Zusammenfassung

- Man unterscheidet zwischen primärer und sekundärer Hyperhidrose
- Die primäre Hyperhidrose ist häufig, tritt in jungen Jahren auf und ist meist familiär
- Die sekundäre Hyperhidrose muss ausgeschlossen werden
- Endokrinologisch sind zu erwähnen:
  - Die Menopause
  - Die Hyperthyreose
  - Der NET-Tumor
  - Das Phäochromozytom
  - Die Acromegalie
  - Das Cushing Syndrom
  - Diabetes mellitus
- Bei Ausschluss einer sekundären Hyperhidrose gibt es verschiedene dermatologische Ansatzpunkte zur Therapie

Therapie bei Ausschluss einer sekundären Hyperhidrose

1. Line

- Topisch 20% Aluminium chlorid (Drysol) über Nacht so lange bis die Symptome nachlassen

→ Die Aluminium Salze führen zu einer Obstruktion der ekkrinen Drüsen und Destruktion der sekretorischen Zellen

- Für craniofaziale Hyperhydrose: 2% Glycopyrrolat
- Für palmare oder plantare Hyperhidrose: Iontopheres

→ dabei wird mittels ionisiertes Wasser (mit oder ohne Zusatz) Elekztrizität durch die Haut geführt → der Wirkmechanismus ist nicht klar

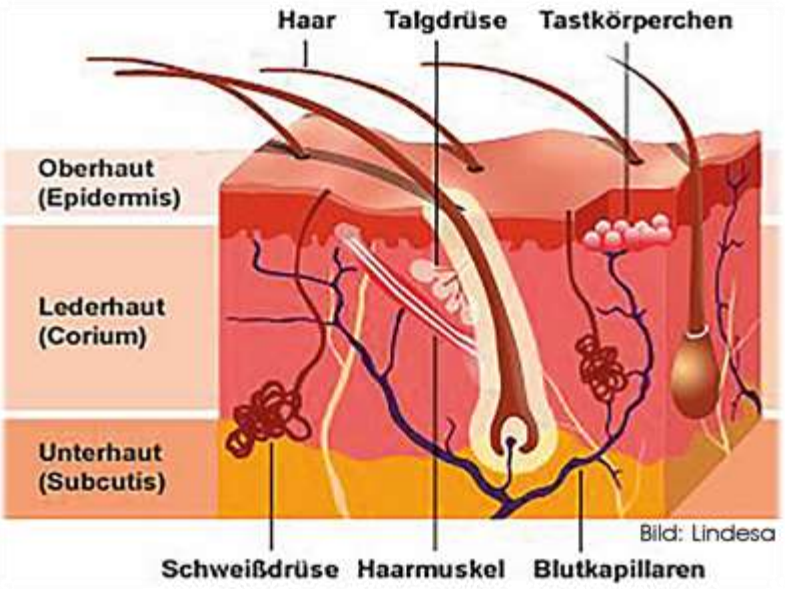
2. Line

- Botox: Zunächst muss mit dem minor starch iodine test die Lokalisation determiniert warden. Schweiss wird violett wenn es mit Strärke in Kontakt kommt

3.4.5 Line

- orale Anticholinergika, Mikrowellen, sympathische Denervation

Schweissproduktion



- Ekkrine und apokrinen bzw. apoekkrine Drüsen der Haut
- Ekkrine Schweissdrüsen am häufigsten (3 Mio), höchste Dichte: axillär, palmar und plantar (Stirn und Wangen)
- Klare, hypotone Flüssigkeit
- pH schwankt zwischen 4 und 7
- 99% Wasser, andere Bestandteile: NaCl, K +, Laktat, kurzkettige Carbonsäuren, Harnstoff, Harnsäure, Bicarbonat, Cholesterin

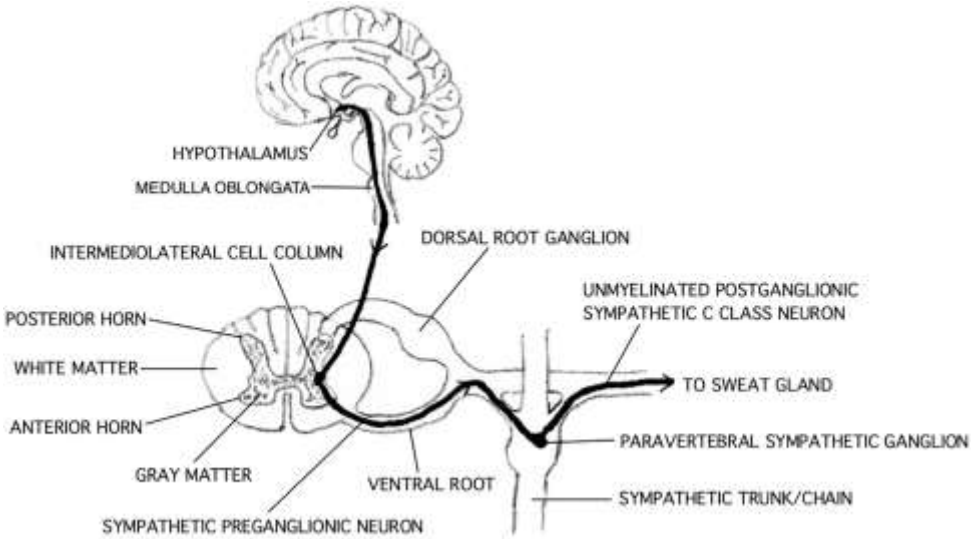
Schweissproduktion und Schweissgeruch

- Ca. 100-200ml Schweiss pro Tag
- Maximale Schweissproduktion: 0.5-2l/h
- ↑ Schweissproduktion wird der Salzgehalt ↓
- Frischer Schweiss ist nahezu geruchlos
- Abbau von langkettigen Fettsäuren wie Ameisensäure (Acidum formicum) oder Buttersäure → typischer Schweissgeruch
- Umwandlung durch Bakterien der Hautflora
- Neben dem optischen, Hauptgrund für die Belastung der Patienten

Pathophysiology of Hyperhidrosis, Christoph H. Schick et al.
Thorac Surg Clin 26 (2016) 389–393

