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Bazex syndrome (acrokeratosis paraneoplastica)

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Abstract Acrokeratosis paraneoplastica (Bazex syndrome) is a rare but distinctive dermatosis associated with carcinomas of the upper aerodigestive tract with possible cervical lymph node metastases. The cutaneous lesions occurring in the syndrome are non-metastatic skin involvement that parallels (as cutaneous marker) the evolution of the malignancy. Since only a few case reports have been published in the otolaryngologic literature, we present our experience and review some of the findings previously reported.

Key words Bazex syndrome · Acrokeratosis paraneoplastica · Head and neck cancer

Introduction

In 1922, Gougerot and Rupp [41] first described a patient with a squamous cell carcinoma (SCC) of the tongue with hyperkeratotic lesions of the nose, ears and palmo-plantar region. In 1965, Bazex et al. [9] described a case of a SCC of the piriform fossa associated with a psoriasislike exanthem. Since then, a number of reports concerning acrokeratosis paraneoplastica have been published, the vast majority of which have appeared in the French dermatology literature. To date, a total number of 112 cases have been described [1–20, 21–36, 37–72, 73–93]. Although the skin eruptions in acrokeratosis paraneoplastica (now known as Bazex syndrome) are usually associated with carcinomas of the head and neck, to our knowledge there have appeared only a few reports in the French, American and German otolaryngologic literature [15, 39, 46, 57, 59, 63, 66, 69, 79]. This is unusual for a rare but distinctive disease in clinical otolaryngology and dermatology. In general, Bazex syndrome belongs to the obligatory cutaneous paraneoplasms that can be grouped together with acanthosis nigricans maligna, erythema gyratum, erythema necrolyticum migrans and hypertrichosis lanuginosa acquisita. The cutaneous paraneoplasia in Bazex syndrome is a non-metastatic skin involvement that parallels the evolution of a co-existing malignancy. Sufficient treatment of underlying neoplasia will improve the cutaneous symptoms significantly. Furthermore, the psoriasiform skin eruption may precede symptoms associated with the neoplasia. Hence, a suspicious diagnosis of Bazex syndrome provides an oportunity for detecting a malignancy at an early asymptomatic stage. Because of this, and since only few of the previous case reports have been published in the otolaryngologic literature, we present another case and review some of the findings on Bazex syndrome.

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Case report

A 61-year-old white male German worker was admitted for evaluation of a 5-month history of hoarseness and dysphagia. He also complained of otalgia and a left cervical tenderness that had begun approximately 6 months before presentation. Past medical history included cardiac dysrhythmia, hypertension, alcohol-induced hepatic disease, as well as scaly skin lesions associated with nail changes, that had started about 5 years previously and were unresponsive to topical therapy. The patient had a 38-pack-year smoking history, but had stopped smoking 6 years previously. On physical examination, acral hyperkeratotic skin lesions were seen and included squamous skin lesions at the elbows. They had ill-defined borders at the hands and feet (palmoplantar). The heels were significantly involved and showed painful fissures and adherent scales. The finger and toenails were dystrophic with a yellowish discoloration and demonstrated a periungual swelling (Fig. 1 a–d). Aural skin lesions were less intense and limited to the upper helix and triangular fossa and were more pronounced in the right ear. Scraping of a skin lesion of the nose provoked some bleeding (Fig. 1 e). Laboratory examination was unremarkable except for slightly raised thyroid stimulating hormone (TSH). Fungal cultures from

