REVIEW

The glucagonoma syndrome and necrolytic migratory erythema: a clinical review

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Abstract

The glucagonoma syndrome is a rare disease in which a typical skin disorder, necrolytic migratory erythema, is often one of the first presenting symptoms. Weight loss and diabetes mellitus are two other prevalent characteristics of this syndrome. Necrolytic migratory erythema belongs to the recently recognized family of deficiency dermatoses of which zinc deficiency, necrolytic acral erythema and pellagra are also members. It is typically characterized on skin biopsies by necrolysis of the upper epidermis with vacuolated keratinocytes. In persistent hyperglucagonemia, excessive stimulation of basic metabolic pathways results in diabetes mellitus at the expense of tissue glycogen stores, and muscle and fat mass. Multiple (essential) nutrient and vitamin B deficiencies develop, which contribute to the dermatosis. In addition, glucagonomas may produce various other products, like pancreatic polypeptide, that add to the catabolic effects of glucagon.

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Introduction

In 1942 Becker *et al.* (1) described a patient with a typical skin disorder who was found to have a pancreatic neoplasm. More than 20 years later, McGavran *et al.* (2) documented hyperglucagonemia in association with the cutaneous eruptions. The combination of symptoms was called the glucagonoma syndrome. The typical skin lesions were called necrolytic migratory erythema by Wilkinson (3, 4). Here, we describe two patients with markedly elevated glucagon concentrations due to a glucagonoma; however, only one patient presented the glucagonoma syndrome. We focus on the skin disorder, a characteristic deficiency dermatosis, and compare it with similar skin disorders. Diagnostic considerations from dermatological and endocrine perspectives are given. Further, we discuss the metabolic consequences of hyperglucagonemia in relation to the characteristic dermatological and pathophysiological findings in this disease.

Patient 1

A 67-year-old man was referred to the Department of Dermatology of the University Medical Center Utrecht because of an extensive, itching cutaneous eruption that had been present for 18 months. His medical history revealed that at age 20 he had

an appendectomy and at age 50 he was operated on because of bilateral inguinal herniae. His medical history was otherwise unremarkable and he was receiving no medication. The skin eruption started at his lower extremities and progressed to involve trunk, upper extremities, head and neck. It had been present with waxing and waning and migrated along the body surface. In addition to the skin problem our patient complained of weight loss (10 kg in 1 year), weakness and a burning mouth. The family history was negative for multiple endocrine neoplasia or diabetes mellitus.

On physical examination, the patient appeared cachectic (weight, 69 kg; height, 183 cm). Along the body surface were cutaneous eruptions of erythematous polycyclic migratory lesions with advancing scaling borders. The centers were hypopigmented or slightly scaly. The chronic lesions showed hyperpigmentation and scaling more than erythema (Fig. 1). Some of the older lesions were crusted (Fig. 2). The patient had a glossy red tongue (Fig. 3); lungs, heart and abdomen were normal. The neurological examination was unremarkable and no visual field defects were found.

Extensive laboratory testing revealed a normocytic anemia (hemoglobin, 7.2 mmol/l). Blood chemistries and electrolytes were all normal, except for a random glucose concentration of 13.6 mmol/l.

A biopsy of the skin (Fig. 4) showed vacuolated keratinocytes in the upper epidermis leading to confluent necrosis of the epithelium. There was a mild

Figure 1 Necrolytic migratory erythema with typical scaling, erythema and hyperpigmentation.

infiltrate of lymphocytes in the superficial dermis. The histological findings on skin biopsy were compatible with the diagnosis of necrolytic migratory erythema and prompted further diagnostic work-up for a pancreatic islet cell tumor. Abdominal ultrasonography showed a process in the tail of the pancreas.

Figure 2 Necrolytic migratory erythema in the face with older crusted lesions (with permission of patient).

