Cutaneous signs of malignant disease

Cutaneous manifestations of underlying malignancies are uncommon but easy to recognise when the physician is aware of them. Recognition means that the possibility of underlying malignancy can be considered and, where appropriate, investigated and treated.

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The following seven conditions have been selected to illustrate the wide range of pathological skin conditions that can be associated with malignant disease:

- dermatomyositis – an interface dermatitis
- Sweet's syndrome and pyoderma gangrenosum – neutrophilic dermatoses
- amyloidosis – a deposition disorder
- acanthosis nigricans – an epidermal proliferative disorder
- pemphigus and pemphigoid – autoimmune blistering disorders.

The common presentations and classic features of these conditions are discussed in this article and summarised in the Table. Further information can be obtained from the review article by Chung and colleagues.[1]

Dermatomyositis

Dermatomyositis is an interface dermatitis. Interface dermatoses, which are also known as lichenoid dematoses, are characterised by cutaneous inflammation with an obscured dermoepidermal junction.

Dermatomyositis is an inflammatory myopathy that is associated with an increased risk of malignancy.[2] The presence of four of the following criteria is consistent with a diagnosis of dermatomyositis or polymyositis, while three criteria suggest a probable diagnosis:[3,4]

- typical cutaneous changes of dermatomyositis
- progressive, symmetrical, proximal muscle weakness
- abnormal findings on muscle biopsy
- elevated muscle enzyme levels
- abnormal electromyogram.

Skin lesions

Gottron's papules, which are erythematous papules over the extensor surfaces of the metacarpophalangeal and interphalangeal joints, are pathognomonic for dermatomyositis (Figure 1). They may also be found on the elbows, knees and feet. Other characteristic skin lesions include

IN SUMMARY

- **Paraneoplastic dermatoses may present in various forms and are associated with underlying malignancy.**
- **Although uncommon, these cutaneous conditions can be easily recognised once the physician is aware of them.**
- **Their recognition should prompt a thorough investigation for the presence of an underlying malignancy.**
- **Recognition of these cutaneous conditions may enable early diagnosis and treatment of malignancy.**

Table. Skin features of paraneoplastic conditions

Condition	Common skin manifestations	Classic skin features
Dermatomyositis	Heliotrope discolouration around eyes	Gottron's papules
Sweet's syndrome	Erythematous plaques	Painful, well-demarcated plaques
Pyoderma gangrenosum	Unexplained nonhealing ulcer	Necrotic ulcer with violaceous border
Amyloidosis	Purpura and petechiae on skin	Smooth, waxy papules on the face
Acanthosis nigricans	Hyperpigmented papules	Velvety plaques in neck and skin folds
Paraneoplastic pemphigus	Flaccid blisters on skin	Painful blisters on mucous membranes
Paraneoplastic pemphigoid	Tense bullae on axillae, thighs and groin	Figurate erythema

lilac (heliotrope) discolouration around the eyelids (Figure 2) and periungual telangiectasia. Patients may also present with diffuse erythema and oedema of the eyelids and periorbital tissue. Hyperkeratotic papules with mucin deposits are often found on biopsy.

Associated systemic disease

Patients with dermatomyositis have an increased risk of developing a carcinoma. In older patients the risk of a carcinoma is higher in those who have dermatomyositis than in those who have polymyositis.[5] One population-based study reported a three-fold increase in the risk of malignant disease after a diagnosis of dermatomyositis had been made, with ovarian, lung, gastric, colorectal and pancreatic cancers having the strongest association with the condition, along with non-Hodgkin's lymphoma.[6] It has been difficult to define precisely the increased risk of cancer in adults with dermatomyositis due to marked differences between reports; however, a risk of 7.7 has been estimated relative to the general population in one study.[7] Malignancy associated with childhood dermatomyositis is relatively rare.

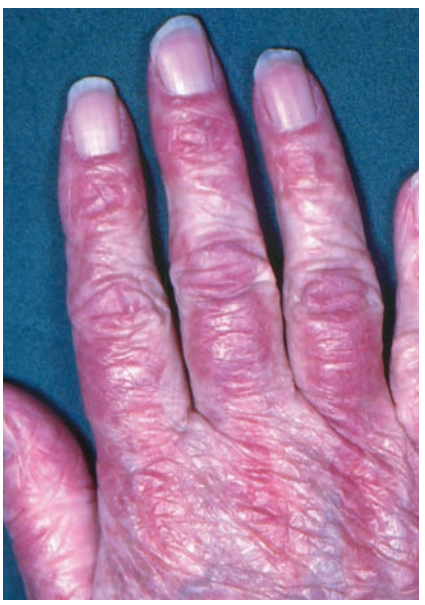

Figure 1. Gottron's papules characteristic of dermatomyositis.

