

Acanthosis nigricans in a patient with metastatic insulinoma post peptide receptor radionuclide therapy

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Summary

Acanthosis nigricans (AN) is a common dermatosis associated with hyperinsulinemia and insulin resistance. However, AN has been rarely reported in patients with insulinoma, a state of persistent hyperinsulinemia. We present a case of metastatic insulinoma, in whom AN manifested after the first cycle of peptide receptor radionuclide therapy (PRRT). A 40-year-old man was diagnosed with metastatic insulinoma after 5 months of symptomatic hypoglycemia. Within 1 month post PRRT, the patient became euglycemic but developed a pigmented, pruritic rash which was confirmed on biopsy as AN. We discuss the rare manifestation of AN in subjects with insulinoma, the role of insulin in the pathogenesis of AN, malignant AN in non-insulin-secreting malignancies and association with other insulin-resistant endocrinopathies such as acromegaly.

Learning points:

- Acanthosis nigricans (AN) is a common dermatosis which is typically asymptomatic and associated with the hyperinsulinemic state.
- Malignant AN can rapidly spread, cause pruritus and affect mucosa and the oral cavity.
- AN is extremely rare in patients with insulinoma despite marked hyperinsulinemia.
- Peptide receptor radionuclide therapy might have triggered TGF- α secretion in this subject which led to malignant AN.
- Rapid spread or unusual distribution of pruritic AN warrants further investigation to exclude underlying malignancy.

Background

Acanthosis nigricans (AN) is a common dermatosis characterized by generalized cutaneous thickening with a pigmented velvety appearance (1). Although pathogenesis remains unclear, it is associated with hyperinsulinemic conditions such as type 2 diabetes and polycystic ovarian syndrome. Despite the marked persistent hyperinsulinemia seen in metastatic insulinoma, AN is a rarely reported. We report a case of metastatic insulinoma

who developed symptomatic AN shortly after peptide receptor radionuclide therapy (PRRT) treatment. The resolution of AN was incongruent with circulating insulin concentration and disease progression. This prompts the possibility of malignant acanthosis nigricans (MAN), a rare paraneoplastic syndrome usually associated with non-insulin-producing adenocarcinoma which heralds a poor prognosis.

Case presentation

A 41-year-old man of Indian descent presented with 5 months of presyncopal episodes, diaphoresis and altered cognition. He gained 10 kg over 2 months leading up to the presentation (BMI=32.3 kg/m²). Investigations captured a hypoglycemic episode with inappropriate hyperinsulinemia (plasma glucose=2.4 mmol/L, insulin=100.5 mU/mL (2.6–24.9 mU/mL), C-peptide=2.28 nmol/L (0.3–2.3 nmol/L), HbA1c of 4.9%/26.8 mmol/mol). Imaging revealed primary pancreatic neuroendocrine tumor (NET) with FDG and 68-Gallium DOTATATE avid nodal metastasis. Immunohistochemistry of lymph node biopsy was positive for insulin, chromogranin and synaptophysin with a Ki-67 index of 10%. Octreotide, prednisolone and diazoxide were commenced for his grade 2 metastatic insulinoma. Within 1 month post ¹⁷⁷Lu-DOTATATE (LuTate) PRRT, he observed hyperpigmented, pruritic skin changes on the hands, which rapidly progressed to involve neck, axillae and the lips (Fig. 1).

Investigation

Histopathological evaluation of skin biopsy confirmed acanthosis nigricans (Fig. 1). Post PRRT, the patient was mostly euglycemic as reflected by HbA1c of 6.3%/45.4 mmol/mol and plasma glucose of 5.5 mmol/L. Insulin (44.3 mU/mL) and C-peptide (1.45nmol/L) concentrations were reduced compared to baseline results.

Treatment

He completed four cycles of LuTate PRRT induction with a partial response on DOTATATE and FDG-PET imaging. He remained on prednisolone 10 mg and somatostatin analog therapy 12 months post PRRT.

Outcome and follow-up

Follow-up at 15 months post PRRT showed resolution of pruritus and fading of hyperpigmentation in the affected areas. However, he noted an increased frequency of hypoglycemia, and progressive disease was confirmed on functional imaging and biochemistry results (insulin = 109.6 mU/mL, c-peptide 3.69 nmol/L). Recurrent hypoglycemia persisted despite dexamethasone, 50% dextrose infusion, octreotide infusion and cytoreduction efforts with CAPTEM chemotherapy, everolimus and repeat PRRT induction. Patient deceased 2 years after the initial diagnosis of malignant insulinoma.

Discussion

AN is a common dermatosis characterized by brown to black velvety hyperpigmented lesions with symmetrical distribution in the skin folds such as groin, axilla or posterior neck, but it may also affect eyelids, lips and mucosal surfaces. It is generally asymptomatic and is more frequently observed in darker skin people (1). The etiology of AN is still not clearly defined, but it is likely related to hyperinsulinemia and insulin resistance. At high levels, insulin crosses the dermoepidermal junction, activates the insulin-like growth factor (IGF) receptor and reduces IGF binding proteins. Subsequently, increased free circulating IGF promotes local proliferation of keratinocytes and fibroblasts (2). AN may be associated with endocrine disorders including acromegaly, gigantism, polycystic ovarian syndrome, Cushing's syndrome and type 2 diabetes. Medications such as glucocorticoids, insulin and estrogen can exacerbate hyperinsulinemia and lead to iatrogenic AN (3). In this setting, AN can resolve with improvement in insulin resistance via weight loss or by cessation of the offending medication (1).