Thermale Regulation

- Erzeugung von Verdunstungskälte → Thermoregulation
- Film über der Haut, wirkt antibakteriell
- Regulation: Neurovegetativ vor allem durch den Sympathikus
  - Wärmerezeptoren überall im Körper: Haut, Organe
  - Die Signale erreichen den Hypothalamus über die afferenten Nervenfasern via laterales Rückenmark
  - Hypothalamus → zentraler Regulator
  - Die efferenten Fasern vom Hypothalamus kontrolliert, aktivieren die Drüsen mittels Acetylcholin aber auch durch Adrenalin/Noradrenalin stimuliert
- Triggerung der Sekretion:
  - Umgebungstemperatur
  - Psychische Einflüsse wie Stress
  - Körperliche Anstrengung
  - Gustatorische Auslöser



Pathophysiology of Hyperhidrosis, Christoph H. Schick et al. Thorac Surg Clin 26 (2016) 389–393

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Definition und Epidemiologie der Hyperhidrose

- Sekretion stärker als physiologisch nötig für die Thermoregulation
- Unterscheidung zwischen primärer (idiopathischer) und sekundärer Hyperhidrose
- Primäre Hyperhidrose
  - Häufig: 0.6-2.8% der Gesamtbevölkerung
  - Meist axillae, plantar oder palmar
  - Beide Geschlechter gleich betroffen
  - familiär in 35-56%
  - Meist vor dem 25. Lebensjahr
  - Paroxysmal oder kontinuierlich, aber meist nicht nachts
- Sekundäre Hyperhidrose
  - Selten
  - Zugrunde liegende Ursache
  - Meist generalisiert

Diagnose einer Hyperhidrose

- Gravimetrie; Schweiss mittels eines Filterpapiers gesammelt und gewogen
- Sudometrie/Sudoscan: Die Feuchtigkeit der Haut mittels einer Messkammer mit getrocknetem Gas gemessen, welche an der Hand befestigt wird
- Minor Stärke-Iod Test : Reaktion zwischen Iod und Stärke mit Schweiss und somit Schweisslokalisation
- Ninhydrintest: Reaktion von Aminosäuren im Schweiss mit Ninhydrin
- Qualitative Tests wie: Hyperhidrose Disease Severity scale

Medikamente

Klasse	Beispiele
Trizyklische Antidepressiva	Amitryptilin
Anxiolytika	Diazepam
Antipsychotika	Quetiapin
SSRI	Citalopram, Fluoxetin
Antibiotika	Ciprofloxazin
Antivirale Medikamente	Acyclovir
Hypoglykäme Substanzen	Insulin
Triptane	Sumatriptan
Antipyretika	Paracetamol
NSAR	Ibuprofen
Antiemetika	Ondansetron
Adrenerge oder cholinerge Substanzen	Noradrenalin
Drogen	Alkohol, Kokain, Heroin

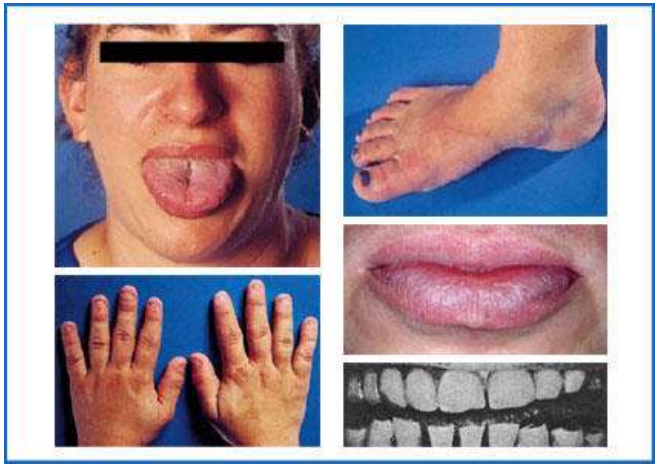
Endokrinologische Differentialdiagnose und Diagnostik

Erkrankung	***Diagnostik***
Menopause	FSH, LH, Estradiol
Hypogonadismus beim Mann	Testosteron, LH, FSH, SHBG
Hyperthyreose	TSH, fT4, (fT3)
Diabetes mellitus	HbA1c
Phäochromozytom	Metanephrine im Plasma
NET-Tumor	5-Hydroxyindolessigsäure im Plasma
Cushing Syndrom	Dexamethason-Hemmtest. Falls pathologisch wiederholen, Mitternachtspeichelcortisol, Cortisol im 24h Urin
Acromegalie	IGF1
(Insulinom)	Kontinuierliche Blutzuckermessung (Bildgebung)
(Medulläres Schilddrüsenkarzinom)	Ultraschall Schilddrüse, Calcitonin, (CEA)
(Diabetes insipidus)	Na+, Urinmenge, Arginin-Copeptin-Stimulationstest/3% NaCl-Belastungstest

The etiology, diagnosis and management of hyperhidrosis, Shiri Nawrocki, et al, 2019 American Academy of Dermatology, Vol 81, Number 3

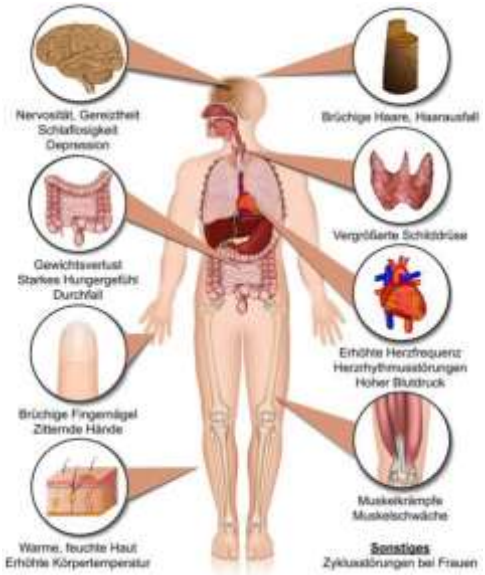
Acromegalie

- 50-88% der Patienten berichten über übermässiges Schwitzen
- Stark riechender Schweiss
- Bopsien zeigten **keine Vermehrung** der Talg- und Schweissdrüsen, aber eine **Vergrösserung** (unterschiedliche Daten)
- GH-Rezeptoren auf den Schweiss und Talgdrüsen
- GH stimuliert die Differenzierung der Schweissdrüsen
- Patienten leiden auch nach Normalisierung des Wachstumshormon unter vermehrtem Schwitzen



Clinics in Dermatology Anat Ben-Shlomo MD, V24, I4, 2016, p256-259
Sweat secretion rates in growth hormone disorders Simone B. Sneppen, 2000 Blackwell Science Ltd, Clinical Endocrinology, 52, 601-608

