

NECROLYTIC MIGRATORY ERYTHEMA AND GLUCAGON CELL TUMOUR OF THE PANCREAS: THE GLUCAGONOMA SYNDROME

Report of Two Cases

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Abstract. Two cases of necrolytic migratory erythema are described. Both patients also suffered from anaemia, weight loss, hypersedimentation and carbohydrate intolerance. A solitary pancreatic tumour was found in both cases—at autopsy in one and at laparotomy in the other. Microscopic examination of skin biopsies showed necrolysis of superficial epidermis. Both patients had extremely elevated plasma concentrations of pancreatic glucagon. By means of specific staining and immunofluorescence techniques the tumours were shown to consist of glucagon-containing α_2 -cells. It is concluded that these patients suffered from the newly described glucagonoma syndrome.

Key words: Glucagon; Pancreatic neoplasma; Islet cell tumour; Skin manifestations

In 1942 Becker et al. (1) described a patient suffering from weight loss and necrotic skin eruptions which resembled chemical burns and showed a specific histological picture. Post-mortem examination revealed an islet-cell carcinoma of the pancreas. Since then a number of cases of the same peculiar skin eruption have been published (2, 3, 4, 7, 14, 15, 16, 17, 18). Invariably these patients also had an islet cell tumour of the pancreas. In addition, weight loss, anaemia and diabetes mellitus were common features. Recently, extremely elevated concentrations of immunoreactive glucagon were found in plasma and tumour extracts (4, 12, 13).

In 1974 Mallinson et al. reviewed 9 cases and suggested the condition to be a nosological entity—the glucagonoma syndrome (12).

In the present report 2 patients with skin eruptions and general symptoms similar to the previous cases are described. In both patients hyperglucagonaemia and a glucagon cell pancreatic tumour were found.

CASE REPORTS

Case 1

A 71-year-old woman who was admitted to a psychiatric department in 1948 because of mental depression. In 1956 she was operated on for a suprasellar meningioma. In the same year rheumatoid arthritis developed. In 1964 pernicious anemia was suspected, and she has since been treated with vitamin B₁₂.

In 1965 general pruritic skin eruptions developed, and one year later she was referred to the Department of Dermatology in Gothenburg. Two and three years later she was again examined at the clinic because of a progression of the skin symptoms. Excoriated papules and nodules were found on the extremities. In 1969 the patient had a sudden eruption of disseminated erythematous macules which cleared following systemic prednisolone therapy. At the same time there was a drop in the haemoglobin concentration in blood from 11 g/100 ml to 8.4 g/100 ml though without any signs of haemolysis or gastrointestinal bleeding.

During the subsequent years the dermatosis progressed and the patient was repeatedly hospitalized with a bewildering array of excoriations, erythema, papules, vesicles, erosions, squamas and pigmented scars. Several symmetrical exanthematous eruptions were noticed, often attended by aggravated anaemia. There were recurrent episodes of red oedematous eruptions, mainly on dependent parts of the body, showing central erosions and superficial necrolysis with a tendency to peripheral extension and gyrate configuration. The lesions resembled chemical burns, and it was thought for some time that the condition might be self-inflicted. Lesions were also found in the groins and between the buttocks, with secondary candida infection. Most of the skin lesions healed in a couple of weeks on topical treatment with conventional preparations containing steroids and clioquinol. In 1972 a stomatitis with a fiery red tongue was observed. During the years 1968-74 there was a loss of weight from 57 to 37 kg. In 1973 the patient was treated for suspected pulmonary embolism. In 1974 it was realized that the patient's condition resembled that of earlier cases described in connection with islet cell tumours in the pancreas, and



Fig. 1. Case 2. Polymorphic skin changes with both collapsed blisters and blisters where superficial necrosis is shed. The slightly hyperpigmented areas correspond to older healing lesions.

the level of plasma glucagon was determined. The patient died shortly afterwards. At post-mortem examination a tumour, 5×6×7 cm, was found in the body of the pancreas. No metastases were found.

Laboratory findings. On repeated occasions anaemia was found. Levels of serum iron and iron-binding capacity were normal. Bone marrow aspirates in 1969 and 1974 were normal as far as cells and iron stores were concerned. In 1974 a Schilling test without intrinsic factor proved abnormal, since only 0.8% of radioactive vitamin B₁₂ administered orally was excreted during the first 24 hours. The sedimentation rate was most often above 100 mm. In 1974 a fasting blood glucose concentration of 120 mg/100 ml was found and an oral glucose tolerance test was diabetic. Antibodies against dermo-epidermal junction or against intra-epidermal intercellular substance could not be demonstrated, using indirect immunofluorescence technique. The concentrations of 16 plasma amino acids were all extremely low. Plasma pancreatic glucagon measured by means of a specific radioimmuno-assay (9)

was 6600 pg/ml (normal range 50–120 pg/ml). Patch test with standard substances (ICDRG) was negative.

