

Paraneoplastic Acrokeratosis (Bazex Syndrome): Unusual Association With In Situ Follicular Lymphoma and Response to Acitretin

Elena Conde-Montero, MD; Ofelia Baniandrés-Rodríguez, MD; Celia Horcajada-Reales, MD; Verónica Parra-Blanco, MD; Ricardo Suárez-Fernández, MD



PRACTICE POINTS

- Paraneoplastic acrokeratosis may mimic palmo-plantar acrokeratosis in both clinical presentation and treatment.
- Uncommon associations of paraneoplastic acrokeratosis with different types of lymphoma have been described.

To the Editor:

Paraneoplastic acrokeratosis (PA), also known as Bazex syndrome, is a rare paraneoplastic dermatosis first described in 1965 by Bazex et al.¹ This entity is clinically characterized by dusky erythematous to violaceous keratoderma of the acral sites and commonly affects men older than 40 years. In most reported cases, there has been an underlying primary malignant neoplasm of the upper aerodigestive tract²; however, some other associated malignancies also have been reported. Skin changes tend to occur before the diagnosis of the associated tumor in 67% of cases. The cutaneous lesions usually resolve after successful treatment of the tumor and relapse in case of recurrence of the malignancy.³

A 53-year-old woman who was a smoker with no relevant medical background was referred to the dermatology department with an itching psoriasiform dermatitis on the palms and soles of 2 months' duration. There were no

signs of systemic disease. Physical examination revealed well-demarcated, dusky red, thick, scaly plaques on the soles with sparing of the insteps (Figure, A). Scattered symmetric hyperkeratotic plaques were present on the palms (Figure, B). We also detected onychodystrophy on the hands. Other dermatologic findings were normal. Histologic examination of a biopsy specimen of the left sole showed hyperkeratosis, focal parakeratosis, acanthosis, hypergranulosis, and a predominantly perivascular dermal lymphocytic infiltrate.

With the diagnostic suspicion of PA, blood tests, chest radiograph, and colonoscopy were performed without revealing abnormalities. Positron emission tomography and computed tomography also was performed, showing cervical, mesenteric, retroperitoneal, and inguinal adenopathies. Histologic examination of both inguinal adenectomy and cervical lymph node biopsy revealed Bcl-2-positive in situ follicular lymphoma (ISFL). Examination of an iliac crest marrow aspirate showed minimal involvement of lymphoma (10%). Follow-up imaging performed 4 months after diagnosis showed no changes. The patient was diagnosed with a low-grade chronic lymphoproliferative disorder with small disperse adenopathies and minimal bone marrow involvement. The hematology department opted for a wait-and-see approach with 6-month follow-up imaging.

The skin lesions were first treated with salicylic acid cream 10%, psoralen plus UVA therapy, and methotrexate 20 mg weekly for 2 months without remission.

Dr. Conde-Montero is from the Department of Dermatology, Hospital Universitario Infanta Leonor, Madrid. Drs. Baniandrés-Rodríguez, Horcajada-Reales, Parra-Blanco, and Suárez-Fernández are from the Department of Dermatology, Hospital Universitario Gregorio Marañón, Madrid, Spain.

The authors report no conflict of interest.

Correspondence: Elena Conde-Montero, MD (elenacondemontero@gmail.com).



Paraneoplastic acrokeratosis with well-demarcated, dusky red, thick, scaly plaques on the soles with sparing of the insteps (A) and symmetric hyperkeratotic plaques on the palms (B).

Replacing the other therapies, we initiated acitretin 25 mg daily, achieving sustained remission after 6 months of treatment, and then continued with a scaled dose reduction. The patient remained lesion free 1 year after starting the treatment, with a daily dose of 10 mg of acitretin.

Paraneoplastic acrokeratosis has been traditionally described as a paraneoplastic entity mainly associated with primary squamous cell carcinoma (SCC) of the upper aerodigestive tract or a metastatic SCC of the cervical lymph nodes with an unknown origin.^{4,5} However, uncommon associations such as adenocarcinoma of the prostate, lung, esophagus, stomach, and colon; transitional cell carcinoma of the bladder; small cell carcinoma of the lung; cutaneous SCC; breast cancer; metastatic thymic carcinoma; metastatic neuroendocrine tumor; bronchial carcinoid tumor; SCC of the vulvar region;

simultaneous multiple genitourinary tumors; and liposarcoma also have been described.⁶ Regarding the association with lymphoma, PA has been reported with peripheral T-cell lymphoma⁷ and Hodgkin disease⁸; however, ISFL underlying PA is rare.

