SECTION EDITOR: MICHAEL E. MING, MD

Tender Nodules on the Legs of a Cardiac Transplant Recipient

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REPORT OF A CASE

A 40-year-old white woman presented with a 2-week history of fever, myalgia, diffuse arthritis, and nausea and vomiting, and a 1-week history of tender, warm nodules on her lower extremities. She had undergone orthotopic cardiac transplantation 4 months earlier and had experienced multiple episodes of rejection, which required immunosuppressive therapy. Physical examination revealed approximately twenty 5- to 10-cm erythematous, warm, tender nodules on her lower extremities (**Figure 1** and **Figure 2**) She was febrile (temperature, 39.5°C) and had arthralgias and myalgias. The findings of the rest of the physical examination were normal; in particular, there was no palpable lymphadenopathy or hepatosplenomegaly.

Laboratory tests revealed the following values: white blood cell count, 5.5×10^9/L (0.90 neutrophils, 0.06 lymphocytes, 0.03 monocytes, 0.01 basophils, and no eosinophils); hemoglobin, 85 g/L (reference range, 120-160 g/L); and hematocrit, 0.27 (reference range, 0.37-0.47). The results of a routine chemistry profile were within normal limits except for the lactate dehydrogenase level, which was elevated at 1031 U/L (reference range, 300-600 U/L). Additional evaluation included radiography of the chest; computed tomography of the brain, abdomen, and pelvis; endoscopy of the upper and lower gastrointestinal tract; and biopsies of the stomach and small bowel; the results were unremarkable. An 8-mm punch biopsy specimen was obtained from a lesion on the left thigh (**Figure 3**).

What is your diagnosis?

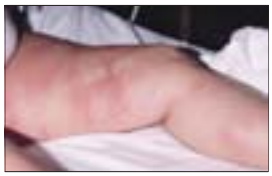


Figure 1.

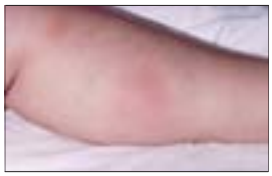


Figure 2.

Figure 3.

Multiple Light-Yellow Papules

Judith B. Romero, MD; James E. Rasmussen, MD; Lyndon D. Su, MD; University of Michigan, Ann Arbor

REPORT OF A CASE

An 81-year-old woman presented with a 2-year history of small, white papules coalescing on the neck and antecubital fossa. She denied any symptoms or previous trauma to the involved areas. She noticed a gradual increase in the number of papules over time. Her medical history was significant for hypercholesterolemia, coronary artery disease, angioplasty, and cataract surgery. She has a strong family history of coronary artery disease affecting multiple family members. Her mother died of heart disease at the age of 68 years, and a brother similarly died at the age of 50 years.

Physical examination revealed many soft, 1- to 3-mm, light-yellow, nonfollicular papules symmetrically distributed on the lateral aspect of the neck and on the antecubital fossae, coalescing to form a cobblestone appearance (**Figure 1**). The findings of a detailed ophthalmologic examination were within normal limits. A review of systems failed to elicit any other complaints. A biopsy specimen was obtained (**Figure 2**). An elastic tissue stain was performed (**Figure 3**).

What is your diagnosis?

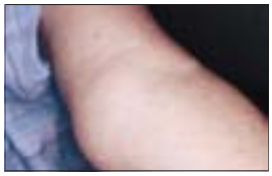


Figure 1.

Figure 2.

Figure 3.

Symmetrical Black Plaques on the Toes

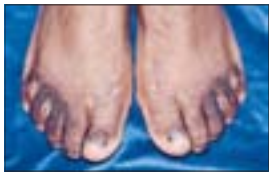
Chemene Robinson, MD; Brian Y. F. Yee, MD; A. Paul Kelly, MD; King/Drew Medical Center, Los Angeles, Calif

REPORT OF A CASE

A 52-year-old African American woman presented with a 3-year history of a progressively thickening "black rash" on her toes and a 5-year history of tinea pedis. Five months before her initial visit, she underwent a total mastectomy for poorly differentiated infiltrating ductal breast carcinoma and had begun a course of chemotherapy (methotrexate, cyclophosphamide, and fluorouracil). She also had a 10-year history of type 2 diabetes mellitus, which was controlled by glipizide therapy.