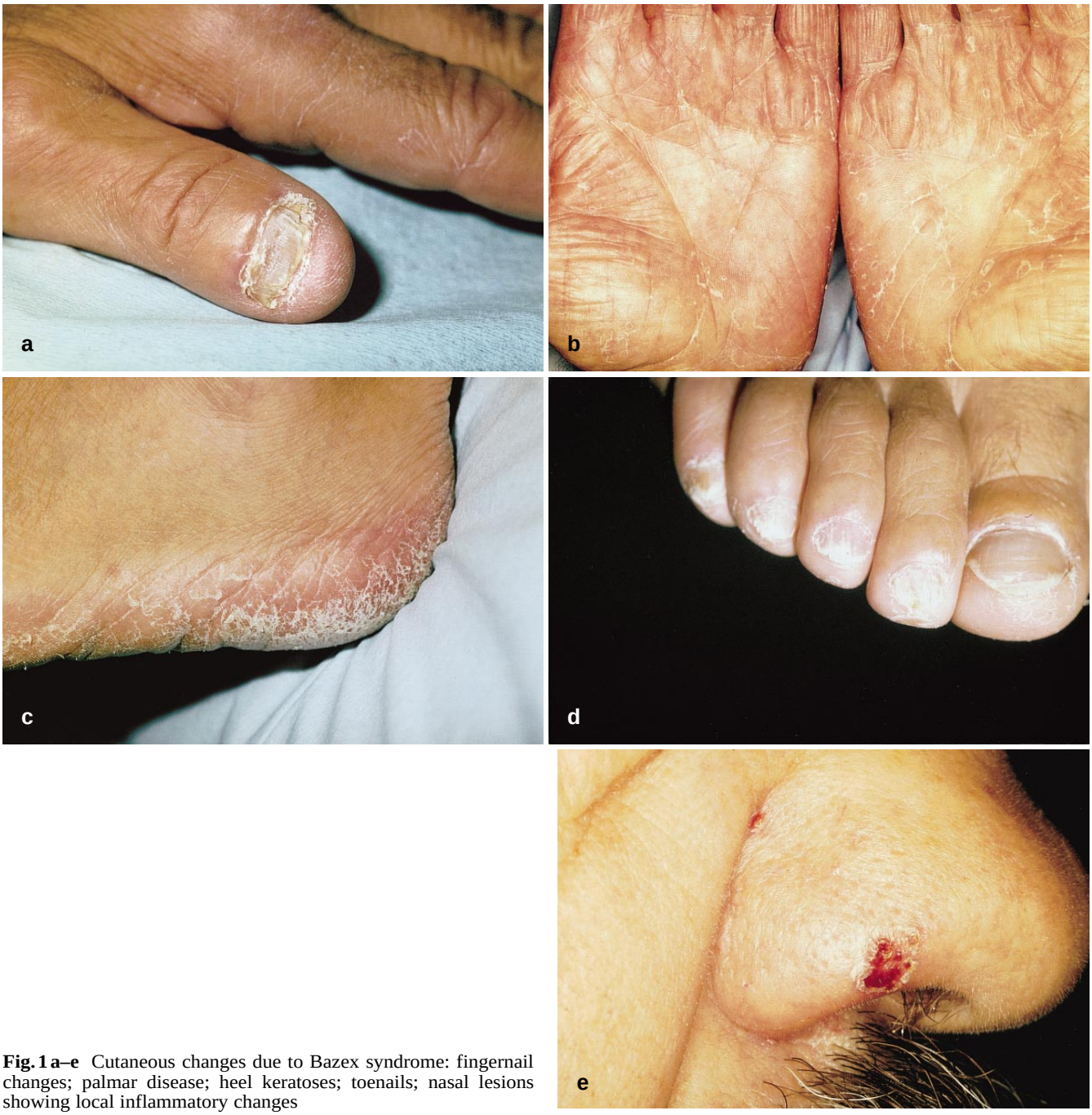

Fig. 1 a–e Cutaneous changes due to Bazex syndrome: fingernail changes; palmar disease; heel keratoses; toenails; nasal lesions showing local inflammatory changes

nails and from squamous lesion of the heel were negative. Human lymphocyte antigen state included A24, A28, B7, B14, Cw8. Panendoscopy revealed a cauliflower-shaped tumor of the left piriform sinus that extended to the left vallecula and epiglottic border. Multiple biopsy specimens confirmed a moderately differentiated SCC of the left piriform sinus and was staged T3N0M0. The patient underwent a total laryngectomy, partial pharyngectomy and left radical neck dissection. The post-operative course was without complications. Radiation therapy to 60 Gy was planned.

