducing the secretion of vasoactive mediators (10,12,15,26,27,28). Histamine-induced flushing may be treated with H1 and H2 receptor blockers (10). Alternatives in management include various combinations of isotope therapy, addition of interferon, 5-HT antagonist ketanserin, and use of chemotherapy (10).

2. Pheochromocytoma and Paraganglioma

Pheochromocytoma and paraganglioma (PPGL) are neuroendocrine tumors that arise from the chromaffin cells of the adrenal glands, and ganglia along the sympathetic and parasympathetic chain, respectively (29). PPGL affect about 1 in 2500–6500 individuals, with 500–1600 cases diagnosed annually in the United States (30). Pheochromocytomas typically produce catecholamines (epinephrine, norepinephrine, and dopamine) and can lead to secondary diabetes mellitus or hypertension, while paragangliomas that arise from the parasympathetic ganglia do not produce catecholamines, and rarely are PPGL's biochemically silent. Hypertension is the most frequent finding, and can be sustained or paroxysmal, or associated with flushing or pallor. The typical PPGL attack, which is seen in approximately 30% of patients (29,31,32), presents with headaches, sweating, palpitations, and with or without flushing. Such paroxysms may be precipitated by medications such as glucocorticoids or β-adrenergic receptor blockers, which may be used in the treatment of flushing before a diagnosis is established.

Several factors may be responsible for the generation of flushing in PPGL. The most convincing mechanism is the production of catecholamines that lead to thermal vasodilation of the face and other bodily areas (33,34). Other recognized factors include general blood pressure lability and episodes of increased cardiac output, and the production of flushing mediators, such as calcitonin gene-related peptide (35), vasoactive intestinal polypeptide (VIP) (36–38), and adrenomedullin (39,40), a potent vasodilatory peptide with significant vasodilatory effects on skin.

Syndromic PPGL may also present with flushing and their frequency is unknown (29). These conditions include; multiple endocrine neoplasia type 2A (MEN2A; medullary thyroid cancer, primary hyperparathyroidism, and cutaneous lichen amyloidosis); multiple endocrine neoplasia type 2B (MEN2B; medullary thyroid cancer, mucocutaneous neuromas, skeletal deformities (e.g., kyphoscoliosis or lordosis), joint laxity, myelinated corneal nerves, and intestinal ganglioneuromas (Hirschsprung disease); von Hippel-Lindau syndrome (VHL; hemangioblastoma that involve the cerebellum, spinal cord, or brainstem, retinal angioma, clear cell renal cell carcinoma, pancreatic neuroendocrine tumors and serous cystadenomas, endolymphatic sac tumors of the middle ear, papillary cystadenomas of the epididymis and broad ligament) and Neurofibromatosis type 1 (neurofibromas, multiple café-au-lait spots, axillary and inguinal freckling, iris hamartomas (Lisch nodules), bony abnormalities, central

nervous system gliomas, macrocephaly, and cognitive deficits). Plethora can develop when neurogenic polyglobulia occurs via hemangioblastomas expressing erythropoietin or via other VHL-associated tumors secreting erythropoietin (41). Plethora is a sign of other endocrine conditions, like Cushing syndrome (see below).

The diagnosis of PPGL is established by measurements of plasma free or 24-hour urinary fractionated metanephrines (29). These tests are superior to other tests of catecholamine excess, as free metanephrines are produced continuously within adrenal chromaffin cells (or the tumors derived from these cells) and are specific markers of chromaffin tumors.

3. Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) is a rare malignant tumor of the parafollicular C cells of the thyroid gland (42). MTC is derived from the neural crest and secretes a variety of biologically active substances including calcitonin, prostaglandins, histamine, substance P, ketacalcin, levodopa, adrenocorticotropic hormone (ACTH), and corticotropin-releasing hormone, that can cause flushing and sweating. MCT is caused by mutations in the *RET* proto-oncogene, and may be sporadic or inherited in an autosomal dominant pattern in approximately 25% of cases as part of multiple endocrine neoplasia (MEN2A and MEN2B) or familial MTC. Most patients with MTC are asymptomatic; in the symptomatic patient, secretory diarrhea is the most prominent hormone-mediated clinical feature, while protracted flushing of the face and upper extremities, discoloration, and telangiectasias, is seen less frequently (42). Examining a fine needle aspirate from a thyroid nodule initially makes the diagnosis of MTC with 95–98% accuracy (42). Serum calcitonin levels are usually elevated and often establish the diagnosis of MTC. Carcinoembryonic antigen (CEA) may be elevated in advanced MTC and could be used as a marker for possible later recurrence of disease. Total thyroidectomy with central lymph node dissection is the minimum recommended operation for MTC. Genetic testing of the proband and all first-degree relatives should include *RET* mutation analysis (43,44).

4. Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (PNETs) are rare neuroendocrine neoplasms from pluripotent cells of the pancreas with an incidence of les than 1 per 100 000 persons per year (45,46). Their prevalence ranges from 0.8% to 10% in patients undergoing a postmortem examination, suggesting that people frequently harbor asymptomatic PNETs (47). When PNETs are malignant, they are called pancreatic endocrine cancer or islet cell carcinoma.

PNETs secrete several hormones and peptides, including VIP, gastric inhibitory polypeptide, prostaglandin, insulin, gastrin, glucagon, ACTH, somatostatin, growth hormone–releasing factor (GRF), neurotensin, parathyroid hormone-related peptide, pancreatic polypeptide, and melanocyte-stimulating hormone (48,49). Most individuals usually only have symptoms relating to the hormone that is chiefly produced. Flushing can be seen in all forms of PNETs and resembles that of gastric carcinoid syndrome (pruritic reddish-brown with variegated margination over the entire body). As with CS, chronic flushing from PNETs may develop thick skin changes with venous telangiectasia and bluish coloration of the chin, nose, and malar area.

PNETs are divided into several subtypes. VIPomas classically present with Verner-Morrison syndrome that manifest with watery diarrhea, hypokalemia, achlorhydria, and rarely flushing. A VIP tumor is diagnosed by demonstrating a high plasma VIP level in the setting of stool volume greater than 1 L per day. Neurotensinomas are rare forms of PNETs that are usually malignant and manifest with hypotension, hypokalemia, weight loss, flushing, and hyperglycemia, while calcitoninomas, another rare form, cause watery diarrhea and facial flushing, as one would see with MTC. Flushing is a rare clinical finding in: gastrinomas which are usually malignant and form in the head of the pancreas (often referred to as Zollinger-Ellison syndrome); insulinomas which are usually benign tumors in the head, body, or tail of the pancreas that may produce flushing during hypoglycemic episodes; glucagonomas which are usually malignant and located in the tail of the pancreas and present with hyperglycemia and a characteristic necrolytic migratory erythema rash; and somatostatinomas which lead to hyperglycemia, gallstones, and steatorrhea.

Evaluation of PNETs requires biochemical workup of the various secretory peptides and amines, and advanced imaging techniques. Abdominal and pancreatic ultrasound, as well as computed tomography and aortography, could be performed to localize the tumor or metastases (50). Therapy for PNETs is primarily surgical resection for localized disease and selected patients with metastatic disease. Although somatostatin analogues have proven to be very effective in ameliorating symptoms of hormone overproduction, options regarding systemic therapy for advanced disease continue to be limited (10,12,49).

5. Endogenous Cushing syndrome

Endogenous Cushing syndrome is the result of chronic glucocorticoid excess from either an ACTH-secreting pituitary tumor, cortisol producing adenoma, adrenal hyperplasia, or ectopic production of ACTH and/or CRH from a neuroendocrine tumor (51,52). Endogenous Cushing syndrome is rare with an overall incidence of approximately 0.7–2.4 per million population per year (53,54). Patients classically present with facial plethora (Image 2), central body weight gain with limb thinning, glucose intolerance or diabetes with extensive acanthosis nigricans, hypertension, proximal muscle weakness, easy bruising and striae. Flushing is rarely a presenting complaint and is usually subjective. Facial plethora is consistent and unlike flushing rarely episodic; it is also decreased after surgery, due to reduction of blood volume perfusion (Image 2) (55).

