

GLUCAGONOMA PRESENTING AS NECROLYTIC MIGRATORY ERYTHEMA IN A LONG-STANDING TYPE II DIABETIC PATIENT

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ABSTRACT

We report a case of glucagonoma in a 60-year old diabetic lady who was seen by a dermatologist for a superficial erythematous skin eruption with flaccid bullae over both legs of recent onset. These findings warranted further investigations that revealed a pancreatic mass lesion involving the distal body and tail with three metastatic deposits within the right lobe of the liver. Distal pancreatectomy and splenectomy were performed and histological examination of the excised specimen confirmed the diagnosis of pancreatic glucagonoma with liver metastasis. Blood sugar levels became more controlled postoperatively. The skin lesion disappeared completely six months after surgery. The lady enjoys fairly good health, and is maintained on Somatostatin analogues for control of metastasis that are stable after 18 months of follow up.

Key words: Diabetes mellitus type II, glucagonoma, necrolytic migratory erythema

JRMS August 2009; 13(2): 47-50

Introduction

Glucagon is a 29 amino acid peptide secreted by the pancreatic alpha cells in islets of Langerhans. Its main effect is to keep normal blood glucose levels counteracting the actions of insulin. Pharmacological administration of glucagons is effective in the treatment of hypoglycemia but extrahepatic effects are also well known.⁽¹⁾ Glucagonoma is a rare neuroendocrine tumor arising from alpha islet cells of the pancreas,⁽²⁾ it is extremely rare but well-known with a current prevalence estimated at 1/20 millions.⁽³⁾ Glucagonoma is associated with a characteristic syndrome caused by glucagon hypersecretion. Patients typically present in their fifth or sixth

decade. Classical clinical features of glucagonoma syndrome include: diabetes mellitus, cheilitis, normocytic anemia, painful glossitis, gastrointestinal disturbances, thromboembolism and weight loss.⁽⁴⁾ The characteristic skin manifestation is necrolytic migratory erythema, which is an erythematous painful and pruritic rash. It begins as macules that coalesce and develop central bullae before eroding and leaving hyperpigmentation and crusts at the periphery.⁽⁵⁾ Necrolytic migratory erythema usually starts at the perirectal area and subsequently spread to the perineum, buttocks, thighs, and lower extremities. It is a pathognomonic feature of glucagonoma.⁽⁶⁾ Necrolytic migratory erythema is typically characterized on skin biopsies by

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Manuscript received August 24, 2006. Accepted February 1, 2007

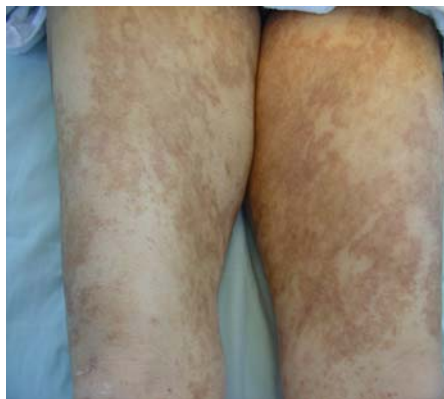


Fig. 1A. Showing the necrolytic migratory erythema on lower limbs

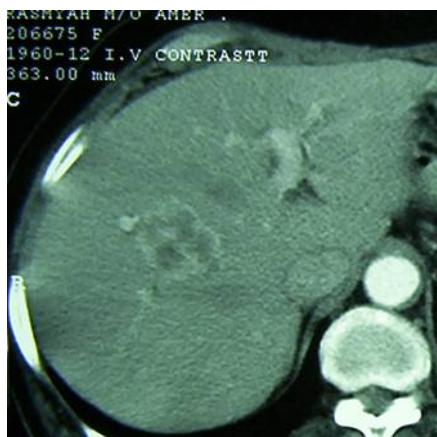


Fig. 1B. Showing the pancreatic lesion and the metastatic lesions in liver



Fig. 1 C. Octreotide scan showing the three metastatic lesions in the liver

necrosis of the upper epidermis with vacuolated keratinocytes.⁽⁷⁾ Glucagonoma usually becomes evident within 1-2 years of developing diabetes mellitus. We present here a rare case of glucagonoma presenting with a typical skin eruption in a lady with long standing Type 2 DM that became more controlled after tumor removal.