The patient was subsequently referred to the endocrinology department on suspicion of having the glucagonoma syndrome. An abdominal computed tomography scan reported a large pancreatic mass with a diameter of 13 cm (Fig. 5). No evidence of metastases in the liver or elsewhere was found.

Hormone analyses showed that both glucagon levels (700 pmol/l; normal, 14–40 pmol/l) and pancreatic polypeptide (6000 pmol/l; normal, <100 pmol/l) were grossly elevated. An octreotide test (100 µg s.c.) was performed and resulted in strong suppression of both hormones.

Treatment was initiated with somatostatin, and surgical removal of the glucagonoma was subsequently performed in our hospital by distal pancreatectomy. During the operation there were no signs of lymph node involvement or other metastases. On histological examination the pancreas showed an islet cell tumor with a size of 14 cm. There was vaso-invasive growth of tumor cells. The peri-pancreatic lymph nodes were negative. Immuno-histochemical stainings showed the tumor to be positive for glucagon, synaptophysine and chromogranine. Genetic analysis of the glucagonoma

Figure 3 Glossitis in the glucagonoma syndrome.

Figure 4 Skin biopsy in necrolytic migratory erythema showing a large zone of necrosis in the upper epidermis (double headed arrows) and vacuolated keratinocytes (single headed arrows).

revealed no mutation of the multiple endocrine neoplasia type-1 (MEN1) gene.

Postoperatively, the necrolytic migratory erythema disappeared almost immediately. After 1 week no sign of skin disease was left. The glucagon concentrations returned to normal values (19 pmol/l) within 1 week, and remained normal. Nineteen months after surgical treatment, a slight increase in pancreatic polypeptide level (118 pmol/l) was found, while the other hormone levels were still normal. Five months later, the patient complained of weakness in his legs. Magnetic imaging revealed a tumor at the level of thoracic vertebrae 8 to 11. Needle biopsy showed a neuro-endocrine tumor, most probably a relapse of the glucagonoma

although the glucagon level was still normal. Within a few weeks our patient was not able to walk alone. Shortly thereafter he was found dead at home. Autopsy was not performed.

Patient 2

A 16-year-old boy was found to have hyperglucagonemia (145 pmol/l; normal, 14–40 pmol/l) during regular screening visits at our outpatient clinic. He is a carrier of a mutation in the MEN1 gene and comes from a family with MEN1. His father suffered from Cushing's syndrome and died at the age of 39 due to the consequences of Zollinger–Ellison syndrome. His brother had recurrent epileptic insults at age 13, due to an insulinoma.

He had no complaints and his physical examination, with special attention to skin problems, was unremarkable. An abdominal magnetic resonance imaging scan and angiography showed a mass with a diameter of 2 cm in the corpus of the pancreas. Because of potential malignancy a subtotal pancreatectomy was performed. Histological examination revealed multiple islet cell tumors positively staining for insulin, glucagon and pancreatic polypeptide. Plasma concentrations of insulin were not increased. Pancreatic polypeptide levels were not determined. As a consequence of the MEN1 syndrome he developed hyperparathyroidism and the Zollinger–Ellison syndrome. Currently, 15 years after removal of the glucagonoma, he is in good health.

Figure 5 CT scan of the abdomen of patient 1, revealing a large tumor in the tail of the pancreas.

