Glucagonoma: how the misdiagnosis of a paraneoplastic cutaneous manifestation affects the clinical outcome: a case report

Elena Parlagreco[1], Irene Persano[1*], Anna La Salvia[2], Anna Pia[3], Giorgio Vittorio Scagliotti[1], Maria Pia Brizzi[1]

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ABSTRACT

Background: Glucagonoma is a rare functional pancreatic neuroendocrine tumor. Necrolytic migratory erythema (NME) is a paraneoplastic manifestation of glucagonoma and is often the first presenting symptom. The misdiagnosis of this rare entity can affect the patient's quality of life and his life expectancy.

Case Presentation: We report a case of a 48-year-old man presenting with pruritic scaly rash, ulcerated skin lesions, and periorbital edema, who was diagnosed and treated for atopic eczema for a 7-year period. Despite treatment, his dermatitis and general conditions progressively worsened, until he was admitted to the emergency department due to weight loss and fatigue. An uncontrolled diabetes was found and the computer tomography scan of the abdomen revealed a tumor located in the tail of the pancreas with liver metastases. Subsequently, liver biopsy and high levels of glucagon confirmed the diagnosis of glucagonoma. The patient was treated with short-acting subcutaneous octreotide for 2 weeks and then with intramuscular slow-release octreotide every 28 days, with a significant improvement of the symptoms.

Conclusion: This case provides further knowledge about NME, since a timely recognition and treatment of this misleading disease can prevent morbidity from the dermatitis and mortality from the malignancy itself.

Keywords: Glucagonoma, neuroendocrine tumors, glucagonoma syndrome, necrolytic migratory erythema (NME), quality of life, dupilumab, somatostatin analogs (SSA).

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Correspondence to: Irene Persano
*Department of Oncology, University Hospital San Luigi Gonzaga, University of Turin, Orbassano, Italy.
Email: irenepersano@gmail.com
Full list of author information is available at the end of the article.

Background

Glucagonoma is a rare pancreatic α-cell tumor that oversecretes glucagon, resulting in a syndrome with distinct clinical features such as weight loss, diabetes, anemia, mucosal abnormalities, thromboembolism, gastrointestinal symptoms, and neuropsychiatric disorders [1].

A paraneoplastic skin erythematous rash known as necrolytic migratory erythema (NME) can be a presenting symptom of glucagonoma. Since NME is usually present at the early onset of glucagonoma syndrome, the dermatologist may be the first specialist consulted by the diseased patient [2]. The punctual recognition and treatment will prevent morbidity from the epidermal dysfunction and mortality from the tumor itself [3]. Herein, we report a case of glucagonoma with NME that well illustrates how the delayed diagnosis of this rare disease can affect the patient's quality of life and the clinical outcome.

Case Presentation

A 48-year-old man presented with generalized pruritic scaly rash, ulcerated skin lesions (Figure 1) and periorbital edema. The rash was prominent in the lower and upper extremities, perioral areas, and areas of increased