Case Report

A 60 year old Jordanian lady, a mother of 11 children, consulted her doctor for an itchy

erythematous skin rash that started over both feet, then extended up to the gluteal area over a two weeks period. She lost eight kilograms of body weight in the last four months prior to presentation. The patient has had type II diabetes for the past 10 years and essential hypertension for the last five years. She had no history of surgeries or allergies. She smokes 20 cigarettes a day since the age of 30. Her current medications include: Glibenclamide 5mg bid, Metformin 850mg bid and Enalapril 5mg bid. Clinical evaluation revealed a middle aged lady

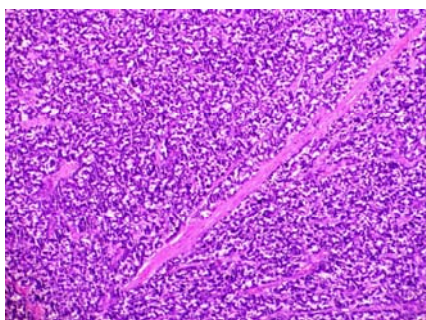
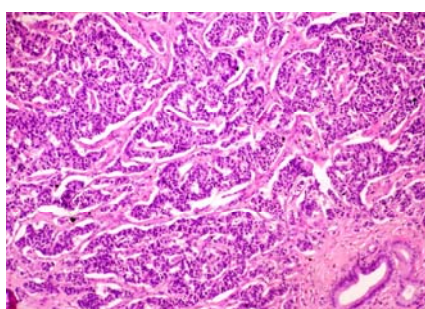
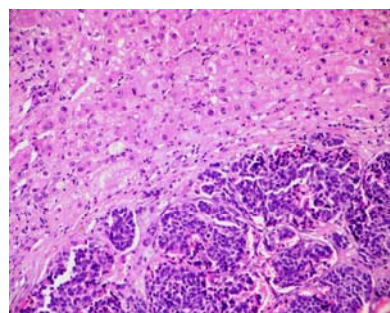


Fig. 2A. Glucagonoma and normal pancreatic tissue (Right of the picture)



2B



2C

Fig. 2B. The tumor arranges in trabecular and gland-like growth pattern (composed of small, round, uniform cells with hyper chromatic nuclei and scant granular eosinophilic cytoplasm), **Fig. 2C.** Liver with metastatic glucagonoma

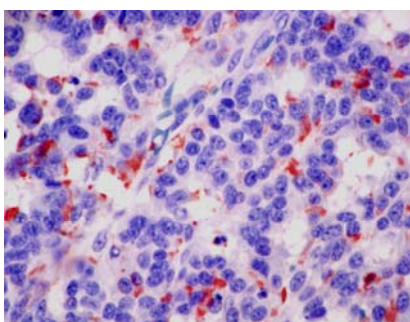


Fig. 2D. Tumor cells reactive for chromogranin

with pale conjunctivae, blood pressure of 136/88 mmHg, no goiter and no palpable abdominal organs or masses. Examination of the lower limbs showed an erythematous rash over the posterior aspect of both lower limbs from the heels upward to the gluteal region with superficial flaccid bullae and minute pustules, scratch marks were also seen (Fig. 1A).

She was treated initially with systemic as well as topical antibiotics and antihistamines but without improvement. Laboratory work up revealed normochromic normocytic anemia, normal other blood counts, normal liver and kidney function tests. The glucagon level was not done due to laboratory factors, her diabetes was uncontrolled with

glycosylated hemoglobin of 10.6%. Scraping of the skin rash showed no evidence of bacterial or fungal overgrowth. Radiological imaging showed a normal chest X-ray, abdominal ultrasound followed by computerized tomography scan revealed a well defined lobulated, heterogeneously enhancing soft tissue mass lesion arising from the distal body and tail of the pancreas measuring 5.5x4.5x3 centimeters, partially encasing the splenic vessels and indenting the posterior aspect of the fundus of the stomach. There were also three metastatic deposits in the right lobe of the liver (Fig. 1B) which were confirmed by octreotide liver scan (Fig. 1C).

The lady underwent surgery with excision of the spleen and distal part of the pancreas.

Histopathological examination confirmed the diagnosis of glucagonoma (Fig. 2A, 2B, 2C, 2D).

Follow up visit at six months post surgery showed complete disappearance of the rash and controlled blood sugar (HbA1c 6.8%). She enjoys a good health, kept on twice monthly intramuscular injections of somatostatin analogue (Lanreotide LA 30mg) as well as one tablet of glibenclamide 5mg and antihypertensive drugs. She is under close follow up. Octrotide scan after one year showed stable liver metastases with no new lesions.