Histology of skin lesions. A number of biopsies were taken. As a rule there was necrosis of superficial epidermal cells with remaining pycnotic nuclei. There was a sharp borderline between necrotic superficial epidermis and basal epidermis, which could sometimes be acanthotic. Some biopsies also showed dilatation of capillaries and infiltration of leukocytes and histiocytes.

The tumour consisted of alpha₂-cells as demonstrated both by Grimelius' (6) and by Phospho-Tungstic-Acid-Haematoxylin staining methods. By means of immunofluorescence and using an antiserum specific for pancreatic glucagon, the cells were shown to contain glucagon (10). The glucagon content of the tumour, as calculated from radioimmuno-assay of an acid-ethanol extract, was 266 µg/g. The concentration of glucagon in pancreatic autopsy specimens from patients without signs of pancreatic disease is 3–5 µg/g.

Case 2

A 69-year-old retired farmer. For the last 10 years he had suffered from a hyperplasia prostatae, and for some years there were symptoms of a mild Parkinson's disease. Slight diabetes mellitus was found in 1969 and was at first treated with diet and tolbutamide (Rastinon, Hoechst), but during the last 2 years with diet alone.

Since 1968 the patient experienced periodic skin symptoms, often starting in the autumn and healing spontaneously in the winter. He was only slightly disabled by his dermatosis, which was treated successfully by a general practitioner. In September 1974 the patient was referred to the Department of Dermatology, Lund, with erythematous, gyrate, scaling skin changes of groins, perineum and fore legs (Fig. 1). On the back of one foot a collapsed blister was seen corresponding to the rim of his shoe. For 2–3 weeks there was a slow progression with peripheral extension of new lesions consisting of small crusts and sometimes small collapsed blisters covered by a white blister roof which was shed in a couple of days and was replaced by a slightly weeping surface. As the new eruptions slowly progressed in the periphery, the oldest, central lesions healed up with formation of new epithelium, which was often slightly hyperpigmented. On one occasion there was a sudden outbreak of 1–2 cm round exanthema-like eruptions on the body and subsequently similar more confluent elements on the arms. In the erythema on the arms small pustules were also seen. Later a scaling eruption developed in the face (Fig. 2). No stomatitis was found. The skin lesions cleared following topical steroid treatment. During an intermediate stay in another hospital for treatment of his Parkinsonism, there was an episode with clinical signs of deep vein thrombosis of the left lower extremity. The plasma pancreatic glucagon levels were elevated, and angiography of the arteria coeliaca and arteria mesenterica superior was performed, which revealed a tumour in the tail of the pancreas. The patient was operated on and a 3×4×5 cm firm, light grey tumour was removed. There were no signs of metastases.

Laboratory findings. Haemoglobin/blood was 10 g/100 ml. The concentration of serum iron was slightly decreased, i.e. 65 µg/100 ml, as well as the iron-binding

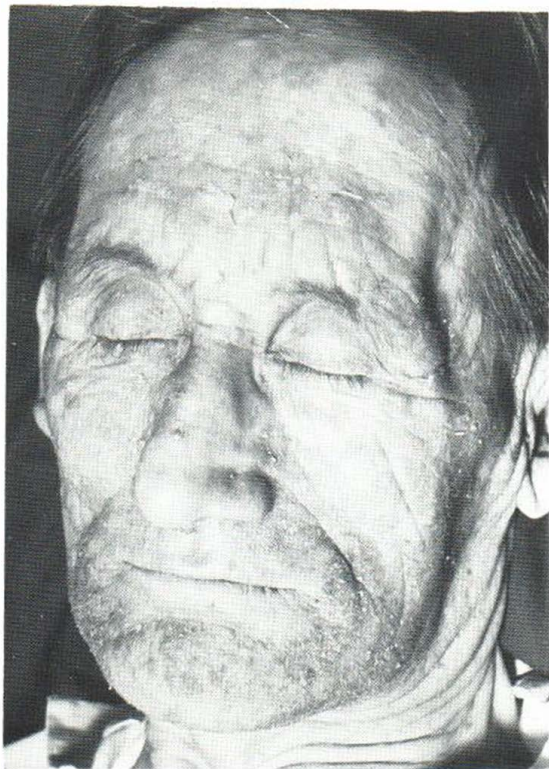


Fig. 2. Case 2. Dermatitis of face with erythema and crusts.

capacity, 200 $\mu\text{g}/100\text{ ml}$. Folic acid and vitamin B₁₂ plasma levels were normal. The sedimentation rate was around 80 mm. There was a normal amount of fat in the faeces. Fasting blood glucose was normal, but an intravenous glucose tolerance test was clearly diabetic. There were no antibodies against dermo-epidermal junction or intercellular epidermal substance when measured by indirect immunofluorescence technique. The levels of 16 plasma amino acids were all abnormally low. On several occasions plasma glucagon concentrations were measured by specific radioimmuno-assay (9) and found to vary between 700 and 1800 pg/ml (normal range value 50–120 pg/ml).