Schwitzen bei Hyperthyreose



- Vermehrtes Schwitzen in 50-91%
- Hitzeintoleranz in 41-89%
- Mechanismus:
  - Die Schildrüsenhormone erhöhen die Genexpression von Na+/K+ -ATP-Asen in verschiedenen Körperteilen
  - ATP-Verbrauch führt zu überschüssiger Energie → wird als Wärme abgegeben
  - Vermehrung von Betaadrenergen-Rezeptoren
  - Gesteigerte Sensitivität auf Catecholamine

Uptodate: Betablockers in the treatment of hyperthyreoidism
Physiology of thyroid hormones Muhammad A Shahis et al.
Calculation of the role of the Na+, K+-ATP-ase
Thermogenesis, Ronald J. Calrek, 1827, 10, 2013, p1205-1212

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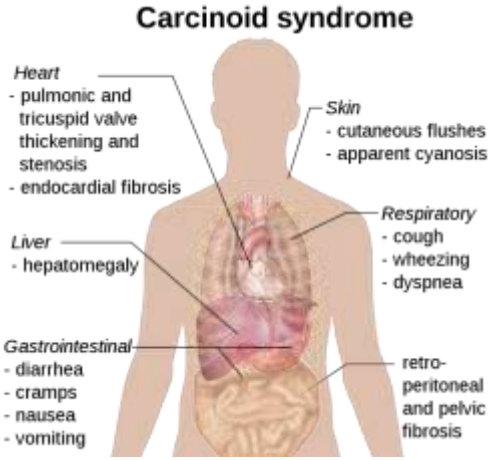
Carcinoid Syndrom

- Das Carcinoid-Syndrom: Symptomkomplex → Freisetzung verschiedener Produkte
- Produkte werden durch NET-Tumoren ausgelöst
- Manche dieser Produkte sind für das Carcinoidsyndrom verantwortlich, aber die relative Kontribution bleibt unklar

Carcinoid symptoms and their putative mediators

Organ	Symptom	Frequency (%)	Putative mediator
Skin	Flushing	85	Kinins, histamine, kallikreins, other
	Telangiectasia	25	
	Cyanosis	18	
	Pellagra	7	Excess tryptophan metabolism
Gastrointestinal tract	Diarrhea and cramping	75 to 85	Serotonin
Heart	Valvular lesions		Serotonin
	Right heart	40	
	Left heart	13	
Respiratory tract	Bronchoconstriction	19	Unknown



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Produkte von gut differenzierten neuroendokrinen Tumoren

- Über 40 Produkte sind identifiziert worden
- Die prominentesten sind:
  - Serotonin
  - Histamin
  - Tachykinin
  - Kallikrein
  - Prostaglandin
- Bei den meisten ist der Tryptophanmetabolismus gestört
- Dieser ist wahrscheinlich für die Diarrhoe, nicht jedoch für die hot flushes verantwortlich

Products of well-differentiated neuroendocrine tumors

Amines
Serotonin
5-Hydroxytryptophan
Norepinephrine
Dopamine
Histamine
Polypeptides
Kallikrein
Pancreatic polypeptide
Bradykinin
Motilin
Somatostatin
Vasoactive intestinal peptide
Neuropeptide K
Substance P
Neurokinin A
Neurokinin B
Corticotropin (ACTH)
Gastrin
Growth hormone
Peptide YY
Glucagon
Beta-endorphin
Neurotensin
Chromogranin A
Prostaglandins

Graphic 79329 Version 2.0

Uptodate: Clinical features of carcinoid syndrom

Für die Flushes wahrscheinlich mitverantwortlich bei NET

- Histamin, dafür spricht das H1 und H2 Antagonisten eine Besserung bringen
- Kallikrein: spaltet Kinin von Plasma-Kininogen. Ein Spaltprodukt davon ist Bradykinin, welches ein potenter Vasodilatator ist
- Tachykinin

Uptodate: Clinical features of carcinoid syndrom

Schwitzen bei Menopause

Epidemiologie:

- Hot flushes oder Nachtschweiss betrifft 80% der Frauen
- Die ersten hot flushes treten 3.8 Jahre vor Menstruationsunregelmässigkeiten auf
- Der peak ist bei 1 Jahr vor der letzten Menstruation
- Die durchschnittliche Dauer ist 7.4 Jahre
- 10%-30% leiden 12 Jahre oder mehr darunter

Risikofaktoren

- Übergewicht, afrikanischer Herkunft, Rauchen, St. n. prämenstruellem Syndrom
- Wahrnehmung der hot flushes ist sehr unterschiedlich (kulturell)

The menopausal hot flush a review, D.W. Sturdee et al.
Climacteric 2017, Vol 20, No 4, p 296-305

Schwitzen bei Menopause

Symptomatik:

- Plötzlich: Tag oder Nacht
- Getriggert oder ungetriggert: Trigger können sein: emotional, Temperaturveränderung, Stress, Alkohol, warme Getränke
- Meistens plötzliches Gefühl von Wärme (teilweise objektivierbar), begleitet von Schwitzen, gerötete Haut, manchmal Palpitationen
- Meist Beginn am Oberkörper und dann Ausbreitung über den ganzen Körper
- Dauer: wenige Sekunden bis zu 1h, meist 3-4 Minuten

The menopausal hot flush a review, D.W. Sturdee et al.
Climacteric 2017, Vol 20, No 4, p 296-305

Schwitzen bei Menopause

Mechanismus:

- Die meisten Studien: 1970-80 Jahren
- Störung der Temperatur regulierenden Mechanismen
- Die Konzentration an Östrogen nicht direkt verantwortlich (nimmt im Alter ab, die Flushes auch)
- Akute Veränderungen des Östrogens (z.B. Ovarektomie) → mehr Beschwerden

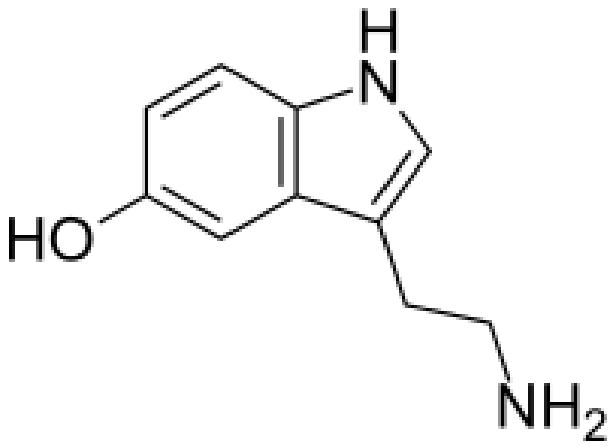
Hypthesen

- 1.): Pulsatile LH Sekretion als Auslöser nicht bestätigt → GnRH Analoga Therapie keine Besserung
- 2.): die hypthalamischen Neuronen für LHRH funktionell verlinkt mit der Thermoregulation → anatomisch mit den Neuronen im präoptischen anterioren Nukleus verwandt