Discussion

We have described two patients with distinctly elevated glucagon concentrations but only one had the glucagonoma syndrome. Thus, glucagonoma producing islet cell tumors can present with various clinical manifestations ranging from asymptomatic (patient 2) to the full-blown glucagonoma syndrome (patient 1). The most common features of this syndrome are weight loss, the necrolytic migratory erythema and diabetes mellitus (5). The prognosis of this disease varies greatly according to the stage at which the disease is diagnosed. Early recognition of the symptoms of the glucagonoma syndrome is therefore important (6). Glucagonomas due to MEN1 syndrome are rare and comprise not more than 3% of the glucagonomas (7). They probably carry a better prognosis due to early recognition by periodic screening visits (8, 9). Sporadic cases are diagnosed much later in the course of the disease. By the time of diagnosis, 50% (10) to 100% (5) of patients already present with metastatic disease and a cure is often impossible. The tumor is resistant to chemotherapy and metastatic disease is often not amenable to surgical resection (11). However, since this island cell tumor is slow growing, prolonged survival (more than 20 years) is possible (12) and in metastatic disease most causes of death appear to be unrelated to the tumor (5). Successful palliative treatment is possible with long-acting somatostatin analogs (13) and/or interferon alpha (14). In addition, supplementation with zinc, amino acids and essential fatty acids appears to be beneficial in some cases (15–17) together with topical dermatological therapy (10). We will now focus on the challenge of diagnosing the glucagonoma syndrome from two points of view.

The dermato-pathologic perspective

Necrolytic migratory erythema: characteristics of a deficiency dermatosis The necrolytic migratory erythema is the presenting problem in roughly 70% of the patients with a glucagonoma (5). The lesions consist of an intense erythema with superficial epidermal necrosis. This leads to shedding of the skin with flaccid bullae and crusted erosions. Central healing occurs, which gives the lesions an annular appearance. The lesions primarily affect the perineum and other intertriginous sites. The trunk, legs, perioral skin and sites of minor trauma can also be involved. Onychoschizia is reported (12). The most specific feature on histological examination of the skin, is necrolysis of the upper epidermis with vacuolated keratinocytes, leading to focal or confluent necrosis (18). In fact, the histology of the skin is very similar to the biopsy findings in other deficiency states like pellagra (19), zinc deficiency (20) and necrolytic acral erythema (21). We will discuss

these conditions because they are the histopathological differential diagnosis of necrolytic migratory erythema.

Pellagra Pellagra develops as a consequence of inadequate amounts of niacin (nicotinic acid) in the tissues. It is a multi-system nutritional disorder resulting from a primary dietary deficiency, malabsorption, use of chemotherapeutic agents, or from abnormalities of tryptophan metabolism (22, 23). An example of this latter category is the carcinoid syndrome, in which tumor cells divert tryptophan metabolism toward serotonin and away from nicotinic acid. In Hartnup disease there is a congenital defect in tryptophan absorption and transfer. Initially, there is a burning erythema in sun-exposed areas. The lesions are sharply demarcated and have a symmetrical distribution. Particularly affected are the dorsum of the hands, the forearms, the face and the neck; blistering may occur. The final stage of the lesions is an intense hyperpigmentation with sharp margination and areas of epithelial desquamation. Other features include glossitis and angular cheilitis, comparable with lesions in the glucagonoma syndrome. Pellagra is sometimes called the 'disease of the four Ds': dermatitis, diarrhea, dementia and, if untreated, death.

Zinc deficiency Zinc deficiency usually presents in infancy. The cutaneous lesions are eczematous, crusted, sometimes vesico-bullous or pustular eruptions with an acral and periorificial distribution. The skin lesions are accompanied by alopecia and diarrhea. This recessively inherited condition, due to a rare disorder of zinc metabolism, is known as acrodermatitis enteropathica and may occasionally present itself in adulthood (24). Stomatitis, photophobia, nail dystrophy, hair shaft abnormalities, short stature and emotional disturbances can also be seen. Other causes of an acrodermatitis-enteropathica-like eruption are zinc deficiency in advanced cancer and in Crohn's disease, intestinal bypass procedures, gastrectomy, advanced alcoholic cirrhosis, the acquired immunodeficiency syndrome, isoleucine deficiency, anorexia nervosa, cystic fibrosis and artificial feeding in premature infants. This condition is rarely seen in breast-fed infants. Low body stores of zinc and a poor capability to absorb zinc from the gut make premature infants more vulnerable to the development of zinc deficiency than full-term infants. An acrodermatitis-enteropathica-like dermatosis is also described in patients with parenteral nutrition without zinc supplementation. The rare aminoacidopathies (methylmalonic and propionic acidemia) may cause a periorificial dermatitis resembling acrodermatitis enteropathica. Biotin deficiency, which can be due to an inborn error in metabolism such as biotinidase deficiency, can also mimic zinc deficiency.

