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OPEN ACCESS JOURNALS

Archives of Clinical & Experimental Dermatology

Case Series | Vol 4 Iss 2

Two Unusual Cases of Acanthosis Nigricans

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Received: July 01, 2022; **Accepted:** July 18, 2022; **Published:** July 26, 2022

Abstract

***Acanthosis nigricans (AN)* presents as thickened, velvety or verrucous hyperpigmentation in skin folds, especially the neck and axilla. It is most commonly associated with endocrine disorders, obesity, and insulin resistance. However, AN that has sudden onset and is widespread should raise concern for malignancy. We present two cases to highlight the appearance of AN as a paraneoplastic syndrome. In cases of atypical AN, the importance of a more thorough malignancy work-up, apart from age-related cancer screening, cannot be understated. This work-up may include CT chest abdomen pelvis or PET scan.**

Keywords: ***Malignancy; Acanthosis nigricans; Paraneoplastic; Cancer therapy***

1. Abbreviations

AN: Acanthosis nigricans; Hb A1C: Hemoglobin A1C; CT: Computed tomography; MRI: Magnetic resonance imaging; CK: Cytokeratin; TTF-1: Thyroid transcription factor; EGD: Esophagogastroduodenoscopy; PET: Positron emission tomography.

2. Introduction

AN is a cutaneous disorder characterized by thickened, velvety, hyperpigmented skin in intertriginous areas, particularly the neck and axilla. Prevalence of AN varies from 7% to 74% of the population depending on factors such as age, race, type of AN, degree of obesity, and presence of associated endocrine issues. On histopathologic exam, papillomatosis and hyperkeratosis is seen. It is most commonly associated with insulin resistance.

However, AN can be a marker of other systemic disorders, including other endocrine disorders, such as metabolic syndrome, and malignancy [1].

3. Case One

3.1 Presentation

A 69-year-old female presented with a pruritic hyperpigmented eruption with associated skin thickening involving neck, face, bilateral axilla, and palms. The patient stated the rash appeared after receiving a steroid injection in her hip seven months prior and had not improved. The patient had tried Triamcinolone ointment and Hydrocortisone Valerate without relief. The patient denied a history of diabetes. Physical exam showed velvety hyperpigmented acanthotic plaques involving the face, neckline, mid-chest, mid-back, distal fingers, palms, hard palate, and gingiva (FIG. 1 & 2). The rest of the skin exam was normal. Patient reported she was up to date on age-appropriate cancer screenings, including a mammogram that was normal within the past year.

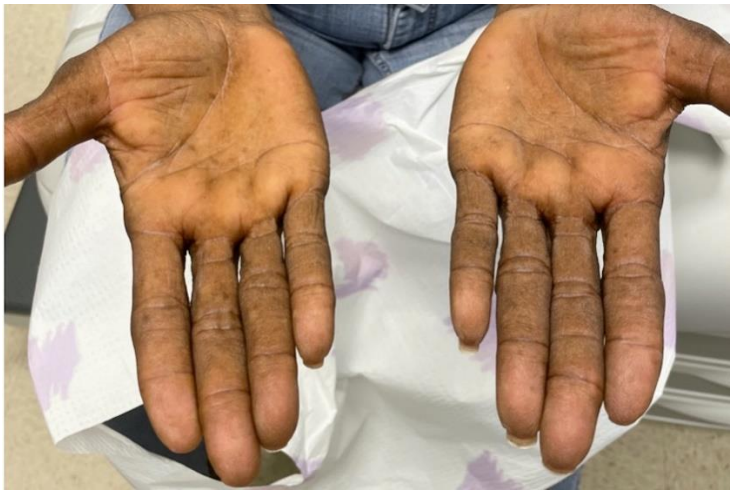

FIG. 1. **A 69-year-old female presented with thickened and hyperkeratotic plaques on the palms, consistent with atypical AN.**

