Bazex Syndrome (Acrokeratosis Paraneoplastica) Diagnosed in a Patient with Oral Persistent Ulcerations

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Abstract Paraneoplastic syndromes associated with head and neck cancer are rare and have been reported under dermatological, endocrine, hematological, neurological and rheumatological disorders. Bazex syndrome is an intriguing paraneoplasia that can be associated with head and neck squamous cell carcinomas. A range of symmetrical dermatological manifestations, with a clear predilection to extremities, that encompasses erythematous squamous plaques, skin scaling and nail dystrophy can provide a psoriasiform pattern in Bazex syndrome. In addition to these tricky clinical features, the rarity of the disease and the lack of understanding on Bazex syndrome generally make such cases to be mismanaged as psoriasis or lichen planus, causing an important delay in the diagnosis of the underlying malignancy. The authors describe a case of Bazex syndrome that occurred in a patient with a recently diagnosed tongue squamous cell carcinoma. Clinicians should consider paraneoplasia when assessing skin and/or oral persistent lesions.

Keywords Bazex · Acrokeratosis paraneoplastica · Paraneoplastic · Oral cancer · Squamous cell carcinoma

Introduction

Bazex syndrome, also known as acrokeratosis paraneoplastica, is an uncommon condition characterized by dermatological disorders associated with an underlying malignancy. The main features of this paraneoplasia is the presence of symmetrical papulosquamous eruptions (psoriasiform cutaneous eruptions), nail dystrophy and skin scaling usually localized in the body extremities (acral distribution) which may affect ears, nose, cheeks, hands, feet, fingers, toes, elbows and knees [1]. Less frequently, skin bullae and vesicles as well as mucosa alterations can occur concomitantly to the more typical cutaneous lesions [1, 2].

Most frequently, squamous cell carcinoma (SCC) of the head and neck, particularly of the oral cavity, oropharynx, larynx and esophagus are associated with Bazex syndrome. Likewise, regional or distant metastasis of head and neck SCC are often present. Although rare, association with other malignant tumours has been reported, including cutaneous squamous cell carcinoma, transitional cell carcinoma of the bladder, metastatic thymic carcinoma, ductal carcinoma of the breast, adenocarcinomas of the colon and prostate, liposarcomas, Hodgkin's disease, peripheral T-cell lymphoma, metastatic neuroendocrine tumour, bronchial carcinoid tumour and tumours of the liver, stomach, thymus, uterus, vulva, genitourinary tract and bone marrow [1–9].

Remarkably, in the majority of the reported cases, cutaneous lesions precede the diagnosis of malignancy by several months and if they were recognized on time, it

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could represent an important predictor of malignant disease [3, 7]. Based on these peculiar features of the disease that highlight its relevance, the authors present a unique case of Bazex syndrome diagnosed in a patient with a recent history of tongue SCC in which persistent and multiple oral ulcerations led to the recognition of an exuberant range of clinical signs of paraneoplasia that resulted in the diagnosis of a malignant tumour in the patients' mediastinum.

Case Report

A 61-year-old Caucasian man was referred for evaluation of multiple painful persistent oral ulcerations. The patient had a recent history of SCC on the lateral border of the tongue, which was treated by the combination of surgery (left hemiglossectomy and supraomohyoid neck dissection on the same side) and post-operative radiotherapy. The clinical stage of the tumour was T₂N₀M₀. According to the medical group responsible for the patient's treatment, oral ulcerations were initially noticed during the eighth day of radiotherapy. Since then, the ulcers quickly progressed causing severe pain and limited oral overall function, thus, the radiotherapy protocol had to be discontinued in the 11th day due to the severity of these lesions. The oral lesions were locally managed as radiation-induced mucositis but no improvement was achieved even after radiotherapy was interrupted for 60 days. Notwithstanding, it was decided to resume the radiotherapy, however, after two additional sessions radiation had to be permanently discontinued because of the worsening of the oral ulcers and the poor quality of life of the patient, who was unable to speak or eat because of generalized oral pain.

After sixty additional days of medical management and follow-up, a gradual worsening was observed and the patient was referred to a second opinion in our clinic with a provisional diagnosis of 'persistent radiation-induced mucositis'. He had no other relevant medical issues apart from the recently diagnosed tongue SCC and had never been under continuous medical treatment.

