Received: 10 February 2017 | Accepted: 17 April 2017
DOI: 10.1111/dth.12498

WILEY DERMATOLOGIC THERAPY

Necrolytic migratory erythema associated with glucagonoma treated successfully with cyclosporine

1 | INTRODUCTION

Glucagonoma syndrome is a rare paraneoplastic syndrome characterized by elevated serum levels of glucagon, the presence of glucagonoma, and dermatological clinical findings such as necrolytic migratory erythema (NME) (John & Schwartz, 2016; Luber, Ackerman, Culpepper, Buschmann, & Koep, 2016). The main challenge associated with the diagnosis of glucagonoma syndrome is that at diagnosis, metastasis has already occurred in more than 50% of cases. However, this tumor tends to exhibit slow growth; median survival is 3–7 years and patients have survived for up to 24 years (John & Schwartz, 2016; Mendoza-Guil, Hernández-Jurado, Burkhardt, Linares, & Naranjo, 2005). Furthermore, NME significantly affects patients' quality of life and is characteristically resistant to treatment (Thomaidou, Nahmias, Gilead, Zlotogorski, & Ramot, 2016). In this sense, additional knowledge regarding effective drugs for treating persistent NME is needed.

2 | CASE REPORT

A 57-year-old man presented with a 2-year history of persistent cutaneous rash affecting the lower limbs and intertriginous areas. His medical history featured a diagnosis in 2014 of stage IV glucagonoma of the tail of the pancreas with multiple hepatic and splenic metastases. For this reason, the patient did not undergo surgery. The Oncology Department provided two years of treatment with different chemotherapy regimens including cisplatin, etoposide, fluorouracil, irinotecan, temozolomide, and capecitabine. Octreotide was added to these treatments. The aforementioned treatments did not control the patient's NME lesions. Dermatologic examination revealed well-demarcated erythematous scaly and erosive plaques with serohematic scabs on their surface that mainly affected the lower extremities and the intergluteal and inguinal regions (Figure 1). Angular cheilitis and glossitis were observed. Laboratory tests indicated elevated levels of glucagon (619 pg/ml; reference range, 60–170 pg/ml), chromogranin A (1,556 ng/ml; reference

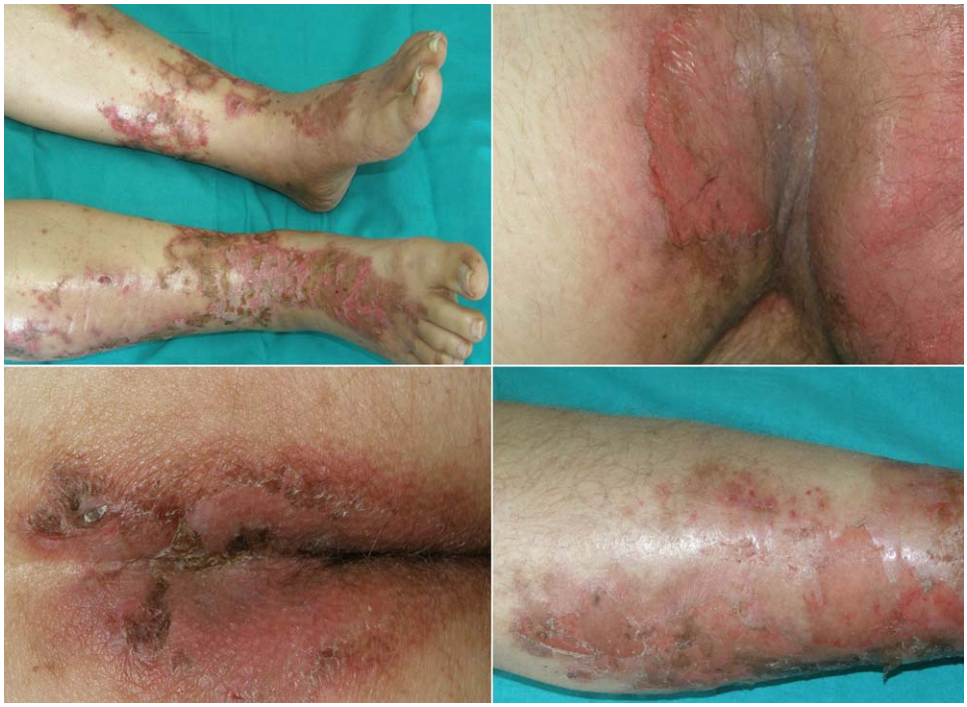

FIGURE 1 Clinical image of NME caused by glucagonoma. Well-demarcated erythematous and scaly plaques with an eroded and scabby surface affecting the lower extremities and intertriginous areas

