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Skin manifestations of systemic disease

Background
Dermatologic complaints are a common reason for presentation to a general practitioner. In some cases, one needs to determine if the complaint may be a manifestation of a more serious underlying systemic disease.

Objective
This article aims to highlight common dermatologic presentations where further assessment is needed to exclude an underlying systemic disease, to discuss classic cutaneous features of specific systemic diseases, and to outline rare cutaneous paraneoplastic syndromes.

Discussion
Skin manifestations of systemic disease are wide, varied, specific and nonspecific. Generalised pruritus and cutaneous vasculitis are more common cutaneous presentations where an underlying systemic disease may be present and will influence management. In certain chronic diseases such as connective tissue disease and chronic liver disease, there are characteristic cutaneous findings. Internal malignancies such as multiple myeloma may present with distinctive cutaneous findings, which need to be recognised to institute a search for the underlying neoplasm. The skin has the potential to provide a window into the patient and aid in the diagnosis of diseases of all organ systems.

Dermatologic complaints are a common reason for presentation to a general practitioner. In such cases, one needs to determine if the complaint may be a manifestation of a more serious underlying systemic disease. Disorders of the every organ system may cause skin symptoms and signs, some of which are due to treatment of these conditions. It is beyond the scope of this review to cover all potential skin manifestations of systemic disease. This article highlights the more common, classic and important manifestations in three different groups:

- **'When to look further' – where dermatologic presentations require further assessment to exclude underlying systemic disease, and guide appropriate management**
- **'What to look for' – where certain systemic diseases have classic cutaneous findings**
- **'What not to miss' – where specific cutaneous signs might be the initial presentation of an underlying malignancy.**

When to look further

Generalised pruritus

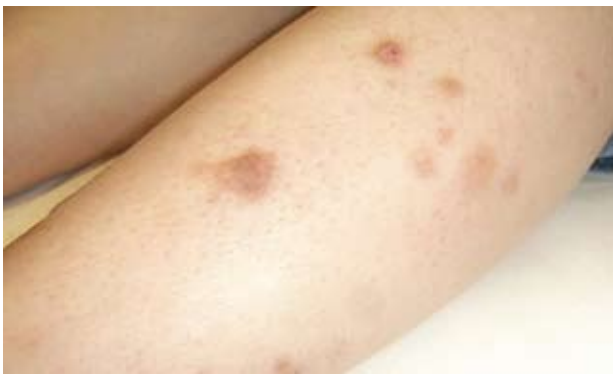
Pruritus or itch is a common complaint of dermatologic disease. Generalised pruritus in the absence of a rash requires investigation and exclusion of an underlying systemic disorder (*Table 1*).[1,2] Many patients will develop excoriations, and with time some may develop prurigo nodules and it is important to distinguish these from an underlying primary skin disease such as scabies or eczema (*Figure 1*).

In some patients, addressing xerosis (dry skin) with simple measures including soap substitutes and emollients will reduce the itch. In others, it is clear that the pruritus developed in a temporal relationship to the commencement of a new medication, and cessation or substitution will result in resolution of the symptom. In patients where the pruritus persists, a thorough clinical history, examination and pruritus screen is necessary to exclude an underlying systemic disorder. An approach to a patient who presents with generalised pruritus is shown in *Figure 2*. Management is targeted at

Table 1. Causes of generalised pruritus[1,2]

Causes of pruritus	
Haematologic disorders	Iron deficiency anaemia Myeloproliferative disorders including polycythaemia, leukaemia Monoclonal gammopathy and multiple myeloma Lymphoma
Renal disorders	Uraemia due to any cause
Liver disorder	Cholestasis due to any cause
Endocrine disorders	Either hyperthyroidism or hypothyroidism

Figure 1. Excoriations and prurigo nodules may be seen in a patient with pruritus in the absence of primary skin pathology



the underlying systemic disorder if found. Other therapeutic options reported to be of benefit include antihistamines, doxepin, selective serotonin reuptake inhibitors and mirtazepine.[1,2]

Practice tips

- Generalised pruritus in the absence of rash and dry skin may have an underlying systemic cause
- Treatment of the cause is necessary, in addition to symptomatic measures.