Extraoral assessment detected mild peri-oral erythematous changes and evident ulcers with crusts affecting upper and lower lips (both in vermillion and mucosa). Intra-oral evaluation was impaired because of a limited ability of mouth opening caused by the pain associated with widespread ulcers involving buccal mucosa, tongue, hard and soft palate (Fig. 1a, b). Regional and full body examinations were able to detect inconspicuous white scales on the dorsal surfaces of the metacarpophalangeal and proximal interphalangeal joints of the hands (Fig. 2). The skin of the legs was also altered and papulosquamous eruptions were noticed showing a symmetrical distribution. Nail thickening, onycholysis, dystrophic changes and vertical ridging of

Fig. 1 **a** Erythematous areas and discreet desquamative changes of the lower lip. Ulcerations and crusts affecting vermillion and mucosa of upper and lower lips. **b** Limited mouth opening and widespread ulcerations involving lips, buccal mucosa and tongue

hands and feet nails were also noticed (Fig. 3a–c). The patient reported that skin lesions were asymptomatic, with rare episodes of itching. He was unable to determine the exact time when these lesions appeared. However, his wife and himself confirmed that they only became noticeable after the tongue SCC surgery was performed and during the course of radiotherapy. They also reported that skin scales started simultaneously to the onset of oral ulcers.

Considering the widespread pattern of these lesions that affected oral mucosa and skin surfaces, further mucosa involvement was investigated. No ocular changes were found, however, the patient reported alterations on the penis mucosa. Examination identified erosive areas on the glans penis mucosa that were marked by diffuse red patches associated with white plaques. According to the patient, such lesions were noticed a few weeks after the beginning of the radiation therapy (Fig. 4). Other symmetrical papulosquamous eruptions were observed in the thigh's skin adjacent to the pubic region (Fig. 5).

Taking all signs together, the main diagnosis hypothesis included lichen planus and psoriasis. As an attempt to promote improvement of the oral ulcers and pain relief, it was prescribed systemic oral prednisone (40 mg/day for 1 week). However, no signs of improvement were observed. Subsequently, a skin biopsy was performed and showed hyperkeratosis, acanthosis, focal dyskeratosis, precocious keratinization, subepithelial lymphocytic infiltrate, deep perivascular and perianexial lymphocytic infiltrate as well as necrotic keratinocytes at the dermoepidermal junction

Fig. 2 Scales on the dorsal surfaces of the metacarpophalangeal and proximal interphalangeal joints of the hand

Fig. 4 Mucosa of the glans penis exhibiting erosive areas marked by diffuse red patches associated with white plaques

Fig. 3 **a** Onycholysis and dystrophic changes on the hand's nails. **b** Detail of vertical ridging affecting the hand nails. **c** Feet's nails showing widespread thickening, onycholysis and dystrophic changes

(Fig. 6a, b). After realizing that the lesions were recalcitrant to local management and systemic corticosteroids and noticing that the microscopic features of the skin specimen were unspecific and not compatible with the provisional diagnosis, the hypothesis of paraneoplasia was considered.

The medical group was warned about the possibility of Bazex syndrome and before they had the chance to perform a tumour screening in the patient, he was hospitalized in an emergency character with crisis of persistent and acute cough suggestive of pneumonia. In this same occasion all the previously mentioned skin and mucosa lesions were present and additional scaling was observed on the nose skin. At that point, the medical team performed a complete screening of the upper aerodigestive tract including a

computed tomography (CT) that failed to detect signs of recurrence, second tumours or regional metastasis (neck) of the recently treated tongue SCC. CT images also included the lung fields for assessment of distant spread. Surprisingly, it was seen an extensive image of mixed attenuation showing central areas of hypoattenuation, suggesting necrosis in the mediastinum (Fig. 7). Subsequently, two bronchoscopies with transbronchial biopsies were performed but none of these procedures were able to collect representative material apart from necrotic tissue.