Discussion

The underlying neoplasia in Bazex syndrome is usually located in the upper aerodigestive tract: SCC of the pharynx, larnyx, bronchi and esophagus. Review of the 112 published cases shows that nearly half of the malignancies were located in the oral cavity, pharynx and larynx (54 of 112). There were 19 cases of lung cancer and another 15 cases of a malignancy of the esophagus. Carcinoma from an unknown primary site (CUP) with lymph node metastases was also frequently observed (18 of 112). Adenocar-

Table 1 Primary sites and types of malignancy reported in patients with Bazex syndrome (*SCC* squamous cell carcinoma, *Ca* carcinoma)

Primary site	No. cases	Type
Oral cavity/pharynx/larynx	54	45 SCC
Lung	19	5 SCC
Unknown primary	18	11 SCC
Esophagus	15	6 SCC
Liver	1	Hepatoma
Prostate	1	Adeno-Ca
Stomach	1	Adeno-Ca
Thymus	1	SCC
Uterus	1	Adeno-Ca
Vulva	1	SCC
Total	112	

cinoma of the prostate [71], stomach [35], uterus [1], as well as SCC of the thymus or vulva [84], and carcinoid tumor of the lung [21] were considered to be exceptions. Gago et al. [38] described a case of paraneoplastic acrokeratosis in which no SCC or adenocarcinoma was found, but a malignant hepatoma (Table 1). Nearly all of the reported cases of Bazex syndrome have occurred in males (105 of 112). Only 7 patients were female [1, 6, 42, 47, 48, 64, 84]. The mean age of the patients was 61 ± 10 years. Five cases were described in patients with an age less than 45 years [6, 15, 32, 63, 92]. The youngest patient was a 25-year-old woman with a small-cell carcinoma of the lung [6].

Evolution of skin lesions

The most frequently involved sites of skin lesions in Bazex syndrome are the hands, feet, ears, and nose. The skin eruptions consist of squamous hyperkeratotic and erythematous to violaceous lesions. According to Bazex [7, 8], the disorder evolves in three stages. The first stage is characterized by the occurrence of a symmetrically localized erythemato-squamous eruption at the fingertips and toes. This is followed by involvement of the nose and usually the helices. The fingernails and toenails become dystrophic and show paronychia and subungual keratotic debris, as well as possible onycholysis. Although an underlying tumor may have already metastasized to cervical or mediastinal lymph nodes, the neoplasm per se is commonly asymptomatic in this stage. During its second stage tumor growth or cervical lymph node metastases usually become obvious and skin lesions spread centripetally. The cheeks, forehead, elbows, thighs and knees might be involved. In general, the borders of the cutaneous lesions are ill-defined. Scraping of a skin lesion may provoke slight bleeding. In the last (third) stage persistance of the underlying malignancy leads to involvement of the extremities and trunk. The psoriasislike skin lesions tend to develop rhagades. Although pruritus is frequent, it tends to be of less severity. Additional or deviating forms and sites of skin lesions have been reported. These descriptions include erythrodermia [49, 61], lichenification [71, 73, 87], acrocyanosis [15, 51, 55, 81, 91], periungual erythematous swelling [18, 47, 87, 93] and complete onychoatrophy [13, 17, 19, 23, 27]. Bullous skin lesions have been described [15, 19, 30, 40, 56], as well as vesicles [51, 68, 87] and pustules [31, 92]. Hyperpigmentation has also been in some cases, although this has tended to occur in darkly pigmented patients [6, 14, 17, 18, 37]. Three cases were reported by Handfield-Jones et al. [47] that did not show any erythematosquamous lesions of the ears and nose. In another case, *Candida albicans* was isolated in cultures of scrapings from hyperkeratotic finger nails. The nail changes proved to be unresponsive to treatment with cotrimazole [52], suggesting secondary fungal invasion of the dystrophic nails. Histologic examination of skin lesions will usually reveal hyperkeratotis, parakeratosis, acanthosis and/or vacuolar degeneration of keratinocytes. Less often thickening of the basal layer can be seen with papillomatosis, spongiosis, a loss of melanin pigment into dermis or atrophy. Non-specific vascular alterations with lymphocytic or mixed-cell perivascular infiltration can be regularly found. Infiltrations may also contain neutrophils or eosinophils [6]. Direct and indirect immunofluorescence of lesional skin has either shown negative findings or non-specific reactions such as the deposition of immunoglobulins, C3 or fibrin at the basement membrane zone [45, 47, 73, 79, 80, 87, 90]. In one case, the amino acid composition of affected nails was found to be abnormal in comparison to normal and psoriatic nails [54]. In nearly all cases, a skin eruption was present when the diagnosis of a malignant neoplasia was made. In general, cutaneous lesions preceded tumor symptoms or diagnosis for an average period of 2–6 months. Longer periods were involved in some cases, ranging from 1 year to 6 years [14, 32, 33, 55, 61, 71, 75, 86]. There have been a few cases, in which skin lesions developed after treatment for a malignancy. These were associated with recurrence of tumor or metastases [28, 39, 69]. The patient's history as well as the characteristic distribution and non-specific histologic findings of the skin lesions in Bazex syndrome usually exclude an acral form of psoriasis, a pytiriasis rubra pilaris, lupus erythematodes, Reiter's disease, hyperkeratotic-rhagadiform hand and foot eczema, and hereditary palmoplantar keratosis. Mycosis of the nails or tinea of the hands and feet regularly reveals positive fungal cultures, most often dermatophytes.