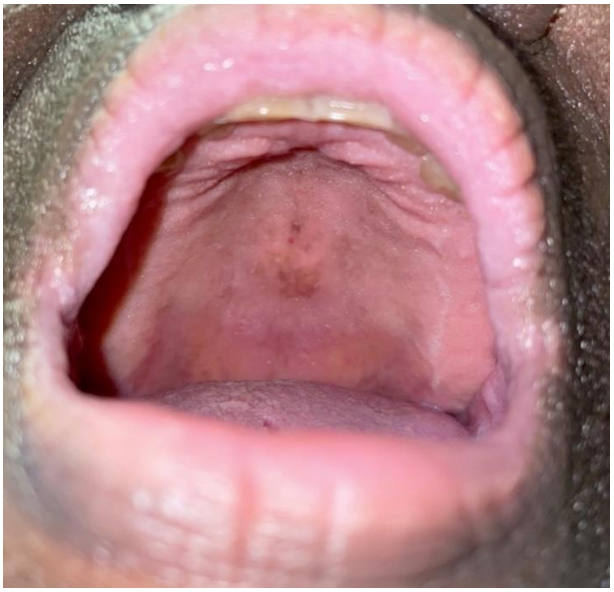

FIG. 2. **Velvety, hyperpigmented, acanthotic plaques on the hard palate of a 69-year-old female patient. Plaques had been present for about 7-months. She was up to date on age-appropriate cancer screenings.**

3.2 Diagnosis

A shave biopsy was performed and revealed acanthosis and papillomatosis with focal spongiosis, compatible with the clinical impression of AN.

3.3 Clinical course

Hb A1C was normal.

Given the patient had no underlying diabetes and the eruption of AN appeared suddenly, was widespread, and involved atypical locations, additional malignancy workup was pursued.

Chest CT with contrast showed right axillary adenopathy measuring up to 2.9 cm with asymmetric glandular tissue in the right breast. Mammogram was significant for right axillary lymphadenopathy and additional imaging was recommended. Bilateral breast MRI with and without contrast showed non mass enhancement in the right lower inner breast that was suspicious for malignancy.

Ultrasound-guided biopsy of right axillary lymph node showed invasive ductular breast cancer. Biopsy markers showed estrogen receptors 72%, progesterone receptor-negative, HER-2 negative, and Ki-67 65%.

Abdominal CT with contrast showed scattered sub centimeter hepatic hypodensities. Abdominal MRI with and without contrast showed 6 hepatic lesions suspicious for metastatic disease involvement. Liver biopsy was positive for malignant cells consistent with metastatic carcinoma and the patient underwent image-guided heat-based ablation of segment 6 metastatic hepatic lesions.

3.4 Treatment

The patient was ultimately diagnosed with stage IV breast cancer metastatic to the liver, and the patient was started on Letrozole and Ibrance. The patient was also started on urea cream twice daily for AN.

4. Case Two

4.1 Presentation

A 70-year-old female with a history of papillary thyroid cancer presented for a rash over the entire body. The rash had been present for three months and had progressively worsened. She reported that it was very itchy at night and reported the skin texture on her palms had changed. In addition, she had a 60-pound weight loss she related to decreased food intake secondary to pain from oral lesions.

Physical exam was significant for hyperkeratotic itchy papules on the bilateral dorsal hands and feet, as well as thickened and hyperkeratotic plaques under the breasts, axilla, posterior neck, gluteal crease, and palms (FIG. 3). She also had papillomatous lesions on the oral mucosa with a thickened tongue (FIG. 4). She denied a history of diabetes and had a recent normal A1c. She was up to date on age-appropriate cancer screenings.

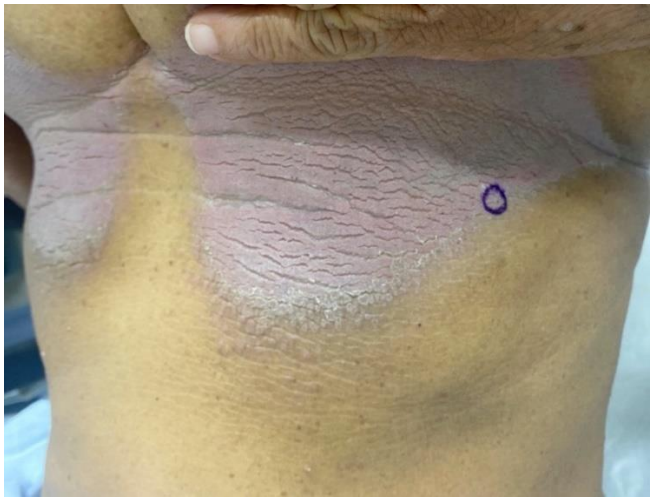

FIG. 3. **A 70-year-old female presenting with new onset rash for three months, found to have thickened and hyperkeratotic plaques under the breasts, consistent with AN.**