Once a diagnosis of dermatomyositis has been made, clinical assessment should include investigations for any underlying malignancy. A prostate-specific antigen test is recommended for men, and a gynaecological examination, Pap smear and mammography are recommended for women. Other investigations, such as a chest x-ray or endoscopy, should be guided by the patient's medical history and examination findings.

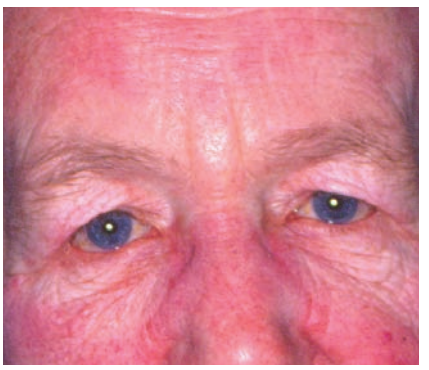

Figure 2. Heliotrope changes around the eyelids in dermatomyositis.

Treatment

As with any paraneoplastic disease, it is essential to identify the carcinoma and remove it. This may result in remission of the dermatomyositis. High doses of oral corticosteroids (e.g. prednisone 1 mg/kg/day) are the mainstay of treatment and the dose should be slowly tapered to reduce the risk of relapse. An oral corticosteroid-sparing agent such as azathioprine, methotrexate (Methoblastin), cyclophosphamide (Cycloblastin) or cyclosporin (Cicloral Neoral, Sand - immun) may also be introduced.

Sweet's syndrome

Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, is a disease characterised by painful, well-demarcated plaques on the skin. Fever, arthralgia, malaise and leukocytosis accompany these skin lesions. Sweet's syndrome is often mistaken for a cutaneous infection.

Diagnosis is based on the presence of two major and two out of five minor

criteria.[8,9] The major criteria are:

- an abrupt onset of tender erythematous plaques or nodules
- a predominant neutrophilic infiltration in the dermis without leukocytoclastic vasculitis.

The minor criteria are:

- preceded by fever or infections
- accompanied by fever, arthralgia or underlying malignancy
- leukocytosis greater than 10,000/mm^3
- an erythrocyte sedimentation rate (ESR) greater than 50 mm/hour
- a good response to systemic steroids and not to antibiotics.

Skin lesions

The skin lesions appear rapidly and are tender, often pustular, erythematous plaques or nodules that commonly occur over the face, neck, arms, hands and legs (Figure 3). Central clearing can give the plaques a target-like appearance. The whole plaque heals without scarring. There are no signs of vasculitis, such as infiltration and vessel wall destruction by inflammatory cells. Some lesions can develop at a site of minor trauma (pathergy).

Associated systemic disease

Sweet's syndrome is associated with a haematological malignancy in 20% of cases, with acute myelogenous leukaemia being the most common type noted.[10] Associated lymphomas, other myeloproliferative and myelodysplastic disorders, and carcinomas (usually genitourinary) have also been reported.[11]

Lung, kidney and liver infiltrates may be present. Lung infiltrate may be seen on chest x-ray and a lung biopsy will demonstrate extensive neutrophilic infiltrate. Proteinuria is the most common renal abnormality but patients may also present with, or develop, haematuria and mesangiocapillary glomerulonephritis. Liver involvement can be confirmed by biopsy, which shows infiltration of the portal triad and ducts.

A chest x-ray, bone marrow aspiration if the full blood count is abnormal, and investigations such endoscopy may be indicated during clinical assessment. A skin biopsy should be taken, which typically shows neutrophilic infiltrate and papillary dermal oedema.

Treatment

Oral corticosteroids are very effective at treating this condition. Oral anti-inflammatory drugs such as indomethacin (Arthrexin, Indocid) and colchicine (Colgout, Lengout), or oral corticosteroid-sparing agents such as dapsone and cyclosporin, are also useful.

