Necrolytic migratory ulceration

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ABSTRACT

Endocrine tumors of the gastroenteropancreatic system associated with specific skin manifestations are rare. We report a 53-year-old female who presented with migratory annular and arcuate ulcers on her limbs. Histopathology was similar to necrolytic erythema family which includes necrolytic migratory erythema (NME). Though initial CT scans were normal, follow up scans revealed multiple mass lesions in the tail of pancreas. Her skin lesions responded to oral zinc sulphate and monthly injections of octreotide. Prior to planned FNAC from the mass lesion, patient developed altered sensorium and succumbed to the disease. This case report seems to differ from NME clinically, due to unique finding of deep migrating ulcers which heal with scarring. 'Necrolytic migratory ulceration' thus appears to be a new paraneoplastic manifestation, secondary to pancreatic malignancy.

Key words: Migratory ulcers, necrolytic erythema, necrolytic migratory erythema, pancreatic tumor

INTRODUCTION

Endocrine tumors of the gastroenteropancreatic system are rare.[1] Many cutaneous manifestations of pancreatic tumors have been described.[2] But we came across a case, who presented with an unusual and hitherto unreported skin manifestation associated with mass lesions in the tail of pancreas.

CASE REPORT

A 53-year-old unmarried woman presented to us with history of recurrent episodes of erythematous scaly plaques over face, trunk and extremities of 12-year duration. Since 1 year she noticed vesicles at the margins of such plaques on the lower limbs, which broke down to form erosions and painful ulcers. These ulcers extended peripherally with tendency to heal centrally forming arcuate and annular patterns. Some of the lesions on the leg and hands developed thick waxy scales. She had been treated earlier as a case of psoriasis with no relief. She gave history of diabetes mellitus, weight loss and chronic diarrhea for the past 1 year.

Examination revealed multiple scaly erythematous plaques of size 1-15 cm over the face, trunk and extremities and multiple annular plaques with thick waxy scales on the thighs, legs, palms and periorbital area [Figure 1]. There were also multiple crusted plaques over the dorsum of both feet and ankles [Figure 1]. This later progressed to multiple arcuate and annular ulcers of size 3-7 cm with irregular borders, marginal vesiculopustules, sloping edges and floor covered with granulation tissue and hemorrhagic crusting over feet and

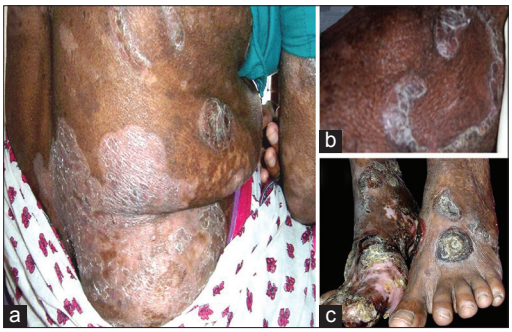

Figure 1: (a) Scaly erythematous plaques of size 1-15 cms over the trunk (b) Annular plaques with thick waxy scales on the thighs (c) Crusted plaques over the dorsum of feet

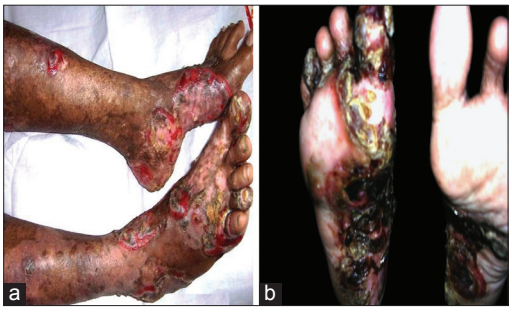

Figure 2: Arcuate and annular ulcers over (a) the legs and dorsum of feet (b) plantar aspect of feet

Access this article online
Website: www.idoj.in
DOI: 10.4103/2229-5178.115518
Quick Response Code:

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legs [Figure 2]. Additional findings included pallor, angular chelitis and ichthyosis. We investigated the patient with a differential diagnosis of psoriasis, Reiter's disease, pyoderma gangrenosum and acral necrolytic erythema.