Necrolytic acral erythema A variant of necrolytic erythema is the so-called necrolytic acral erythema,

presenting with erythematous patches with erosions and blisters; there is a predilection for the lower limbs. Zinc levels are normal. This condition is strongly associated with hepatitis C (21) and responds to treatment with interferon alpha and oral zinc.

In conclusion, when a dermatopathologist notes the characteristic *vacuolization* of keratinocytes in the upper epidermis, he should think of the deficiency dermatoses mentioned above. If a clinical description or, even better, a clinical differential diagnosis including one of the deficiency states is given, it is possible to differentiate between the different types. However, frequently the condition will not be recognized by the clinicians and in these cases the best conclusion is: 'Biopsy of the skin suggestive for a deficiency dermatosis. Are there clinical indications for necrolytic migratory erythema, pellagra or zinc deficiency?'

The endocrine perspective

Diagnostic considerations Our first patient presented with cachexia, normocytic anemia, diabetes mellitus and a process in the tail of the pancreas. The differential diagnosis of pancreatic tumors includes, among other factors: pancreatic carcinoma, islet cell tumors (e.g. insulinoma or gastrinoma), abscesses or metastases. The combination of diabetes mellitus and a pancreatic tumor (especially in the tail of the pancreas) should prompt the clinician to think of an endocrine tumor. Although diabetes mellitus can develop as a consequence of a pancreatic carcinoma in 50% of cases, one should also think of glucagon- or somatostatin-producing tumors. The somatostatinoma syndrome consists of diabetes mellitus, cholecystolithiasis and steatorrhea (25); skin manifestations have not been described. Impaired fasting glycemia or diabetes mellitus is found in 80% of patients with the glucagonoma syndrome. As mentioned before, a typical skin disorder is part of this disease. Without having knowledge of a pancreatic process, recognition of the glucagonoma syndrome largely depends

on appreciation of the skin disorder by clinician or pathologist. However, in most cases of the glucagonoma syndrome other potentially diagnostic clues are present. In our first patient weight loss and anemia were suggestive of neoplastic disease. Thus, careful radiological examination in the diagnostic work-up would eventually have revealed a pancreatic tumor. Furthermore, one should keep in mind that the development of diabetes in a patient without obesity can be the consequence of an endocrinopathy.

The hormonal origins and metabolic effects

Glucagon and the glucagon-like peptides are encoded within a larger precursor, proglucagon. The proglucagon gene is expressed in the pancreas (A cells), intestine (L cells) and brain (solitary tract), giving rise to a single proglucagon mRNA transcript that is identical in all tissues. Tissue-specific post-translational processing of proglucagon accounts for the different molecular forms of the glucagon-related peptides present in each tissue (26, 27). In the pancreas it gives rise to glucagon, the major proglucagon fragment (MPGF) and glicentin-related polypeptide. In the intestine, proglucagon peptide cleavage results in glicentin, oxyntomodulin and the glucagon-like peptides I and II (26). Hypoglycemia, most amino acids, many gut hormones and the autonomous nervous system promote pancreatic glucagon secretion directly or indirectly. Hyperglycemia, insulin and somatostatin exert an inhibitory influence. Glucagonomas secrete a disproportionate amount of proglucagon-like material (28–31).

