LECTURE

Newer skin signs of systemic disease

William D. James

Department of Dermatology, University of Pennsylvania, Philadelphia, PA, USA

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Abstract. The skin is a well-known reflection of internal disease states. It provides the astute clinician with clues that lead to the diagnosis of systemic illness. While skin disease is rarely life-threatening, serious morbidity and mortality may be avoided by early recognition of subtle cutaneous signs signaling internal problems. The recent literature was reviewed to glean new findings that either added new associations to older syndromes or described completely new diseases. While entire books are written regarding the "Skin Signs of Internal Disease", this article focuses only on the newest of such findings.
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Hepatitis C-related Conditions

The incidence of hepatitis C infection is rising worldwide. There have been many conditions associated with this life-threatening liver disorder, including necrolytic acral erythema, mixed cryoglobulinemia, porphyria cutanea tarda, lichen planus, pruritus, periarteritis nodosa and the red finger syndrome.[1] The first three are most dramatically linked to hepatitis C, while the latter four are characteristic enough to suggest the need for hepatitis serology upon diagnosis.

Necrolytic acral erythema was first described by El Darouti and El Ela in 1996.[2] Seven patients with predominantly lower extremity tender well-defined velvety or scaly surfaced red plaques were reported. Since then, an eighth patient has been documented.[3] Five were women and their ages ranged from 12 to 58. The hands were also affected in many by this distinctive change. Biopsy revealed a pallor of the superficial acanthotic, hyperkeratotic epidermis which may lead to blistering, both clinically and histopathologically. These microscopic findings suggest a nutritional deficiency or the glucagonoma syndrome. However, as necrolytic acral erythema has acral predominance and spares the perioraficial skin, investigation for hepatitis C infection should be done. Herein lies the importance; the chance to diagnose a communicable disease with potential disastrous long-term sequelae. Treatment with interferon can alleviate both the systemic illness and the cutaneous eruption.

Mixed cryoglobulinemia and porphyria cutanea tarda are highly indicative of hepatitis C infection while lichen planus, pruritus and periarteritis nodosa are variably associated with this infection. Studies from different countries with widely varying background rates of infection in the populace continue to suggest a generally low but real risk above the norm for the latter three conditions.[1] Hepatitis C serologies are a part of the workup for the etiology of all of these diseases.

The red finger syndrome has recently been defined as chronic striking well-defined painless distal erythema of the fingers and toes with multiple telangiectasias.[4–6] First thought to be a sign of HIV infection, it has become more closely associated with hepatitis C infection, similar to the manner in which porphyria cutanea tarda was finally appreciated to be more closely associated with hepatitis C rather than HIV disease. The red finger syndrome is also seen in connective tissue disease patients, particularly those with dermatomyositis and lupus erythematosus.

Connective Tissue Diseases

Two recent articles regarding signs of connective tissue disease are highlighted. Five patients, four girls and

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Reprint requests to: Dr. William D. James, Program Director of the Residency Program, Director of Clinical Services, and Vice Chairman, Department of Dermatology, University of Pennsylvania Health System, 2 Maloney Building, 3600 Spruce Street, Philadelphia, PA 19104-4283, USA

a boy, were reported with juvenile dermatomyositis (DM) and striking gingival telangiectasias.[7] All had prominent nail fold telangiectasias. Additionally, other oral findings of DM were noted, including edema, erythema, ulcers and white plaques. These oral findings join the shawl sign, the Samitz sign (cuticular fraying), mechanic's hands, and ulcerations as newer signs of DM. These complement the heliotype swelling of the periocular tissues, nail fold telangiecetiasis, Gottron papules and the Gottron sign as indicators of this disease with a plethora of skin signs.

Tumid lupus erythematosus was described over 70 years ago but it has attracted little attention over the years.[8] After only a small number of case reports and small case series Kuhn *et al*. reported 40 patients with this disease.[9] The definition they use includes smooth red-violet patches, papules, or plaques (Fig. 1) of the face, neck, upper trunk, and arms (sun-exposed sites) which on biopsy reveal superficial and deep perivascular lymphohistocytic infiltrates with abundant mucin interstitially. These patients generally noted the onset of the eruption in the summer (70%) between the ages of 30 and 50. Interestingly, men and women were equally represented. While some patients also exhibited discoid lupus erythematosus lesions, associated systemic lupus erythematosus was rare. The skin disease clears regularly with antimalarial treatment with no scarring. If one adheres to their disease definition, reticulated erythematous mucinosis and plaque-like erythematous mucinosis would be included under the designation tumid erythematosus. The lumping together of these disorders is reasonable.