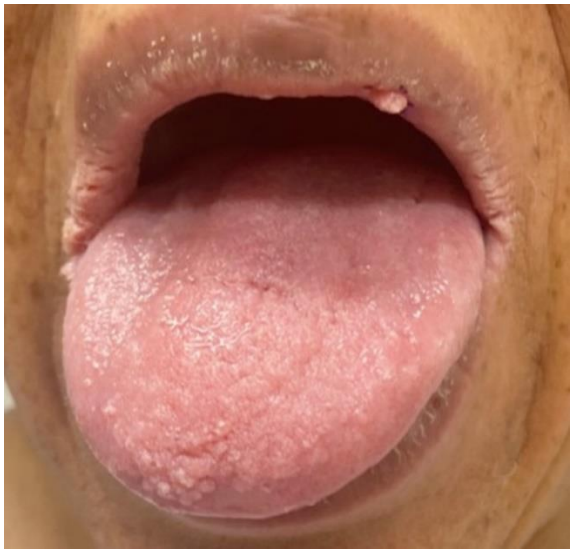

FIG. 4. **Papillomatous lesions of the oral mucosa with a thickened tongue in a 70-year-old female presenting with atypical AN, found to have metastatic, poorly differentiated adenocarcinoma of unknown primary.**

4.2 Diagnosis

A shave biopsy was performed, and histopathologic examination was significant for papillomatosis and hyperkeratosis, consistent with the clinical impression of AN.

4.3 Clinical course

Given the widespread and sudden onset of AN with associated weight loss, CT soft tissue neck, chest, and abdomen and pelvis were ordered. Her CT scans were notable for diffuse lymphadenopathy including retroperitoneal, mesenteric, periportal, mediastinal, supraclavicular, and left axillary/subpectoral nodes. She underwent ultrasound-guided core biopsies of a retroperitoneal node that was significant for metastatic, poorly differentiated adenocarcinoma. Immunohistochemical markers were cytokeratin (CK) 7-positive, villin-positive, AE1/AE3-positive, CK20-negative, thyroid transcription factor (TTF)-1

negative, and GATA 3-negative, most consistent with an upper gastrointestinal or pancreaticobiliary primary malignancy. CA 19-9 was elevated at 321. CEA and CA 125 were within normal limits. The patient subsequently underwent Esophagogastroduodenoscopy (EGD) which showed the AN involving the entirety of the oral mucosa and esophagus. Biopsies of the esophagus and stomach were negative for malignant cells. The patient also had a PET/CT which again demonstrated diffuse lymphadenopathy but was unable to identify the primary tumor.

4.4 Treatment

A primary tumor has not been identified. She was started on modified FOLFOX6, consisting of leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin. CT scans will be repeated after four cycles.

5. Discussion

AN normally presents as velvety or verrucous hyperpigmentation in skin folds that is most commonly associated with endocrine disorders, obesity, and insulin resistance [2]. Eruptive AN with mucosal involvement and palmar involvement should prompt the clinician to consider malignancy associated AN. Malignancy associated AN is theorized to result from tumor secretion of cytokines such as transforming growth factor-a (TGF-a), which can bind to epidermal growth factor receptor (EGFR) in skin cells and cause the hyperkeratosis and papillomatosis seen in AN [1].

Gastrointestinal adenocarcinoma is the most common malignancy reported with this condition, but other reports have shown associations with pulmonary carcinoma, hepatic carcinoma, esophageal carcinoma, and ovarian cancer [3]. Most cases are detected concurrently with the underlying cancer, however AN may also pre-date or post-date the malignancy by years. Red flags which should trigger evaluation for malignancy in patients with AN include unintentional weight loss and rapid onset of extensive AN [1]. In malignant instances, the locations of AN can be unusual, and can be associated with eruptions like tripe palm and Leser-Trélat sign [4]. Clinical diagnosis of AN is typically straight forward given its classic appearance. Morphologically similar cutaneous diseases such as epidermal naevi, psoriasis, and reticulated papillomatosis should be differentiated using proper history, clinical examination, and histopathological examination [1]. Numerous treatment options are available including topical retinoids and keratolytics, lasers, and systemic treatments like isotretinoin [1].

In malignancy associated AN, therapy is focused on treatment of the underlying neoplasm. Notably, the majority of cases of malignant AN reported in the literature seem to be presented in female patients and may be of interest for future studies.

6. Conclusion

These cases serve as a reminder that AN can be an indicator of malignancy. Diagnosis at earlier stages could lead to a better prognosis. With more atypical presentations of AN, a more extensive work up beyond age-appropriate cancer screenings should be considered, such as a CT chest abdomen pelvis or PET scan.

7. Conflict of Interest

The authors have no conflicts of interest to disclose.

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