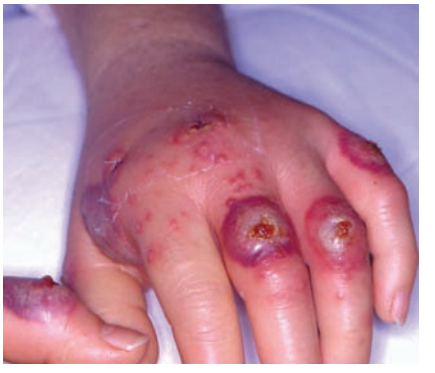

Figure 3. Ulceration on the hands of a patient with Sweet's syndrome.

Pyoderma gangrenosum

Pyoderma gangrenosum is an uncommon, severe, ulcerative condition of uncertain aetiology (Figure 4). It shares some features with Sweet's syndrome in that it is an inflammatory neutrophilic dermatitis that is not due to infectious causes and is associated with myeloproliferative disease. Up to 50% of cases are idiopathic; the remainder are associated with systemic diseases, most often inflammatory bowel disease (Crohn's disease, ulcerative colitis), rheumatoid arthritis, and myeloproliferative disorders.[12] Pyoderma gangrenosum may occur at any age, but predominates in the fourth and fifth decades of life.

Skin lesions

The skin lesions begin as a pustule with an erythematous halo, which often affects the lower legs (Figure 5). It is usually a single lesion, but multiple small lesions may coalesce and ulcerate. The ulcer base is necrotic with a haemorrhagic exudate, a violaceous border and an undermined edge. The ulcers may become very large before they heal into thin, atrophic scars. A superficial variant exists that affects either the dorsum of the hands, the extensor surface of the forearms or the face. Lesions may also occur after minimal trauma,

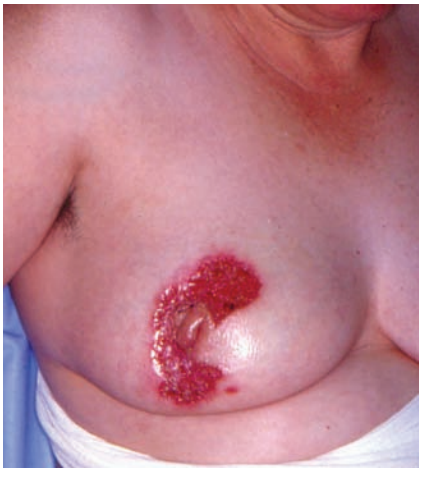

Figure 4. Pyoderma gangrenosum resulting in ulceration of the breast.

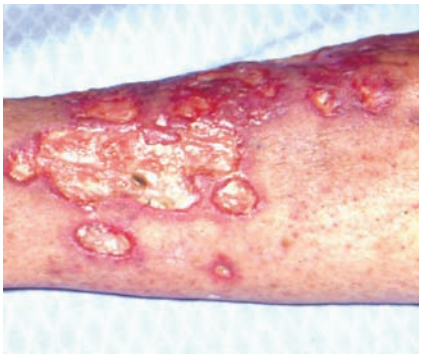

Figure 5. Erythematous halo in pyoderma gangrenosum of the leg.

such as a bone marrow aspiration, which can account for up to 30% of cases.

Associated systemic disease

Inflammatory bowel disease and polyarthritis are often associated with pyoderma gangrenosum. Malignant associations include leukaemia, predominantly myelocytic leukaemia, monoclonal gammopathy (usually the immunoglobulin A type) and multiple myeloma.[13]

Treatment

It is important to treat the underlying cause, if found, especially if it is inflammatory bowel disease as this tends to improve the skin lesions. Topical therapies include wound dressings, corticosteroid preparations and tacrolimus ointment (Prograf). Oral anti-inflammatory antibiotics such as dapsone and minocycline (Akamin, Minomycin) should be sufficient to treat small ulcers. Larger ulcers may require immunosuppressive therapies, including oral corticosteroids, cyclosporin, and tumour necrosis factor alpha inhibitors such as etanercept (Enbrel), given subcutaneously, or infliximab (Remicade), given intravenously.

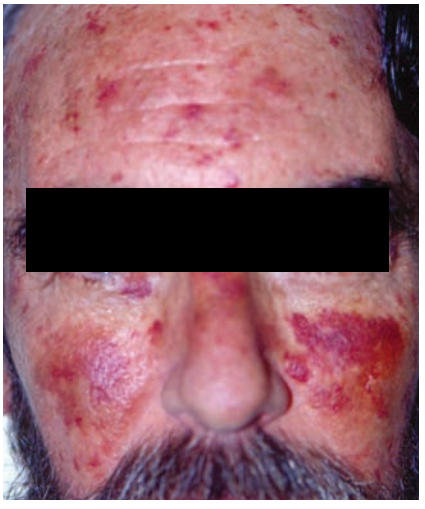

Figure 6. Waxy papules characteristic of amyloid deposition on the face.