Physical examination revealed a slightly obese, but otherwise healthy-appearing woman. There were bilateral, symmetrical hyperpigmented papillomatous plaques on the dorsum of the toes. The plaques extended from the metatarsal phalangeal joint to the proximal nail fold, and there was brown discoloration of all toenails (**Figure 1** and **Figure 2**). The hyponychium was normal. She denied pruritus of the involved areas. A 3-mm punch biopsy specimen was obtained (**Figure 3**).

What is your diagnosis?



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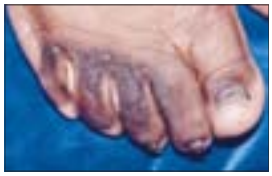

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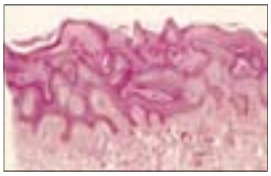


Figure 3.

Diffuse and Progressive Papules and Nodules

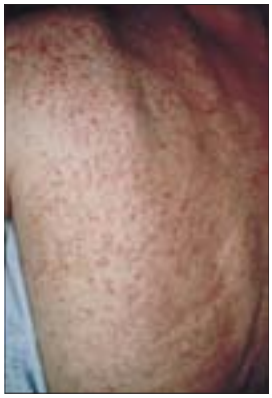
Christine M. Adamick, MD; Debra L. Breneman, MD; University of Cincinnati, Cincinnati, Ohio

REPORT OF A CASE

A previously healthy 67-year-old white man presented with a 10-week history of a diffuse asymptomatic cutaneous eruption that began on his trunk and progressed to involve his extremities. His primary care physician initially treated him with topical corticosteroids for presumed dermatitis, with continued worsening of his disease. A review of systems revealed mild fatigue and a 4.5-kg weight loss over a 3-month period.

Physical examination revealed diffusely scattered erythematous and violaceous smooth-surfaced papules and nodules (**Figure 1**). A biopsy specimen was obtained from a lesion on the right flank (**Figure 2** and **Figure 3**).

What is your diagnosis?



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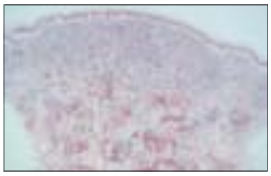

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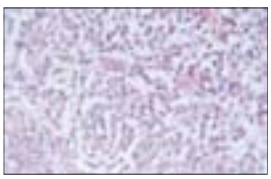

Figure 3.

Tender Nodules on the Legs of a Cardiac Transplant Recipient

Diagnosis: *Toxoplasma gondii* infection.

MICROSCOPIC FINDINGS AND CLINICAL COURSE

The biopsy specimen from the left thigh demonstrated an unremarkable epidermis, with an edematous papillary and reticular dermis. There was a moderate interstitial dermal lymphocytic infiltrate, with the greatest intensity in the upper dermis. Occasional large histiocytes within the dermis were noted to contain abundant trophozoites that were consistent with *T gondii* (Figure 3, arrows). Trophozoites were also noted within the subcutis, without associated reaction.

During the hospital course, the patient underwent a myocardial biopsy for routine evaluation of graft rejection. The myocardial tissue also demonstrated trophozoites, consistent with toxoplasmosis.

The patient was treated initially with clindamycin and pyrimethamine, and her fever had abated 5 days after admission. However, after 16 days of therapy, the patient's regimen was switched to sulfadiazine and pyrimethamine. Over a 3-week period, the skin nodules became erythematous and indurated, then became vesiculated, and desquamated.

DISCUSSION

Dermatologic manifestations of toxoplasmosis were first described in 1940 by Pinkerton and Weinman, with demonstration of the parasite.[1,2] The following year, the same authors performed extensive histological and clinical studies of the skin of 2 patients with fatal toxoplasmosis. There were macular, papular, maculopapular, and hemorrhagic eruptions, followed by desquamation.[2] However, since these early reports, there have been few documented cases of skin manifestations of this infection. This paucity of cases in the literature may be attributable to its rare occurrence, the lack of clinical suspicion by physicians, or its varied clinical presentation.