Erythema nodosum

Erythema nodosum is an acute, reactive inflammation of the subcutis, or panniculitis. This most commonly affects young women, presenting as symmetric tender, hot erythematous nodules over the extensor legs (*Figure 3*). Patients may also complain of fever, arthralgias and malaise. Most cases follow a self limiting course.

When a patient presents with erythema nodosum, there are a number of investigations which should be performed to look for an associated cause (*Table 2*). In some cases there is no underlying cause found. Atypical cases in which:

- the process does not resolve
- the lesions ulcerate, cause atrophy or scarring, or
- extend beyond extensor surfaces of the legs

require further investigation including biopsy of the skin to look for other

Figure 2. An approach to a patient with generalised pruritus[1,2]

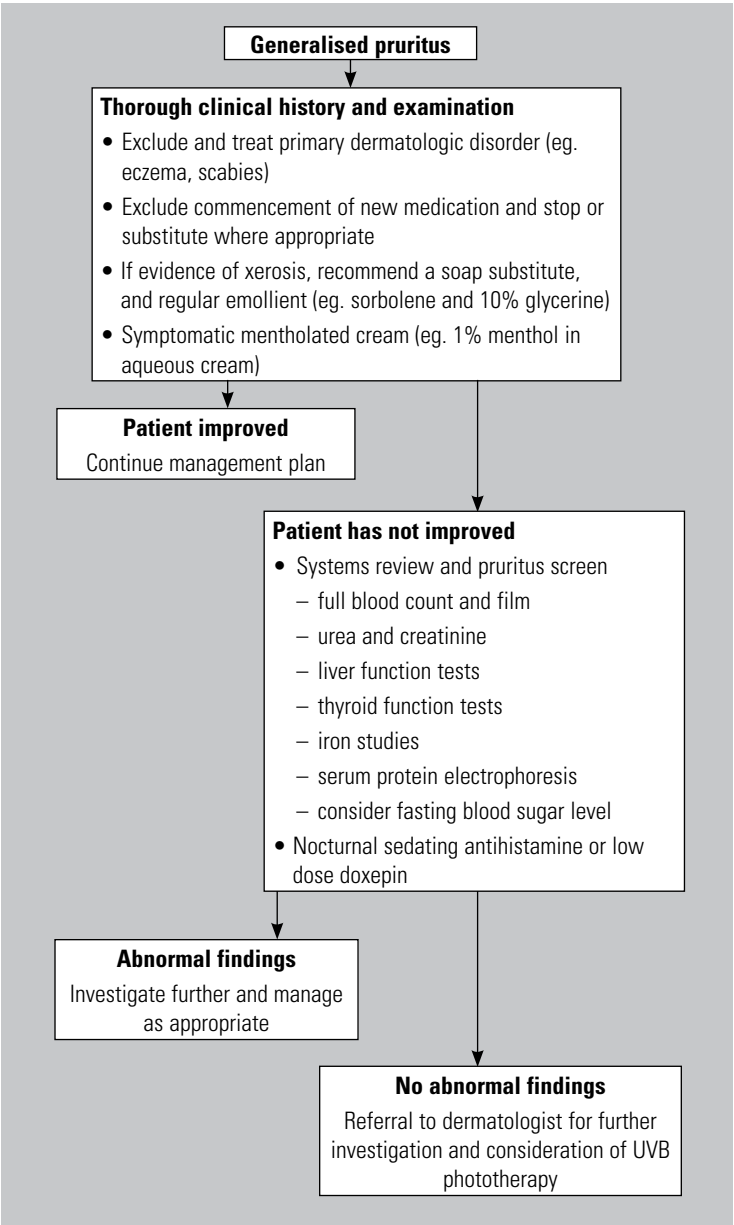


Figure 3. Tender erythematous nodules over the extensor legs in erythema nodosum

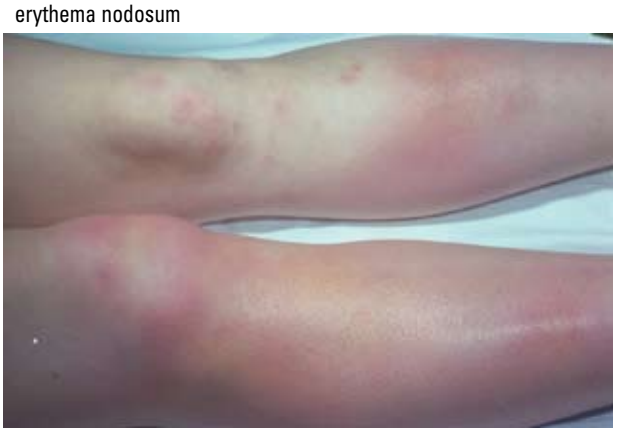
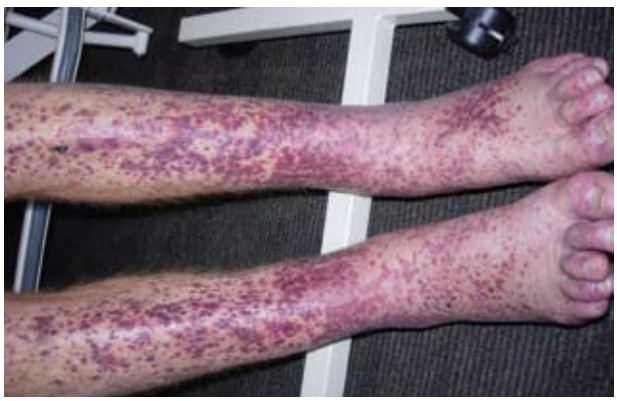


Table 2. Causes and investigation of erythema nodosum[3]

Causes of erythema nodosum	Approach and investigations
Infections • Bacterial, eg. Streptococcus, Yersinia, Salmonella, Campylobacter • Viral, eg. Epstein Barr virus • Mycobacterial	 • Throat swab, anti streptolysin O titre (ASOT), anti-double stranded DNA antibodies • Serology and stool cultures where appropriate • Serology where appropriate • Investigate if clinical suspicion – chest X-ray, Mantoux, Quantiferon gold
Sarcoidosis	Chest X-ray, serum angiotensin converting enzyme inhibitor (ACEI), calcium and referral if abnormal
Inflammatory bowel disease	History and examination
Malignancy Leukaemia, lymphoma (rare) Postradiotherapy	Full blood count and film
Pregnancy	History, ßHCG level