Amyloidosis

Amyloidosis comprises a group of diseases that are characterised by an increased deposition of amyloid fibrils in tissues. Amyloidosis may result in macroglossia and 'baggy' fingers. The clinical presentation and type of amyloid fibril deposition can be used to differentiate amyloidosis types. Primary amyloidosis is associated with haematological malignancies, whereas secondary amyloidosis is not.[14] Primary systemic amyloidosis involves the deposition of insoluble monoclonal light chains or light chain fragments into various tissues, including smooth and striated muscle, connective tissue, blood vessels and peripheral nerves. It is a plasma cell dyscrasia that usually affects elderly adults.

Skin lesions

Skin lesions are seen in about 30% of cases of primary amyloidosis. Petechiae, purpura or ecchymoses may occur spontaneously or following minor trauma. Lesions are characteristically smooth, waxy papules or nodules on the face, especially around the eyes and on the tongue (Figures 6 and 7). They may also occur on the extremities, axilla and umbilicus, and in body folds such as the perianal region.

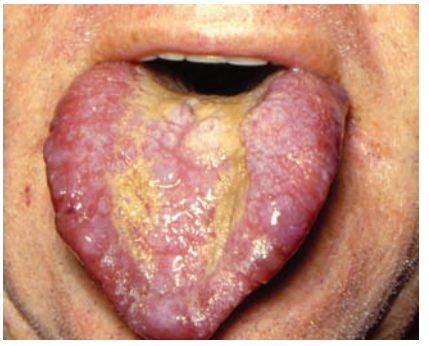

Figure 7. Amyloidosis of the tongue.

Associated systemic disease

Primary systemic amyloidosis is usually associated with multiple myeloma and monoclonal gammopathy of unknown significance. It is estimated that between 13 and 16% of patients with primary amyloidosis will also have multiple myeloma.[15]

Treatment

Treatment is directed towards the affected organ. Diuretics may be used for heart failure, and dialysis commenced for renal failure. Kidney transplantation is also a consideration, but amyloid may reaccumulate in the transplanted kidney. Bone marrow ablation and transplantation can be considered for patients with multiple myeloma.

Intermittent oral therapy with prednisone and melphalan (Alkeran) may be used to treat the skin lesions. Topical and intralesional corticosteroids may provide some relief.

Acanthosis nigricans

Acanthosis nigricans is a condition in which symmetrical, pigmented, warty skin lesions manifest in the axillae, pubic, neck and umbilical regions. Hyperpigmentation gives the skin a dirty appearance. There are two types of acanthosis nigricans: benign and malignant. Benign acanthosis nigricans is associated with obesity and commonly occurs in patients who have diabetes mellitus or another endocrine disorder. Insulin resistance is a frequently associated feature. Malignant acanthosis nigricans is more common in older, nonobese patients, whereas the benign form occurs more often in darker skinned people.

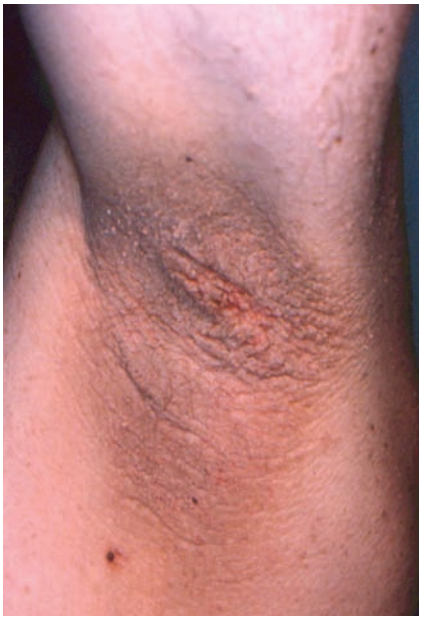

Figure 8. Acanthosis nigricans in the axilla.

Skin lesions

The lesions begin as hyperpigmented papules that develop into velvety plaques located on the neck or axillae or in other body folds (Figure 8). The lesions develop abruptly in the malignant form. Eruptive seborrhoeic dermatoses may also be associated with acanthosis nigricans.