Neoplasia of the oral cavity, pharynx and larynx

Our review of the available literature uncovered 54 patients whose malignancies were in the oral-pharyngeal-larnygeal region (Table 2). These tumors in 45 cases (83%) were of the squamous type and in 5 cases poorly differentiated. In the other 4 patients the cell type was not futher specified.

Table 2 shows sites and cell types of the malignancy of the 54 cases. Overlapping or incoherence of anatomical specification was due to different methods of reporting

Table 2 Primary sites of malignancy described in patients with Bazex syndrome

Primary site	No. cases	SCC
Tonsil	13	11
Piriform sinus	9	7
Pharynx	8	6
Larynx	7	5
Tongue	7	7
Epiglottis	4	3
No specific site	3	3
Palate	2	2
Floor of mouth	1	1
Total	54	45

data that have been published in the literature. The most commonly involved sites have been the tonsillar region (in 13 cases), piriform sinus (9 cases), pharynx (8 cases), larynx (7 cases) and tongue (7 cases). The epiglottis, soft palate and floor of mouth have been less frequently involved. Metastases to cervical lymph nodes were found in 60 cases. The most commonly involved nodes in the neck were the jugulodigastric, anterior jugular, and submandibular group. In 13 cases, other or additional sites of metastatic involvement included the lymph node regions of the axilla, paratracheal-mediastinal and inguinal region [6, 17, 33, 47, 54, 58, 61, 71, 79, 85, 87]. Other sites have included the skeleton, lung, liver, and skin [1, 17, 35, 38, 60, 71]. Cervical metastases were found in 3 cases each from malignant primaries of the lung [57, 83, 87] and esophagus [15, 43, 63]. On the other hand, except for one patient with mediastinal lymph node involvement [79], all of the metastases in the 18 cases of carcinoma of unknown primary (CUP) were located in the cervical lymph nodes, with most derived from a squamous cell carcinoma. Thus, it seems likely that the majority of the underlying carcinoma would be located in the larnygopharyngeal region. In only 12 of 112 cases was it explicitly stated that there was no metastatic involvement of lymph nodes or of other organs. Several authors have described the occurrence of synchronic or metachronic carcinomas (as a second primary) in a few patients [15, 32]. Other cutaneous signs that may reflect an underlying malignancy include acquired ichthyosis [14, 35, 68], bullous pemphigoid [80], or Leser-Trèlat syndrome [82]. In one patient a cutaneous porphyria was found [40]. Poskitt et al. [77] reported one case of Bazex syndrome associated with a carpal tunnel syndrome and concomitant evolution and resolution of skin lesions and neurological symtoms. Data on typical risk factors for the development of carcinomas of the upper aero-digestive tract were available for 22 patients only. Except for 2 cases [6, 71], all patients had a history of smoking and/or alcohol.