Glucagon has various important effects on glucose, fat and protein metabolism (Fig. 6). It stimulates hepatic gluconeogenesis and inhibits glucose breakdown (glycolysis); glycogen synthesis is inhibited. In adequately fed people, glucagon also promotes glycogen breakdown (glycogenolysis) in the liver. In adipose tissue it activates hormone-sensitive lipase, the rate-limiting step in triglyceride degradation. Thus, it increases the free fatty acid delivery for hepatic

Figure 6 Metabolic effects of persistent hyperglucagonemia.

ketogenesis while, at the same time, blocking liver-derived lipoprotein production. In muscle, enhanced protein breakdown results in the flow of the gluconeogenic amino acids alanine and glutamine from muscle to liver. Urea synthesis in patients is increased (32). Hyperglucagonemia in healthy subjects and in the glucagonoma syndrome reduces plasma amino acid concentrations and enhances essential amino acid catabolism (32–35). As a consequence, in persistent hyperglucagonemia diabetes mellitus develops at the expense of tissue glycogen stores, muscle and fat mass.

The etiology of the necrolytic migratory erythema

The exact cause of the skin rash remains unknown. Normalization of glucagon concentrations by surgery or somatostatin analogs almost invariably results in rapid disappearance of the skin disorder. Studies on treatment of various nutritional deficiencies have yielded limited success. However, it is likely from the physiological function of glucagon, as well as from the histopathological findings on tissue biopsy, that the necrolytic migratory erythema is a true deficiency dermatosis. Hypovitaminosis B develops through persistent stimulation of the carbohydrate metabolism as a result of hyperglucagonemia. Indeed, the glucagonoma syndrome exhibits several features of vitamin B₂ (riboflavin) deficiency (angular stomatitis, cheilosis and glossitis), vitamin B₃ (niacin) deficiency (dermatitis, diarrhea and dementia), vitamin B₆ (pyridoxine) deficiency (disturbances in amino acid metabolism, hypochromic microcytic anemia, secondary pellagra; also exhibited are disturbances in the central nervous system like depression and convulsions) and panthothenic acid (pigmentation disorders), biotin (dermatitis), folic acid and vitamin B₁₂ (cyanocobalamin) deficiencies (macrocytic anemia, neurological symptoms and dermatitis). Interestingly, relatively few symptoms have been described that suggest vitamin B₁ (thiamine) deficiency – such as heart failure or Wernicke–Korsakoff syndrome. Furthermore, enhanced lipolysis may lead to deficiencies of essential fatty acids, which have been reported to result in a dermatitis with scaly lesions (36). Enhanced protein breakdown leads to essential amino acid deficiency which may result in a deficit of dopamine, (epi)nephine, thyroxine, tri-iodothyronine and serotonin. All this may contribute in a complex way to the glucagonoma syndrome. Furthermore, post-translational processing may be different in pancreatic islet cell tumors, resulting in several bioactive polypeptides such as the glucagon-like peptides 1 and 2, with profound effects on carbohydrate metabolism, intestinal motility and food intake (37–40). Pancreatic polypeptide is very often co-secreted in glucagonomas, as was the case in patient 1. Pancreatic polypeptide has known actions in gastrointestinal motility and secretion (41) and has recently been found to also inhibit food intake and stimulate energy expenditure following peripheral

administration (42). Thus, high levels of pancreatic polypeptide and other proglucagon fragments may be important additional factors in the appearance of the glucagonoma syndrome, potentiating the catabolic effects of glucagon. However, hyperglucagonemia *by itself* is also sufficient for the development of necrolytic migratory erythema as evidenced by recent case reports of iatrogenic necrolytic migratory erythema after intravenous administration of glucagon in the treatment of persistent hypoglycemia (43–45). Perhaps, as in the carcinoid syndrome, systemic and not portal concentrations of glucagon are determinants of disease symptoms.

In conclusion, hyperglucagonemia provokes multiple nutrient and vitamin B deficiencies, which in turn are the probable cause of this typical skin disorder. Deficiencies may develop depending on the duration and degree of hyperglucagonemia and on the (pre-existing) nutritional status of the patient. In addition, other bioactive polypeptides may be co-secreted, potentially adding to the effects of glucagon. These factors all may contribute to the variable clinical expression of the glucagonoma syndrome.

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