Vascular Processes

Four cases of a new disease process called diffuse dermal angiomatosis have been described.[10–12] Three of the four have had painful ulcerations of the thigh within violaceous, hyperpigmented thickened plaques. Severe peripheral vascular disease and exertional pain were present in these three patients. On biopsy, a dermal proliferation of endothelial cells was present. All of these three patients' ulcers healed after revascularization. A fourth case involved the upper extremity of a renal dialysis patient with an arteriovenous access. Again revascularization led to disease remission. It is felt that this process is a subtype of reactive angioendothelomatosis.

Reactive erythemas have been the subject of new reports. Pustular vasculitis of the dorsal hands was defined by Strutton, *et al*. in 1995 as ulcerative lesions with a pustular border that involved the dorsal radial aspect of the hands of six women.[13] Some had associated fever and leukocytosis, but none had leukemia or inflammatory bowel disease. They reported that the biopsies were Sweet-like, however leukocytoclastic vasculitis was clearly evident in all lesions. A rapid response to steroids was characteristic and left no residual scarring. I have seen several such patients with identical clinical lesions limited to the dorsal hands (Fig. 2). None of the biopsies revealed vasculitis and I consider this to be a subset of Sweet syndrome.[14] Thus far no associated disease has been seen with this distinctive eruption.

Rheumatoid neutrophilitic dermatitis is another recently defined inflammatory disorder.[15] It is characterized as chronic erythematous plaques affecting primarily the trunk with fibrotic nodules of the extremities (Fig. 3). It affects patients with longstanding rheumatoid arthritis. Biopsies revealed a neutrophilic infiltrate of the dermis with intact neutrophils infiltrated between collagen bundles. There was no vasculitis or leukocytoclasis. This disorder is in clear contrast to Sweet syndrome and other neutrophilic reactive processes such as pyoderma gangrenosum, vasculitis and erythema elevatum diutinum.

Renal Disease

Scleromyxedema is a well-known, well-defined disorder consisting of infiltrated papules and plaques of the head and neck, trunk, and at times the limbs. In 90 percent of patients, a circulating paraprotein is present. The mucinous infiltrate may involve the viscera. Cooper, *et al*. reported a new subset of scleromyxedema, that was associated with renal dialysis.[16] They have seen 15 patients with primarily extremity papules and plaques which were thickened and hyperpigmented. Some patients had localized solitary lesions while others had diffuse thickening of the skin with flexion contractures. None had an associated paraprotein, or visceral involvement, and only some had trunkal lesions. All 15 patients, who were aged 31 to 74 years and mostly men, were receiving or had received renal dialysis. My experience with four such patients mirrors their report (Fig. 4).

Tumor-related Conditions

Birt, Hogg and Dube in 1977 reported 15 patients in one family who had multiple small skin-colored dome-shaped papules, which on biopsy revealed perfollicular fibrosis and epithelial proliferation.[17] Many subsequent patients with multiple familial fibrofolliculomas have been documented (Fig. 5). A triad of these lesions associated with acorchordons and trichodiscomas was originally thought to exist, but my experience and that of others point out that the latter two papules are also fibrofolliculomas if sectioned horizontally.[18,19]

The recently appreciated fact is that this skin disease

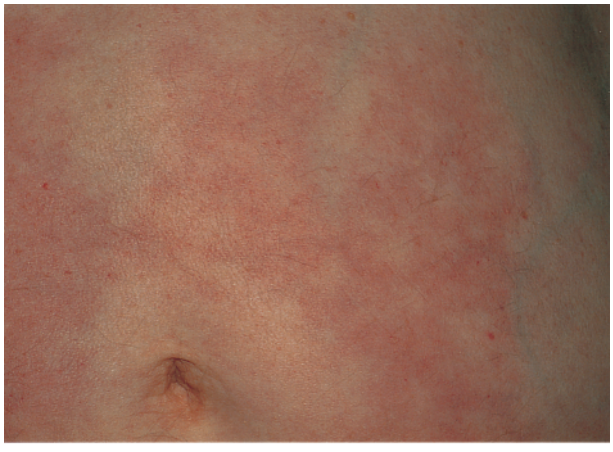

Fig. 1 Reticulate erythematous patch in a man with lupus erythematosus.

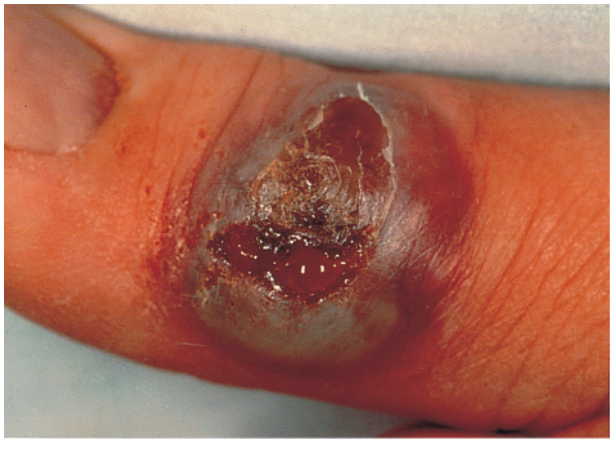

Fig. 2 Pustular erosive lesion on the dorsal radial aspect of the hand.