Behcet syndrome	History of oral and genital aphthous ulcers and examination
Drugs	Recent commencement in particular oral contraceptive pill, tetracycline antibiotics, sulphur based drugs, bromides and iodides

Figure 4. Multiple palpable purpuric papules and plaques – a case of a florid small vessel cutaneous vasculitis



causes of panniculitis. These cases should be referred for specialist assessment.

Management is supportive, including bed rest, the use of support stockings, and nonsteroidal anti-inflammatory drugs. In more severe cases, systemic corticosteroids may be needed.[3]

Practice tips

- In all cases, consider and exclude an underlying systemic disorder, in particular sarcoidosis
- Atypical clinical presentations require a skin biopsy to look for other causes of panniculitis
- Treatment is both supportive and aimed at the underlying disorder.

Cutaneous vasculitis

Vasculitis refers to an inflammation of the blood vessels, which can affect small, medium or large vessels. Both small and medium vessel vasculitis may present with cutaneous findings. In any patient who presents with a cutaneous vasculitis, it is important to look for any evidence of systemic vasculitis, which has more serious implications.

Table 3. Causes of cutaneous vasculitis[5,6]

Infections	
Bacterial	• Streptococcal, meningococcal, urinary tract infections
Viral	• Hepatitis B and C, HIV
Mycobacterial	• Tuberculosis
Connective tissue disorders	• SLE and related conditions • Rheumatoid arthritis • Systemic sclerosis, Sjogren syndrome • Dermatomyositis • Medium vessel vasculitides (Wegener granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome)
Malignancy	• Haematologic – myeloproliferative – lymphoma – monoclonal gammopathy – multiple myeloma
Drugs	Including antibiotics, antihypertensives
Idiopathic	Henoch-Schonlein purpura