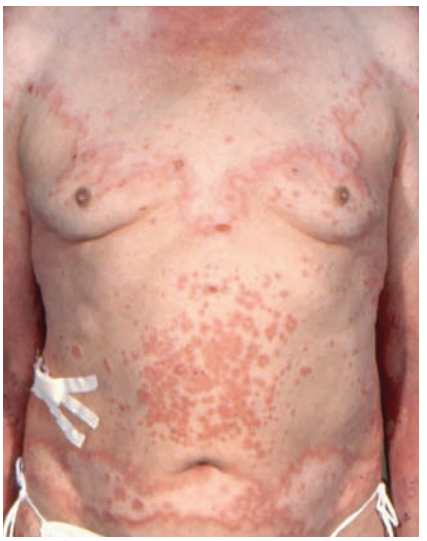

Figure 10. Figurate erythema of the lower abdomen in paraneoplastic pemphigoid.

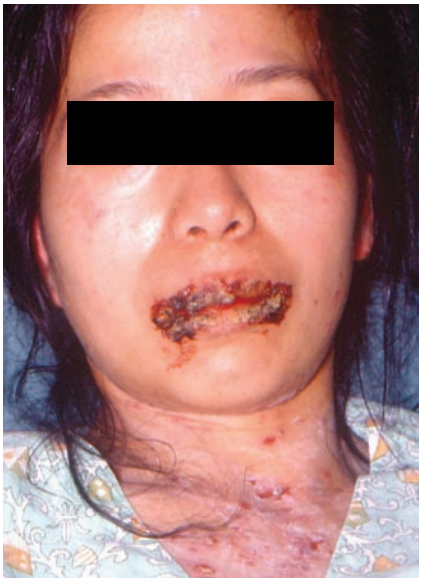

Figure 9. Mucosal ulceration in paraneoplastic pemphigus.

Associated systemic disease

Malignant acanthosis nigricans is mainly associated with gastrointestinal carcinomas, particularly gastric ones. There is also a reported association with oral cancers (especially of the lip and tongue), bronchogenic carcinomas and lymphomas.[16]

Treatment

Patients with acanthosis nigricans may be treated with topical keratolytics for cosmesis. Regression of acanthosis nigricans parallels that of the tumour in the malignant form.

Paraneoplastic pemphigus

Paranoeoplastic pemphigus is an auto - immune blistering disease of skin and mucous membranes with specific immunoglobulin G antibodies directed against the intercellular surfaces of the keratinocytes.

Skin and mucosal lesions

Patients commonly present with stomatitis due to blistering in the mouth (Figure 9). The primary skin lesion is a flaccid blister, which usually appears on normal skin but it may develop on erythematous skin. Patients may have a widespread lichenoid eruption with intermittent blister formation. The lichenoid reaction can resemble a drug eruption or even erythema multiforme.

Associated systemic disease

Paranoeoplastic pemphigus is associated with lymphoma and thymoma. A few reported cases have also linked the condition with carcinomas.[17,18]

Treatment

Treating paranoeoplastic pemphigus is difficult but should aim to decrease blister formation and prevent infection. Oral corticosteroids (e.g. prednisolone) are often used to treat the skin disease but immunosuppressants such as oral azathioprine are useful corticosteroid-sparing agents. The novel approach of treating a patient with paraneoplastic pemphigus with rituximab (Mabthera) for follicular B-cell lymphoma has also been reported.[19]

Paraneoplastic pemphigoid

Bullous pemphigoid is a chronic, autoimmune, subepidermal blistering disease that, unlike pemphigus, rarely involves mucous membranes. It is estimated that up to 18% of patients with pemphigoid have malignant disease, classically those with figurate erythema.[20]

Skin lesions

Patients most often present with tense bullae, usually on the axillae, thighs, groin and abdomen, but sometimes the forearms and legs can be involved. There is a characteristic figurate erythema accompanying the blisters (Figure 10). Oral lesions are unusual, but when present they are less painful than in pemphigus.

Associated systemic disease

Paraneoplastic pemphigoid has been associated with carcinomas of the lung, stomach and colon.[21-23]

Treatment

If the associated carcinoma is removed, then the pemphigoid may remit. Predni - solone can be given alone or in combination with azathioprine. Local recurrence can be treated with topical corticosteroids.

Summary

Paraneoplastic dermatoses may present in various forms. These skin conditions are associated with underlying malignant diseases, and their diagnosis in patients should prompt a thorough investigation for the presence of malignancy. Recognition of these cutaneous conditions may enable early diagnosis and treatment of malignancy.

