Case of delayed diagnosis of necrolytic migratory erythema

Wissal Abdelli1 | Fatima Alaoui1 | Asmahan Souissi1 | Wiem Sassi1 | Ines Chelly2 | Slim Haouet2 | Mourad Mokni1

1Dermatology Department - Rabta Hospital, Tunis, Tunisia
2Anatomopathology Department – Rabta Hospital, Tunis, Tunisia

Correspondence
Wissal Abdelli, Rabta Hospital
Dermatology Department, Jebel Lakhdar street 1007- La Rabta
Jebbari - Tunis - Tunisia.
Email: abdelliwissal7@gmail.com

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1 INTRODUCTION

Necrolytic migratory erythema (NME) is a rare cutaneous paraneoplastic manifestation of glucagonoma. Estimated incidence of glucagonoma is 1/20,000,000/year. Elevated glucagon level can cause a variety of clinical manifestations including weight loss, diabetes, and NME. This skin rash has a cyclic nature, and lesions exist simultaneously at different stages. Misdiagnosis of paraneoplastic cutaneous manifestation could delay the diagnosis of glucagonoma. We report an interesting case of a female patient with a 6-year history of delayed diagnosis of glucagonoma.

2 CASE REPORT

A 36-year-old Tunisian woman had been followed in our dermatology department for 6 years. She was referred to us for chronic prurigo. Laboratory testing revealed hypochromic microcytic anemia. Serum glucose, HBA1C, and liver plasma tests were normal. She had normal serum zinc, albumin, and lipid levels. Abdominal ultrasound was normal. She was treated with topical steroid intermittently with variable response. Since this episode, she had returned several times with polymorphous skin lesions such as papules, erythematous squamous and crusty plaques, vesicles, pustules, and erosions accompanied by severe pruritus. At that time, we thought she had prurigo (Figure 1A), eczema (Figure 1B), insect bites (Figure 1C), or even drug eruption (Figure 1D).

The eruption was episodic with spontaneous exacerbations and remissions. The patient had no abdominal pain, gastrointestinal symptoms, or weight loss. Multiple skin biopsies were performed. They concluded to drug eruption, eczema, prurigo, and erythema multiforme. During the course of the outbreaks, the patient developed angular cheilitis and gingivitis, a deep vein thrombosis in the leg, and psychological problems which affected her social and professional life. Six years later, she presented with acute abdominal and pelvic pain. Abdominal computed tomography (CT) was performed, and hyperdense mass was confirmed on body-tail pancreatic of 15 cm in maximum diameter with mild degree of contrast enhancement. Removal of the tumor was indicated and the cutaneous lesions vanished 1 week after surgery. Pathology report indicated a tumor in the pancreatic alpha...
cells. Immunohistochemistry showed expression of glucagon and chromogranin A in tumor cells (diagnosis of glucagonoma). No metastases were detected.

Retrospectively, on reviewing the patient’s photos, in addition to the deceptive lesions, our patient presented a unique clinically and histologically typical episode in which we missed unfortunately in the diagnosis. She had an annular-circinate, erythematous, scaly rash with areas of hyperpigmentation and skin sloughing, mainly involving the extremities, buttocks, and perineum (Figure 2A). The lesions were highly suggestive of NME. Skin biopsy revealed psoriasiform acanthosis and abrupt necrosis of the upper layers of stratum; whereas the lower half of epidermis appears viable, the detached necrolytic portion appears pale with pyknotic nuclei. Perivascular lymphocytic infiltration and scattered extravasated red blood cells were present in the upper dermis (Figure 2B).

The absence of diabetes and gastrointestinal symptoms led to misdiagnosis.

Two years after surgery, the patient presented with typical skin signs of NME (Figure 3) and diabetes. Magnetic resonance imaging (MRI) and abdominal CT were normal. We asked for a review of the MRI and CT scan because we were sure that the tumor had recurred. Two nodules were visualized on MRI: a retropancreatic nodule (13 mm) and a nodule opposite the tail of the pancreas (11 mm), with heterogeneous T2 signal, diffusum hyper-signal, without intense arterial enhancement, homogeneous at both portal and late phases. The octreoscan did not show distant metastases. The patient was referred to
surgery for surgical resection of the tumor. The cutaneous lesions vanished 2 weeks after surgery. No tumor recurred during 11 months of follow-up.

3 | DISCUSSION

Glucagonoma syndrome (GS) is a rare paraneoplastic phenomenon. Its most common features are weight loss, NME, and diabetes mellitus. The pathogenesis of the NME is mainly due to the elevated level of serum glucagon that induces inflammatory mediators in the skin, which are responsible for epidermal necrosis. It is likely from the physiological function of glucagon and the histopathological findings on tissue biopsy that the NME is a true deficiency dermatosis. Excess glucagon leads to hypovitaminosis B, amino acid deficiency, zinc deficiency, and free fatty acid deficiency.