Schwitzen bei Menopause

3.) Hypothese

- Serotonin
- Serotonin nimmt um 50% ab mit erniedrigtem Östrogen
- Serotonin inhibiert die Produktion von Noradrenalin
- Konzentration↓ Produktion von Noradrenalin nicht mehr inhibiert → Balance gestört



The menopausal hot flush a review, D.W. Sturdee et al.
Climacteric 2017, Vol 20, No 4, p 296-305

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Vielen Dank für die Aufmerksamkeit

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Sweating and Flushing: Evaluation and Management

M58
Tuesday, June 18
11:15 AM to 12:00 PM

Pierre-Marc Bouloux, BSC, MD, FRCP
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London, United Kingdom
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SIGNIFICANCE OF THE CLINICAL PROBLEM

Flushing describes episodic attacks of redness of the skin together with a sensation of warmth or burning of the face, neck, and less frequently the upper trunk and abdomen. Attacks are typically transient, contrasting with flushing from the persistent erythema of photosensitivity, sunburn or acute contact reactions. Repeated flushing can, over time, result in telangiectasia or occasionally facial rosacea.

Both flushing and sweating are frequently an exaggeration of a physiological process, and a biochemical work-up of every case of every presentation is neither practical nor cost-effective. While a thorough anamesis frequently identifies an obvious cause (e.g. vasomotor instability of the menopausal, alcohol induced flushing), often the diagnosis is far from obvious, and it becomes incumbent on the practitioner to exclude a potentially serious underlying cause of symptoms, which can have a profound effect on the patient's quality of life.

A structured anamnesis lies at the heart of accurate diagnosis, and coupled with physical investigations and targeted investigations, will generally lead to a high probability of a correct diagnosis.

The vasodilatation of flushing may be due to a direct action of a circulatory vasodilator substance, for example histamine, or it may be caused by dysregulated vasodilator autonomic neural activity to cutaneous vasculature of face (travelling with the trigeminal nerve), neck, and upper trunk, where flushing is most frequent. The neurological control of vascular tone is predominantly exerted by autonomic vasodilator nerve fibers. Autonomic nerve fibers also supply eccrine sweat glands, and neurally mediated flushing is frequently associated with sweating (wet flushing) as opposed to isolated (dry) flushing due to the actions of circulating vasodilator substances. The presence or absence of sweating may serve as a clinical guide to the mechanisms of flushing, though not an invariable one. Examples of wet flushing are physiological and menopausal flushing. Niacin-provoked flushing is an example of drug induced 'dry flushing.'

BARRIERS TO OPTIMAL PRACTICE

The causes of flushing and sweating are potentially myriad, but history and examination, may yield important diagnostic clues. In an age of defensive medical practice, the attending clinician may (reflexly) perform a bewildering number of complicated and often expensive investigations to rule out rare pathologies. Perseverance, and unhurried history taking are essential to eschew this pitfall. Patients with flushing and sweating may reach the endocrinologist 'to rule out an endocrine cause' having initially been referred to dermatologists, gastroenterologists, gynaecologists, neurologists, neuroendocrine tumor departments and even psychiatrists without a prior definitive diagnosis. An impoverished patient may then be desperate, and it behooves the endocrinologist, with common sense and a sound knowledge of internal medicine to elucidate the diagnosis.

LEARNING OBJECTIVES

- Learn the value of accurate anamnesis
- The key physical signs to be elicited to reach

a diagnosis
- To familiarize you with the range of disorders and drugs liable to cause flushing/ sweating
- To understand the place of botulinus toxin and endoscopic thoracic sympathectomy (ETS) in selected cases

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Diagnostic Evaluation of the Patient With a Flushing/Sweating

With flushing and sweating, several characteristics of these symptoms should be elicited prior to embarking on expensive laboratory evaluation. These include: (1) provocative and palliative factors, (2) morphology, (3) associated features, and (4) temporal characteristics.

Provocative or palliative factors

Certain agents that precipitate a flush may suggest an aetiological underlying systemic disease e.g., mastocytosis and carcinoid syndrome. Drugs are a particularly common cause of flushing *(see Table 1)*, as is alcohol, particularly in certain racial groups. A recent review has highlighted the fact that some 620 drugs have been associated with flushing!

Morphology of flush/ distribution of sweat
- Is it stereotyped and does it come and go? Can the patient provide photographic evidence ?
- Is the redness patchy or confluent?
- What is the color of the flush?
- Is there cyanosis?
- Is the flushing preceded or followed by pallor?
- Which parts of the body is affected by sweating?

The morphology of the flushing may suggest not only the cause of the flushing but also, in the case of carcinoid tumors, the anatomical origin of the disorder.

Associated features

These could include respiratory symptoms (e.g., wheezing), gastrointestinal symptoms (colicky pain and diarrhoea), headache, urticaria, facial oedema, hypertension, hypotension, palpitations, or sweating.

Temporal characteristics

What is the frequency and duration of the flush/sweat? Patients may not have thought carefully about these questions, and important information can be obtained from a 2-4 week diary in which the patient records qualitative and quantitative aspects of the flushing / sweating event and lists exposure to all exogenous agents. If the diagnosis remains obscure after evaluation of a 2-4 week diary, an exclusion diet can be suggested, paying attention to foods high in histamine, foods and drugs that affect urinary 5-HIAA tests, and foods and beverages that cause flushing. If the flushing reactions completely disappear, restoring the excluded items individually (rechallenge) can identify the causative agent. If the flushing/sweating reactions continue unabated, further metabolic work up may be mandated.

Physical examination of the patient with flushing/ sweating disorder

A thorough general examination of the patient should be undertaken, and vigilance paid to certain key physical signs: telangiectatic lesions, *urticarial pigmentosa*, venous pressures, right sided cardiac valvular signs, goitre and thyroid nodules (painful neck masses can occur with medullary carcinoma of the thyroid), lymphadenopathy in the neck, features of thyrotoxicosis, hepatosplenomegaly, Darier's sign.