Small vessel vasculitis affects the arterioles, capillaries and venules and classically presents as palpable purpuric papules and plaques (*Figure 4*). This is the most common form of cutaneous vasculitis, typically affecting the lower legs and dependent areas. There are a large number of causes reported (*Table 3*).[4,5]

Medium vessel vasculitis is much less common and often associated with a systemic vasculitis and connective tissue disorder including systemic lupus erythematosus (SLE), Wegener granulomatosis,

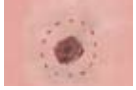
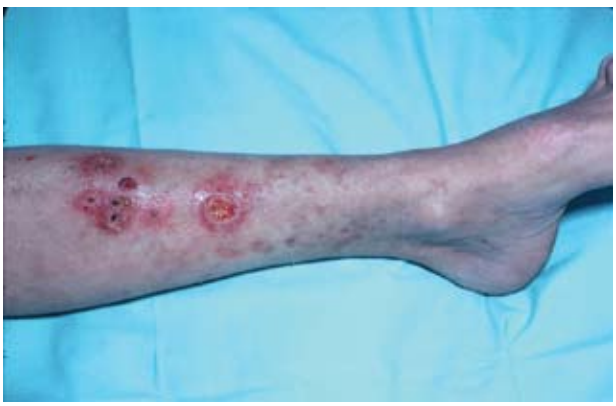


Table 4. Investigations in a patient with cutaneous vasculitis[4,5]

Vasculitis screen	
All patients	**Selected patients where appropriate**
• Full blood count and film	• Hepatitis B and C serology
• Urea, electrolytes and creatinine (UE&C)	• Serum protein electrophoresis
• Liver function tests (LFTS)	• Streptococcal serology – antistreptolsyin O titre – anti-DNAse antibodies
• Anti nuclear antibodies (ANA)	• Throat swab – microscopy and culture
• Extractable nuclear antibodies (ENA)	• Blood cultures
• Antineutrophil cytoplasmic antibodies (ANCA)	• Midstream urine – microscopy and culture
• Rheumatoid factor (RF)	• Skin biopsy – gram stain, culture, special stains and cultures for other organisms (eg. fungal)
• Urinalysis	• HIV serology
• Urine – phase contrast microscopy (glomerular red cells)	• Other serology – cryoglobulins, serum complement levels – lupus anticoagulant anticardiolipin antibodies – faecal occult blood test (for Henoch-Schonlein purpura) – chest X-ray, Quantiferon gold, Mantoux test
• Skin biopsy – histology and consider direct immunofluorescence	

Figure 5. Features of a medium vessel vasculitis – inflammatory ulcers, ulcerated nodules and distal broken livedo



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polyarteritis nodosa and Churg-Strauss syndrome. These diseases affect both medium and small vessels. Cutaneous findings of a medium vessel vasculitis include subcutaneous nodules, livedo reticularis and ulcers (*Figure 5*).[4,5]

The most important factor in managing patients with cutaneous vasculitis is detection of systemic involvement, as this will require specialist management, and has much greater potential for morbidity. A thorough history, in particular asking about arthralgias, gastrointestinal and systemic symptoms supplemented by a full clinical examination is needed. A biopsy of lesional skin for histopathology is needed to confirm the diagnosis. *Table 4* outlines investigations needed for a patient who presents with vasculitis, both to look for the cause and any systemic involvement.

In patients with palpable purpura, a second biopsy may be taken for direct immunofluorescence if Henoch-Schonlein purpura (HSP) is suspected. The presence of IgA in the vessel wall confirms the diagnosis of HSP, which can also affect the joints, bowel and kidneys, and needs long term monitoring of renal function, as involvement may develop years after the episode of cutaneous vasculitis.[6]

A systemically unwell, septic patient should be treated as meningococcaemia until proven otherwise.

Practice tips

- If the patient is septic and unwell, exclude meningococcaemia
- It is important to look for any evidence of systemic vasculitis, in particular renal involvement
- Treatment is directed at the underlying cause.

