Ind J Dermatol Venereol Leprol 1996; 62 : 246-9

GLUCAGONOMA SYNDROME

V L Aswani, R H Malkani

A case of glucagonoma is being presented. The patient presented with erosions, crusts, bullous dermatitis, glucose intolerance and weight loss.

Key Words: Glucagonoma syndrome, Necrolytic migratory erythema, Glucagon cell tumour of the pancreas

Introduction

Changes in the skin can provide clues to the presence of internal malignant neoplasms. When cutaneous signs or symptoms antedate other manifestations of a malignancy, awareness of the relationship between dermatosis and neoplasm may lead to early diagnosis and possible cure. Necrolytic migratory erythema (NME) is a distinctive eruption associated with glucagon secreting islet cell tumour of the pancreas (glucagonoma).

The earliest report of a case of this type was by Becker et al in 1942.[1] Wilkinson in 1973 coined the term NME,[2] and Mallinson et al in 1974[3] published the first series of 9 patients and established the glucagonoma syndrome as a distinct entity.

Case Report

A 38-year-old married businessman from Surat presented to us in August 1994 with reddish scaly, itchy skin rash and skin lesions resembling chemical burns for 2 years on the genitals, perineum, buttocks, thighs and legs with variable periods of waxing and waning. There was history of fluid filled lesions on the legs off and on. One year prior to presentation progressive weight loss and weakness began and there was history of oedema of the feet on dependency off and on. The rash used to respond to systemic steroid therapy.

There was no history of fever, malaise, headache, joint pains, nausea, vomiting. diarrhoea or jaundice, oral cavity involvement, drug ingestion or previous skin diseases. His family history was non-contributory.

The patient was averagely built, afebrile, but looked chronically ill. His pulse and blood pressure were normal. He had pallor. An eruption consisting of erythematous erosions with peripheral scales was seen on the legs extending onto the dorsum of the feet and toes. Occasional intact flaccid bullae could be identified on the legs. The lesions resembled chemical burns (Fig.1). Annular, erythematous, scaly lesions, crusts, scaly papules were seen on the buttocks, thighs, back and extensor aspect of the forearms. Crusting was seen on the shaft of the penis. The lesions healed with hyperpigmentation. Hair, nails and mucous membranes were normal. Investigation disclosed the following laboratory values: Hb was 12.1 gm% (normocytic, normochromic); ESR 40 mm in 1st hour; CBC 4400/mm3, N-57, L-40, E-2. Platelet count was normal, blood sugar fasting was 90 mg% and after 75 gm of glucose was 188mg%, s amylase was elevated to 896. Serum iron, TIBC, and transferrin saturation were normal. ANF, thyroid function tests, s cholesterol, LDH, CPK, uric acid, serum calcium, BT, CT, PT, RFT, LFT were

From the Department of Dermatology, Jaslok Hospital and Research Centre, 15, Dr G Deshmukh Marg, Mumbai-400026, India.

Address correspondence to : Dr V L Aswani

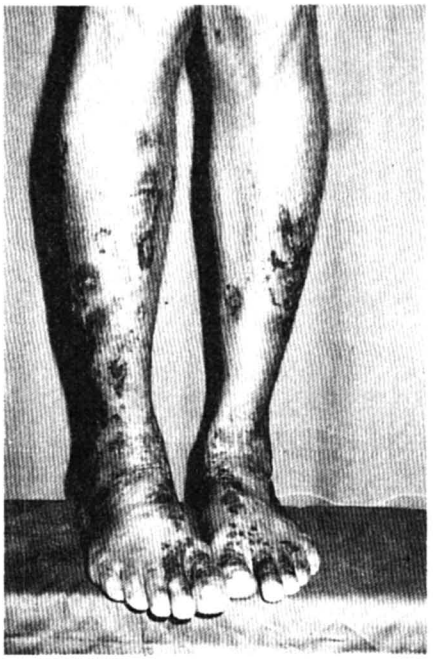

Fig. 1. Erosions with collarette scale and crusts resembling chemical burns.

normal. HBsAg and Elisa test for HIV I and II were negative. Urinalysis was normal. Stool examination revealed occult blood and ova of E histolytica.

