Case Reports in Dermatology

Case Rep Dermatol 2022;14:307–312
DOI: 10.1159/000525381
Received: January 28, 2022
Accepted: May 29, 2022
Published online: October 20, 2022

Single Case

Acrokeratosis Paraneoplastica (Bazex Syndrome): A Case Report

Julia Holzgruber[a] Jacqueline Oberneder-Popper[a] Emmanuella Guenova[b] Wolfram Hötzenecker[a]

[a]Department of Dermatology, Kepler University Hospital Linz, Johannes Kepler University, Linz, Austria; [b]Department of Dermatology, University of Lausanne, Vaud, Switzerland

Keywords
Bazex syndrome · Acrokeratosis paraneoplastica · Malignancy-associated skin disorders · Paraneoplastic syndrome · Case report

Abstract
Acrokeratosis paraneoplastica Bazex is a rare paraneoplastic skin manifestation, typically causing acral psoriasiform lesions. Patients usually show erythematous hyperkeratosis with yellowish, adherent scales on the hands and feet or other acral locations such as ears or nose. We herein report a case of Bazex syndrome in a male patient, who was previously diagnosed with hepatocellular carcinoma. Our case report highlights this rare condition as early diagnosis may impact the patient's course of tumor disease and prognosis.

Introduction

Acrokeratosis paraneoplastica or Bazex syndrome is a rare, obligate paraneoplastic skin manifestation, typically characterized by rapid appearance of acral exfoliative, psoriasiform lesions, and palmoplantar keratosis [1]. Patients usually show erythematous hyperkeratosis with yellowish, adherent scales on the hands and feet or on other acral locations (e.g., ears, nose) [2]. Bullous lesions of Bazex syndrome are rare and most common in acral areas [3]. The first known case of palmoplantar hyperkeratosis associated with internal malignancy was reported in 1922 by Gougerot and Rupp [4]. In 1965, Andre Bazex et al. [5] first described acrokeratosis paraneoplastica as "paraneoplastic syndrome with hyperkeratosis of the extremities" in a patient with head-neck cancer and cervical lymph node metastases, whose skin lesions resolved after treating the primary tumor.

Correspondence to:
Julia Holzgruber, julia.holzgruber@kepleruniklinikum.at

Case Rep Dermatol 2022;14:307–312
DOI: 10.1159/000525381

Bazex syndrome is related to internal malignancies, and in two-thirds of cases, cutaneous lesions precede the symptoms or diagnosis of the tumor. Less common, the skin disorder can develop contemporaneously or after diagnosis of malignancy. In most cases, it affects Caucasian men over forty with an underlying neoplasm, which is frequently diagnosed as a squamous cell carcinoma of the upper aerodigestive tract or metastatic cervical lymphadenopathy [6]. Due to a similar clinical appearance, the cutaneous psoriasiform lesions can often be misdiagnosed as psoriasis or eczema but do not respond well to standard dermatological treatment, such as topical corticosteroids. Remissions after successful treatment of the primary malignancy are often seen [7].

Case Presentation

A 69-year-old male patient with a toxic-nutritive-induced liver cirrhosis (Child-Pugh A) was diagnosed with a hepatocellular carcinoma (HCC) in September 2017. The diagnosis was based on two different imaging methods, as well as on an elevated tumor marker α-fetoprotein (AFP). Two suspect foci were detected in both liver lobes. The tumor in segment VII was treated with microwave ablation and the other one in segment IVb/V with irreversible electroporation (NanoKnife®) in November 2017. A follow-up CT scan was performed in December 2017, showing a necrosis of the two treated liver lesions and a thrombosis of the portal vein. Within 4 months after initial treatment, a fulminant progressive disease was noted. The liver magnetic resonance imaging showed a multilocular HCC in segment V, VI, VII, and VIII with a dramatic serological increase of AFP up to 28,000 IU/ml. As surgical hemi-hepatectomy was not possible, a therapy with sorafenib, a multikinase inhibitor, was initiated in March 2018 according to the recommendation of the Barcelona-Clinic Liver Cancer criteria. One month later, the patient presented at the Department of Dermatology of the University Hospital Linz. On examination, almost symmetrical papulopustular plaques at the dorsum of both hands, on the lateral forearms, and most pronounced pretibial at the lower legs were observed. On the soles of the feet, desquamations with blistering were present. There was no involvement of the nails. In context to the current HCC treatment, we first suspected an exfoliate dermatitis (or Hand-Foot Syndrome) commonly associated with sorafenib treatment. The oral tyrosine kinase inhibitor was stopped and topical corticosteroids were prescribed. The dermatitis improved; however, several psoriasiform, hyperkeratotic, yellowish scaly eruptions and partly verrucous plaques on the palm and dorsum of both hands remained unchanged (Fig. 1, 2). There was no history of other dermatological skin disorders, especially no psoriasis vulgaris or atopic eczema. Due to the patient's medical history (HCC) and the lack of improvement after discontinuation of sorafenib, we diagnosed Bazex syndrome (acrokeratosis paraneoplastica). In light of a palliative setting of HCC, no further cancer treatment was started, and the skin disorders persisted. The patient was lost in follow-up and last seen by the hepatologist in April 2019 with a stabile palliative disease. An overview of the case is shown in Table 1.