Histology of skin lesions. In a biopsy from a blister on the back of the foot there was a pronounced intracellular oedema and necrosis in epidermis corresponding to stratum granulosum with separation of the parakeratotic horny layer from the epidermis (Fig. 3). In a biopsy from a pustular reaction on the arm, the same necrosis and oedema of superficial epidermis was found as described above and also an inflammatory reaction in dermis with pronounced infiltration of leukocytes and histiocytes (Fig. 4).

A Grimelius stain revealed that the tumour of the pancreas consisted mainly of α_2 -cells, which contained glucagon as demonstrated by immunofluorescence. The glucagon content of the tumour was 82 $\mu\text{g/g}$ tissue as compared with 1.4 $\mu\text{g/g}$ in the surrounding normal pancreatic tissue.

DISCUSSION

Including the present 2 cases, 8 verified cases of glucagonoma syndrome have now been reported (4, 12, 13). Furthermore, 10 cases of typical dermatosis and islet cell tumour of the pancreas have been described (1, 2, 3, 7, 12, 16, 18). The first of these reports (1) was published in 1942, but the syndrome is now more frequently recognized and 12 of the 18 cases have been reported during the last 5 years. Most of the patients were post-menopausal women. The youngest patient described was a woman 31 years old at onset of the disease (2). Becker et al. (1), Wilkinson (17) and Sweet (14) described in detail the dermatological and histological features of their cases, and Wilkinson (17) gave the skin disease its striking name—necrolytic migratory erythema.

The skin lesions in the present cases showed a varying morphology. There were eruptions of dis-

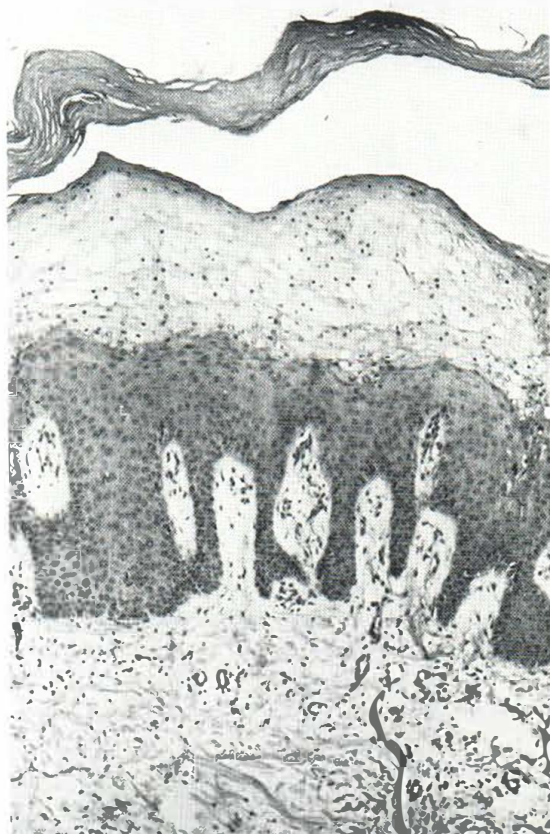


Fig. 3. Case 2. Skin biopsy from the back of the right foot showing the sharp borderline between necrotic and pyknotic cells in superficial epidermis, and the vital cells in the acanthotic basal epidermis.

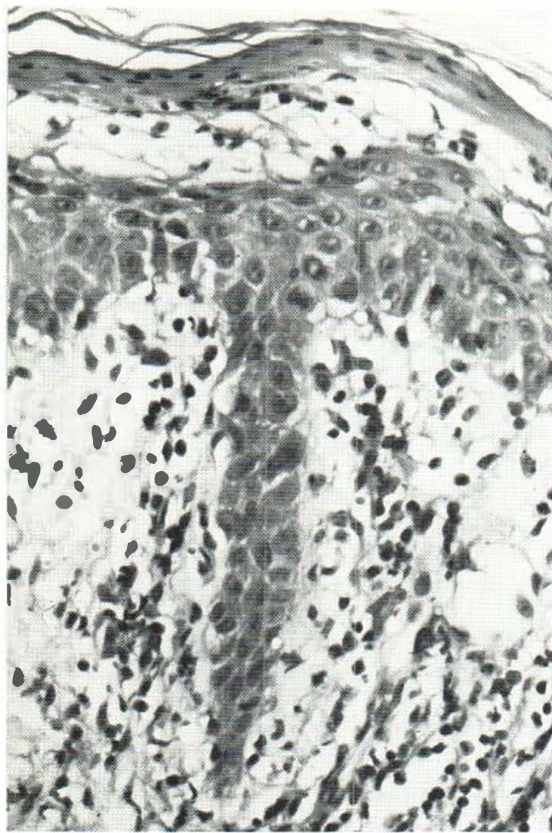


Fig. 4. Case 2. Skin biopsy from an erythematous and pustular area on the left arm shows both superficial epidermal necrosis and severe inflammatory changes in the dermis with infiltrates of leukocytes and histiocytes.