6. Other causes

Several comorbidities may be associated with neuroendocrine disorders and are known to cause flushing, including; central hypogonadism in men (56); POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes) (57); malignant histiocytoma, neuroblastoma, and ganglioneuroma, from increased production of VIP; TSH-secreting pituitary adenoma causing hyperthyroidism (58); dysautonomia, orthostatic hypotension, migraines; anxiety and panic attacks presenting with hot flashes and sweating; and vascular pulsation in inflammatory skin diseases, examples of which are spider arterial angiomas, acquired pulsating arteriovenous angiomas and arteriovenous capillary shunt in inflamed lesions or in local trauma (only visible in inflamed skin implicating the roles of neuropeptides) (59, 60). More than two thirds of

perimenopausal women experience hot flashes which may represent a marker of underlying cardiovascular disease (61); a recent study examined the role of genetic variation in the tachykinin receptor 3 (*TACR3*) as a contributor to hot flashes (62). Treatment should be individually tailored and includes use of systemic hormone therapy (estrogen +/− progestogen), selective serotonin reuptake inhibitors, gabapentin, clonidine, and other modalities (63,64).

Conclusion

The differential diagnosis of cutaneous flushing in neuroendocrine disorders is limited, yet encompasses a broad spectrum of benign and malignant entities. A thorough history and physical examination to elicit the characteristics of the underlying syndrome associated with flushing, and laboratory and radiographic investigations to ascertain the cause, are mandatory. Several neuroendocrine disorders are associated with flushing, including CS, PPGL, MTC, and endogenous Cushing syndrome, among others. It is imperative for the clinician to separate benign from potentially life-threatening conditions associated with flushing and to provide an appropriate workup and treatment to decrease morbidity and mortality that are associated with neuroendocrine disorders.

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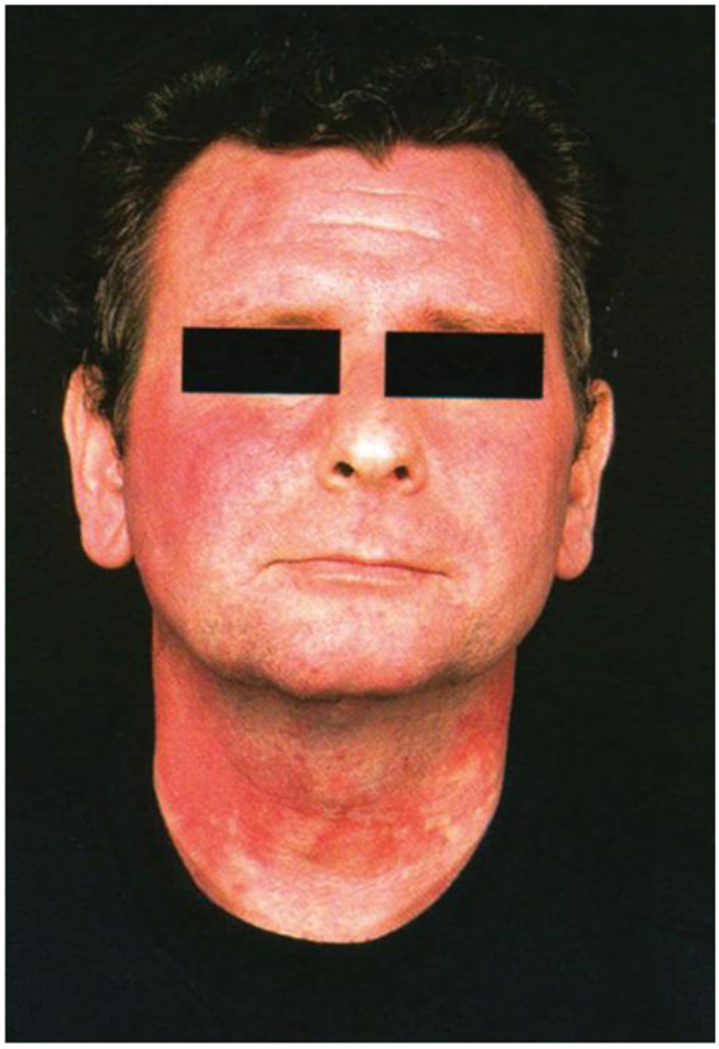

Image 1.
Flushing from a carcinoid tumour in the foregut due to histamine release. With permission from John Wiley and Sons

Image 2.
Facial plethora in a patient with Cushing syndrome before and after surgery. With permission from Ali Afshari and Constantine A. Stratakis, NIH

Table 1

Neuroendocrine causes of flushing.

