Oral Diseases (2005) 11, 326–329

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CASE REPORT

Paraneoplastic pemphigus: a case report and review of literature

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Paraneoplastic pemphigus (PNP) is an autoimmune mucocutaneous disease frequently associated with lymphoproliferative disorders. The rare combination of the disease with other malignancies such as different types of carcinomas, sarcomas, melanoma and skin tumours has also been reported. Most patients develop very severe oral ulceration and conjunctival ulceration with or without genital ulceration resembling the features of Steven's Johnson's syndrome or most severe forms of drug eruptions. The possibility of PNP should be borne in mind when a patient presents with extensive oral ulceration if clinical, histopathological and results of direct immunofluorescence are not pathognomonic for a specific diagnosis. The issue becomes even more important as some patients with PNP have no diagnosed malignancy at the time of presentation. We document a case of PNP in a 29-year-old female who suffers from non-Hodgkin's lymphoma.
Oral Diseases (2005) **11**, 326–329

Keywords: paraneoplastic; pemphigus; oral mucosa; neoplastic; immunofluorescence; refractory

Introduction

Paraneoplastic pemphigus (PNP) is an autoimmune mucocutaneous disease frequently associated with lymphoproliferative disorders. The rare combination of the disease with other malignancies such as different types of carcinomas, sarcomas, melanoma and skin tumours has also been reported (Kaplan *et al*, 2004). PNP was first described by Anhalt *et al* (1990) in 1990 and proposed a set of criteria in order to arrive at the diagnosis. The proposed criteria which are valid up to date are (1) mucocutaneous blistering and ulcerations, (2) histopathological features such as acantholytic changes of the epithelium and epidermis with interface dermatitis, (3) deposition of immunoglobulin (Ig)G and C_3 in intercellular areas and/or along the basement membrane, (4) presence of serum antibodies and (5) demonstration of various desmoplakins and desmogleins in the serum.

Most patients develop very severe oral ulceration and conjunctival ulceration with or without genital ulceration resembling the features of Steven's Johnson's syndrome or most severe forms of drug eruption (Hashimoto, 2001). Imunopathology of PNP has been extensively studied during the last few years (Hashimoto, 2001).

Although the treatment of choice for PNP is Oral prednisolone, significant percentage of patients need adjuvant treatment. However a large majority of patients are refractory to treatment and the survival with associated malignancy is invariably poor (Mimouni *et al*, 2002). The present paper documents a case of PNP in a patient with non-Hodgkin's lymphoma.

Case report

Twenty-nine-year-old female presented to the Dermatology clinic of teaching Hospital Kandy, Sri Lanka with painful oral and genital ulcers. The patient also had redness of eyes. The lesions have been there for last 2 months.

Two and half months prior to the development of ulcers the patient had presented with generalized lymphadenopathy, especially in axillary and inguinal areas. Fine needle aspiration biopsy was performed followed by excision of one axillary node for histology as the cytology was suggestive of a malignancy. The histopathology and immunohistochemistry confirmed that as a non-Hodgkin's lymphoma. Subsequent bone marrow biopsy did not reveal any abnormalities.

A week after the biopsy of the lymph node, blisters started to appear on both palms and oral ulcers soon followed. Genital ulceration and redness of eyes appeared subsequently.

Her family history revealed a tendency towards developing malignancies in the family as both father

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Received 14 September 2004; revised 9 January 2005; accepted 11 January 2005

