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CASE REPORT

Occult cause of paraneoplastic acanthosis nigricans in a patient with known breast DCIS: case and review

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ABSTRACT

Paraneoplastic acanthosis nigricans (PAN) is an infrequently encountered cutaneous manifestation of internal malignancy. Here, we describe a case of PAN in the setting of a known breast ductal carcinoma *in situ,* which, to our knowledge, had not been described in association with PAN. As a result, thorough investigation was undertaken to search for another concurrent neoplasm that would better explain the development of PAN. In so doing, we identified a coexisting metastatic cholangiocarcinoma. We thus conclude that when PAN is observed in an uncommon association with a known malignancy, further investigation should be undertaken to explore whether a more likely occult culprit exists.

KEY WORDS

Acanthosis nigricans, paraneoplastic acanthosis nigricans, cholangiocarcinoma, ductal carcinoma *in situ*

1. CASE DESCRIPTION

A 51-year-old woman was seen in consultation in the dermatology clinic for progressive pruritic skin changes affecting the axilla, groin, and neck. She had been referred by her oncologist, who was managing her recently diagnosed breast cancer. Definitive treatment had been initiated and consisted of left breast lumpectomy, sentinel node biopsy, and adjuvant radiation therapy. Final pathology had demonstrated a microinvasive ductal carcinoma *in situ* with a negative sentinel lymph node.

On clinical assessment, the patient was asymptomatic with respect to her breast cancer, and she had recovered completely from surgery. She had no symptoms apart from the pruritus associated with the cutaneous findings. Physical examination revealed velvety dark rugose changes in the axillae bilaterally [Figure 1(A-B)], the perineum (Figure 2), and neck, although no lymphadenopathy was evident. The features of this exanthem were consistent with a diagnosis of acanthosis nigricans.

Given the patient's absence of metabolic risk factors and the rapidity of onset of the cutaneous findings, paraneoplastic acanthosis nigricans (PAN) was considered. To our knowledge, PAN is most often associated with gastrointestinal tract malignancies and has not been reported in the setting of a ductal carcinoma *in situ*. Investigations were therefore undertaken to rule out a second occult malignancy that might be a better explanation for the findings.

Chest computed tomography (CT) imaging, esophagogastroduodenoscopy, and colonoscopy were all normal, but carbohydrate antigen 19-9 (a tumour marker for pancreatic adenocarcinoma and colorectal cancer) was elevated at 209 kU/L. Abdominal CT revealed a large dilated cystic structure in the gallbladder fossa in which lobulated soft tissue was noted; large masses in the pancreatic bed and porta hepatis were also observed. Marked retroperitoneal adenopathy consistent with metastatic cancer was also noted in the para-aortic region bilaterally.

A CT-guided biopsy of the retroperitoneal lymph nodes demonstrated carcinoma of an undetermined primary. On staining, tumour cells were positive for epithelial membrane antigen and carcinoembryonic antigen, but negative for cytokeratins 7 and 20, estrogen receptor, thyroid transcription factor 1, and calretinin. This staining pattern pointed toward tumours of biliary, pancreatic, and gastric origin, and was not consistent with metastatic breast cancer.

The local Tumour Board reviewed the patient's case and concluded that the intra-abdominal findings were most consistent with metastatic cholangiocarcinoma arising from the choledochal cyst. The patient was deemed to have non-curable disease and was offered treatment with palliative chemotherapy.

