Necrolytic Migratory Erythema with Cryosurgery Intervention

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ABSTRACT
Necrolytic migratory erythema (NME) is a rare skin condition, which is the first presenting manifestation in almost 70% of the patients with glucagonoma. It is characterized by well-defined scaly erythematous patches with crusted erosion in annular appearance. The predominant areas are genital area, intertrigenous sites and lower extremities. This article has presented the case who had a 5-month history of progressive erythematous scaling patches with crusted erosion on acral, trunk and intertriginous areas. He had been treated for several months at another hospital without definite diagnosis. Our investigations revealed diabetes mellitus and a 6.5x5.7x6.0 cm mass at pancreatic head without liver metastasis. Percutaneous biopsy revealed monomorphic round cells with pleomorphic nuclei which immunohistochemical staining revealed strongly positive for neuroendocrine tumor. The diagnosis of probable glucagonoma associated with NME was established. Zinc supplement was initiated resulting in marked improvement of his rash. He went to Fuda Hospital in China to receive cryosurgery for his pancreatic tumor. Up until now, there has been no recurrence of his rash and his general condition remains stable for 3 years. However, CT scan at 3 years after cryosurgery showed slight increase in size of pancreatic mass and increased degree of diffuse dilatation of main pancreatic duct and side-branch. Thus, long term follow-up is mandatory to conclude the outcome of cryosurgery for pancreatic cancer.

Keywords: Cryosurgery; glucagonoma; necrolytic migratory erythema (Siriraj Med J 2017;69:44-46)

INTRODUCTION
Necrolytic migratory erythema (NME), a rare skin condition, is the first presenting manifestation in almost 70% of the patients with glucagonoma.1,2 It is characterized by well-defined scaly erythematous patches with crusted erosion in annular appearance.2-5 The predominate areas are genital area, intertrigenous sites and lower extremities. Angular cheilitis and glossitis are frequent mucosal manifestations.1,3,6 Glucagonoma syndrome (GS) is a paraneoplastic syndrome, which comprises of the three most common findings including diabetes mellitus (DM), NME and weight loss.1,6 The majority of patients with GS usually present with metastatic disease by the time of diagnosis.1,3,6 Early diagnosis is mandatory to prolong survival.

CASE REPORT
A 51-year old Asian man presented with a 5-month history of unexplained progressive skin eruptions that initially involved his lower extremities and then progressed to the whole body especially the intertriginous areas. He had been treated for several months at another hospital before referring to our hospital for definitive diagnosis. From systematic review, he had hypertension, hepatitis B carrier and weight loss (8 kg/5 months). Physical examination revealed cheilitis and erythematous scaling patches with crusted erosion on acral, trunk and intertriginous areas (Fig 1). Skin biopsy revealed focal parakeratosis and scattered necrotic keratinocytes (Fig 2). Laboratory testing demonstrated diabetes mellitus (fasting blood sugar 160...
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mg/dL), and elevated level of serum amylase (212 U/L). A contrast-enhanced computed tomography (CT) of abdomen showed a 6.5 x 5.7 x 6.0 cm. enhancing mass at pancreatic head (Fig 3). A few mesenteric and peripancreatic lymph nodes, size up to 0.7 cm. were found. No liver or spleen metastases were detected. Percutaneous biopsy revealed monomorphic round cells with pleomorphic nuclei which immunohistochemical staining revealed strongly positive for neuroendocrine tumor. The diagnosis of probable glucagonoma associated with NME was established. Zinc supplement has been successfully tried to control his rash.

However, our patient denied surgical resection and went to Fuda Cancer Hospital, Guangzhou, China to receive percutaneous argon-helium cryoablation for pancreatic tumor. Adjuvant chemotherapy (gemcitabine and cisplatin) was initiated one week after cryosurgery. His rash was gradually cleared within 2-months of treatment. Up until now, there has been no recurrence of his rash and his general condition has remained stable for 3 years. Follow-up abdominal CT scan at 3 months and 18 months after cryosurgery showed no change in size of pancreatic tumor. However, CT scan at 3 years after cryosurgery showed slightly increase in size of pancreatic mass and increased degree of diffuse dilatation of main pancreatic duct and side-branch. Our patient denied the surgical intervention and decided to go back to China for another cryosurgery session.