Discussion

Acrokeratosis paraneoplastica (Bazex syndrome) represents a rare dermatological manifestation of internal malignancy and is mainly descripted in form of case reports in the current literature. By now, there are about 150 published cases of Bazex syndrome. The typical patients' characteristics are middle-aged Caucasian men, women are less likely affected [8]. A systematic review published in 2017 illustrates that in most cases of acrokeratosis paraneoplastica, the underlying neoplasm was squamous cell carcinoma of the upper aerodigestive tract (head-neck

Case Rep Dermatol 2022;14:307–312
DOI: 10.1159/000525381

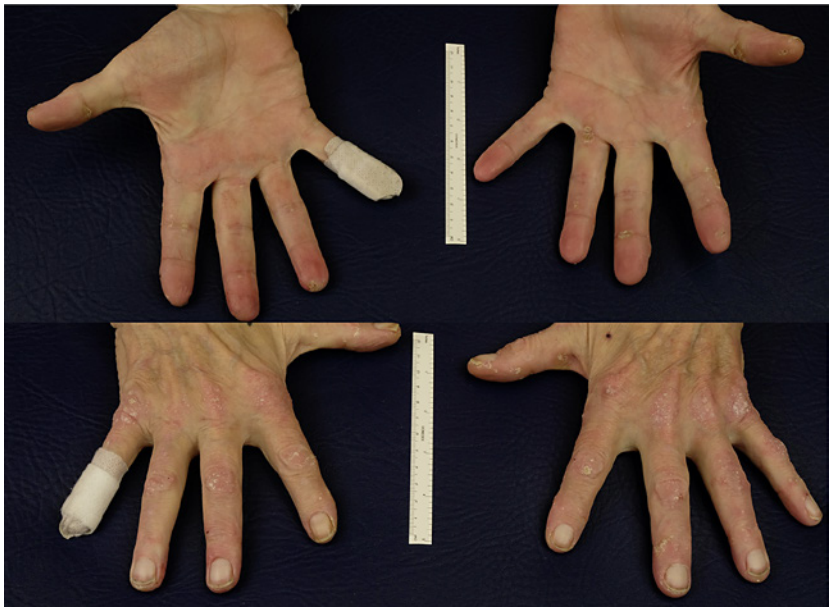

Fig. 1. An overview of the dorsum and palm of the hands, suggesting Bazex syndrome.

cancer, lung) or cervical lymph node metastases with an unknown primary tumor, followed by gastrointestinal and genitourinary tumors. More rarely, the liver, stomach, or bone marrow is affected [2].

The pathogenesis of acrokeratosis paraneoplastica is still unclear. One hypothesis suggests that tumor cells produce growth factors, such as epidermal growth factor (EGF) or insulin-like growth factor (IGF), which may lead to cross-reactivity between antigens in the skin and the tumor. EGF and IGF are autocrine growth factors for keratinocytes [9]. Other authors postulate an immune-mediated pathomechanism based on a close correlation between SCC antigen levels and severity of cutaneous lesions. Furthermore, T cell-mediated immune response to tumor-like antigens in the epidermis is discussed [10], and a vitamin A or zinc deficiency may serve as a potential risk factor for the development of Bazex syndrome [11].

The clinical appearance consists of nonpruritic, psoriasiform plaques at the acral site such as finger, toes, ears, or nose. In contrast to psoriasis, the helical rim of the ear and nasal tip can be affected. Nail involvement occurs simultaneously with cutaneous lesion in about 75% of patients with Bazex syndrome. The most common manifestations are thickening of the nail plate, subungual hyperkeratosis, onycholysis, or longitudinal streaks with yellow or brown pigmentation. Two or more types of nail changes are common [12]. Blistering is a rare clinical manifestation and only occurs in the minority of patients with Bazex syndrome. Typically, bullae and vesicles are located on the hands and feet but also on the trunk. In those cases, skin biopsy is essential to exclude a concomitant autoimmune bullous disorder, especially bullous pemphigoid [3].