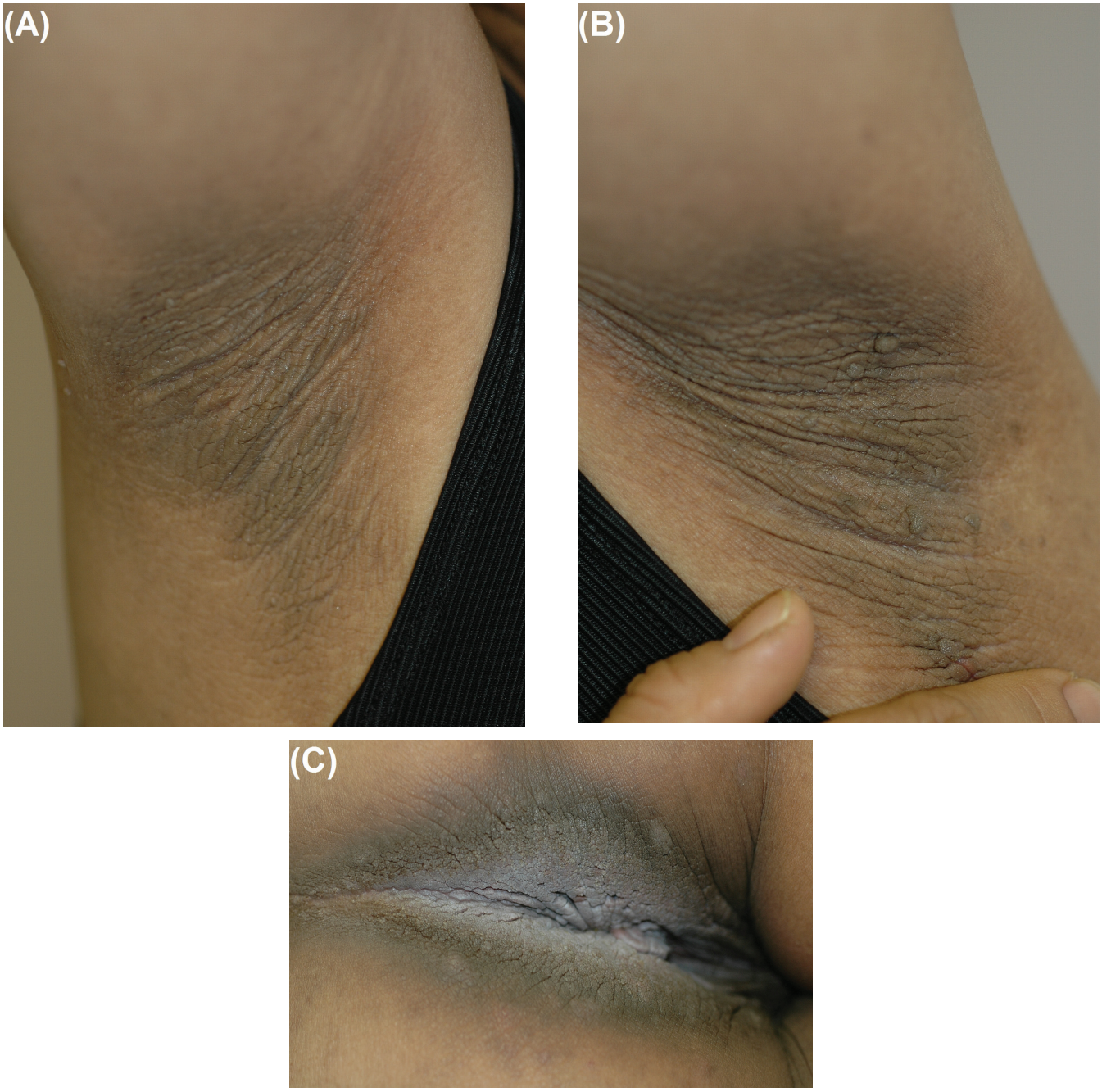

FIGURE 1 *Acanthosis nigricans: characteristic hyperpigmented rugose changes involving the (A) right and (B) left axilla, and the more prominent changes in (C) the skin of the perineum.*

2. DISCUSSION

Acanthosis nigricans is characterized by hyperpigmented velvety plaques affecting intertriginous areas, including the neck, axilla, and inframammary and inguinal regions[1,2]. These clinical findings alone are adequate for making a diagnosis of acanthosis nigricans, but biopsy demonstrates the histology findings of mild acanthosis with hyperkeratosis and dermal papillomatosis[2]. Acanthosis nigricans is observed most often in association with insulin-resistant states[3] and endocrine disorders[4], in which it represents a benign but cosmetically problematic finding. However, acanthosis nigricans can occasionally portend the presence of an internal malignancy. In this context, it is called malignant acanthosis nigricans or PAN.

Unlike typical acanthosis nigricans, PAN tends to affect middle-age or older patients and can be rapidly

progressive with extensive mucocutaneous involvement. This major feature distinguishes it from benign acanthosis nigricans, in which the symmetrically distributed lesions tend to appear at a younger age and do not evolve with time. In addition to systemic features such as weight loss and cachexia, PAN may also be seen along with other cutaneous manifestations of internal malignancy, including florid cutaneous papillomatosis[5], tripe palms[6], and the sign of Leser–Trélat[2,7,8]. These features, when present, also aid in differentiating between benign acanthosis nigricans and PAN.

Among the neoplastic associations with PAN, abdominal carcinomas are the most frequent (the preponderance being gastric adenocarcinomas[2,9,10]), although a broad spectrum of cancers have been documented, including (but not limited to) neoplasia of the urinary bladder[11], esophagus[12], adrenals[13], lung[5], liver[14], gall bladder[15], ovaries[7], and endometrium[6,16]. In the context of breast carcinoma, PAN is rare[10]. It has, however, been reported in the setting of cholangiocarcinoma[17].

The pathophysiology of PAN is poorly understood, but several theories have been posited. The role of insulin-like growth factors, either produced directly by cancerous cells or released in response to stimulatory factors secreted by cancer cells, has been surmised. Alternatively, conjecture has implicated transforming growth factor α and its action on epidermal growth factor receptors[18–20]. The fact that PAN regresses after surgical debulking (which correlates with depressed levels of transforming growth factor α) further supports the latter hypothesis[18]. As suggested by Yeh *et al.*[9], a more all-encompassing explanation is a "three-hit" model, which proposes that a combination of the presence of malignancy, secretion of growth factors, and cellular susceptibility all contribute to the pathogenesis of PAN.

Paraneoplastic acanthosis nigricans may precede or follow diagnosis of the causative malignancy, and it usually parallels the underlying cancer in progression[10]. Patients may complain of pruritus, though acanthosis nigricans is usually asymptomatic[1,2]. Topical therapies can aid in symptom management, but interventions targeting the underlying malignancy are most definitive. Despite disease-modifying measures such as surgical resection, chemotherapy, and radiation, the prognosis for patients with PAN is poor because of the aggressive nature of the underlying malignancy.

3. CONCLUSIONS

We present a unique case of PAN in the setting of two primary malignancies. Rather than attributing the PAN to the patient's known diagnosis of ductal carcinoma *in situ,* this case illustrates the importance of investigating the more common associations of rare phenomena rather than accepting seemingly convenient explanations that are less plausible.

4. ACKNOWLEDGMENTS

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5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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