**DISCUSSION**

Glucagonoma is a slow growing alpha-cell tumor of the pancreatic islets of Langerhans, which is a rare neuroendocrine tumor with an estimated incidence of one in 20 million. Hyperglucagonemia due to glucagonoma can cause multiple systemic manifestations that are called glucagonoma syndrome, for example, NME, DM, weight loss, anemia, cheilitis, glossitis, diarrhea, steatorrhea, thromboembolic tendency, and psychiatric disorder. Angular cheilitis and glossitis are frequent mucosal manifestations. Even though blood for glucagon level and tissue staining for glucagon could not be tested in our hospital, our patient did have NME, cheilitis, weight loss, and DM which were suggestive of glucagonoma.

The exact pathogenesis of NME remains unknown. It was postulated that hyperglucagonemia can provoke hypoaminoacidemia, vitamin B deficiency or other nutritional deficiencies that are the probable reasons of this cutaneous lesion. NME has been the pathognomonic of a glucagonoma for a long time. The differential diagnosis includes intertrigo, zinc deficiency, pellagra, other nutritional deficiency, pemphigoid, and psoriasis. Uncommonly, NME can occur without pancreatic tumor. This condition is termed pseudoglucagonoma syndrome which is often associated with malabsorptive state, inflammatory bowel disease, chronic liver disease,
pancreatitis, various malignant neoplasms and heroin abuse.4,6

The most typical histopathology of NME is the necrolysis of the upper spinous layer with vacuolated keratinocytes leading to focal or confluent necrosis.1,2,4,6 These are consistent with our patient’s findings. However, these findings are nonspecific because of resemblance to findings in pellagra, zinc deficiency, and necrolytic acral erythema causing NME to be an under-recognized condition for several months to years.1,2,4,6 Chronic recurrent skin eruptions and systemic manifestations, especially weight loss and DM as in our patient, are the hints to suspect this condition.

Glucagonoma can be curable by surgical resection, but only when the tumor is localized and without metastases.4,5 Although an alpha-cell tumor of the pancreatic islets is slow-growing, 50-100% of patients present with metastatic disease at the time of diagnosis.1,3,6 The most common site of metastasis is liver, followed by peripancreatic lymph nodes, bone, adrenal gland, kidney, and lung.6 Overall the survival rates are 20% in 1-year and 5% in 5-years.7 Prolonged survival is possible with early recognition and correct diagnosis.2,3 Palliative treatment for metastatic disease with chemotherapy, radiotherapy, chemoradiotherapy, long-acting somatostatin analogue and supplementation with zinc, amino acids, and essential fatty acids may be helpful.2,6,9 Chemotherapy is used to reduce the tumor growth rate while radiotherapy is most often used to relieve pain.5 Gemcitabine is the most commonly used chemotherapy agent in pancreatic cancer.3 However, these palliative treatments are pessimistic.5,9

Because of the poor prognosis of the disease, novel treatment is necessary. In 1970, Korpan reviewed this and showed that there was a good efficacy of cryosurgery for pancreatic cancer. Xu et al., reported that 59 patients with pancreatic cancer at Fuda Hospital underwent percutaneous cryoablation. The survival rate at 3, 6 and 12 months was 89.7%, 61.1% and 34.5% respectively. It should be noted that the survival rates of 40 patients without liver metastases were 92.4%, 84.2% and 62.1% at 3-, 6- and 12-months respectively. It is believed that cryosurgery initiates poor blood flow in the pancreatic tumor and a systemic immunological response that might promote anti-tumor effects. However, more research with a greater number of patients is needed to support this encouraging outcome.

In conclusion, we have reported the case of a glucagonoma patient who underwent cryosurgery intervention. Early recognition of this rare skin condition and prompt treatment of pancreatic tumor are mandatory to improve outcome. Cryosurgery is a novel treatment for locally advanced pancreatic cancer. Long term follow-up is needed to elucidate the outcome of cryosurgery in this patient.

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REFERENCES