Skin biopsy specimen showed hyperkeratosis, necrolysis of the upper stratum malphighii resulting in the formation of upper epidermal blister (Fig.2). The necrolytic epidemal cells appeared pale with pyknotic nuclei (Fig.3). These changes occurred in the midst of psoriasiform hyperplasia with occasional spongiosis. There were no acantholytic cells. Sparse upper dermal lymphocytic infiltrate was seen.

USG showed focal hypoechoic lesion in the region of the head of the pancreas measuring 5 x 3.5 x 5 cm. A speck of

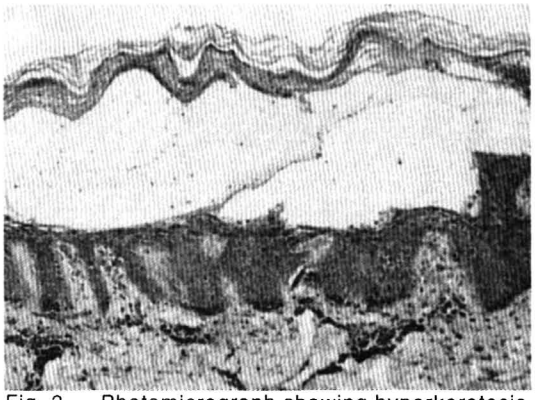

Fig. 2. Photomicrograph showing hyperkeratosis, necrolysis of upper stratum malphighii and upper epidermal blister (H&E x 20).

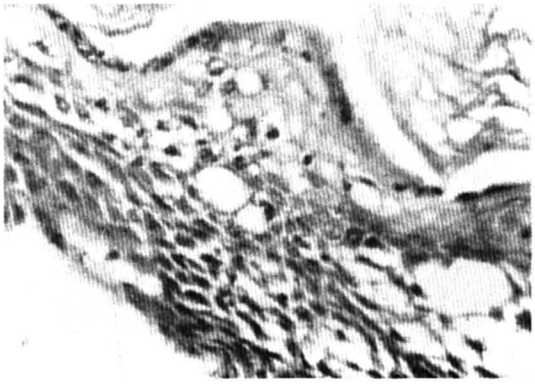

Fig. 3. Histopathology showing necrolytic epidermal cells with pyknotic nuclei and marked intra and intercellular oedema (H&E x 400).

calcification was seen within the mass. CT scan showed soft tissue mass in the head of the pancreas with dilatation of the pancreatic duct. A small calculus was also seen.

The patient underwent Whipple's pancreatico-duodenectomy. The skin lesions disappeared few days after the operation. Histopathology confirmed the diagnosis of malignant islet cell tumour of the pancreas. A mesentric nodule revealed a metastatic islet cell tumour. Subsequently the patient received radiotherapy and chemotherapy.

Discussion

The pancreas is composed of two major

types of tissues (1) the acini, which secrete digestive juices and (2) islets of Langerhans, which secrete insulin and glucagon directly into the blood. The islets contain two major types of cells, the alpha and beta cells. The beta cells produce insulin and glucagon is secreted by the alpha cells. Glucagon causes glycogenolysis and gluconeogenesis.

NME is a peculiar cutaneous reaction with a prolonged fluctuating course characterised by dermatitis, glucose intolerance and hyperglucagonaemia caused by an alpha cell tumour of the pancreas. Glucagonomas occur in the middle age or in the elderly, and are slightly more common in females.

The major diagnostic criteria for diagnosis of glucagonoma syndrome are:

(1) Weight loss, often profound weakness

(2) NME

(3) Glossitis, stomatitis, angular cheilitis

(4) Histopathology showing subcorneal and mid-epidermal clefts with fusiform keratinocytes with pyknotic nuclei

(5) Diabetes mellitus

(6) Elevated plasma glucagon level

(7) Alpha cell tumour of pancreatic islets with or without metastasis. Glucagonoma may be a rare component of multiple endorcine neoplasia (MEN) either type I or II.

Out of all the features of the syndrome the cutaneous component, necrolytic migratory erythema,appears most often. Cutaneous lesions often precede the diagnosis of the syndrome for long periods, with a mean of 6-8 years and a maximum of 18 years. Characteristically the skin lesion starts as an erythematous area typically at peri-orificial or intertriginous areas such as groin, buttocks, thighs or perineum and then spreads laterally. The lesions subsequently become raised with superficial central blistering which breaks down to leave an eroded area that crusts.The lesion tends to heal in the centre with peripheral spread. This entire sequence takes 1 to 2 weeks, and while new lesions are developing, others are healing. In a few cases rash has had the appearance of eczema craquele, or may resemble chemical burns. Drier lesions may show a collarette of scale or an entire erythematous plaque may be surmounted by scale, giving a psoriasiform appearance. Perioral and paranasal crusting is almost invariably present at sometime. Thinning of nails with distal friability, decrease in hair density, atrophic glossitis, stomatitis, and angular cheilitis are frequently associated findings. Typically the skin lesions wax and wane, responding poorly to therapy of any type, yet regressing without apparent cause.