Histologic findings of Bazex syndrome are unspecific and can include spongiosis, acanthosis, dyskeratotic keratinocytes, vacuolar degeneration and in the dermis, a lichenoid, perivascular, lymphocytic, or histiocytic infiltrate [9]. Immunofluorescence usually appears negative [3]. The unspecific findings emphasize that the diagnosis is strongly related to the clinical appearance in combination with the course of disease and patient's comorbidities. By now, there is no specific marker for a clear histopathological differentiation.

Bazex syndrome mainly responds to treatment of the underlying neoplasm and should always be considered as primary therapy. Topical ointment therapy includes corticosteroids,

Case Rep Dermatol 2022;14:307–312
DOI: 10.1159/000525381

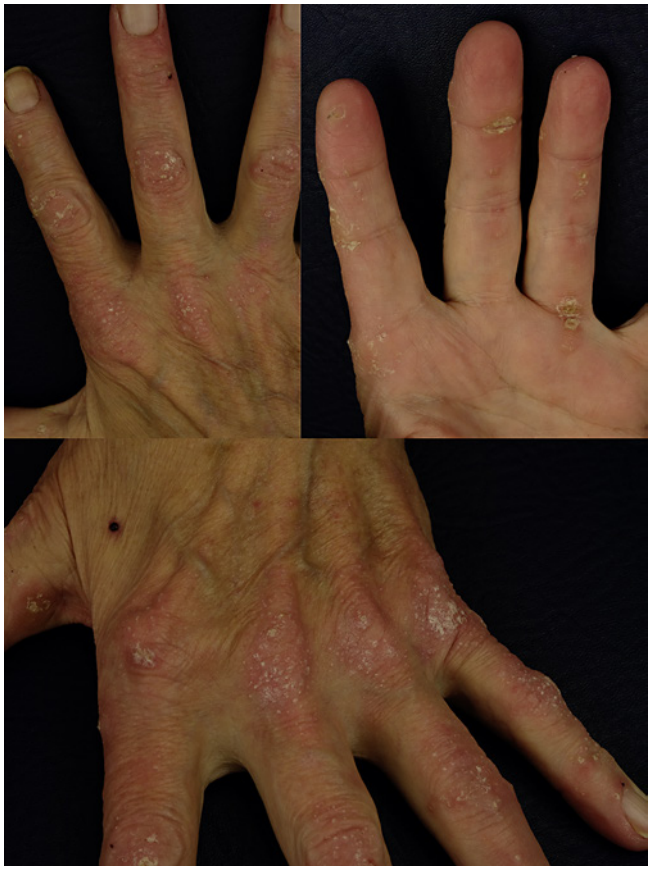

Fig. 2. Detailed view of atypical, psoriasis-like, yellowish, and partly verrucous plaques on the hands.

Table 1. Bazex syndrome case details

	Case report
Gender	Male
Age	69
Race	Caucasian
Risk factors	Alcohol, smoking
Malignancy	HCC
Clinical presentation	Figures 1 and 2 Atypical, psoriasis-like, yellowish, and partly verrucous plaques on both hands
Time of diagnosis	Oncological diagnosis preceded
Oncological treatment	Palliative (radio frequency ablation, sorafenib), treatment stop due to side effects and patient's request
Dermatological outcome	Skin condition remained, loss of follow-up

itraconazole, fluconazole, isosorbide dinitrate, cephalexin, keratolytics, neomycin, or zinc ointments [2]. Some authors even suggest oral steroids such as prednisolone 0.5 mg/kg/day, slowly tapering over 4 weeks [13]. In case of ineffective treatment of the primary tumor, oral retinoids can be used to reduce hyperkeratosis [14]. There are encouraging results of PUVA therapy in the treatment of Bazex syndrome [15].

We here present a case of acrokeratosis paraneoplastic in a male patient with HCC. The early recognition of typical cutaneous stigmata of Bazex syndrome is important for detection

Case Rep Dermatol 2022;14:307–312
DOI: 10.1159/000525381

of the responsible neoplasm and an immediate start of anticancer therapy. An early diagnosis may have an impact on patient's prognosis, and therefore Bazex syndrome should constantly be considered as a differential diagnosis in case of an atypical acral psoriasiform dermatitis.