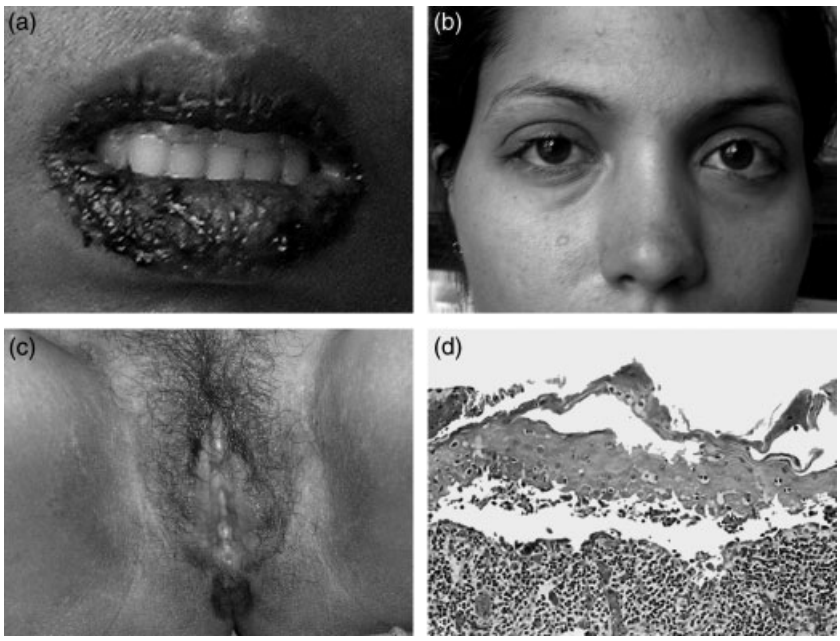

Figure 1 (**a**) Severe oral ulceration. (**b**) Redness of eyes. (**c**) Mild genital ulceration. (**d**) Intraepithelial blistering and necrosis of keratinocytes, H&E, 100×

and one brother have died from carcinoma and leukaemia respectively.

At the time of presentation to the skin clinic the patient had extensive and painful oral ulceration with crusting and spots of bleeding (Figure 1a), redness of eyes (Figure 1b) and mild genital ulceration (Figure 1c). The oral ulcers were mainly on lips with mild ulceration of buccal mucosae. Conjunctival ulceration was evident after a period of redness of eyes. However the severity of ulcers was much less than the oral ulcers. An incisional biopsy was performed for histology and direct immunofluorescence (DIF). The histopathology revealed intraepithelial blistering with mild degree of acantholysis and necrosis of keratinocytes (Figure 1d). There was a prominent mostly lymphocytic infiltrate beneath the epithelium showing features of interface dermatitis (Figure 1d). DIF revealed weak to moderate intercellular positivity of IgG mainly in the lower part of the epithelium (Figure 2). IgA, IgM and C_3 were negative. The diagnosis of PNP was confirmed with the help of clinical features, histopathological features and the findings of DIF.

She was on a regimen of chemotherapy for lymphoma and the patient was prescribed oral prednisolone and steroid ophthalmic suspension. However the patient showed no significant improvement.

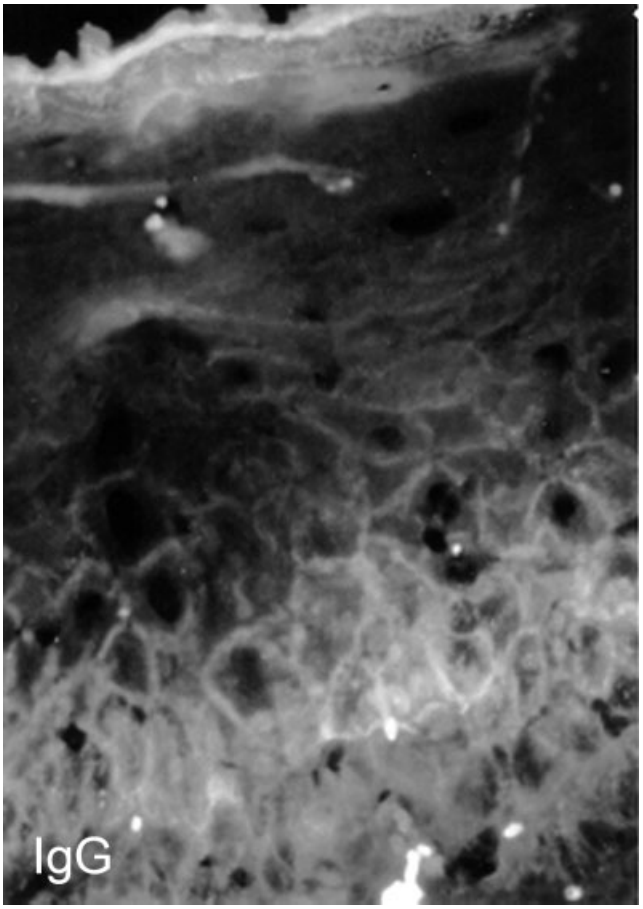

Figure 2 Moderate positivity of immunoglobulin G in intercellular areas

Discussion

Although there had been case reports of unusual pemphigus in the literature, the term PNP was proposed with sound criteria for diagnosis only in 1990 by Anhalt *et al* (Anhalt *et al*, 1990; Hashimoto, 2001). The disease is of paramount importance to Dental clinicians as oral ulceration is the most consistent feature of the disease.