Follicular lymphoma is the second most common non-Hodgkin lymphoma in Western countries and comprises approximately 20% of all lymphomas.⁹ It is slightly more prevalent in females, and the majority of patients present with advanced-stage disease. Generally considered to be an incurable disease, a watchful-waiting approach of conservative management has been advocated in most cases, deferring treatment until symptoms appear.⁹

Histology of PA is nonspecific, as in our case. However, it facilitates a differential diagnosis of major dermatoses including psoriasis vulgaris, pityriasis rubra pilaris, and lupus erythematosus.

Paraneoplastic palmoplantar keratoderma also is characteristic of Howel-Evans syndrome, which is a rare inherited condition associated with esophageal cancer. In contrast to our case, palmoplantar keratoderma in these patients usually begins around 10 years of age, is caused by a mutation in the *RHBDF2* gene, and is inherited in an autosomal pattern.¹⁰

The diagnosis in our case was supported by a typical clinical picture, nonspecific histology, and the concurrent finding of the underlying lymphoma. Treatment of PA must focus on the removal of the underlying malignancy, which implies the remission of the cutaneous lesions. Taking into account that a recurrence of the primary tumor leads to a relapse of skin manifestations while distant metastases do not cause a reappearance of PA, it could be suggested that pathogenetically relevant factors are produced by the primary tumor and by lymph node metastases but not by metastases elsewhere.

In this case, due to the wait-and-see approach, a specific treatment for the skin lesions was established. Although management of the skin itself generally is ineffective, there are isolated reports of response after corticosteroids, antibiotics, antimycotics, keratolytic measures, or psoralen plus UVA therapy.⁶ Wishart¹¹ used etretinate to achieve an improvement of PA. We also achieved good response with acitretin. Retinoids are known to have antineoplastic activity, which may have been helpful in both the patient we presented and the one reported by Wishart.¹¹ In summary, we propose adding ISFL to the expanding list of malignant neoplasms associated with PA, noting the response of skin lesions after acitretin.

REFERENCES

1. Bazex A, Salvador R, Dupré A, et al. Syndrome paranéoplasique à type d'hyperkératose des extrémités. Guérison après le traitement de l'épithélioma laryngé. *Bull Soc Fr Dermatol Syphiligr.* 1965;72:182.
2. Bazex A, Griffiths A. Acrokeratosis paraneoplasticae—a new cutaneous marker of malignancy. *Br J Dermatol.* 1980;103:301-306.
3. Bologna JL. Bazex syndrome: acrokeratosis paraneoplastica. *Semin Dermatol.* 1995;14:84-89.

4. Witkowski JA, Parish LC. Bazex's syndrome. Paraneoplastic acrokeratosis. *JAMA*. 1982;248:2883-2884.
5. Bologna JL. Bazex's syndrome. *Clin Dermatol*. 1993;11:37-42.
6. Sator PG, Breier F, Gschnait F. Acrokeratosis paraneoplastica (Bazex's syndrome): association with liposarcoma [published online August 28, 2006]. *J Am Acad Dermatol*. 2006; 55:1103-1105.
7. Lin YC, Chu CY, Chiu HC. Acrokeratosis paraneoplastica Bazex's syndrome: unusual association with a peripheral T-cell lymphoma. *Acta Derm Venereol*. 2001;81:440-441.
8. Lucker GP, Steijlen PM. Acrokeratosis paraneoplastica (Bazex syndrome) occurring with acquired ichthyosis in Hodgkin's disease. *Br J Dermatol*. 1995;133:322-325.
9. Jegalian AG, Eberle FC, Pack SD, et al. Follicular lymphoma in situ: clinical implications and comparisons with partial involvement by follicular lymphoma. *Blood*. 2011;118:2976-2984.
10. Sroa N, Witman P. Howel-Evans syndrome: a variant of ectodermal dysplasia. *Cutis*. 2010;85:183-185.
11. Wishart JM. Bazex paraneoplastic acrokeratosis: a case report and response to Tigason. *Br J Dermatol*. 1986;115:595-599.