seminated erythematous macules in both cases and in Case 2 also pustules, at first interpreted as drug eruptions. These pustules never developed into blisters, but dried up in a couple of days. The bizarre skin changes with flaccid bullae were suspected to be self-inflicted in Case 1 and at first thought to be pemphigus in Case 2. In both cases the characteristic necrolytic migratory erythema was located on dependent parts of the body and places where the skin was easily traumatized, such as skin folds in axillae and groins and on the foot corresponding to the rim of the shoe (Fig. 1). The spontaneous course of the necrolytic migratory erythema was like that also described by Wilkinson (17) and Sweet (14), that is, the duration of the erythema developing into a blister, a squama and a pigmented scar was around 2 weeks. There was regularly a good response to topical therapy with steroids.

The main features of the histologic changes of bullous lesions were intra- and intercellular oedema in the epidermis corresponding to stratum granulosum and lucidum. Necrosis of cells in these layers was also noticed. In a biopsy from the pustular lesions of Case 2, necrosis of superficial cells in epidermis was also observed. Furthermore, there was a severe inflammation of the dermis with dilatation of vessels and a pronounced infiltrate of leukocytes and histiocytes (Fig. 4). Thus, necrosis of superficial epidermis was found in lesions of varying macroscopic appearance. This skin histology, as well as macroscopic skin changes, seems to be unique for the glucagonoma syndrome. Wilkinson (17) described the changes as "sudden death" of superficial epidermal cells.

Besides skin lesions, other symptoms of the glucagonoma syndrome are weight loss, a normochromic normocytic anaemia, stomatitis and a diabetic carbohydrate metabolism. Our patients also suffered from these symptoms, except that Case 2 showed no stomatitis.

The symptoms are presumed to be caused by secretion products of the pancreatic tumour or indirectly by the hypoaminoacidaemia (12). Zdanov (18) was the first to hint at the possibility of glucagon production by the pancreatic tumour, as this consisted of alpha-cells. Gössner & Korting (7) found that the tumour contained large amounts of tryptophan, a constituent of glucagon but not of insulin. Besides, an extract of the tumour had a pronounced hyperglycemic effect when injected in a rabbit. McGavran et al. (13), who reported on a case of bullous eczematoid dermatosis, diabetes mellitus, anaemia and an alpha-cell carcinoma of the pancreas, were the first to describe increased levels of plasma glucagon as well as an increased amount of glucagon in the tumour compared with normal pancreatic tissue. Freedberg & Galdabini (4) found an abnormally high level of plasma glucagon in their case. This was also found by Mallinson et al. (12) in all of the 4 cases where radioimmunoassay was performed. In the present 2 cases glucagon was found to be 70 and 10–20 times the normal value. In both cases the levels of sixteen plasma amino acids were abnormally low.

The tumours of the pancreas of the present 2 cases were solitary adenomas. Both malignant and benign tumours have been described. Mallinson et al. (12) described two adenomas and six tumours showing malignant features. One patient had a sol-

itary adenoma (14), which was removed. All symptoms disappeared within a month, including high blood levels of glucagon and low levels of amino acids (11, 12). There have been other reports on glucagon-producing tumours in connection with a polyglandular adenoma syndrome or alpha-cell hyperplasia, together with other endocrine abnormalities, but no skin changes are described in these syndromes (5, 8).

In untreated cases there seems to be an increased frequency of venous thrombosis and emboli (1, 3, 7, 16, 17). In the present 2 cases there was an episode of suspected pulmonary embolism and deep venous femoral thrombosis. Although the progress of symptoms is usually slow, the prognosis is grave. Untreated, the patients succumb from the catabolic condition caused by the increased production of glucagon or from thrombo-embolic complications, while on the other hand early diagnosis may lead to successful surgical treatment. The diagnosis based on characteristic macroscopic and microscopic skin changes, weight loss and anaemia is supported if hypoaminoacidaemia is found and confirmed by measurement of plasma glucagon.

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ADDENDUM

Case 2 was re-examined 3 months after the operation. All skin eruptions had disappeared, and the level of plasma glucagon as well as the intravenous glucose tolerance test were normal.

A third case, a 62-year-old man, is now being investigated in Lund. He has had diabetes mellitus for 8 years and skin eruptions during the last 3 years. Plasma pancreatic glucagon is 1400 pg/ml.