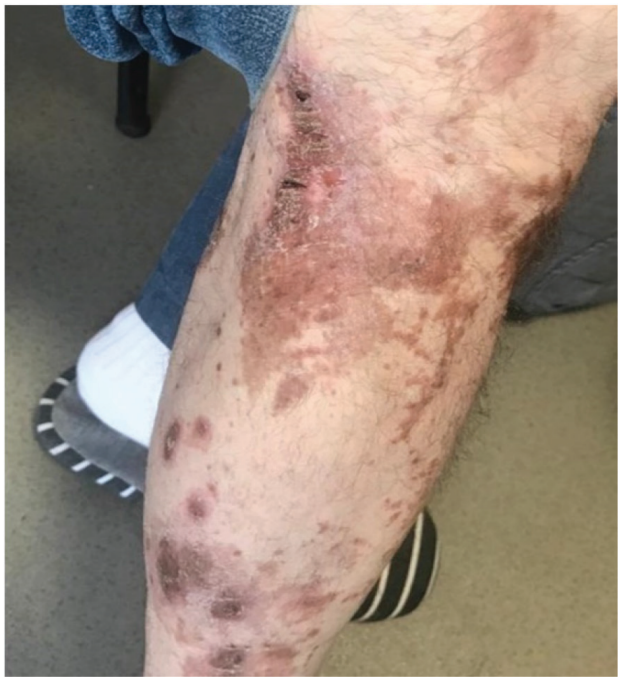

Figure 1. *Necrolytic migratory erythema with scaly and ulcerated skin lesions.*

friction and pressure (i.e., inguinal creases and popliteal fossa). Due to his severe clinical conditions, he was referred to a dermatological center. A skin biopsy was carried out, reporting a non-specific inflammatory pattern: epidermal psoriasiform hyperplasia, parakeratosis, and lymphocytic perivascular infiltrate (Figure 2). Based on the clinical and histological features, he was diagnosed with atopic eczema and then treated for a 7-year period with a sequence of topical and oral steroids, methotrexate, cyclosporine A, and the humanized monoclonal antibody dupilumab. Despite the best sequential dermatology treatment, the dermatitis progressively worsened in extent and severity, limiting the patient's activities of daily living. In August 2019, he was admitted to the emergency department of our center for fatigue, weight loss (33 pounds in 3 months) and hyperglycemia (>300 mg/dl). The computed tomography (CT) scan of the abdomen showed a mass in the pancreatic tail and multiple liver metastasis (Figure 3). A liver biopsy was carried out and confirmed a G1 neuroendocrine tumor (NET) with a Ki67 of 2%, while the immunohistochemical staining was positive for synaptophysin, chromogranin, and focally for glucagon. The patient was referred to our neuroendocrine multidisciplinary tumor board. Serum glucagon was higher than 1,000 pg/ml (normal range < 100 pg/ml) and the cutaneous rash was recognized as NME. Gallium-68 somatostatin receptor positron emission tomography (^{68}Ga-DOTATATE PET/CT) revealed intense uptake in the body and tail of the pancreas and liver (Figure 4). An inherited syndrome was excluded. Since the tumor was judged surgically unresectable, the patient was promptly started on a somatostatin analog therapy (SSA) with subcutaneous octreotide (0.5 µg three times a day), and intramuscular long-acting octreotide acetate every 28 days. After 15 days, a decrease in glucagon levels and a meaningful improvement of skin lesions were achieved (Figure 5A and B), with a highly positive impact on the patient's quality of life. The clinical improvement was sustained after four cycles of SSA with good glycemic control and evidence of stable disease at the restaging CT scan.

Discussion

Glucagonoma is a rare functioning pancreatic neuroendocrine neoplasm with an annual incidence of 0.01-0.1 new cases per 100,000/persons [4]. The neuroendocrine α cells tumor produces an uncontrolled secretion of glucagon,

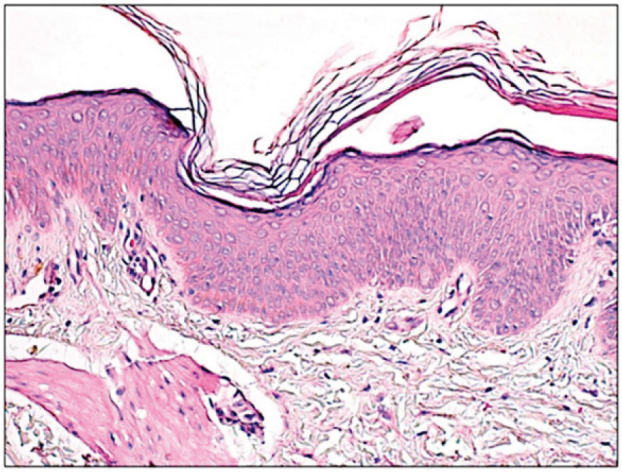

Figure 2. *Skin biopsy reporting a non-specific inflammatory pattern: epidermal psoriasiform hyperplasia, parakeratosis, and lymphocytic perivascular infiltrate.*

