

Acrokeratosis of Bazex as a sign of thyroid cancer: first description and review of thyroid-associated paraneoplastic dermatoses

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Abstract. – **OBJECTIVE:** Bazex syndrome is a rare paraneoplastic skin disorder of unknown pathogenesis. Cutaneous findings are usually noticed before the diagnosis of the underlying malignancy, more frequently squamous cell carcinomas of the upper aerodigestive tract or metastasis to cervical lymph nodes. Association with other malignancies has been reported.

CASE REPORT: Herein, we describe a case in course of metastatic papillary thyroid carcinoma and review the relevant literature.

RESULTS: A bibliographic search was conducted and a total of 8 studies concerning the association were reviewed.

CONCLUSIONS: Physicians be aware of unexpected cutaneous conditions as a possible sign of underlying tumors.

Key Words:

Bazex syndrome, Paraneoplastic dermatoses, Thyroid cancer.

Introduction

Paraneoplastic acrokeratosis (Bazex syndrome) is a rare skin disorder of unknown pathogenesis that typically affects men older than 40 years¹. The common histopathology is psoriasiform, however other non-psoriasiform features have been described¹. Clinically, it is characterized by symmetrical erythematous squamous lesions involving the acral sites². At the advanced stage, the lesions may affect the upper/lower limbs, face, and scalp, with a centripetal distribution². Cutaneous findings are usually noticed before

the diagnosis of the underlying malignancy, more frequently squamous cell carcinomas of the upper aerodigestive tract or metastasis to cervical lymph nodes¹, although other malignancies have been reported¹⁻³. Differential diagnosis includes psoriasis/chronic eczema². Skin manifestations show resistance to conventional treatments and improve or subside spontaneously after complete treatment of the malignancy^{2,3}; recrudescence may suggest tumor recurrence².

Case Report

A 62-year-old man came to our department in May 2021 with 12-months history of itchy skin lesions unresponsive to systemic steroids. He complained of malaise and fatigue following total thyroidectomy with right latero-cervical and paratracheal lymphadenectomy for a metastatic papillary thyroid carcinoma in September 2007. The patient had undergone radiometabolic treatment with iodine 131 due to extensive metastasis to the neck lymph nodes. Secondaries to the cranial theca, ribs, vertebral column, and sacrum were also detected on bone scan. After 5 sessions, metastases did not regress, and the patient refused further endocrinological checks. Physical examination revealed cachexia and erythematous scaly lesions homogeneously distributed over the entire skin surface. His hands and feet also had thickened skin, longitudinal streaking, and severe subungual hyperkeratosis (Figure 1A-D). Based on patient's history and cutaneous findings we diagnosed paraneoplastic Bazex syndrome.



Figure 1. A-D, Erythematous scaly lesions with skin thickening, longitudinal streaking, and severe subungual hyperkeratosis on the hands and feet.

Materials and Methods

A bibliographic search was conducted on PubMed database (<https://ncbi.nlm.nih.gov/> PubMed – accessed on 21 February 2022) using the key words: “thyroid cancer” AND “paraneoplastic dermatoses”. Basing on the abstract content, we collected papers concerning this association. No restrictions for language, type or year of publication were applied.

Results

The overall search yielded 38 articles. Among these, 30 were excluded as not relevant and/or because the full text was not available, and 8 papers were selected as matching our search.

Discussion

Paraneoplastic dermatoses represent a heterogeneous group of skin disorders occurring with malignancies and possibly manifesting with a suspect chronological link⁴. The pathogenesis is complex and discussed⁴. These skin manifestations may often appear unspecific and be characterized by extreme clinical polymorphism⁴. Early recognition may contribute to the diagnosis and timely treatment of the underlying malignancy.

Acanthosis nigricans (AN) is the most reported cutaneous paraneoplastic marker of internal malignancy. Although gastrointestinal adenocarcinomas of gastrointestinal have been commonly associated with AN, lymphomas, sarcomas, squamous cell carcinoma and endocrine carcinomas may also occur^{5,6}. Dealing with thyroid cancer, Buzdar et al⁵ described the case of a young girl affected by AN and papillary thyroid cancer in whom the severity of insulin-resistance represented the main feature. Even if the pathophysiology of cancer related AN remains unknown, the release of peptide growth factors by the tumor may cause skin atrophy⁵. Hyperinsulinemia and C-peptide levels rapidly decreased within 1 month after targeted therapy⁵.