Statement of Ethics

The authors have no ethical conflicts to disclose. All patients have given written informed consent to publication of their case details and any accompanying images. Every precaution has been taken to protect the privacy of research subjects and confidentiality of their personal information. Ethical approval is not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. The publication of this paper has no direct or indirect financial implication for the authors, their relatives, or their institution.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Julia Holzgruber performed analysis of the information and wrote the manuscript. Jacqueline Oberneder-Popper and Emmanuella Guenova aided in the acquisition of medical data and critical revision of the manuscript. Wolfram Hötzenecker reviewed the manuscript and supervised the project. Julia Holzgruber, Jacqueline Oberneder-Popper, Emmanuella Guenova, and Wolfram Hötzenecker have read and agreed to the published version of the manuscript.

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author

References

1 Poligone B, Christensen SR, Lazova R, Heald PW. Bazex syndrome (acrokeratosis paraneoplastica). Lancet. 2007; 369(9560):530.
2 Räßler F, Goetze S, Elsner P. Acrokeratosis paraneoplastica (Bazex syndrome: a systematic review on risk factors, diagnosis, prognosis and management. J Eur Acad Dermatol Venereol. 2017;31(7):1119–36.
3 Duran-Vian C, Gómez C, Navarro I, Reguero L, Alonso L, González-Vela MC, et al. Acrokeratosis paraneoplastica (Bazex syndrome) with bullous lesions. Indian J Dermatol Venereol Leprol. 2020;86(3):335.
4 Gougerot H, Rupp C. Dermatose érythémato-squameuse avec hyperkératose palmoplantaire, porectasies digitales et cancer de la langue latent. Paris Med. 1922;43:234–7.
5 Bazex A, Griffiths A. Acrokeratosis paraneoplastica: a new cutaneous marker of malignancy. Br J Dermatol. 1980; 103(3):301–6.
6 Hempen A, Samartzis EP, Kamarachev J, Fink D, Dedes KJ. Acrokeratosis paraneoplastica in serous ovarian carcinoma: case report. BMC Cancer. 2015;15:507.

Case Rep Dermatol 2022;14:307–312
DOI: 10.1159/000525381

7 Humphrey SR, Hussain AS, Chandran R, Wilson B, George B. Acute onset of acrokeratosis paraneoplastica (Bazex syndrome). JAMA Dermatol. 2015;151(6):677–8.
8 Eckstein J, Healy E, Jain A, Hawkins D, Ho QA, Agrawal A, et al. A series of typical and atypical cases of Bazex syndrome: identifying the red herring to avoid delaying cancer treatment. Clin Case Rep. 2020;8(11):2259–64.
9 Bolognia JL, Brewer YP, Cooper DL. Bazex syndrome (acrokeratosis paraneoplastica): an analytic review. Medicine. 1991;70(4):269–80.
10 Hara M, Hunayama M, Aiba S, Suetake T, Watanabe M, Tanaka M, et al. Acrokeratosis paraneoplastica (Bazex syndrome) associated with primary cutaneous squamous cell carcinoma of the lower leg, vitiligo and alopecia areata. Br J Dermatol. 2006;133(1):121–4.
11 Karabulut AA, Şahin S, Şahin M, Ekşioğlu M, Üstün H. Paraneoplastic acrokeratosis of Bazex (Bazex's syndrome): report of a female case associated with cholangiocarcinoma and review of the published work. J Dermatol. 2006;33(12):850–4.
12 Roy B, Lipner SR. A review of nail changes in acrokeratosis paraneoplastica (Bazex syndrome). Skin Appendage Disord. 2021;7(3):163–72.
13 Medenica L, Gajić-Veljić M, Škiljević D, Peško P. Acrokeratosis paraneoplastica Bazex syndrome associated with esophageal squamocellular carcinoma. Vojnosanit Pregl. 2008;65(6):485–7.
14 Esteve E, Serpier H, Cambie MP, Armingaud P, Huet C, Penouil MH, et al. [Bazex paraneoplastic acrokeratosis. Treatment with acitretin]. Annales de dermatologie et de venereologie; 1995.
15 Gill D, Fergin P, Kelly J. Bullous lesions in Bazex syndrome and successful treatment with oral psoralen phototherapy. Australas J Dermatol. 2001;42(4):278–80.