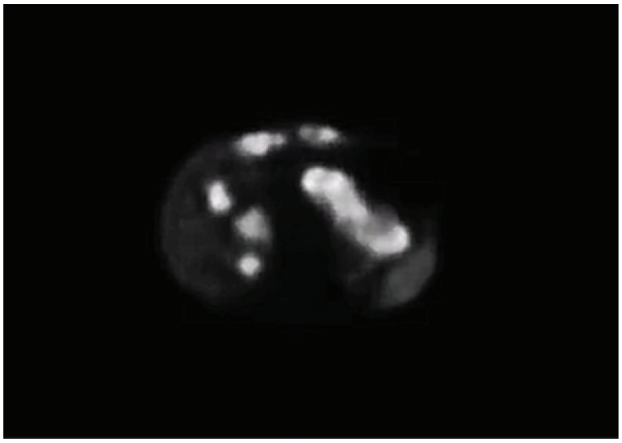

Figure 4. *Gallium-68 somatostatin receptor positron emission tomography revealing intense uptake in the body and tail of pancreas and liver.*

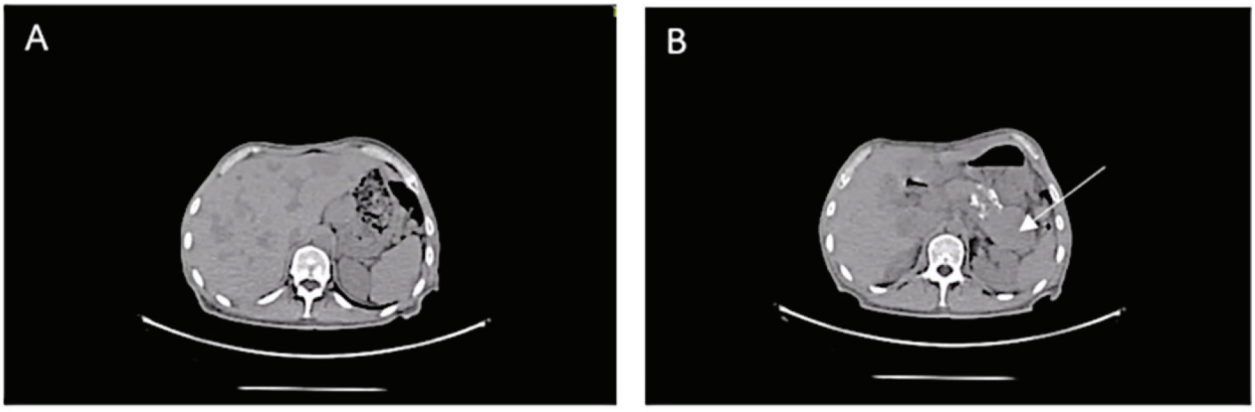

Figure 3. *Computed tomography scan of the abdomen showing multiple liver metastasis (A) and a mass in the pancreatic tail (B).*

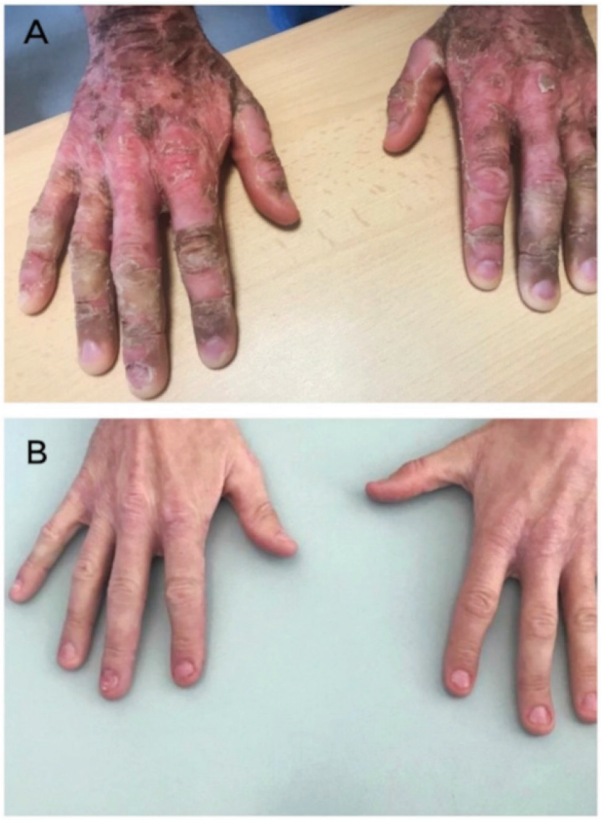

Figure 5. *(A) Necrolytic migratory erythema before and (B) after 15 days of SSA.*