Specific causes of flushing and sweating

Blushing

Embarrassment or anger may cause blushing in individuals with a low threshold for this response. The reaction itself may be unusually intense. Explanation and reassurance are usually sufficient. If necessary, propranolol or nadolol may be used to alleviate the symptom.[1]

Thermal stimuli

Heat provokes flushing in many, and overheating can lower the threshold to flushing due to other causes such as menopause. Overheating, such as after exercise or a sauna,

and hot drinks can induce physiological flushing due to the action of a rise in blood temperature on the anterior hypothalamic thermoregulatory center The temperature of hot coffee rather than its caffeine content causes flushing. A useful maneuver for patients faced with a brief thermal exposure is to suck on ice chips carried in an insulated cup, and this will attenuate flushing.

Menopausal flushing/sweating

About 80% of postmenopausal women experience flushing associated with sweating, and a similar syndrome may also occur in men with prostate cancer receiving treatment with gonadotropin-releasing hormone analogues such as buserelin. About 65% of post-menopausal women have hot flushes for 1 to 5 years, 26% for 6 to 10 years, and 10% for more than 11 years. There is considerable variation in the frequency, intensity, and duration of hot flushes within and among individuals. A typical hot flush begins with a sensation of warmth in the head and face, followed by facial flushing that may radiate down the neck and to other parts of the body; it is associated with an slight increase in temperature and pulse rate and followed by a decline in temperature and profuse perspiration over the area of flush distribution. Visible changes occur in about 50% of women, and each flush lasts for 1 to 5 minutes. Rapid oestrogen withdrawal rather than a low oestrogen level by itself is likely to induce hot flushes. A pulse of luteinizing hormone appears to be released at the onset of each flush, but this is not responsible per se for the hot flush since flushing can occur after hypophysectomy. Rather, the synchronization is likely to be with GnRH release. The anterior hypothalamus has oestrogen and progesterone receptors, and both hormones can be used effectively to treat hot flushes. α2 noradrenergic pathways appear participate in the pathogenesis of hot flushes since the α2-adrenergic agonist clonidine attenuates hot flushes by suppressing noradrenaline release. A number of drugs can induce a 'pharmacological menopause' with associated flushing including danazol, tamoxifen, clomiphene citrate and leuprolide.

Certain characteristics suggest the diagnosis of climacteric flushing: drenching perspiration, a prodromal sensation of overheating before the onset of flushing and sweating, and waking episodes at night with the typical symptoms. Alcohol can enhance a menopausal flush. Veralipride, a dopamine antagonist, can attenuate the frequency and intensity of menopausal flushing in premenopausal women pre-treated with goserelin (gonadotropin-releasing hormone agonist) for endometriosis.

Drug induced flushing

A large number of drugs can be associated with flushing *(Table 1)*. Other medications that can cause flushing are corticotrophin-releasing hormone, doxorubicin, niacin and calcium antagonists. Some 5-15% of patients taking PDE5 inhibitors (sildenafil, vardenafil, tadalafil) complain of flushing also. Systemic administration of morphine can cause histamine mediated flushing of the face, neck, and upper thorax. Some patients develop facial flushing and/or generalized erythema after epidural or intra-articular administration of triamcinolone; this is counter-intuitive, as glucocorticoids are usually vasoconstrictors.

Alcohol induced flushing

Certain Asian genotypes evince extensive flushing in response to modest alcohol exposure, due to higher plasma levels of

TABLE 1. Some Causes of Drug-Induced Flushing

All vasodilators (e.g., nitroglycerine, prostaglandins)
Calcium channel blockers (nifedipine etc.)
Nicotinic acid (not nicotinamide)
Morphine and other opiates
Amyl nitrite and butyl nitrite
Cholinergic drugs
Bromocriptine used in Parkinson's disease
Thyrotropin releasing hormone (TRH)
Tamoxifen, clomiphene
Cyproterone acetate
Oral triamcinolone
Cyclosporin
Rifampin
Sildenafil citrate, vardenafil, tadalafil

acetaldehyde caused by deficiency of an isoenzyme of liver aldehyde dehydrogenase. This population can be detected by using an ethanol patch test which produces localized erythema. A special type of alcohol flush is also associated with chlorpropamide. Even small amounts of alcohol provoke intense flushing within a few minutes of ingestion. This flushing is not associated with sweating, but in some cases tachycardia, tachypnoea, and hypotension may be seen. The flush is mediated by elevated acetaldehyde plasma levels and possibly by release of prostaglandins.

Alcohol ingestion can trigger flushing in carcinoid tumors, mastocytosis, medullary thyroid carcinoma, and certain lymphoid tumors. Trichloroethylene, a chemical that has been abandoned in recent years because of carcinogenic potential, can cause flushing. When inhaled following ingestion of alcoholic beverages, a striking cutaneous reaction results, consisting in the sudden appearance of erythema of the face, neck, and shoulders—a reaction that has been termed "degreaser's flush." Nausea and vomiting may also occur.

Food associated flushing/sweating

Eating spicy or sour foods can cause gustatory facial flushing, due to a neural reflex involving branches of the trigeminal nerve. The flushing may curiously be unilateral. The flushing of monosodium glutamate (MSG: sino-cibal syndrome) is controversial. Oral challenge with MSG often fails to induce flushing in volunteers with a history of MSG flushing, and it may be appropriate to look at other dietary agents, such as red pepper, other spices, nitrites and sulphites (additives in many foods), thermally hot foods and beverages, and alcohol. Scromboid fish poisoning (tuna and mackerel) is due to the ingestion of fish that was left in a warm temperature for hours. In addition to flushing, patients with scromboid fish poisoning have sweating, vomiting, and diarrhea. These symptoms are due to intoxication with histamine, which is thought to be generated by histidine decarboxylation by bacteria in spoiled fish.

TABLE 2. Factors That Can Precipitate Flushing in the Carcinoid Syndrome

Hot food/beverage
Spicy food
Chocolate
Cheeses
Tomatoes
Avocados
Red plums
Walnuts
Eggplant
Alcohol
Emotional Stress
Valsalva maneuver: Straining and vigorous coughing
Sudden direct pressure on a large carcinoid tumor