In contrast, MAN is induced by malignancy (most commonly adenocarcinoma originating from the

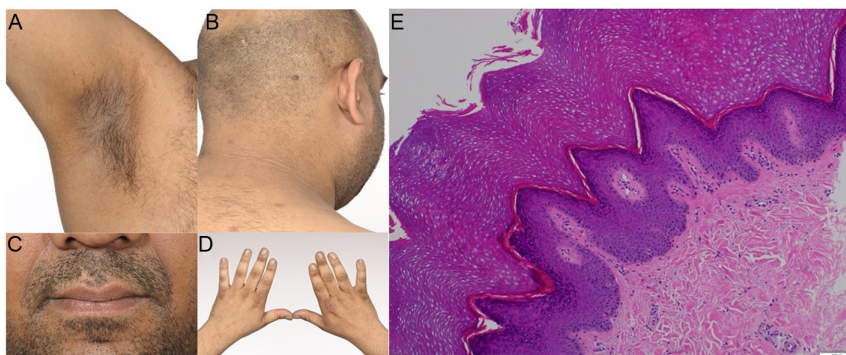


Figure 1
Acanthosis nigricans of axillae (A), neck (B), lips (C), dorsal hands (D), biopsy specimen showing papillomatosis, hyperkeratosis and acanthosis in the epidermis (E).



Table 1 Summary of this case and other case reports of AN in insulinoma patients.

Author	Year	Age	Ethnicity/ phototype	Gender	BMI (kg/m ²)	Site of AN	Insulin (2.6–24.9 mU/mL)	C-peptide (0.3–2.3 nmol/L)	Benign vs metastatic/size of tumor (cm × cm)	Treatment/outcome of AN
Pfeifer (11)	1999	16	Caucasian	Female	39.8	Neck, abdo, axillae	697	3.645	Benign/N/A	Surgical excision/resolution of AN 11 years post operation
Tran (12)	2003	64	N/A	Female	43	Eyes, lips, axillae, groin	171	3.9	Metastatic/5.0 × 4.0	Surgical excision/N/A
Ghosh (13)	2008	35	N/A	Male	31	Neck	79	5.297	Benign/1.5 × 1.2	Surgical excision/resolution of AN 8 weeks post operation
Jyotsna (14)	2014	14	Skin type 4	Male	29	N/A	133.5	4.019	Benign/1.8 × 1.1	Surgical excision/N/A
Patra (7)	2016	14	Skin type 5	Female	36.5	Neck	16.8	1.146	Benign/3.1 × 2.9	Surgical excision/significant reduction of AN 4 weeks post operation
Gudala (15)	2017	15	Hispanic	Female	32.8	Neck	63.2	1.821	Benign/1.2 × 1.2	Surgical excision/N/A
Yun (current case)	2021	41	Skin type 4	Male	32.3	Lips, neck, axillae, hands	100.5	2.278	Metastatic/3.7 × 1.7 × 4.1	PRRT/resolution of pruritus and improved hyperpig- mentation

N/A, not available.



gastrointestinal tract and pancreas) and can precede (18%), accompany (60%) or follow (22%) the onset of the malignancy. Visually indistinguishable from AN, these lesions are often pruritic, involve the oral cavity and have a rapid onset. The malignant tumor cells in the primary tumor and metastases secrete cytokines including transforming growth factor- α (TGF- α), IGF, fibroblast growth factor and α -melanocyte-stimulating hormone which pathologically stimulates fibroblasts, keratinocytes and melanocytes (4).

Insulinomas are rare neuroendocrine tumors, with an incidence of four cases per million patients per year. They are generally benign, but 5.8–15% are malignant tumors. In a series of 31 insulinoma patients, none had AN despite significant hyperinsulinemia (5). To date, there are only six case reports of AN and insulinoma (Table 1). Only half of the reviewed cases reported significant improvement and/or resolution of AN post-surgical enucleation of insulinoma. We did not find a temporal relationship between AN onset/severity and the circulating insulin concentration or tumor load in our case. AN was absent at diagnosis when his insulin was at its peak, thereafter AN appeared after PRRT treatment and then faded when disease progressed. Of the seven cases of AN and insulinoma in Table 1, the average insulin concentration was 181.7 mU/mL, a level typically seen in obese PCOS subjects post glucose load (6). Furthermore, other than our case, AN has only been reported in one other case with metastatic insulinoma. Therefore, AN in insulinoma patients might be a neoplastic phenomenon rather than an insulin hypersecretion issue per se. Patra *et al.* also questioned hyperinsulinemia as the sole mechanism given the rare prevalence of AN in insulinoma patients (7).

To our knowledge, our case is the first described case of AN observed after the commencement of insulinoma treatment. PRRT is a relatively new mode of therapy for malignant insulinomas. The first cycle of PRRT can trigger a peptide storm as the targeted insulin-producing neuroendocrine cells die, resulting in transient insulin release and potentially intractable hypoglycemia (8). TGF- α expression has been demonstrated in NETs (9). Large quantities of TGF- α can bind to the EGF receptor to promote proliferation and differentiation of keratinocytes, thereby leading to AN. It is plausible that the peptidome secretion post PRRT triggered the AN in our case (10).

In summary, we report a rare manifestation of AN post PRRT treatment for malignant insulinoma. The temporal course, rapid onset and distribution suggest MAN due to peptidome secretion post PRRT rather than insulin hypersecretion as a cause. Since AN is common amongst

patients with obesity or diabetes, clinicians should be wary of atypical AN presentation which might uncover the underlying malignancy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

The patient provided written informed consent for publication of the submitted article and accompanying deidentified images.

Author contribution statement

JY collected data and composed the manuscript, and the senior co-authors C C, C M and M G assisted with the analysis and provided critical revision of the manuscript for important intellectual content.

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