Necrolytic migratory erythema also occurs outside the context of a glucagonoma, and in these cases, it is termed pseudoglucagonoma syndrome. This may occur in pancreatitis, inflammatory bowel disease, non-pancreatic malignancies, liver disease, malabsorption with villous atrophy, celiac sprue, hypoproteinemia, zinc and essential fatty acid deficiency, and iatrogenic causes.

Necrolytic migratory erythema is considered a hallmark clinical sign of glucagonoma syndrome, present in approximately 70% of patients. The dermatosis evolves in 7–14 days, occurring in spontaneous exacerbations and remissions. Cutaneous features can mimic bullous dermatitis; it may also present as psoriasiform or eczematosus plaques. Our patient’s cutaneous lesions were underrecognized, and we misinterpreted the skin manifestations as more common entities such as prurigo, eczema, and drug eruption for 6 years. Indeed and during several years, our patient presented with prurigo, eczema, insect bites, or even drug eruption-like lesions. Only one episode was typical with a necrolytic migratory erythema. Unfortunately, we missed the diagnosis. The polymorphism of the cutaneous features and the rarity of glucagonoma delayed the recognition of the clinical syndrome. The absence of diabetes and the normal abdominal ultrasound also contribute to erroneous and delayed diagnosis in our patient.

There are many reports of delayed diagnosis of glucagonoma due to misdiagnosis or delayed diagnosis of skin lesions. The average time from recognized symptoms to diagnosis is about 4 years. Histology may show nonspecific dermatitis, requiring multiple biopsies to confirm the diagnosis. The most specific feature includes superficial epithelial necrosis of the upper spinous layer with vacuolated keratinocytes. Lack of specific findings on biopsy and the rarity of the pancreatic tumor can attribute to delay in the diagnosis.

Necrolytic migratory erythema is a valuable cutaneous presentation in this disease, when the skin lesions relapsed, we were convinced of the recurrence of the tumor, even though the scan was normal.

By the time of diagnosis, 50%–100% of patients already present with metastatic disease, and a cure is often impossible. However, since this islet cell tumor is slow-growing, prolonged survival (more than 20 years) is possible, and in metastatic disease, most causes of death appear to be unrelated to the tumor. The causes of death are correlated with thromboembolism, sepsis, and gastrointestinal bleeding. Skin changes appear early in the course of GS and are reason for seeking medical help for the first time. They are followed by systemic symptoms such as...
weight loss, diarrhea, diabetes mellitus, neuropsychiatric disorders, anemia, and thrombosis.

Diabetes mellitus is found in 80% of patients with the GS.3 Our patient had no diabetes and this delayed the recognition of the clinical syndrome.

Glucagonoma syndrome is associated with a high incidence of thromboembolism, estimated between 10% and 30% of patients18 which is responsible for the immediate cause of death in up to 50% of patients.19 Our patient was diagnosed with deep vein thrombosis in the leg.

Vitamin B6 (pyridoxine) deficiency due to excess glucagon explains the hypochromic microcytic anemia and the disturbances in the central nervous system like depression as in our patient.3 Complete resection of the tumor is the best treatment. Our patient’s cutaneous lesions vanished 1 week after surgery. Patients who underwent resection had longer median survival than patients who did not receive surgery, even when diagnosed with later stages of disease.20

4 | CONCLUSION
The observed patient was diagnosed with a high delayed diagnosis but fortunately before metastases occurred. It highlights the atypical clinical features and non-specific histology of NME which makes the diagnosis difficult. The absence of diabetes, the polymorphism of clinical and histologic presentation, and the psychological features contribute to erroneous and delayed diagnosis in our patient.

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CONFLICT OF INTEREST
The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS
Abdelli Wissal wrote the article. Souissi Asmahen, Alaoui Fatima, and Sassi Wiem were involved in drafting the manuscript and revising it critically. Chelly Ines and Haouet Slim have made contributions to examine the histology slides. Mokni Mourad gave final approval of the version to be published.

ETHICAL APPROVAL
I testify on behalf of all co-authors that our article submitted to the clinical case reports: a case of delayed diagnosis of necrolytic migratory erythema. This material has not been published in whole or in part elsewhere. The manuscript is not currently being considered for publication in other journals. All authors have been personally and actively involved in substantive work leading to the manuscript and will hold themselves jointly and individually responsible for its content.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy on the title page of the manuscript.

DATA AVAILABILITY STATEMENT
The data used to support the findings of this study are included within the article.

ORCID
Wissal Abdelli https://orcid.org/0000-0001-6431-105X

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