What to look for

Chronic liver disease

Chronic liver disease is associated with a number of cutaneous manifestations. Some of these occur in any patient, while others are more specific to the nature or cause of the liver disease. Any patient with chronic liver impairment may have multiple spider naevi, palmar erythema, an acquired ichthyosis or macular purpura in association with a coagulopathy. Cholestasis may be associated with jaundice and generalised pruritus, which can result in secondary changes such as excoriations and prurigo nodules (*Figure 1*). Hepatitis C infection has been associated with a range of cutaneous manifestations (*Table 5, Figure 4, 6*).[7,8]

Connective tissue disorders

Connective tissue disorders often have classic cutaneous findings, some of which are disease specific. Recognising these signs will help to differentiate between the different diseases, although overlap between them can be seen. The different specific and nonspecific cutaneous signs are detailed in *Table 6*, and illustrated in *Figures 7–10*.[9–12]

Table 5. Reported cutaneous manifestations of hepatitis C infection[7,8]

Cutaneous vasculitis – uritcarial, leucocytoclastic, cryoglobulinaemic
Polyarteritis nodosa
Porphyria cutanea tarda
Lichen planus
Necrolytic acral erythema

Figure 6. Lichen planus – violaceous flat topped papules have been reported in hepatitis C infection

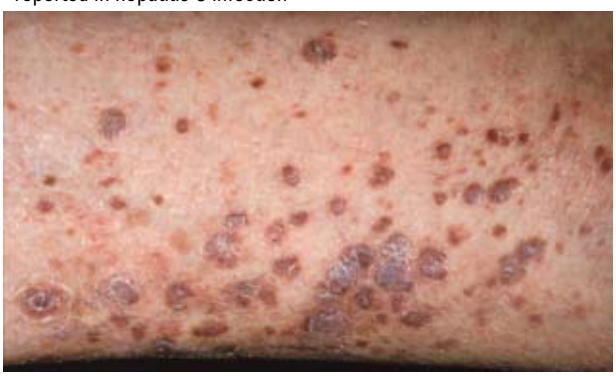

Figure 7. Malar erythema of systemic lupus erythematosus

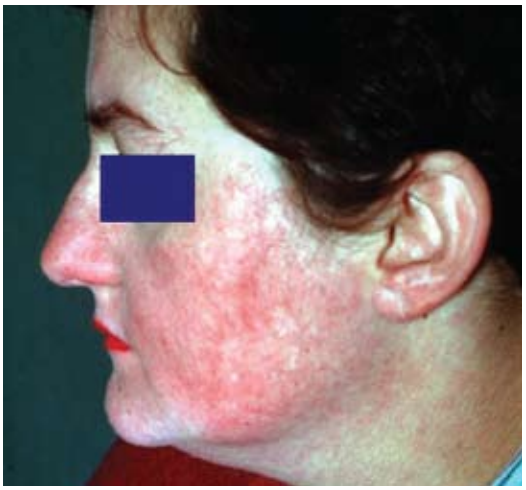

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Table 6. Classic and more common cutaneous findings in connective tissue disorders[9–12]

Connective tissue disease	Cutaneous manifestation
Lupus erythematosus	
Systemic lupus erythematosus	• Malar erythema (Figure 7), lupus hairs
Subacute cutaneous lupus erythematosus	• Annular/psoriasiform rash affecting arms and 'V' chest (Figure 8) • Well demarcated plaques with adherent scale causing a scarring or a scarring alopecia (Figure 9)
Discoid lupus erythematosus	
Dermatomyositis	• Heliotrope rash • Gottron papules and sign (violaceous macules and papules over interphalangeal and metacarpophalangeal joints) • Macular violaceous or poikilodermatous rash over shoulders and hips • Mechanics hands (hyperkeratosis on ulnar border of fingers) • Calcinosis
Systemic sclerosis, CREST syndrome (Figure 10)	• Calcinosis • Raynaud phenomenon • Sclerodactyly • Telangiectasia • Digital infarcts
Rheumatoid arthritis	• Rheumatoid nodules • Linear subcutaneous bands • Rheumatoid neutrophilic dermatitis
Other cutaneous changes of connective tissue disease	• Photosensitivity • Vasculitis and ulcers • Nail fold changes (periungual erythema, ragged cuticles, nail fold telangectasia) • Pyoderma gangrenosum

