Bullous pemphigoid in a patient with giant squamous cell carcinoma of the groin

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SUMMARY

Bullous pemphigoid is considered by some authors to be a paraneoplastic syndrome.

A 47-year-old male was referred to our department because of disseminated tense vesicles and blisters, and multiple erosions all over the body. Two years before admission the patient noticed for the first time a tumor in the left groin. Seven months later the lesion was surgically removed, and the histopathology revealed squamous cell carcinoma. Four months after removal of the tumor a local relapse occurred.

The skin lesions were slightly itchy and painful. On the left buccal mucosa solitary erosions were present. In the left groin a huge, partly ulcerated tumor was present.

The immunohistochemical and histopathologic examinations confirmed the clinical diagnosis of bullous pemphigoid. No distant metastases were detected by x-ray examination. The patient was treated with intramuscular injections of methylprednisolone acetate (80mg/week) and oral cyclophosphamide (50mg/day) that failed to yield a satisfactory response. The tumor was surgically removed. After resection a marked improvement of the skin lesions was observed.

KEY WORDS

bullous pemphigoid, squamous cell carcinoma, paraneoplastic syndrome

Introduction

Bullous pemphigoid (BP) is an acquired, autoimmune, subepidermal blistering disease with subepidermal blisters that occur mainly in the elderly (1). Although some epidemiological studies have shown that the frequency of malignancies in patients with BP is spread in similar proportion throughout the population (2,3), some authors consider BP to be a paraneoplastic syndrome as there are many reports in medical literature that document the coexistence of various malignancies and BP (4-7). In addition, in some cases the successful treatment of malignancy has achieved as a result control of the skin lesions (4,5). We present a patient with giant cutaneous squamous cell carcinoma, who developed lesions typical for BP.

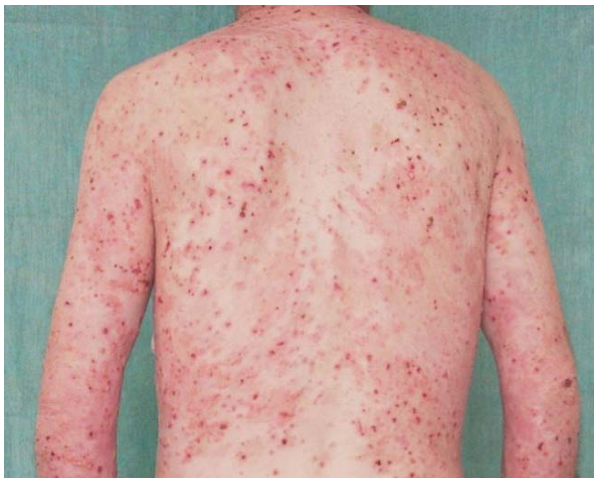

Figure 1a. Clinical manifestation of bullous pemphigoid with numerous tense vesicles and erosions with an erythematous background.

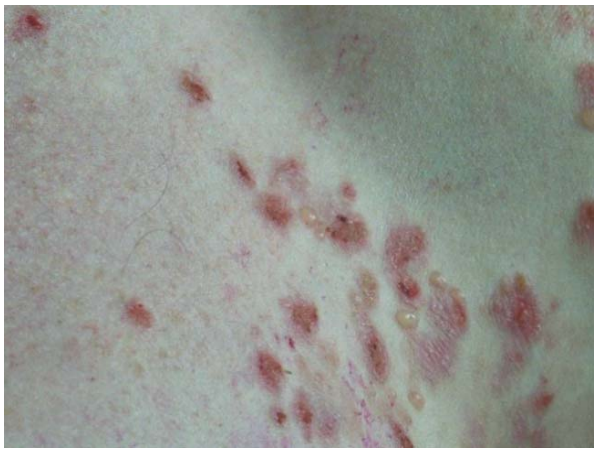

Figure 1b. Higher magnification showing the vesicles, crusts and erosions.

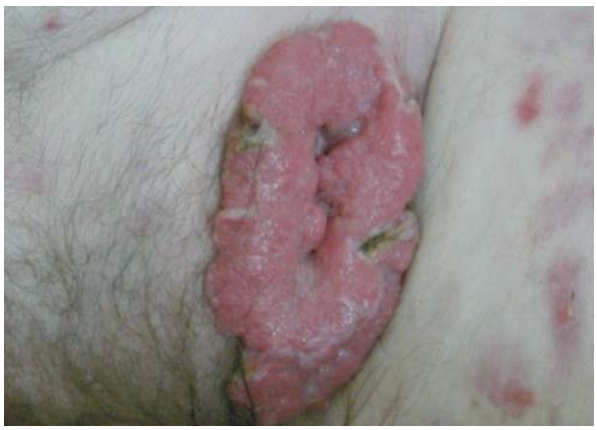

Figure 2. Ulcerated, giant squamous cell carcinoma of the groin in a patient with bullous pemphigoid.