Investigations showed hemoglobin level of 9.5 gm/dl; total leucocyte count of 13,300 with a differential count of 82% polymorphs and 16% lymphocytes; ESR of 100 mm; low serum zinc and albumin levels; elevated blood sugar levels; and negative HIV, HBsAg, VDRL and HCV serology. Other biochemical parameters were normal. No organism could be isolated despite repeated cultures for bacteria, mycobacteria and fungi. Skin biopsies from the plaque and margin of ulcers showed psoriasiform hyperplasia of the epidermis with focal parakeratosis, dyskeratotic cells and upper epidermal pallor with hydropic degeneration of keratinocytes [Figure 3]. The histopathology was suggestive of the family of necrolytic erythemas, which includes glucagonoma syndrome. But CT scan of the abdomen failed to detect any pancreatic tumors at the time. Due to monetary constraint the patient refused serum glucagon estimation.

During the 3-month hospital stay the patient failed to improve with antibiotics, vitamin supplementation, injection human insulin and general supportive measures. The presence of chronic psoriasiform skin lesions, histologically belonging to the family of necrolytic erythemas[2] and coexistent diabetes, made us consider the possibility of undetected glucagonoma. So we treated the patient empirically with oral zinc sulphate 220 mg thrice daily, amino acid infusions and monthly injections of 20 mg octreotide acetate. The skin lesions improved and healed completely in 1 month with residual pigmentary changes and scarring [Figure 4]. On discontinuation of treatment the skin lesions recurred, but responded again to the same line of management. One year later a repeat CT scan showed multiple hypodense lesions in the tail of the pancreas. A diagnostic FNAC from the mass lesion was planned from department of gastroenterology. But prior to the procedure patient developed altered sensorium of one day for which she was readmitted in that department. But her condition progressively worsened and she expired the next day despite resuscitative measures.

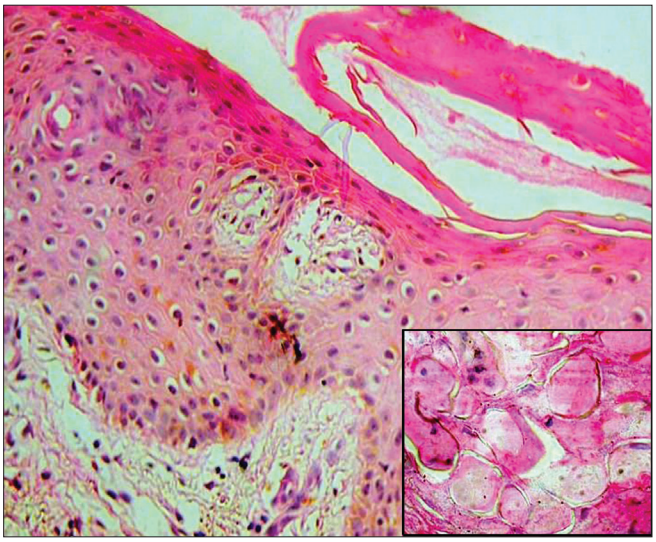

Figure 3: Skin biopsy from the edge of the ulcer showing psoriasiform hyperplasia of the epidermis with focal parakeratosis, dyskeratotic cells and upper epidermal pallor with hydropic degeneration of keratinocytes [H & E, original magnification ×40]. Inset shows high power view of the hydropic degeneration of keratinocytes [H & E, original magnification ×100]

DISCUSSION

Necrolytic migratory erythema (NME) belongs to the recently recognized family of deficiency dermatoses of which zinc deficiency, necrolytic acral erythema and pellagra are also members.[2] NME is characterized clinically by intense erythematous skin lesions with superficial epidermal necrosis that leads to shedding of the skin with flaccid bullae and crusted erosions and central healing giving rise to annular appearance over the perineum, other intertriginous sites, trunk, legs, perioral skin and sites of minor trauma. Histologically the most specific feature is necrolysis of the upper epidermis with vacuolated keratinocytes, leading to focal or confluent necrosis.[2] NME was originally described in association with glucagonoma syndrome, whose clinical constellation apart from NME includes diabetes mellitus, anemia, weight loss, glossitis, cheilitis, steatorrhea, diarrhea, venous thrombosis and neuropsychiatric disturbances in the presence of a glucagon producing α-cell tumor of the pancreas.[3] But NME can also occur in association with other conditions.