resulting in distinct paraneoplastic phenomena that might occur together in a syndromic pattern. The so-called 4D syndrome associated with glucagon oversecretion consists of diabetes, a typical dermatosis named NME, deep venous thrombosis, and depression [5]. Other manifestations such as weight loss, stomatitis, steatorrhea, anemia, gastrointestinal symptoms, and neuropsychiatric disorders can be less frequently reported [6]. Our patient suffered from typical cutaneous eruptions, diabetes, and weight loss. The diagnosis is based upon clinical findings and requires elevated serum glucagon levels (>1,000 pg/ml) and imaging data confirmed a pancreatic tumor. Despite being a slow-growing tumor, glucagonoma is frequently a late diagnosis: the reported average time from symptoms onset to diagnosis of glucagonoma is 31.4 months. This was the case for our patient, who was diagnosed with glucagonoma syndrome after 7 years from the onset of the dermatitis. Fortunately, even in the metastatic setting, survival is relatively favorable: a recent review of 623 cases reported a median overall survival of 32.1 months [7]. The misdiagnosis of this entity can be justified by the subtle and often non-specific initial symptoms, as in the case of the NME. NME is a characteristic cutaneous paraneoplastic manifestation of glucagonoma and can be the only presenting feature in approximately 70% of the patients. This rash is commonly characterized by pruritic, painful, erythematous, and well-demarcated plaques that usually spread in a centrifugal pattern, comparable to those developing in our patient. Similar cutaneous manifestations can be associated with other skin disorders, such as acrodermatitis enteropathica, zinc deficiency, essential fatty acid deficiency, kwashiorkor disease, pellagra, psoriasis, eczema, seborrhoeic dermatitis, candidiasis, and pemphigus, making the diagnosis really challenging [8]. Although no histologic feature is pathognomonic, the hallmarks of NME are necrosis of the upper spinous layer of the epidermis, confluent parakeratosis and irregular acanthosis, with loss of the granular layer [9]. These relatively non-specific findings can make it difficult to distinguish NME from other common dermatoses, especially from chronic inflammatory dermatitis such as psoriasis and eczema. For instance, the characteristics of our patient's rash, combined with the periorbital edema, suggested a diagnosis of atopic eczema. Thus, the patient underwent standard treatment for atopic eczema over a 7-year period, with the use of topical anti-inflammatory medications and subsequent systemic treatment with oral glucocorticoids, methotrexate, ciclosporine A, and the humanized monoclonal antibody dupilumab. Nevertheless, the cutaneous eruptions of our patient and the general condition progressively got worse, since the pathogenesis of NME differs from that of the other, most reported, chronic inflammatory skin diseases. Moreover, a potential role of the long-term immunosuppressive therapy on the tumor progression cannot be completely excluded. Although the exact pathogenesis of NME is still not fully understood, hyperglucagonemia, along with several other interplaying factors (including hypoaminoacidemia, zinc, and essential fatty acids deficiency), contributes to the epidermal dysfunction. The catabolic state induced by excess serum glucagon results in derangement of a common metabolic pathway involving the above-mentioned nutrients; thus, NME can be classified as a deficiency dermatosis [10]. In this context, zinc seems to play a major role in the pathogenesis of NME, as its supplementation has been shown to improve the cutaneous eruptions seen in glucagonoma syndrome [11]. It has been reported that the zinc deficiency, as a required co-factor in the delta-6 desaturation of linoleic acid, results in the blockage of polyunsaturated fatty acids pathway. Consequently, the precursors shift to the production of arachidonic acid with an increased production of inflammatory mediators, such as prostaglandins and leukotrienes, in the epidermis [12]. Similarly, it is postulated that the depletion of amino acids as well leads to a decrease in peptide synthesis in the epidermis, with subsequent increased arachidonic acid production, and thus an increased tendency toward inflammation [13]. Despite a relatively good survival rate, glucagonoma is a malignant disease and treatment should be undertaken as soon as possible after diagnosis. Surgery is currently the only curative approach for glucagonoma. The removal of the primary tumor, in the absence of distant metastases, has demonstrated to completely resolve the paraneoplastic