Unfortunately, before the medical group had enough time to perform an open biopsy, the patient had died. Since the family refused permission for necropsy, it was not possible to collect tissue samples from the mediastinal

Fig. 5 Papulosquamous eruptions in the thigh's skin

Fig. 6 **a** Microscopical analysis performed in one of the papulo-squamous eruptions depicting hyperkeratosis, acanthosis, focal dyskeratosis, precocious keratinization, subepithelial inflammatory infiltration, deep perivascular and perianexial lymphocytic infiltrate (HE stain, scanning). **b** Dyskeratosis and necrotic keratinocytes at the dermoepidermal junction (HE stain, high power)

tumour and consequently to achieve the final diagnosis of the mediastinal mass that was highly suggestive of malignant tumour.

Fig. 7 Computed tomography of the mediastinum displaying an extensive mass extending from the pulmonary artery trunk and characterized by areas of mixed attenuation with central areas of hypoattenuation that suggests necrosis and a malignant tumour

Discussion

Associations between acral hyperkeratosis and malignancy were initially depicted by Bazex et al. [4]. Since the first description, Bazex syndrome has been reported almost exclusively in men over the age of 40 years and has unanimously been associated with malignancies. There are nearly 140 published cases of Bazex Syndrome, and the majority has been reported in the French literature [3, 5].

The etiology of Bazex syndrome is still unknown, although, several hypotheses have been suggested such as immunologic mechanisms in which antibodies directed against the tumour cross-react with antigens in the epidermis or basement membrane; a possible tumour's capability to secrete growth factors, e.g., TGF- α that may affects epidermal growth and epithelial differentiation; and genetic susceptibility due to the occurrence of the same HLA types (A3 and B8) in many cases of the disease [8, 10–12].

Clinical features may be tricky in Bazex syndrome, prompting a misdiagnosis as in the present case. Additionally, skin biopsies generally provide a mixture of findings that may be found in several more common disorders (hyperkeratosis, acanthosis, spongiosis, mononuclear perivascular infiltrate, dyskeratotic keratinocytes and vacuolar degeneration of keratinocytes), which increase the chances to confuse it with diseases that may be similar both clinically and microscopically such as psoriasis and less frequently, lichen planus [1].

The most frequently neoplasia associated with Bazex syndrome is SCC, which is responsible for about 64% of the cases, arising particularly on the aerodigestive tract,

with 80% affecting oral cavity, larynx, pharynx, lung, and esophagus. Remarkably, 50% of the reported malignancies have metastasis to the cervical lymph nodes. On the other hand, approximately 16% of the cervical lymph nodes metastasis associated with Bazex syndrome have unknown primary tumour. There are isolated cases of other malignancy associations in the literature, including cutaneous squamous cell carcinoma, transitional cell carcinoma of the bladder, metastatic thymic carcinoma, ductal carcinoma of the breast, adenocarcinomas of the colon and prostate, liposarcomas, Hodgkin's disease, peripheral T-cell lymphoma, metastatic neuroendocrine tumour; bronchial carcinoid tumour and tumours of the liver, stomach, thymus, uterus, vulva, genitourinary tract and bone marrow [1–7].

The importance of any paraneoplasia is the obvious association with an underlying malignancy. In Bazex syndrome's this association is even more important, inasmuch as cutaneous eruptions can predate clinical evidence of cancer by several months or even years in approximately 75% of the patients [2]. Any clinical sign that could suggest Bazex syndrome should automatically guide a cutaneous biopsy followed by a complete screening of the upper aerodigestive tract. If no tumour is found in the head and neck region, further investigation of other possible affected primary sites or metastasis should be performed, such as mediastinum, colon, bladder, prostate, uterus and vulva [3].

Mucosa lesions are not considered a common feature of Bazex syndrome and to the best of the author's knowledge, only one case of oral lesions and another case describing penis lesions have been reported to date. Both cases are included in an analytic review conducted by Bolognia et al. [1]. The presence of mucosal lesions associated with skin changes in the current case may be supported by previously published cases that reported the co-existence of two paraneoplastic disorders, e.g., Bazex syndrome associated with paraneoplastic pemphigoid or paraneoplastic pemphigus [1, 2]. In a similar way, Gill et al. [2] provided various explanations for the vesicles and bullae that may appear simultaneously to Bazex syndrome, including coexisting porphyria cutanea tarda, epidermolysis bullosa acquisita, bullous pemphigoid, bullous lichen planus or paraneoplastic pemphigus associated with the typical skin changes.