Further research may clarify the strength of the association between the cutaneous disorders and the malignancy, as well as the pathogenesis of the skin manifestations. More studies are needed to ascertain the benefits and potential dangers of novel therapies, such as monoclonal antibodies, for these skin conditions. MT

References

1. Chung V, Moschella S, Zembowicw A, et al. Clinical and pathologic findings of paraneoplastic dermatoses. J Am Acad Dermatol 2006; 54: 745-762.
2. Boyce S, Harper J. Paraneoplastic dermatoses. Dermatol Clin 2002; 20: 523-532.
3. Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med 1975; 292: 344-347.
4. Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med 1975; 292: 403-407.
5. Marie I, Hatron PY, Levesque H, et al. Influence of age on characteristics of polymyositis and dermatomyositis in adults. Medicine 1999; 78: 139-147.
6. Hill C, Zhang Y, Sigurgeirsson E, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet 2001; 357: 96-100.
7. Stockton D, Doherty VR, Brewster DH. Risk of cancer in patients with dermatomyositis or poly - myositis, and follow-up implications: a Scottish population-based cohort study. Br J Cancer 2001; 85: 41-45.
8. Su WP, Liu HN. Diagnostic criteria for Sweet's syndrome. Cutis 1986; 37: 167-174.
9. von den Driesch P, Gomez RS, Kiesewetter F, Hornstein OP. Sweet's syndrome: clinical spectrum and associated conditions. Cutis 1989; 44: 193-200.
10. Fitzgerald RL, McBurney EI, Nesbitt LT Jr. Sweet's syndrome. Int J Dermatol 1996; 35: 9-15.
11. Cohen PR, Talpaz M, Kurzrock R. Malignancy-associated Sweet's syndrome: review of the world literature. J Clin Oncol 1988; 6: 1887-1897.
12. Callen JP. Pyoderma gangrenosum. Lancet 1998; 351: 581-585.
13. Bennett ML, Jackson JM, Jorizzo JL, Fleishcer AB Jr, White WL, Callen JP. Pyoderma gangrenosum. A comparison of typical and atypical forms with an emphasis on time to remission. Case review of 86 patients from 2 institutions. Medicine 2000; 79: 37-46.
14. Breathnach SM. Amyloid and amyloidosis. J Am Acad Dermatol 1988; 18: 1-16.
15. Kurzrock R, Cohen PR. Mucocutaneous paraneoplastic manifestations of hematologic malignancies. Am J Med 1995; 99: 207-216.
16. Yeh JS, Munn SE, Plunkett TA, Harper PG, Hopster DJ, du Vivier AW. Coexistence of acanthosis nigricans and the sign of Leser-Trélat in a patient with gastric adenocarcinoma: a case report and literature review. J Am Acad Dermatol 2000; 42: 357-362.
17. Robinson ND, Hashimoto T, Amagai M, Chan LS. The new pemphigus variants. J Am Acad Dermatol 1999; 40: 649-671.
18. Anhalt GJ. Paraneoplastic pemphigus. Adv Dermatol 1997; 12: 77-96.
19. Borradori L, Lombardi T, Samson J, Girardet C, Suarat JH, Hügli A. Anti-CD20 monoclonal antibody (rituximab) for refractory erosive stomatitis secondary to CD20+ follicular lymphoma-associated paraneoplastic pemphigus. Arch Dermatol 2001; 137: 269-272.
20. Hadi SM, Barnetson RS, Gawkrodger DJ, Saxena U, Bird P, Merrett TG. Clinical, histological and immunological studies in 50 Patients with bullous pemphigoid. Dermatologica 1988; 176: 6-17.
21. Graham-Brown RA. Bullous pemphigoid with figurate erythema associated with carcinoma of the bronchus. Br J Dermatol 1987; 117: 385-388.
22. Muramatsu T, Iida T, Tada H, et al. Bullous pemphigoid associated with internal malignancies: identification of 180-kDa antigen by Western immunoblotting. Br J Dermatol 1996; 135: 782-784.
23. Gilmour E, Bhushan M, Griffiths CE. Figurate erythema with bullous pemphigoid: a true paraneoplastic phenomenon? Clin Exp Dermatol 1999; 24: 446-448.

DECLARATION OF INTEREST: Dr Liu: None. Professor Barneston is a medical advisor to Schering-Plough and Stiefel Laboratories.