Carcinoid Syndrome

Manifestations of carcinoid tumors include flushing, bronchoconstriction, gastrointestinal hypermotility, and valvular (usually right sided) cardiac disease. Four types of flushing have been described in the literature: erythematous, violaceous, prolonged and bright red. The sudden, diffuse erythematous flush usually affects the face, neck and upper chest and lasts 1-5 minutes and is reported in 20-70% of patients with midgut tumors. Carcinoid tumors can produce a variety of peptides, hormones, and neurotransmitters many of which are vasoactive. 'Carcinoid syndrome' occurs in about 10% of patients with these tumors, and in 75%, episodes of severe flushing are precipitated by exercise, alcohol, stress, and certain foods (spices, chocolate, cheese, avocados, plums, walnuts, red sausage, and red wine) *(Table 2)*; flushing may however appear without provocation. Foregut tumors (stomach, lung, pancreas) are said to be associated with a bright-red "geographic" flush of a more sustained duration, as well as lacrimation, wheezing, sweating, and a sensation of burning. In ileal tumors, the flush is patchier and more violaceous, intermingled with areas of pallor, and does not last as long. Both may be associated with facial oedema that may progress to telangiectasia and even facial rosacea. Pellagra-like skin lesions can result from excessive utilization of tryptophan by the carcinoid tumor, leaving little for the daily

niacin requirement. These lesions include hyperkeratosis; xerosis; scaling of the legs, forearms, and trunk; angular cheilitis; and glossitis. 70% of patients also have watery diarrhoea, and 35% develop right-sided endocardial fibrosis leading to congestive heart failure. Diarrhoea and other gastrointestinal manifestations may precede or coexist with the flushing.

Ninety-five percent of all carcinoids are found in the appendix, rectum, or small intestine, the remainder arising outside of the intestinal tract (e.g. ovary, testis, lung). In general, the larger the primary tumor, the greater the likelihood of metastasis, which provides prognostic implications. Carcinoids of the appendix and rectum rarely present with the carcinoid syndrome. 40- 50% of patients with carcinoids of the small intestine or proximal colon have manifestations of the carcinoid syndrome. Tumors that secrete their hormonal product into the portal venous system do not cause flushing because the released amines are inactivated by the liver. In contrast, liver metastases may escape hepatic inactivation and deliver their product directly into the systemic circulation and hence cause flushing. Pulmonary or ovarian carcinoids release pharmacological products directly into the venous circulation, bypassing the portal system, and can therefore cause symptoms without metastasizing to the liver. Bronchial carcinoids are associated with the more prolonged type of flushing, lasting several hours to sometimes days.

Pathophysiology

The flushing seen with foregut carcinoids is due to release of histamine. Flushing seen with ileal carcinoids is unlikely to be explained solely by serotonin production, since serotonin may or may not be released into the circulation during flushing, intravenous infusion of serotonin does not cause flushing, and moreover flushing is unaffected by serotonin antagonists such as methylsergide, cyproheptadine, and ketanserin). Foregut carcinoids do not generally secrete serotonin but, instead, its precursor, 5-hydroxytryptophan. Screening should therefore seek this product if the other metabolites are not elevated. Other likely mediators of flushing include prostaglandins and the tachykinins. Tachykinins are believed to be mediators of the flushing in tumors of the midgut. They exert vasodilation and contraction of various types of smooth muscle. These peptides include substance P, substance K, and neuropeptide K. Their release is usually partially blocked by somatostatin analogues. Urine excretion of histamine is usually increased in patients who have gastric carcinoid.

Diagnosis

Clinical diagnosis is not difficult in patients with flushing episodes associated with systemic symptoms (diarrhoea, wheezing, and weight loss) and hepatomegaly. It is more difficult in patients who have occasional flushing and no associated symptoms. Only when there is reasonable clinical suspicion should biochemical testing be done, and localization studies must be reserved for those cases proven biochemically.

Provocative Tests

When in doubt, a carcinoid flush can be provoked by alcohol ingestion (4 mL of 45% ethanol) or the infusion of 6 μg noradrenaline, an effect blocked by phentolamine (5 to 15 mg intravenously). Calcium gluconate, 10 to 15 mg/kg, administered intravenously over 4 hours, may produce a flush mimicking a spontaneous attack. Epinephrine reverses flushing in patients with mastocytosis but provokes flushing in patients with the carcinoid syndrome. The procedure should only be performed in a controlled environment. A 1 μg/mL solution of epinephrine in normal saline is administered by intravenous bolus beginning with an initial dose of 0.05 μg. The dose is doubled at intervals of 10 minutes until flushing appears or a until a maximum of 6.4 μg is given. When flushing occurs, it usually begins within 60 seconds after epinephrine administration and dissipates after 3 or 4 minutes.

Biochemical Diagnosis

The diagnosis is confirmed by determining urinary excretion of 5-hydroxyindoleacetic

acid (5-HIAA), the major metabolite of serotonin, normally excreted at 2 to 10 mg (10 to 50 μmol) per 24 hours. A value of more than 150 μmol/24 hours (30 mg/24 hours) is usually diagnostic, and in carcinoid syndrome it is often above 200 μmol per day. This test has a sensitivity of 75% and a specificity of up to 100%. The degree of elevation of 5-HIAA does not always correlate with the severity of flushing, and other vasoactive substances are clearly at play (vide infra). As excretion may be variable, repeated estimations are mandatory. Some patients with carcinoid cannot convert serotonin to 5-HIAA, and have high blood levels of serotonin but normal urinary 5-HIAA. Dietary factors may cause confusion and patients should receive a diet free of the culprit items for 3 days before the urine collection. Measuring blood serotonin is helpful when urinary 5-HIAA is equivocal. Patients with carcinoid syndrome usually have very high blood levels of serotonin. Measurement of serotonin and its metabolites permits the detection of 84% of neuroendocrine tumors. Even carcinoids that predominantly secrete 5-hydroxytryptophan are associated with increased urinary excretion of 5-HIAA because the released 5-hydroxytryptophan is converted to serotonin in other tissues and is subsequently metabolized to 5-HIAA. Chromogranin A (CgA), an acidic glycoprotein of 439 aminoacids, is co-secreted with serotonin, and is elevated in most patients with carcinoid tumors. CgA can be cleaved into smaller fragments at dibasic cleavage sites, generating multiple bioactive fragments such as vasostatins, chromostatin, and pancreastatin. In the evaluation of flushing with an equivocal 24-hour urinary 5-HIAA, a normal plasma CgA value suggests non-endocrine causes. This test is sensitive but not specific, and its predictive value in carcinoid is still uncertain. Flushing was associated with a rise in circulating substance P in 80% of patients with gastric carcinoid. Neurokinin A levels are elevated in certain patients.