Figure 8. Psoriasiform rash of subacute cutaneous lupus erythematosus affecting the 'V' of the chest

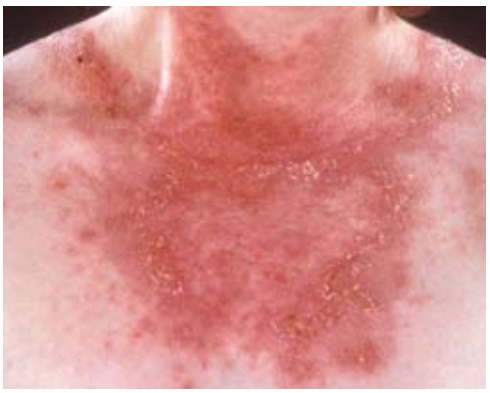


Figure 9. Scarring, hypopigmented and hyperpigmented erythematous well demarcated plaques in sun exposed areas of discoid lupus erythematosus

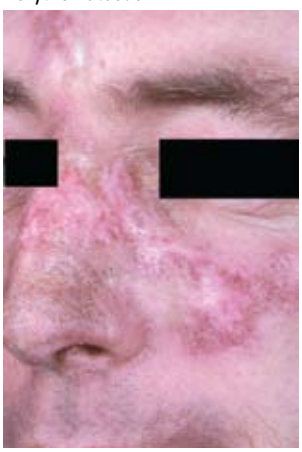


Figure 10. Cutaneous calcinosis, sclerodactyly and telangiectasia of CREST syndrome. Cutaneous calcinosis may also be seen in systemic sclerosis and dermatomyositis

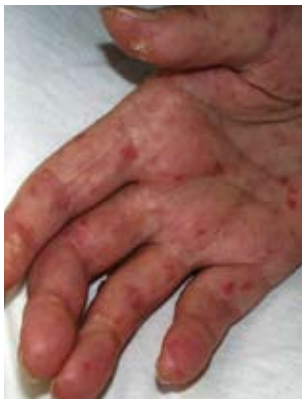


Figure 11. Marked velvety papillomatous thickening of the neck extending onto the face and lips seen in malignant acanthosis nigricans

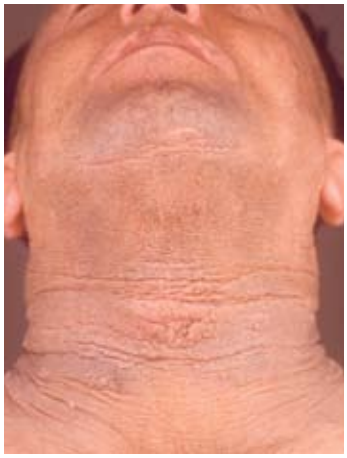
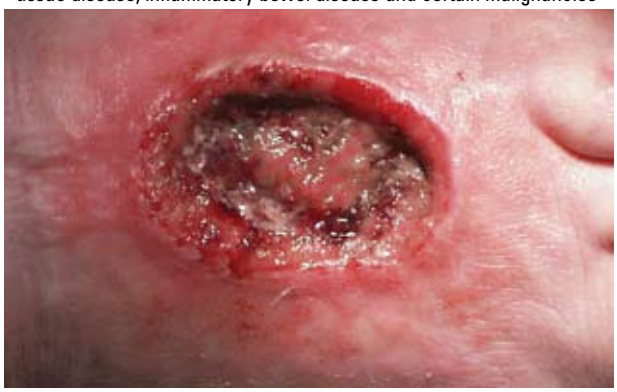


Figure 12. Pyoderma gangrenosum may be associated with connective tissue disease, inflammatory bowel disease and certain malignancies



If a patient presents with any constellation of the cutaneous changes consistent with a connective tissue disease, then it is important to fully investigate to:

- confirm the diagnosis of the connective tissue disease and to distinguish between them using serology including anti nuclear antibodies, extractable nuclear antibodies, double stranded DNA
- look for any evidence of systemic disease – full blood count and film, urea, electrolytes and creatinine, liver function tests, urinalysis, and where appropriate, lupus anticoagulant, anticardiolipin antibody.