Therapy

With the exception of a few cases [23, 28, 64, 67, 71], the cutaneous lesions in Bazex syndrome have usually proved to be unresponsive to topical treatment with steroids, antimycotics or keratolytics. A partial or total spontaneous resolution of the skin lesions without treatment of the malignant neoplasia was reported in 3 cases [43, 79, 83]. Improvement of the cutaneous lesions to systemic therapy with etretinate (Tigason), an aromatic retinoid, was also reported in 2 cases [58, 91]. Conversely, Juhlin and Baran [54] described a progressive worsening of skin lesions following etretinate treatment. Although temporary improvement of cutaneous lesions by topical or systemic drugs has been reported, these treatments nearly always fail to clear lesions in case of tumor persistence. Moreover, in more than 90% of the cases in which the course of the skin eruption has been described, skin lesions showed either significant improvement following antineoplastic treatment or no improvement in cases with tumor persistence. Sufficient treatment of the neoplasia has led to a clearing of skin lesions within months. In some cases this improvement began 3 to 14 days after surgery [6, 16, 61]. Blanchet et al. [15] described a patient with a laryngopharyngeal carcinoma, in whom the cutaneous lesions had cleared after surgery and radiation therapy and did not reappear for more than 8 years. On the other hand, the aforementioned nail changes in Bazex syndrome improve only slowly after successful treatment of the neoplasia, or may even persist [13, 27, 79].

Pathogenesis

The pathogenesis of Bazex syndrome remains to be determined. It is still unclear whether or not the disorder is induced by the primary neoplasm per se or presupposes the prior metastatic involvement of lymph nodes. The occurrence of the skin lesions and cervical lymph node metastasis may prove to be a relevant step in the pathogenesis of the syndrome. Examination of the HLA state of patients with acrokeratosis paraneoplastica has been reported by a few authors [45, 49, 52, 84, 90]. A combination of HLA-A2 and HLA-B8 was found in three out of five cases, while the other two cases showed A2 and B8 alone. Hence, except for our case presented, one or both of these two HLA types were found in each case of Bazex syndrome for which an HLA state was determined. Several authors have proposed that the histopathologic findings of immunoglobulins and inflammatory cells at the basal layer derive from an autoimmune reaction [17, 28, 73, 87]. This is possibly initiated and triggered by a common antigen between tumor cells (usually SCC) and epidermal cells. Immunologic factors in the form of antigen cross-reactivity might prove to be the pathogenic entity in Bazex syndrome. Another explanation for the psoriasiform skin lesions in Bazex syndrome is based on the stimulating effect of transforming growth factor (TGF) alpha produced by the tumor cells present. Partridge et al. [72] suggested that TGF-alpha had a proliferative potential on normal skin, cultured keratinocytes, and SCC. Elder et al. [36] evaluated the genetic overexpression of TGF-alpha in psoriatic skin in comparison to normal skin.

TGF-alpha mRNA and protein in cutaneous lesions were shown to have a four- to sixfold increase, whereas the levels of its antagonist TGF-beta were not significantly different in all skin specimens studied. Hence, an increase in TGF-alpha whether relative or absolute may lead to a dysregulation of the autocrine growth control loop and induce the hyperkeratotic lesions found in Bazex syndrome.

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