Diagnosis	Estimates	Clinical findings	Triggers		Substances
Carcinoid syndrome	10% of patients with carcinoid tumors (incidence rate of 1.9 per 100,000)	Flushing Diarrhea Abdominal cramping Fatigue	**1** **2** **3**	Amine-rich foods: sherry, beer, fermented foods, and chocolate Medications: catecholamines, dopamine, pentagastrin and isoproterenol Increase in adrenergic activity: as seen in pain, anger, embarrassment, or exertion.	Serotonin Substance P Histamine Catecholamines Prostaglandins
Pheochromocytoma and Paraganglioma	1 in 2500–6500 individuals (500–1600 cases diagnosed annually in the United States)	Hypertension is the most frequent finding (sustained or paroxysmal, or associated with flushing or pallor) The typical PPGL attack, which is seen in approximately 30% of patients, presents headaches, sweating, palpitations, and with or without flushing.	**1** **2**	Medications: glucocorticoids or β-adrenergic receptor blockers, glucagon. Increase in adrenergic activity: as seen in pain, anger, embarrassment, or exertion.	Pheochromocytomas: catecholamines (epinephrine, norepinephrine, and dopamine) Paragangliomas: does not produce catecholamines Both may be biochemically silent
Medullary Thyroid Cancer	Rare	Most patients are asymptomatic; in the symptomatic patient, secretory diarrhea is the most prominent hormone-mediated clinical finding, with or without flushing	None		Calcitonin Prostaglandins Histamine Substance P Ketacalcin Levodopa, Adrenocorticotropic hormone Corticotropin-releasing hormone
Pancreatic Neuroendocrine Tumors	<1 per 100 000 persons per year	Most individuals usually only have symptoms relating to the hormone that is chiefly produced.	None		Vasoactive intestinal peptide Gastric inhibitory polypeptide Prostaglandin Insulin Gastrin Glucagon Adrenocorticotropic hormone Corticotropin-releasing hormone Somatostatin Growth hormone–releasing factor Neurotensin Parathyroid hormone-related peptide Pancreatic polypeptide

Diagnosis	Estimates	Clinical findings	Triggers	Substances
				Melanocyte-Stimulating Hormone
Endogenous Cushing syndrome	0.7–2.4 per million population per year	Facial plethora Central body weight gain with limb thinning Acanthosis nigricans Proximal muscle weakness Easy bruising Striae Flushing (rare)	None	Cortisol Adrenocorticotropic hormone and/or Corticotropin-releasing hormone (in Cushing disease or ectopic Cushing syndrome)

Table 2

The characteristics of flushing in neuroendocrine tumors.

Syndrome	Characteristics
Carcinoid syndrome	• Midgut: rapid cyanotic flush that last for less than a minute and commonly associated with a mild burning sensation • Foregut: pruritic reddish-brown with variegated margination or bright red and confluent, with wheals over the entire body, and associated with chemosis, facial edema, or hypotension. • Those with bronchoconstriction are usually bright red and confluent, and associated with chemosis, facial edema, or hypotension. • Accompanying symptoms are common, including diarrhea, dyspnea, abdominal pain or wheezing. • Chronic flushing may lead to thick skin changes with venous telangiectasia and bluish coloration of the face or upper torso.
Pancreatic Neuroendocrine Tumors	• Rapid cyanotic flush that last for less than a minute and commonly associated with a mild burning sensation • Pruritic reddish-brown with variegated margination or bright red and confluent, with wheals over the entire body, and associated with chemosis, facial edema, or hypotension.
Endogenous Cushing syndrome	• Flushing is rarely a presenting complaint and is usually subjective. Facial plethora is consistent and unlike flushing rarely episodic; it is also decreased after surgery, due to reduction of blood volume perfusion.