The pathogenesis of glucagonoma syndrome is a consequence of the glycogenolytic and gluconeogenic effects of glucagon.[4] Venous and pulmonary thromboembolism, observed in patients, is attributable to the production of a molecule similar to coagulative factor X from tumor cells.[4] The exact cause of the skin rash remains unknown. According to one theory NME is caused by the excess circulating glucagon and loss of amino acid tryptophan which regulates cell turnover, capillary tone and the maturation of the epidermis.[4] According to another theory, NME is related to the deficiency of zinc and essential fatty acids secondary to low levels of their carrier protein-albumin caused

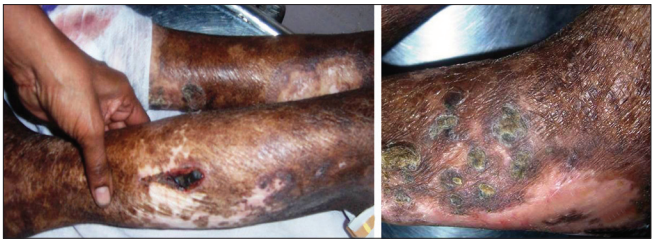

Figure 4: Residual pigmentary changes and scarring on the foot after healing of ulcers

by excess of glucagon.[4] These factors along with deficiency of vitamin B complex and other nutrients essential for skin vitality might lead to inflammatory damage to tissues in areas exposed to friction and pressure.[2,4] Cosecreted bioactive polypeptides such as pancreatic polypeptide and proglucagon fragments, may also play a role in potentiating the catabolic effects of glucagon.[2]

Our patient had several features similar to NME like chronic psoriasiform skin lesions showing waxing and waning course, anemia, diabetes mellitus, weight loss, diarrhea, angular chelitis, anemia, hypoproteinemia, persistently elevated ESR, biopsy consistent with NME and follow-up CT scan showing hypodense lesions in the tail of pancreas. Moreover skin lesions healed with amino acid infusions, zinc sulphate supplementation and octreotide injections. But the development of crusted plaques, migratory annular ulcers which heal with scarring and absence of lesion in intertriginous area makes this case unique. As autopsy could not be performed, we were unable to confirm the histology of the multiple mass lesions in tail of pancreas. We can only speculate that the cause of death could have been worsening hyperglycemia, diabetic ketoacidosis or metabolic encephalopathy secondary to liver metastasis since the relatives give history of decreasing level of consciousness prior to admission, which worsened prior to death.

Multiple tumors in the pancreas associated with glucagonoma can occur in multiple endocrine neoplasia type-1 (MEN-1) syndrome[5] and 'glucagon cell adenomatosis' a newly recognized disease of the endocrine pancreas.[6] We speculate that either of these diseases or production of secondary hormones by the tumor may have led to the unusual skin manifestation in our patient.

The histology of the skin in NME is very similar to the biopsy findings in deficiency states like acquired zinc deficiency, essential fatty acid deficiency, biotin deficiency and pellagra,[2,7] Necrolytic acral erythema, a condition strongly associated with hepatitis C presenting with erythematous patches with erosions and blisters with a predilection for the lower limbs[8] was ruled out in our patient due to a negative hepatitis C serology and presence of generalized skin lesions.

CONCLUSIONS

'Necrolytic migratory ulceration' appears to be a new paraneoplastic manifestation secondary to pancreatic malignancy. More number of reports of this disease along with investigations like serum glucagon estimation, full gut hormone profile analysis, endoscopic ultrasound-guided FNAC and somatostatin receptor scintigraphy may yield answers regarding the exact pathogenesis of this rare paraneoplastic syndrome.

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Cite this article as: Pakran J, Riyaz N. Necrolytic migratory ulceration. Indian Dermatol Online J 2013;4:205-7.

Source of Support: Nil, **Conflict of Interest:** None declared