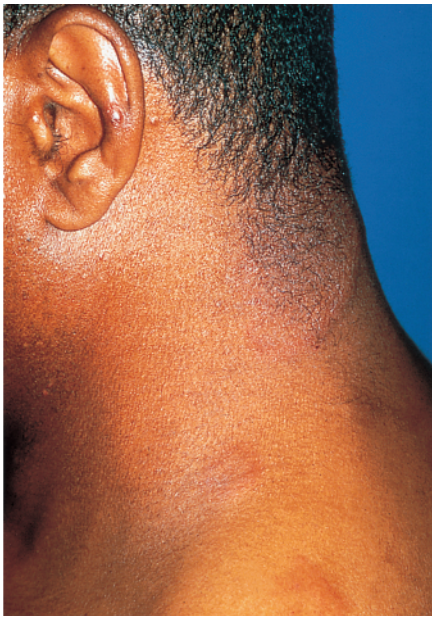

Fig. 3 Erythematous, edematous fixed plaques of rheumatoid neutrophilic dermatitis.

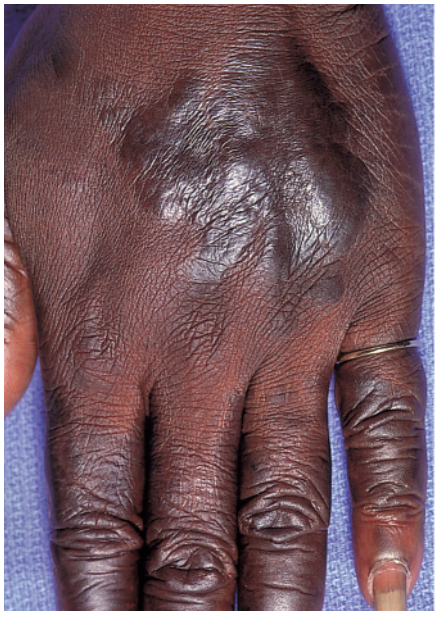

Fig. 4 Hyperpigmented sclerotic plaque of scleromyxedema in a renal dialysis patient.

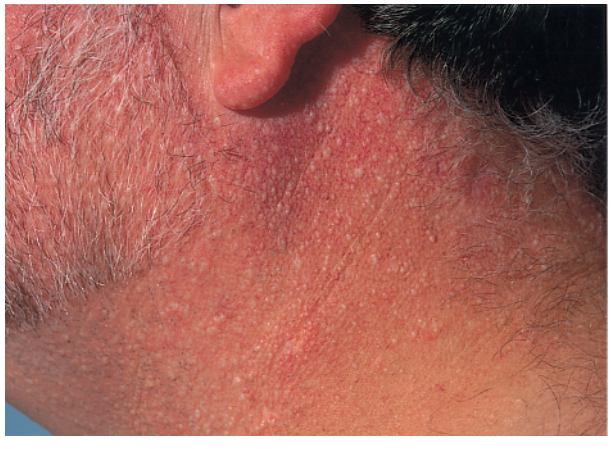

Fig. 5 Form Fibrofolliculomas in a patient with Birt-Hogg-Dube syndrome.

may have internal associations. Familial renal cell carcinomas, recurrent pneumothorax secondary to pulmonary cysts, and possibly colonic polyposis and carcinoma are well documented.[19] I have seen two patients with Birt-Hogg-Dube syndrome and neural derived tumors, a neurothekioma and a meningioma. It is now appreciated that a chest X-ray, an abdominal CT scan and ultrasound, and a colonoscopy should be done in all newly diagnosed patients and their family members. Generally, the pulmonary symptoms predate the onset of the papules (late teens *vs.* early thirties), and the renal and colonic abnormalities frequently occur later in life after the papules become apparent.[19]

Finally, an acral variant of acquired cutis laxa has been defined over the past 10 years. Four patients with easily deformed finger pads that lack elasticity and resiliency, have been reported.[20–22] Two of them, as in a case I recently observed, had associated amyloidosis and myeloma. While generalized acquired cutis laxa is a well-known complication of these associated diseases, this acral variant has only recently been recognized.

Continued vigilance is needed when assessing our dermatology patients, so we do not miss recognizing men and women who come for skin care but are manifesting treatable internal disease.

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