In cases of suspected dermatomyositis appropriate investigations include: creatinine kinase, biopsy, magnetic resonance imaging of affected muscle or electromyogram and, in adult cases, malignancy screen.

A biopsy of the skin may show histologic features specific to SLE, dermatomyositis and scleroderma, and direct immunofluorescence can be used to look for a lupus band.

Treatment of the cutaneous changes requires strict photoprotection and the use of topical corticosteroids. In some cases, systemic treatment is needed. Corticosteroids, hydroxychloroquine, methotrexate, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, intravenous immunoglobulin, and more recently, rituximab, have all been used.[13] Patients with a suspected connective tissue disease should be assessed by a specialist physician.

Practice tips

- Use the clinicopathologic correlation of symptoms, signs, serology and histology to confirm the diagnosis and differentiate between connective tissue disorders
- Always look for the extent of systemic involvement
- Patients will often need a multidisciplinary approach to management.

Table 7. Cutaneous manifestations of internal malginancies[14–22]

Cutaneous feature	Clinical findings	Associated malignancy
Acanthosis nigricans (malignant) (Figure 11)	Velvety hyperpigmented thickening extending beyond the flexures and neck to involve lips, palms	Intra-abdominal adenocarcinoma, lung carcinoma, lymphoreticular malginancies
Acrokeratosis paraneoplastica (Bazex syndrome)	Psoriasiform dermatitis with nail dystrophy affecting hands, feet, ears, nose	Squamous cell carcinoma of upper aerodigestive tract
Erythema gyratum repens	Wood grain pattern annular, scaling erythema	Lung carcinoma
Necrolytic migratory erythema	Eroded erythematous annular polycylic eruption affecting intertriginous areas	Glucagonoma
Sweet syndrome	Plum coloured nodules affecting head, neck and dorsae hands	Can be associated with leukaemia, lymphoma, multiple myeloma
Pyoderma gangrenosum especially bullous variant (Figure 12)	Painful inflammatory ulcers with raised violaceous edge and overhanging borders; associated pathergy	Can be associated with leukaemia, lymphoma, multiple myeloma
Paraneoplastic pemphigus	Bullous, erosive mucosal +/- cutaneous eruption	Haematologic malignancies, thymoma
Necrobiotic xanthogranuloma (Figure 13)	Purpuric yellow plaques in periorbital and flexural areas	Monoclonal gammopathy/multiple myeloma
Diffuse plane xanthomas	Yellow-orange macules and plaques	Monoclonal gammopathy/multiple myeloma
Scleromyxoedema	Scleroderma-like thickening of skin associated with skin coloured or erythematous papular infiltrate	Monoclonal gammopathy/multiple myeloma
Primary systemic amyloidosis	Macroglossia, purpura especially periorbital and infiltrated papules	Monoclonal gammopathy/multiple myeloma

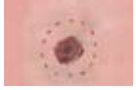
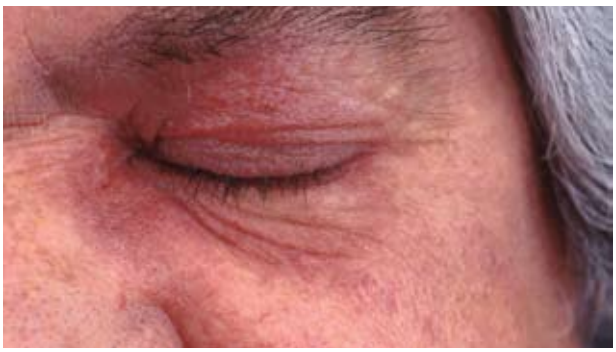


Figure 13. Purpuric plaque of the periorbital area – necrobiotic xanthogranuloma



What not to miss

This section has been included to highlight cutaneous paraneoplastic syndromes. Certain malignancies, in particular haematological malignancies, may often present with specific cutaneous features (*Table 7*). Multiple myeloma, in particular, has been associated with a number of cutaneous syndromes.[14–22] The presence of these paraneoplastic syndromes and cutaneous features should institute a search for the malignancy. The lack of recognition of these features may result in a delay in diagnosis and treatment.

Conflict of interest: none declared.

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