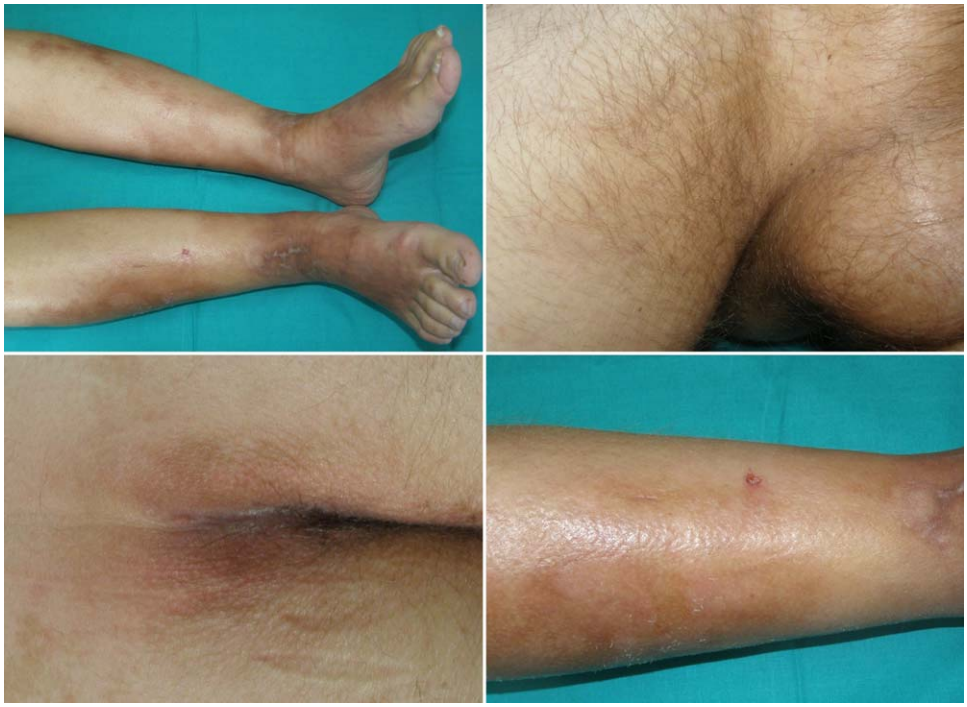

FIGURE 2 Complete and sustained resolution after the administration of oral cyclosporine. Areas of postinflammatory hyperpigmentation persist

range, 0–100 ng/ml), glucose (277 mg/dl; reference range, 71–109 mg/dl), gamma glutamyl transferase (451 U/l; reference range, 8–55 U/l), and alkaline phosphatase (251 U/l; reference range, 40–129 U/l). Normal levels of C peptide, insulin, zinc, and biotin were detected. A cutaneous biopsy revealed spongiotic psoriasiform dermatitis with necrobiosis of the upper third of the epidermis compatible with NME. With respect to the treatment of NME, prednisone at a dose of 1 mg/kg/day achieved clinical remission but dose reduction was quickly followed by the reappearance of NME. Faced with multiple recurrences of NME, we started treatment with cyclosporine at a dose of 3 mg/kg/day which also achieved complete clinical remission of NME (Figure 2). For the last 9 months, the patient's NME has remained in remission with cyclosporine treatment and the metastatic disease has remained stable with capecitabine and temozolomide treatment.

3 | DISCUSSION

The pathophysiology of NME can be explained by a catabolic state involving the hypersecretion of glucagon which increases gluconeogenesis, glucogenolysis, and ketogenesis. This catabolic state is responsible for the cachexia and decreased amino acid levels characteristic of patients with glucagonoma-associated NME. An increase in glucagon and hypoaminoacidaemia trigger an increase in arachidonic acid in the epidermis leading to an inflammatory process responsible for the psoriasiform dermatitis and superficial epidermal necrosis typical of NME (John & Schwartz, 2016; Mendoza-Guil et al., 2005). Peterson, Shaw, Acott, Mueggler, and Parker (1984) demonstrated that glucagon can increase inflammatory mediators such as arachidonic acid in the epidermis causing the cutaneous lesions characteristic of NME. This pathophysiology may explain the three possible approaches for treating NME. The main approach, surgical removal of the tumor, is considered the definitive treatment for glucagonoma and NME. In addition, somatostatin analogues are utilized to address excess glucagon (John & Schwartz, 2016). The intermediate approach involves the administration of intravenous amino acids to counteract patients' hypoaminoacidaemia and deficits in essential amino acids (Thomaidou et al., 2016). Finally, systemic corticosteroids or cyclosporine could be used to affect the inflammatory cascade triggered in the skin.

We report the first case of NME secondary to metastatic glucagonoma and refractory to octreotide and chemotherapy in which complete remission was achieved after the use of oral cyclosporine.

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REFERENCES

John, A. M., & Schwartz, R. A. (2016). Glucagonoma syndrome: A review and update on treatment. *Journal of the European Academy of Dermatology and Venereology*, *30*, 2016–2022.

Luber, A. J., Ackerman, L. S., Culpepper, K. S., Buschmann, C. M., & Koep, L. J. (2016). Paediatric necrolytic migratory erythema as a presenting sign of glucagonoma syndrome. *British Journal of Dermatology*, *174*, 1092–1095.

Mendoza-Guil, F., Hernández-Jurado, I., Burkhardt, P., Linares, J., & Naranjo, R. (2005). Eritema necrolítico migratorio asociado a glucagonoma. *Actas Dermo-Sifiliogrficas*, *96*, 175–178.

Peterson, L. L., Shaw, J. C., Acott, K. M., Mueggler, P. A., & Parker, F. (1984). Glucagonoma syndrome: In vitro evidence that glucagon increases epidermal arachidonic acid. *Journal of the American Academy of Dermatology*, *11*, 468–473.

Thomaidou, E., Nahmias, A., Gilead, L., Zlotogorski, A., & Ramot, Y. (2016). Rapid clearance of necrolytic migratory erythema following intravenous administration of amino acids. *JAMA Dermatology*, *152*, 345–346.