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Case Report

Acanthosis Nigricans in a Patient with Urothelial Carcinoma Treated with PD-L1 Inhibitor Avelumab, and Secondary Adrenal Insufficiency

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Keywords
Acanthosis nigricans · Paraneoplastic condition · Bladder cancer · Metabolic screening · Oncology · Immunotherapy · Immunotoxicities

Abstract
Acanthosis nigricans (AN) describes hyperkeratotic and hyperpigmented skin changes and its pathophysiology is linked to the activation of epidermal growth factor receptors. Current literature shows that AN is most commonly diagnosed at the time of the underlying pathology, which may occur under benign or malignant conditions. This case presentation demonstrates the occurrence of AN in a patient following the diagnosis of urothelial carcinoma and ongoing treatment with PD-L1 inhibitor immunotherapy. Subsequent investigations ruled out a secondary malignancy or disease progression; however, metabolic screening identified secondary glucocorticoid induced adrenal insufficiency. AN was persistent in this patient despite adequate treatment, which highlights its co-occurrence in both benign and paraneoplastic conditions.

Introduction

Acanthosis nigricans (AN) represents a type of skin change where hyperkeratotic and hyperpigmented lesions occur on skin fold areas including nuchal, axillary, and groin regions. Patients are usually asymptomatic, but pruritus has been reported in some people. Sometimes, the mucosal region can also be affected, but this is uncommon [1]. AN can occur in the

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setting of benign or malignant conditions. The former may represent an underlying metabolic or endocrine syndrome such as obesity, insulin resistance, adrenal insufficiency, PCOS, and pituitary tumours [2, 3]. The latter is associated with paraneoplastic syndromes in the presence of malignant tumours, most commonly gastric adenocarcinomas, pancreatic, lung, ovarian, renal, bladder cancers, and lymphomas [4].

Most cases of malignant AN (60%) are detected at the time of diagnosis, and to a lesser extent, before (20%) or after (20%) the diagnosis of cancer [1, 5]. The onset of AN in metabolic causes is not well documented in the literature; however, its association with obesity and insulin resistance has been used to allow early intervention and prevent progression to type 2 diabetes [6]. The pathophysiology of AN is not fully understood, but it has been linked to a multifactorial combination of elevated levels of insulin-like growth factor and transforming growth factor alpha and its action on epidermal growth factor receptors on susceptible cells, leading to hyperproliferation of keratinocytes and fibroblasts [7].

AN can be secondary to a benign or malignant cause. It can also indicate disease relapse in known malignancy. Drug-induced AN can occur following usage such as glucocorticoids, insulin, oral contraceptives, or nicotinic acid. The treatment of AN has not been fully established; however, most cases resolve with the treatment of the underlying cause, e.g., neoplasm. Some patients may require retinoids or photochemotherapy (PUVA) with persistent AN; however, majority only require symptomatic treatment. In addition, the occurrence of AN usually precedes the diagnosis of the underlying cause [1, 8, 9]. However, this case report details that the presence of AN can be in the setting of both benign and paraneoplastic causes.

Case Report

A 54-year-old male initially presented in February 2023 with a 3-day history of nausea, vomiting associated with crampy abdominal pain, and generalised fatigue. He had a background of stage 3A muscle invasive bladder carcinoma currently on PD-L1 inhibitor immunotherapy, Avelumab for the last 12 months. He had a background of muscle invasive urothelial carcinoma diagnosed in 2018, and his treatment to date includes the following:

- Intravesical BCG and TURBT 2018
- Neoadjuvant chemotherapy 2018
- Radical cystoprostatectomy and ileal conduit.
- Left external iliac nodal metastases 2021
- Further chemotherapy and radiotherapy 2021
- Immunotherapy-Avelumab 2022

During his admission, we noted that there were areas of hyperpigmented, velvety rash on skinfolds such as his axillary area, lower abdominal area, as well as the groin area, which was associated with pruritus (Fig. 1–4). The rash started 2 months ago and there were no significant changes since his hospital admission. Of note, he has been on immunotherapy for the last 12 months, without much side effects reported. Prior to this, he also routinely received regular doses of dexamethasone 20 mg during his chemotherapy cycles to help with anticipatory nausea and vomiting. We subsequently checked his Hba1c, cortisol, thyroid function tests (TFTs) to screen for any underlying metabolic causes. Of note, his BMI was also raised at 30; however, his weight was stable prior to oncological treatment and there was no recent weight gain reported. His Hba1c was normal at

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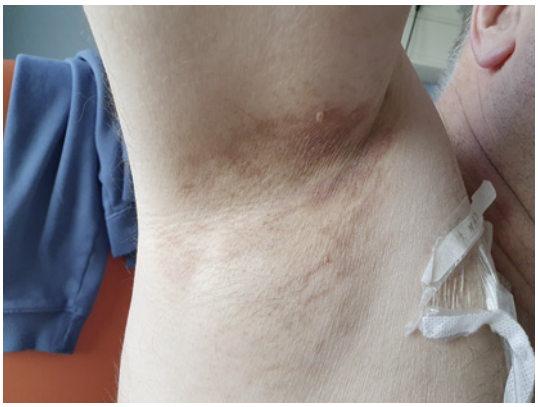

Fig. 1. Right axillary AN.