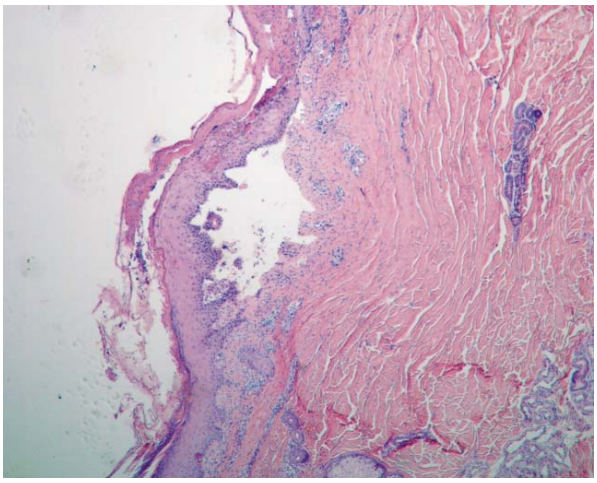

Figure 3. Histopathologic findings of bullous skin lesions showing a subepidermal blister and a mixed infiltrate in dermis (haematoxylin and eosine staining, original magnification 40x).

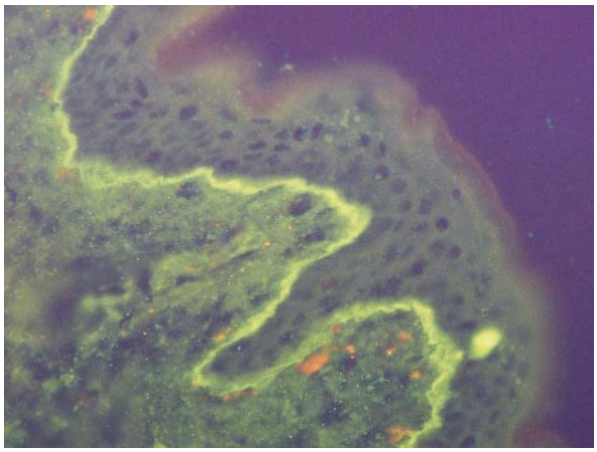

Figure 4. Linear deposits of complement complex - C1q - along the dermoepidermal junction (immunofluorescence, original magnification 400x).

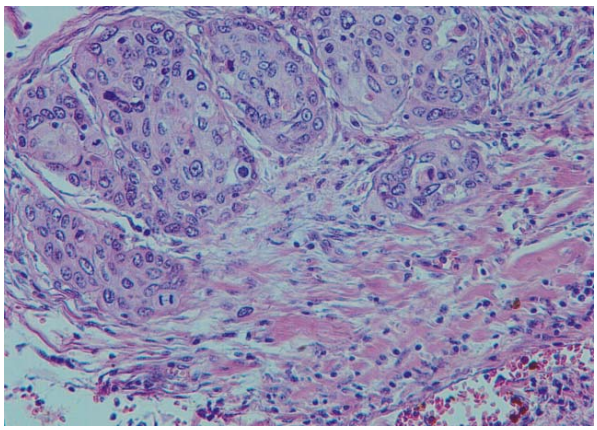

Figure 5. Histopathologic findings of the anaplastic squamous cell carcinoma revealing atypical keratinocytes and numerous mitotic figures (haematoxylin and eosine staining, original magnification 200x).

Case report

History and clinical manifestation

A 47-year old male was referred to our department because of disseminated tense vesicles and blisters, and multiple erosions of the whole skin. He noticed the first blisters on the skin one month before admission. Two years earlier he had first noticed a tumor in the left groin. Seven months later the lesion was surgically removed and sent for microscopic examination. The histopathology revealed squamous cell carcinoma G1. The wound healed without complications. Four months after removal of the tumor a local relapse occurred. Since that time the patient was readmitted several times, and only a palliative treatment applied.

On admission the patient had a chill and a temperature of 37.7°C. Tense vesicles and blisters were spread across the whole body, as well as partly encrusted multiple erosions with an erythematous background (Figs. 1a and 1b). The skin lesions were slightly itchy and painful. On the left side buccal mucosa solitary erosions were present. In the left groin a huge (about 10x20 cm) partly ulcerated tumor was present (Fig. 2). The right inguinal lymph nodes were enlarged up to 1.5 cm. On physical examination they were solitary, soft and not painful. The left side inguinal lymph nodes were not palpable. Examination revealed no significant changes of the other peripheral lymph nodes.

Laboratory examinations

The patient had an elevated count of lymphocytes (12.7x109/l). The other routine laboratory tests were within the normal range or negative, namely: the erythrocyte sedimentation rate, the erythrocyte and blood platelet count, the peripheral blood smear, the serum level of glucose, potassium and sodium, as well as biochemical markers of liver and kidney function. The standard x-ray examination of the chest, abdominal cavity and pelvis revealed no distant metastases. In the left groin no enlarged lymph nodes were observed.