Management

Corticosteroids, phenothiazines, and bromocriptine are sometimes effective in suppressing flushing in patients with bronchial carcinoid tumors, as may cyproheptadine, a serotonin antagonist. Combined administration of H1 and H2receptor antagonists may prevent attacks of flushing in patients with foregut carcinoid tumors that produce histamine. Alpha-interferons may control symptoms of carcinoid syndrome and produce objective biochemical responses (greater than 50% suppression of 5-HIAA) that have a median duration of about 4 weeks. Since catecholamines are known to precipitate attacks, a trial of clonidine is worthwhile. Long acting somatostatin analogues such as octreotide/lanreotide have a much longer half-life, making subcutaneous therapy possible. Octreotide lowers plasma levels of serotonin and tachykinins and relieves both flushing and diarrhoea. Amelioration of these manifestations is accompanied by a marked reduction in the urinary excretion of 5-HIAA. The patient should receive an adequate niacin supplement (nicotinamide rather than nicotinic acid, since the latter causes flushing) and should avoid foods, agents, and activities that precipitate symptoms.

In some patients, failure of medical treatment may necessitate carrying out hepatic artery embolization. This treatment is based upon the dependence of metastatic malignant tissue but not healthy liver parenchyma on an intact hepatic arterial blood supply. Anti-tumor chemotherapy remains experimental. Alpha-interferon causes symptomatic relief accompanied by lowering of urinary 5-HIAA.

Prognosis

About one-fifth of patients with the carcinoid syndrome undergo a protracted course. In the remainder, deterioration can be rapid. The mean survival is about 8 years with some surviving up to 20 years. Mean survival is 36 months after the first flushing episode. Targeted radionuclide therapy may in future extend duration of remission in inoperable cases.

Mastocytoses: Aetiology

Mastocytoses are benign, indolent proliferative disorders of the reticuloendothelial system and due to a hyperplastic rather than a neoplastic process, although some forms are aggressive.

TABLE 3. Factors That Produce False-Positive Results With Urinary 5-HIAA Determination

Foods	Drugs
Avocado	Paracetamol (acetaminophen)
Banana	Acetanilid
Chocolate	Caffeine
Coffee	Fluorouracil
Eggplant	Guaifenesin
Pecan	L-Dopa
Pineapple	Melphalan
Plum	Mephenesin
Tea	Methylamphetamine
Walnuts	Methocarbamol
	Methysergide
	Phenmetrazine
	Reserpine
	Salicylates

Most patients have evidence of cutaneous involvement, most commonly multiple, small, pigmented lesions that produce urticarial on stroking with a blunt object (Darier's sign). They are often self-limited, especially in childhood. Mast cells possess the enzyme histidine decarboxylase which enables them to synthesize and store histamine. Other preformed mediators include tryptase, chymase, and carboxypeptidase. Serotonin has not been detected in the human mast cell.

Histopathology

There are increased numbers of normal-looking mast cells in the dermis. These cells may be predominantly perivascular or may show a nodular distribution. The epidermis is normal, apart from increased melanization.

Biochemical Markers

Symptoms of mastocytosis are mainly the result of release of products of mast-cell activation. Plasma histamine levels are frequently raised in patients with systemic symptoms, and elevated urinary excretion of histamine and its metabolite methyl imidazole acetic acid (MIAA) can also be seen. Plasma tryptase levels can also be elevated. Prostaglandin D2 (PGD2) is another product of mast-cell activation. Urinary excretion of this substance and its major metabolites can be elevated several-fold in patients with mastocytoses. Urine should be collected within a few hours of an attack.

Clinical Presentation

Episodic bright-red flushing occurs either spontaneously or after rubbing the skin or exposure to alcohol or mast-cell degranulating agents. Attacks may be accompanied by headache, dyspnoea and wheezing, palpitations, abdominal pain, diarrhoea, and syncope and may closely resemble the flushing episodes of the carcinoid syndrome, especially the foregut variety, also mediated by histamine. Rosacea may develop rarely. PGD_2 might be associated with the symptoms of flushing and diarrhoea. The flushing of cutaneous mastocytosis typically lasts more than 30 minutes, unlike the typical carcinoid flush which lasts less than 10 minutes. In *urticaria pigmentosa*, the diagnosis is established by demonstrating that gentle rubbing of the lesional skin causes local itching, redness, and whealing (Darier's sign). This reaction is due to local histamine release. Darier's sign may also be demonstrated in non-lesional skin. Bone involvement may manifest as osteoporosis or osteosclerosis, and the systemic form of the disease can involve the GI tract with mucosal nodules in the ileum, stomach and large bowel. Haematological abnormalities include mast cell infiltration of the bone marrow, anaemia, leucocytosis, eosinophilia and occasional lymphadenopathy. A subgroup of patients has mastocytosis secondary to a primary haematological disorder. More than 80% of patients with systemic mastocytosis have activating mutations (D816V) in the tyrosine kinase domain of KIT that alter mast cell growth and differentiation.

Confirmation of the diagnosis is obtained by skin biopsy. In patients with systemic symptoms, bone-marrow biopsy and liver and spleen scans are usually performed. Bone scans should only be carried out in the presence of localized bone symptoms.

Treatment

Treatment of non-localized forms of mastocytosis is mainly symptomatic.

Patients should avoid known histamine-degranulating agents. Antihistamines remain the preferred treatment for most patients with uncomplicated urticaria pigmentosa. Human skin blood vessels possess H1 and H2 receptors, involved in both vasodilation and increased vascular permeability evoked by histamine. Thus, combination treatment with an H1 antihistamine (hydroxyzine, 10 to 20 mg, or cetirizine 10mg tid) and H2antihistamine (cimetidine, 200 to 500 mg) is logical and sometimes effective at controlling the flushing episodes. Oral administration of the mast-cell stabilizing agent disodium cromoglycate has proved effective in some patients. The drug does not decrease urinary excretion of histamine and the histamine metabolite MIAA. Some experts recommend using this agent only in patients with systemic mastocytosis suffering from gastrointestinal symptoms. Photochemotherapy has been reported to cause symptomatic relief as well as objective reduction in the population of mast cells and the urinary excretion of MIAA.

Medullary Thyroid Carcinoma

The range of substances secreted by medullary carcinoma of the thyroid is considerable, whether sporadic or familial and the most common symptom after diarrhoea. Occurring in one-third of the patients with diarrhoea, there is pronounced episodic flushing, which, as in the carcinoid syndrome, may be induced by alcohol ingestion. Calcitonin-gene related peptide, an extremely powerful peripheral vasodilator, is a likely mediator of flushing. The other possible explanation is that calcitonin stimulates prostaglandin secretion which in turn, cause the symptoms. A mass is usually evident in the neck, with evidence of lymph node metastases. In all cases the diagnosis can be confirmed by positive immunostaining of tumor tissue for calcitonin and CEA.