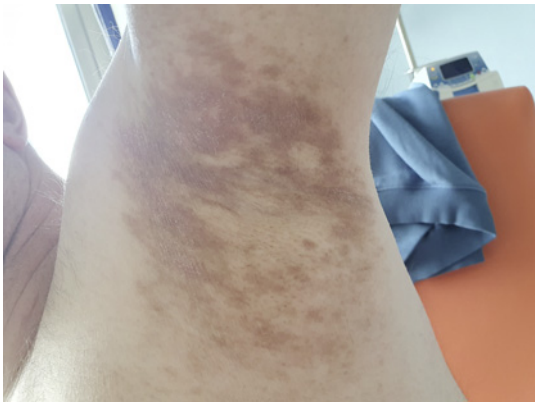

Fig. 2. Left axillary AN.

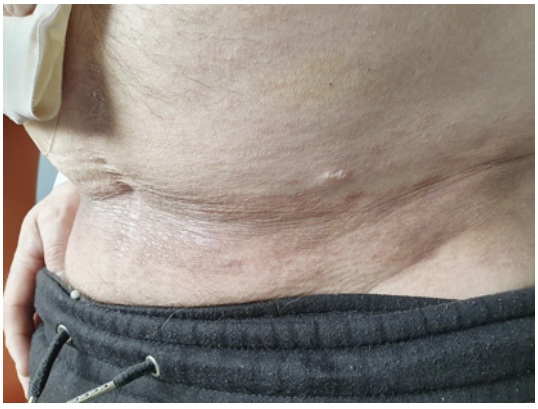

Fig. 3. AN in abdominal skinfolds, left-sided view.

36 mmol/mol, and thyroid function tests were within a normal range. His early morning serum cortisol was found to be low at 61 nmol/L (140–690 nmol/L), and his ACTH was on the lower range of normal at 3.4 pmol/L (1.3–16.7 pmol/L). He was diagnosed with secondary adrenal insufficiency from glucocorticoid use and was subsequently started on hydrocortisone replacement. His AN was treated symptomatically with topical emollients and antihistamines. Follow-up 1 month later showed that his AN was still persistent and unchanged; however, he had no new signs or symptoms of progression of his primary urothelial cancer.

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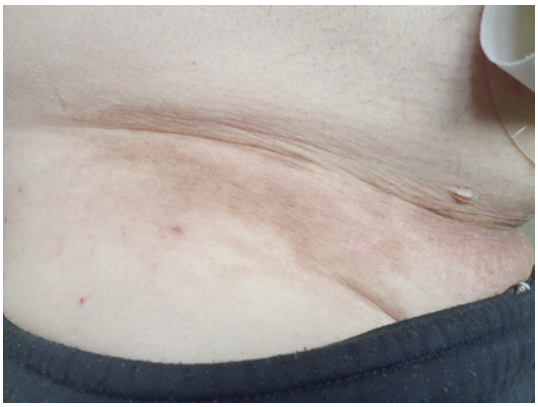

Fig. 4. AN in abdominal skinfolds, right-sided view.

Discussion

The diagnosis of AN is not complete without further investigation into the underlying cause. Given his history of bladder carcinoma, the initial impression was paraneoplastic AN. The main concern was whether there was disease progression; however, a restaging CT TAP showed no interval changes. OGD showed Barrett's oesophagus but no concerning lesions. It is important to rule out other differentials including screening for other primary malignancies, especially in the gastrointestinal tract, and to monitor for any relapse or disease progression which has been reported to correlate with the presence and regression of AN [10]. In addition, most cases of malignant AN are present at the time of cancer diagnosis [11]; however, this case report suggests that AN can occur even few years after the time of diagnosis without disease progression. Despite the good response to his oncological treatment for his underlying urothelial cancer on repeated staging scans, the patient was mainly bothered by the pruritus from the AN rather than the appearance of it. However, he was content with taking antihistamines and topical emollients to control his symptoms on the follow-up review.

On the other hand, the patient had a few risk factors for developing benign AN, such as raised BMI and drug-induced Cushing syndrome from steroid use. The hypothesis is that his AN may be both paraneoplastic, as well as medication-induced. Classically, benign AN is associated with metabolic syndromes including obesity and hyperinsulinemia; however, hypoadrenalism is also an important cause [12]. Immune checkpoint inhibitor therapy has also been linked to primary adrenal insufficiency, with low serum cortisol levels detected in patients [13, 14]. In our case, the patient developed secondary adrenal insufficiency from glucocorticoid use during his chemotherapy. Despite being on steroid replacement therapy, his AN did not resolve completely. Management of persistent AN for some patients can include topical and oral retinoids, calcipotriol, and laser therapy [15].

Conclusion

This case demonstrates the presence of AN in the setting of both benign and malignant causes, as well as the timing of its occurrence. Hence, it is important to investigate and screen for any underlying metabolic disorders in patients with known malignancy, rather than attributing it to a known diagnosis. On the other hand, in patients with known cancer diagnosis, it is important to rule out disease progression. The CARE checklist has been completed by the authors for this case report, attached as supplementary material.

Statement of Ethics

Ethical approval was not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare no conflict of interest for the above study.

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Author Contributions

The first/corresponding author was responsible for the conception and design of the manuscript, data review, collection, manuscript drafting, final approval, and agreement to be accountable for the work done as described. The co-author was responsible for data review and final approval of the manuscript.

Data Availability Statement

The authors confirm that the data supporting the findings are available in this article. Further enquiries can be directed to the corresponding author.

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