Moreover, Talsania et al⁶ reported a case of AN with extensive mucocutaneous involvement, in a 81-year-old man having a follicular thyroid cancer. Even in this case, progressive skin healing was observed with treatment of the underlying malignancy⁶.

Differently from AN, Paraneoplastic Pemphigus (PNP) is a mucocutaneous blistering disease occasionally reported in association with lymphoproliferative tumors^{7,8}. However, fewer cases of PNP occurred with epithelial or mesenchymal tumors^{7,8}. Hong et al⁷ described PNP in course of metastatic lymphoepithelioma-like carcinoma of the thyroid gland in a 59-year-old female. The patient presented flaccid blisters and painful erosions on the whole body, including the oral and genital mucosae⁷. Anti-desmoglein 1 (Dsg1) antibody on Enzyme-linked immunosorbent assay (ELISA) was detected⁷. Despite the improvement of cutaneous lesions after the treatment of the underlying neoplasia, the patient died of multiple brain and lung metastases⁷. Another report of PNP was published by Yamada et al⁸: a 68-year-old man had concomitant malignancies to thyroid, kidney, and retroperitoneal area, in combination with antilaminin-332 mucous membrane pemphigoid (MMP). On possible pathogenesis, the aberrant synthesis of the c2 subunit of laminin-332 by cancer cells may cause MMP through the induction of a secondary autoimmune response against the c2 subunit of laminin-332⁸.

Within the chapter of paraneoplastic bullous disorders, Lombardo et al⁹ reported a case of bullous pemphigoid (BP)-like epidermolysis bullosa acquisita (EBA) refractory to high-dose steroids and dapsone, revealing an underlying papillary thyroid carcinoma in a 52-year-old man. ELISA for BP180 was negative, while ELISA based on collagen VII immunodominant domains was positive⁹. EBA improved with thyroidectomy and radioiodine ablation therapy. Skin disease might be triggered by the cross-reactivity against epitopes shared by tumor cell proteins and type VII dermal collagen⁹.

Dermatomyositis (DM) is also considered as a possible cutaneous sign of internal malignancy¹⁰. The association with thyroid has been rarely described¹⁰. Shah et al¹⁰ reported three cases of DM and papillary thyroid cancer. One out of three experienced improvement in both cutaneous and muscular impairment with the treatment of the tumor. In the other two cases the net effect of treatment was not demonstrated due to poor compliance by the patients¹⁰. It is the authors' opinion that a common autoantigen expression by both the tumor and muscle tissue may exist, although current understanding does not exactly support this hypothesis. Similarly, Nagashima et al¹¹ described two patients with DM and thyroid cancer, treated with high-dose steroid and cyclosporine, in absence of surgical intervention. Patients showed

good response to therapy in both muscle weakness and skin lesions, with no size changing in thyroid cancer¹¹. According to the clinical outcome of their cases and their literature review of epidemiological data, authors stated that DM should not be considered as a paraneoplastic condition. Even in the study of Molina-Ruiz et al¹² the association between thyroid cancer and DM was questioned, given that the complete removal and remission of thyroid cancer in a 53-year-old man resulted in no improvement of the cutaneous disease.

Conclusions

The chapter of paraneoplastic dermatoses is continuously updating. Given the possible link between some cutaneous diseases and internal malignancies, early recognition of the underlying tumor may lead to timely antineoplastic therapy and, in most cases, to the concurrent improvement of skin lesions. Increased vigilance by physicians for thyroid cancer in patients with acanthosis nigricans, dermatomyositis and bulbous diseases may represent an additional ‘task’ in the successful management of these patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

Written consent to image recording for academic purposes was obtained.

Availability of Data and Materials

Study data are available at our University Hospital Archive.

Authors' Contribution

Conceptualization, methodology and writing – original draft preparation. (L.Mac.), data collection (L.Man.), writing — review & editing and supervision (R.T. and C.G.). All authors have read and agreed to the published version of the manuscript.

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