Phaeochromocytoma

Flushing is rare in patients with pheochromocytoma. If flushing occurs at all, it is seen after a paroxysm of hypertension, tachycardia, palpitations, chest pain, severe throbbing headaches, and excessive perspiration. Pallor is typically present during the attack, and mild flushing may occur after the attack as a rebound vasodilation of the facial cutaneous blood vessels.

TABLE 4. Factors That Can Cause False-Negative Results

Corticotrophin
P-chlorophenylalanine
Chlorpromazine
Heparin
Imipramine
Isoniazid
Methenamine mandelate
Methyldopa
MAOI
Phenothiazine
Promethazine
(adapted from Kjell Oberg Williams Textbook of Endocrinology Pages 1809-1828 12th Edition)

Spinal cord lesions above T6

Facial flushing and headache can occur along with sweating of the face, neck, and upper trunk in patients with spinal cord lesions above T-6, particularly as an exaggerated response to bowel or bladder distention.

Miscellaneous causes of flushing

Other causes are certain pancreatic tumors (VIPOMAS), insulinoma, and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes). Transient flushing of the face, chest, or arms has been noted after neurological deterioration secondary to rapid rise in intracranial pressure.

Other endocrine causes of hyperhydrosis

Acromegaly, thyrotoxicosis, hypoglycaemia constitute other causes of sweating *(see Table 4)*.

Idiopathic hyperhidrosis

It is estimated that 0.6 to 1 percent of the population has idiopathic hyperhidrosis, or excessive sweating. The condition may be focal or more generalized. To diagnose idiopathic hyperhidrosis, there must be excessive sweating

for at least six months duration with two of the following criteria:

- Bilateral symmetric sweating
- Impairment of daily activities
- At least one episode per week
- Onset before 25 years of age
- Family history of idiopathic hyperhidrosis
- Focal sweating that stops during sleep

Idiopathic hyperhidrosis is underreported for various reasons. Patient may be too embarrassed to report the symptom or may not even realize the condition is treatable. The Primary Care Physician may also be dismissive of the symptom.

Topical and oral medications that can be used to treat idiopathic hyperhidrosis. Procedures such as Botox and iontophoresis may also be used. When these interventions fail and hyperhidrosis continues to be a debilitating condition, a minimally invasive endoscopic thoracic sympathectomy may help.

MAIN CONCLUSIONS

1. Flushing and sweating are common clinical symptoms.
2. The key to optimal management relies on a thorough anamnesis and clinical examination.
3. Targeted investigation is preferable to a shot-gun approach.
4. Effective treatment is available for most causes of flushing if the correct diagnosis is made.

CASES WITH QUESTIONS

Case 1

A 29-year-old male patient of Irish origin, a nonsmoker and nondrinker, gave a 14 month history of an erythematous skin rash after intake of aspirin. He presented to A and E with abdominal pain, vomiting, and a diffuse erythematous skin rash. OE he was alert and afebrile with no abdominal tenderness. Initially, blood pressure was 170/90 mm Hg and pulse rate was 70/min, but hemodynamic parameters rapidly deteriorated despite fluid infusion. Laboratory investigations revealed acute renal failure (creatinine 211 µmol/L), hypokalaemia (2.6 mmol/l) haemoconcentration (protein 92 g/L), and clotting tests showed prolonged activated partial thromboplastin time (aPTT) (187" versus 30" control value) and prothrombin time (17"2 versus 11"8 control value). Blood count showed leucocytosis (18 × 109/L) with neutrophiia (16 × 109/L) and a normal platelet and eosinophil count. Haemoglobin level was 12.6 g/dL. C-reactive protein was only slightly elevated (14 mg/L). The patient was transferred to the intensive care unit of the university hospital because of anuria and unexplained abnormalities of clotting tests. On admission a diffuse skin rash was still present. Blood pressure fell to 80/60 mm Hg, pulse rate 130/mn, anuria and agitation ensued. Orotracheal intubation was thus performed, and mechanical ventilation and continuous hemofiltration were started. An epinephrine infusion corrected the haemodynamic status, and the skin rash quickly disappeared. Septic or toxic shock were the first hypotheses investigated, but no infection was documented, and there was no evidence for disseminated intravascular coagulation, since the platelet count remained normal. Repeated clotting tests showed however an aPTT up to 200", a prothrombin time raised up to 90", and anti-Xa activity was 2.5 UI/mL. Fibrinogen was 1.8 g/L, antithrombin level was 56%.

Questions

What is your differential diagnosis?
Can you explain the haemostatic abnormalities?
What management would you consider?

Case 2

A 32 year old polish man reports onset of a livid discoloration of the cheeks within 5 minutes of ingesting white wine, and certain spirits. There is a past history of anxiety state but his general health is otherwise good. He takes no recreational drugs and is on no regular medication. He is distressed by this socially disabling symptom.

Questions

1. What is the differential diagnosis?
2. How should he be managed?

Case 3

A 28 year old beautician complains of excessive armpit sweating brought on by

minimal exertion. Recently, her hands have become cold and clammy, so that she has to keep drying them. Her mother suffered from a similar condition. Her general health is good, her weight constant and appetite good. She does not drink alcohol and is on no medication.

Questions
1. What is the differential diagnosis?
2. How is she best managed?

DISCUSSION OF CASES AND ANSWERS

Case 1

Systemic mastocytosis, confirmed by a serum tryptase level up to 200 µg/L (normal < 13) and a bone marrow biopsy showing multifocal infiltrates of spindle-shaped mast cells. The patient was initially treated with fresh frozen plasma and red cell transfusions, and then protamine was infused at a rate of 1200 UI/h combined with IV glucocorticoids, enteral H1 and H2 antihistamines, and imatinib mesylate (400 mg/d). aPTT and prothrombin time were normalized within four days. On clinical examination in the internal medicine unit, urticaria pigmentosa with Darier's sign (urtication reaction at the site of the papulo-macular lesions when scratched) demonstrated on the trunk.. Complementary workup revealed long bones involvement on radiology, diffuse bone abnormality on technetium scintigraphy, diminished bone mineral density (lumbar T-score -1.4; femoral T-score -0.8), and the presence of mastocytic infiltrates in the oesophageal wall. No skin biopsy was performed. C-kit mutation D816V was demonstrated. The patient was discharged on ranitidine, cetirizine, glucocorticoids, alendronate, and imatinib mesylate (200 mg/d). On his last follow-up visit in June 2012, he remained asymptomatic under the same treatment at the exception of steroids which had been discontinued.

Case 2

Most likely a deficiency of isoenzyme of alcohol dehydrogenase.

Case 3

Idiopathic focal hyperhidrosis.

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