cutaneous eruptions, as well as the accompanying symptoms, within a week [14]. Unfortunately, at the time of diagnosis our patient had hepatic metastases and so a palliative medical treatment was the only option. Somatostatin analogs are an effective strategy to decrease serum glucagon levels and they showed anti-growth effects in a randomized, phase III clinical trial on patients with advanced gastroenteropancreatic NETs [15]. So, according to all the international guidelines (European NET Society, North American NET Society), SSAs have been recommended as the first-line therapy in advanced pancreatic NETs (panNETs), including functional panNETs such as glucagonoma [16,17]. Moreover, following the initiation of somatostatin analog treatment, 89%-90% of the patients show a significant improvement in migratory necrolytic erythema rash, whereas 60%-80% have a reduction in glucagon levels [4]. Our case confirmed the following findings: 15 days after being started on short-acting subcutaneous octreotide, the patient had a dramatic decrease in serum glucagon levels, good glycemic control, and a substantial improvement of his dermatitis, while the subsequent use of slow-release somatostatin analogs guaranteed disease control for 4 months. Supplementation with zinc, amino acids, and essential fatty acids also has a biochemical rationale and seems to be beneficial.

In summary, we reported a case of glucagonoma with a clinical presentation of the glucagonoma syndrome: typical NME, weight loss, and diabetes. This case report reinforces how the misdiagnosis of this rare disease can affect the patient's quality of life and his life expectancy. The patient received an immunosuppressive treatment for severe eczema over a 7-year period, without benefit and progressive deterioration of the quality of life. We aimed to provide further evidence of how a timely diagnosis of the glucagonoma syndrome and a prompt treatment initiation can prevent morbidity from the epidermal dysfunction and mortality from the malignancy itself. Furthermore, the role of the NET multidisciplinary tumor board in the management of this misleading disease is crucial; although dermatologists may be at the forefront of the clinical diagnosis and may play a primary role in the differential diagnoses, reporting all suspected patients of glucagonoma to the multidisciplinary tumor board, may contribute to shortening the time to diagnosis.

List of Abbreviations

68Ga-DOTATATE PET/CT	Gallium-68 somatostatin receptor positron emission tomography
CT	computed tomography
MTB	multidisciplinary tumor board
NET	neuroendocrine tumor
NME	necrolytic migratory erythema
PanNETs	pancreatic neuroendocrine tumors
SSA	somatostatin analog

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written consent was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author details

Elena Parlagreco[1], Irene Persano[1], Anna La Salvia[2], Anna Pia[3], Giorgio Vittorio Scagliotti[1], Maria Pia Brizzi[1]

1. Department of Oncology, University Hospital San Luigi Gonzaga, University of Turin, Orbassano, Italy
2. Department of Oncology, University Hospital 12 de Octubre, UCM, Madrid, Spain
3. Department of Biological and Clinical Sciences, Internal Medicine, University Hospital San Luigi Gonzaga, University of Turin, Orbassano, Italy

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Summary of the case

1	**Patient (gender, age)**	Male, 48-year-old
2	**Final diagnosis**	Glucagonoma, glucagonoma syndrome (NME, diabetes)
3	**Symptoms**	Generalized pruritic scaly rash, ulcerated skin lesions and periorbital edema, weight loss, and fatigue
4	**Medications**	Somatostatin analog (SSA) therapy with subcutaneous octreotide (0.5 micrograms three times a day) and intramuscular long-acting octreotide acetate every 28 days
5	**Specialty**	Oncology, neuroendocrinology