Histopathology and immunofluorescence

Histopathologic examination of the bullous skin lession showed a subepidermal blister (Fig. 3). The epidermis showed spongiosis and in some areas it was covered with hemorrhagic crusts. In the dermis a mixed inflammatory infiltrate was observed.

Direct immunofluorescent examination revealed abundant deposits of C3 and C1q, and deposits of IgG within the basement membrane zone (Fig. 4). There were no deposits of IgA, IgM, or C4. Histopathology confirmed bullous pemphigoid. No circulating antibodies, either of pemphigus type or pemphigoid type were detected in the serum.

Treatment and outcome

The patient was treated with intramuscular injections of methylprednisolone acetate (80mg/week) and oral cyclophosphamide (50mg/day). Because of the patient's chill, temperature and leukocytosis on admission, an oral antibiotic was added: 100 mg doxycycline twice a day. Topical therapy included dexamethasone and neomycine in aerosol form. No remarkable improvement of the skin lesions was observed within the first 14 days of therapy. After two weeks the patient was transferred to the department of oncological surgery to remove the tumor. The tumor was removed radically and the histopathologic examination revealed a recurrent anaplastic squamous cell carcinoma (Fig. 5a and 5b). The simultaneously resected lymph nodes had not been infiltrated with malignant cells. After resection of the tumor the patient underwent radiotherapy. The removal of the tumor resulted in the disappearance of the BP skin lesions. Six months after the surgical treatment the patient was lost for further follow-up.

Discussion

The association between BP and malignant diseases remains controversial. Pemphigoid has been reported in numerous patients with malignancies, like parotid carcinoma (4), breast cancer (5), lung cancer (8), gastric cancer (6,8), cancers of colon or rectum (6,8,9), endometrial cancer (8), B-cell lymphoma (7) and many others. Some epidemiological studies have failed to confirm the previous suspicion that BP is etiologically connected with a higher incidence of malignant tumors (2,3). Dissenting reports are also to be found in medical literature. Ogava et al. (10) in a large survey of BP patients in Japan observed a 5.8% incidence of malignancy, which was significantly higher than the rate in age-matched controls (0.6%), and association with gastric cancer was the most commonly observed. Moreover, Egan et al. (8) noted a high incidence of malignancies (28.6%) in patients suffering from an anti-epiligrin cicatrical pemphigoid. This higher proportion is similar to the incidence of cancers in adult patients with dermatomyositis.

In view of the existing data that concerns the paraneoplastic origin of BP, we decided to report the patient with squamous cell carcinoma of the groin, who displayed a remarkable improvement of skin lesions after removal of the tumor. To the best of our knowledge only two reports presenting the coexistence of BP and squamous cell carcinoma of the skin have been published (11,12). In a similar way to these previously described cases of BP accompanied by a malignancy (4,5), our patient did not respond well to standard therapy. An improvement of skin lesions was, however,

observed after surgical removal of the squamous cell carcinoma. In addition, it has been reported that in cases of BP, concurrent malignant disease is more common in patients who have a negative-indirect immunofluorescent examination (13), and this held true in the case of our patient. Therefore, it is possible that the autoimmune disturbances in pemphigoid patients with malignant tumors represent a distinct spectrum of abnormalities.

Recently several types of new bullous diseases in patients with malignancies have been reported. Wong and Ho (14) described a patient with squamous cell carcinoma of the tongue suffering from paraneoplastic pemphigus (PNP) with a pemphigoid-like clinical presentation. The patient presented tense bullae on his skin that were typical of BP with no mucosal involvement, but revealing an intraepidermal blister that was, however, without acantolytic cells. The immunofluorescent examination showed strong positive staining for IgG and C3 throughout the epidermis (14). Musette et al. (15) described a new type of paraneoplastic mixed bullous skin disease in a patient with B-cell lymphoma that was associated with monoclonal IgM kappa paraproteinaemia. In that patient a novel pattern of immunoreactivity was observed – IgG antibodies were directed against desmoplakins I-II and bullous pemphigoid antigen 2 (BPA2), and were associated with antidesmoglein 3 polyclonal IgM antibodies. The clinical features were similar to a "BP-like disease" with tense bullae and urticarial plaques without mucosal involvement or "lichen planus-like" lesions usually observed in paraneoplastic pemphigus. Similarly, the histopathological picture of subepidermal bullae was reminiscent of BP. Direct immunofluorescent examination revealed deposits in the basement membrane zone, but the antidesmoglein 3 antibodies found in the serum were typical for PNP (15).

As many immunological abnormalities have been described in cancer patients, it is probable that such patients may also present the autoantibodies typically found in BP. Moreover, it has even been reported that in squamous cell carcinoma the expression of BPA1 and BPA2 is clearly increased (16,17). This could stimulate the immune system to produce antibodies directed against the antigens that provoke manifestation of BP in patients with such carcinomas.

Conclusion

In view of the available literature and the case study that we have presented, we recommend a precise examination of any patient with BP in order to detect any underlying malignancy. This is specially important in cases with poor response to standard anti-BP therapy or with recurrent BP.

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