Discussion

Glucagonoma is a rare neuroendocrine tumor of the pancreatic α islet cell associated with characteristic syndrome caused by hypersecretion of glucagon. Glucagonoma is often found in the pancreatic body and or tail and is usually large enough to be localized by computed tomography.⁽⁸⁾ It is often both well developed and malignant at detection.⁽⁹⁾ Necrolytic migratory erythema is a characteristic skin condition seen in the presence of pancreatic glucagonoma.⁽¹⁰⁾ The presence of necrolytic migratory erythema in the absence of a pancreatic tumor has been termed the pseudoglucagonoma syndrome. In such cases, necrolytic migratory erythema is commonly associated with conditions, such as liver disease, pancreatitis and malabsorption disorders (celiac disease). There are many theories on the pathogenesis of necrolytic migratory erythema, which include the direct action of glucagon in inducing skin necrosis, a nutritional or metabolic deficiency of zinc or essential fatty acids and glucagon induction of inflammatory mediators.⁽¹⁰⁾ While some improvement of this dermatosis was reported with aminoacid or zinc repletion, almost invariable disappearance of the erythema is the rule after successful removal of the glucagon-producing tumor.^(11,12) Surgery is the main component of the treatment of glucagonoma and in some cases in association with chemotherapy.⁽¹³⁾ Chemoembolization is another option for treatment of metastasis in lesions not amenable for surgery. Early recognition of necrolytic migratory erythema, a clinical feature that may appear in patients with glucagonoma, can lead to possible cure, whereas delayed identification of the disease is associated with metastatic disease and poor prognosis.⁽⁹⁾

Conclusion

As diabetes became well controlled after removal of the glucagonoma tumor, we speculate that

glucagonoma tumor is a contributing cause for uncontrolled diabetes in this case. The tumor was discovered in metastatic stage that needed aggressive approach of treatment to obtain best control of disease.

References

1. **Pollock CV Jr.** Utility of glucagons in the emergency department. *J Emerg Med* 1993; 11: 195-205.
2. **Bouin M, Aoustin LD.** Clinical response of an atypical glucagonoma treated with long acting somatostatin analog. *Gastroenterol Clin Biol* 2002; 26(10): 926-929.
3. **Echenique-Elizondo M, Tuneu Valls A, Elorza Orue JL, et al.** Glucagonoma and pseudoglucagonoma syndrome. *JOP* 2004; 5(4): 179-185.
4. **Chastain MA.** The glucagonoma syndrome: A review of its features and discussion of new prospectives. *Am J Med Sci* 2001; 321: 306-320.
5. **Johnson SM, Smoller BR, Lamps LW, et al.** Necrolytic migratory erythema as the only presenting sign of a glucagonoma. *J Am Acad Dermatol* 2003; 49: 325-328.
6. **Du Jardin P, Cools P, Van der stighelin Y.** Necrolytic migratory erythema: first symptom of glucagonoma. A case report. *Acta Chir Belg* 2004; 104(4): 468-470.
7. **Van Beek AP, de Haas ER, van Vloten WA, et al.** The glucagonoma syndrome and necrolytic migratory erythema: a clinical review. *Eur J Endocrinol* 2004; 151(5): 531-537.
8. **Chen HW, Su DH, Shun CT, Liu KL.** Rare presentation of endocrine pancreatic tumor: a case of diffuse glucagonoma without metastasis and necrolytic migratory erythema. *J Formos Med Assoc* 2005; 104(5): 363-366.
9. **Randy P, Eigentler TK, Soennichsen K, et al.** Metastatic glucagonoma: treatment with liver transplantation. *J Am Acad Dermatol* 2006; 54(2): 344-347.
10. **Tierney EP, Badger J.** Etiology and pathogenesis of necrolytic migratory erythema: review of the literature. *Med Gen Med* 2004; 10; 6(3): 4.
11. **Von Schenk H, Thorell JI, Berg J, et al.** Metabolic studies and glucagons gel filtration pattern before and after surgery in a case of glucagonoma syndrome. *Acta Med Scand* 1979; 205(3):155-162.
12. **Marynick SP, Fagadau WR, Duncan LA.** Malignant glucagonoma syndrome: Response to chemotherapy. *Ann Inter Med* 1980; 93(3):453-454.
13. **Pautrat K, Bretagnol F, de Muret A, de Calan L.** Recurrent glucagonoma 20 years after surgical resection. *Gastroenterol Clin Biol* 2003; 27(12): 1163-1165.