Mallinson et al have suggested that glucagon induced hypoaminoacidaemia may be reseponsible for producing the skin lesions through deprivation, so that epidermal proteins cannot be made.[3]

Glucose intolerance with or without frank diabetes occurs in 83-90% of cases. Tumour resection and normalisation of blood glucagon may not result in normalisation of glucose intolerance.[4] The blood glucose returned to normal in our case after the operation.

Weight loss without noticeable anorexia may be a unique feature of glucagonoma. It is seen even in patients with small tumours without metastatic spread and has been attributed to the known catabolic effects of glucagon. Anaemia occurs in 44-85% of cases, is usually of the normocytic normochromic type. Serum iron is normal as

was in our case. Anaemia may be due to glucagon excess, because prolonged treatment with a long acting glucagon preparation decreases erythropoiesis in animals. ESR is always elevated. Plasma glucagon levels are elevated. A plasma glucagon concentration of 1000 pg/ml is diagnostic of glucagonoma. Due to non-availability, it could not be done in our patient. A normal level of plasma glucagon may be able to exclude pancreatic tumour in patients with NME. Two patients have been described[5] with NME without glucagonoma. Both had normal glucagon levels with small intestinal villous strophy and diarrhoea. Cases have also been described with NME without glucagonomas, but with cirrhosis and chronic pancreatitis.

Skin biopsy reveals irregular acanthosis, spongiosis, and the characteristic, well-demarcated necrolysis (sudden death) of the outer cell layers in the stratum malphighii. Later, clefts and separation occur at the site without acantholysis. Karatinocytes appear fusiform with pyknotic nuclei. Direct immunofluorescence is negative.

The initial procedure of choice for localisation of the tumour is CT scan as was done in our case. For some patients with small tumours, CT or USG may not localize the tumour, and then selective angiography is the procedure of choice.

Since glucagonomas are generally malignant and it is not possible to predict in a given patient when metastasis may develop, surgical resection should be considered in all patients if feasible. Approximately 50-80% of patients have metastasis at the time of diagnosis. To improve the metabolic status before surgery, blood transfusion for severe anaemia and parenteral amino acids to correct hypoaminoacidemia and thereby the skin rash, is recommended. In cases with hepatic metastasis, at the time of diagnosis, streptozocin has proved beneficial in some cases. Successful treatment with dacarbazine has been reported.[6] Octreotide has also been used to improve the skin rash and symptoms of weight loss, abdominal pain and diarrhoea. Octreotide is a synthetic analogue of somatostatin (growth hormone inhibitor). Somatostatin inhibits the secretion of both insulin and glucagon. Streptozocin, dacarbazine and octreotide can thus be used as palliative agents in this condition. Radiotherapy and other chemotherapeutic agents, as used in our case following surgery, have improved the prognosis in these patients.

Acknowledgement

The authors are thankful to Dr V N Shrikhande, Hon Professor and Head of General Surgery, Bombay Hospital for surgical management of the patient.

References

1. Kahan R, et al. Necrolytic migratory erythema: distinctive dermatosis of the glucagonoma syndrome. Arch Dermatol 1977; 113: 792-7.
2. Wilkinson DS. Necrolytic migratory erythema with carcinoma of the pancreas. Trans St John's Hosp Dermatol Soc 1973; 59: 244-50.
3. Mallinson CN, et al. Glucagonoma syndrome. Lancet 1974; ii: 1-5.
4. Leichter SB. Clinical and metabolic aspects of glucagonoma. Medicine 1980; 59: 100.
5. Goodenberger DM, et al. Necrolytic migratory erythema without glucagonoma. Arch Dermatol 1979; 115: 1429-32.
6. Weismann K, Graham RM. Systemic disease and the skin. In: Champion RH, Burton JL, Ebling FJG, editors. Textbook of dermatology. Oxford: Blackwell, 1992: 2430-2.