Interestingly, some reports of Bazex syndrome have found positive direct immunofluorescence results in patients with bullous skin lesions, raising in such cases the doubt whether Bazex syndrome may occurs simultaneously with another bullous diseases or manifests itself in a different and more exuberant way [8, 9]. In the present case, because of the severe oral pain and limited mouth opening, no oral biopsies were taken.

Skin lesions associated with Bazex syndrome seems to be resistant to several therapeutical modalities such as keratolytics, steroids and antibiotics. Apparently, the definitive therapy is the treatment of the underlying tumour. However, nail changes are usually persistent [5].

Bazex syndrome is often diagnosed in the absence of histological confirmation of the primary tumour and in these cases the stigma of the disease is generally associated with neck metastasis of SCC with unknown primary site [1, 5]. In the present case, a well documented history of tongue SCC (T₂N₀M₀) was provided by the patient and the medical team. No clinical or CT assays were able to identify residual tumour, recurrence or second tumour in the tongue or adjacent areas. Likewise, no evidence of cervical metastasis was observed by palpation or CT analysis. On the other hand, surprisingly, an image with high suggestive appearance of malignant tumour was detected in the mediastinum, which could represent a distant metastasis from the primary tongue SCC. However, mediastinum is not considered a normal route for metastasis for head and neck SCC, especially in the absence of neck metastasis. Therefore, it is also worthy to consider that this find could represent another primary tumour, such as a thymus tumour or a lymphoma, that had been previously associated with Bazex syndrome in the literature [1]. Unfortunately, two attempts to collect tissue samples from the mediastinum lesion failed to obtain representative material to establish the diagnosis.

In summary, as rarely reported before, the authors have presented a case where oral recalcitrant ulcers, skin and genital lesions led to the diagnosis of Bazex syndrome, most probably, as a consequence of a distant metastasis from a tongue SCC. Most of all, it is important to bear in mind that oral persistent and unspecific ulcerations associated or not with other disorders could represent a paraneoplastic condition, mainly in patients who have a history of malignant diseases. In such cases, complete screening for residual tumours, recurrences, second tumours or metastasis must be performed.

References

1. Bolognia JL, Brewer YP, Cooper DL. Bazex syndrome (acrokeratosis paraneoplastica). An analytic review. *Medicine* (Baltimore). 1991;70:269–80.
2. Gill D, Fergin P, Kelly J. Bullous lesions in Bazex syndrome and successful treatment with oral psoralen phototherapy. *Australas J Dermatol*. 2001;42:278–80.
3. Poligone B, Christensen SR, Lazova R, et al. Bazex syndrome (acrokeratosis paraneoplastica). *Lancet*. 2007;369:530.
4. Bazex A, Salvador R, Dupre 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.
5. Moore RL, Devere TS. Epidermal manifestations of internal malignancy. *Dermatol Clin.* 2008;26:17–29.
 6. Chave TA, Bamford WM, Harman KE. Acrokeratosis paraneoplastica associated with recurrent metastatic thymic carcinoma. *Clin Exp Dermatol.* 2004;29:430–2.
 7. Sator PG, Breier F, Gschnait F. Acrokeratosis paraneoplastica (Bazex's syndrome): association with liposarcoma. *J Am Acad Dermatol.* 2006;55:1103–5.
 8. Pecora AL, Landsman L, Imgrund SP, et al. Acrokeratosis paraneoplastica (Bazex' syndrome). Report of a case and review of the literature. *Arch Dermatol.* 1983;119:820–6.
 9. Mutasim DF, Meiri G. Bazex syndrome mimicking a primary autoimmune bullous disorder. *J Am Acad Dermatol.* 1999;40: 822–5.
 10. Lucker GP, Steijlen PM. Acrokeratosis paraneoplastica (Bazex syndrome) occurring with acquired ichthyosis in Hodgkin's disease. *Br J Dermatol.* 1995;133:322–5.
 11. Jacobsen FK, Abildtrup N, Laursen SO, et al. Acrokeratosis paraneoplastica (Bazex' syndrome). *Arch Dermatol.* 1984;120: 502–4.
 12. Sarkar B, Knecht R, Sarkar C, et al. Bazex syndrome (acrokeratosis paraneoplastica). *Eur Arch Otorhinolaryngol.* 1998;255: 205–10.