The age range of affected individuals may vary from 7 to 77 years (Anhalt, 1997; Robinson *et al*, 1999). Most patients exhibit very severe and painful oral ulceration. Although some patients may not develop, conjunctival ulceration appears to be a frequent feature. The oral

ulcers mimic the appearance of either severe form of erythema multiforme or severe forms of other types of drug eruptions. Genital ulceration is also a common feature. The involvement of skin in PNP shows variable appearances such as target lesions of erythema multiforme, blisters mimicking bullous pemphigoid or lichen planus like lesions (Joly *et al*, 2000).

The association of an underlying malignancy demands the necessity of correct diagnosis of PNP even quicker, as the existence of a neoplasm is recognized prior to the eruption of lesions only in about two-thirds of the cases (Kimyai-Asai and Jih, 2001).

Out of all the reported cases of PNP, haematologically related malignancies and disorders account for 84% and the commonest malignancy appears to be non-Hodgkin's lymphoma (38%) (Kaplan *et al*, 2004). Chronic lymphocytic leukaemia (18%), Castleman disease (18%), thymoma (5.5%), Waldenstrom's macrogloulinaemia (1.2%) and Hodgkin's lymphoma (0.6%) are the other reported haematologial disorders (Norris *et al*, 1993; Dega *et al*, 1998; Lee *et al*, 1999). It is obvious that PNP can also be associated with non-haematological malignances (16%) such as carcinomas including squamous cell carcinoma of the oral cavity, sarcomas and melanomas (Kaplan *et al*, 2004).

It has been shown that proteins of plakin family and desmogleins play an important role in the pathogenesis of PNP. Truncated recombinant glutathione-S-transferase fusion proteins of envoplakin and periplakin which presented various N- terminal and C-terminal domains have shown to be very strongly reactive with sera from patients with PNP. Further it has been showed that all the PNP antigens identified up to date belong to the plakin family (Hashimoto, 2001). Because of the fact that plakins have cytoplasmic location, they are not directly accessible to autoantibodies in intact cells. Therefore it is believed that the autoantibodies directed towards desmogleins (1 and 3) start the damage of cell membrane exposing the plakins. Flare-up of PNP has been reported to occur with medications to underlying malignancy such as fludarabide and interferon alpha (Bazarbachi *et al*, 1995).

The diagnostic criteria for PNP has been proposed with the introduction of the disease by Anhalt *et al* (1990). They include mucocutaneous blistering and ulcerations, histopathological features such as acantholytic changes of the epithelium and epidermis with interface dermatitis, deposition of IgG and C_3 in intercellular areas and/or along the basement membrane, presence of serum antibodies and finally demonstration of various desmoplkins and desmogleins in the serum. The histopathology is different from that of conventional pemphigus by the presence of keratinocyte necrosis, less pronounced acantholytic changes and a marked interface dermatitis like cell infiltrate. Direct immunofluorence (DIF) usually shows weak or moderate positivity in the intercellular area for IgG and C_3. Some cases may show granular or linear deposits of the same at the basement membrane. One important factor which needs to be stressed is the fact that if PNP is strongly suspected clinically, negative histology and DIF does not completely rule out the possibility of the disease. The present case also did not show C_3 positivity although it is usually positive.

Although the treatment of choice for PNP is oral prednisolone, it is frequent to use adjuvant treatment including cyclophosphomide, azathiaprine, cyclosporine A, gold, dapsone, plasmapheresis, photopheresis and various combinations of the above. However it is not unusual to find that majority of patients become refractory to treatment. Recently, the use of monoclonal antibodies such as anti-CD 20 antibody has also been reported to be of help in order to treat cases with the disease (Schadlow *et al*, 2003). The prognosis of PNP with malignant tumours is generally poor and 90% die within 2 years (Mimouni *et al*, 2002) and the mean survival for majority of the patients is 3 months after the diagnosis (Helm *et al*, 1993).

In summary, the possibility of PNP should be borne in mind when a patient presents with extensive oral ulceration if clinical, histopathological and the results of DIF are not pathognomonic for a specific diagnosis. The issue becomes even more important as some patients with PNP have no diagnosed malignancy at the time of presentation.

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