Recent investigations concerning cutaneous demonstrations of toxoplasmosis have highlighted the variability of its presentation as a possible rationale for underdiagnosis. These presentations may be maculopapular, nodular, papulopustular, lichenoid, purpuric, or erythema multiforme–like. These varied dermatologic manifestations of toxoplasmosis can possibly be attributed to the heterogeneous systemic immune responses to the organism.[3]

Toxoplasmosis is a zoonosis caused by *T gondii*, a crescent-shaped parasite. This ubiquitous protozoan can achieve prevalence rates greater than 50% in many populations and is capable of surviving dormantly in tissues for the life of its host. Toxoplasmosis may occur as a congenital or acquired infection.[2] Congenital toxoplasmosis is due to transmission of infection from the mother to the fetus transplacentally and often leads to stillbirth. Acquired toxoplasmosis is most commonly contracted through ingestion of raw meat or water that is infested with the parasite.[4] Fortunately, most cases of infestation are either asymptomatic or subclinical, with fever, cervical lymphadenopathy, and general malaise. Symptomatic toxoplasmosis is more common in immunocompromised persons. In such individuals, the disease is disseminated and commonly presents with encephalitis, myocarditis, and pneumonia.[5]

Common causes of immunocompromise permitting opportunistic infection include human immunodeficiency virus and immunosuppressive therapy after organ transplantation. Indeed, *T gondii* is one of the major documented complications associated with heart transplantation. In cases of heart transplantation, toxoplasmosis may be attributed to reactivation of a latent infection or to transmission via the donor organ.[6] Although this phenomenon is a known clinical entity in cardiac transplantation, its prevalence in other solid-organ transplants is not well documented.[7] Studies[8-10] suggest that clinical disease occurs in patients who are newly exposed but that it is rare in patients with preexisting antibody who have serologic evidence of recrudescence.

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Multiple Light-Yellow Papules

Diagnosis: Pseudoxanthoma elasticum (PXE)–like papillary dermal elastolysis (PDE).

MICROSCOPIC FINDINGS

Hematoxylin-eosin–stained sections showed focal and slight thickening of collagen in the papillary dermis. Elastic fibers did not appear calcified or fragmented. Sections stained for elastin revealed focal loss of superficial dermal elastic fibers in the central portion of the biopsy specimen.

DISCUSSION

In 1992, Rongioletti and Rebora[1] described 2 patients with lesions that clinically resembled PXE but with a total loss of the elastic network in the papillary dermis. Since then, only a few cases of this unusual acquired elastolytic disorder, termed *PXE-like papillary dermal elastolysis*, have been reported in the literature.[2-6] Pseudoxanthoma elasticum–like papillary dermal elastolysis mainly affects women in late adulthood (60-80 years of age). Cutaneous lesions clinically resemble PXE. Multiple yellowish nonfollicular papules, small in diameter, coalesce to form patches with a cobblestone appearance resembling "plucked chicken skin." They are symmetrically distributed over the antecubital fossae, flexor aspect of the forearms, supraclavicular region, sides of the neck, and lower abdominal area. No systemic involvement has been noted in this disorder. The skin lesions are mostly asymptomatic but slowly increase in number over time.

Hematoxylin-eosin–stained sections of lesional tissue may appear completely normal. Occasionally, as in our case, there is focal thickening of collagen fibers in the papillary dermis. Elastic stains show partial or complete loss of elastic fibers focally in the papillary dermis. Ohnishi et al[6] recently reported that the defect in PDE involves the disappearance of elastin rather than fibrillin 1.

Treatment for PDE is usually not necessary, since the lesions are asymptomatic and progress slowly. Some patients later desire cosmetic treatment. Topical 0.05% tretinoin has been reported to be ineffective in eradicating the papules.

Distinguishing PDE from PXE is of some clinical import. Pseudoxanthoma elasticum is an inherited disorder of connective tissue that predisposes to retinal and gastrointestinal hemorrhage. Both detrimental complications can be delayed with early detection of PXE. Although the skin lesions of PXE and PDE have a similar distribution and appearance, PXE usually presents in early adulthood (usually in the second decade of life), while PDE is seen in older adults and the elderly. When patients present with clinical findings of PXE or PDE, a skin biopsy should be performed, the findings of which will easily distinguish the 2 disorders. Pseudoxanthoma elasticum displays curled and fragmented basophilic elastic fibers in the upper reticular and midreticular dermis that usually spare the papillary dermis (except in perforating forms of PXE). Histologic stains for calcium, such as the von Kossa stain, demonstrate calcification of elastic fibers.

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Symmetrical Black Plaques on the Toes

Diagnosis: Malignant acanthosis nigricans associated with carcinoma of the breast.

MICROSCOPIC FINDINGS

Hematoxylin-eosin–stained sections showed hyperkeratosis, papillomatosis, and irregular acanthosis with minimal basilar hyperpigmentation.

DISCUSSION

Acanthosis nigricans is a symmetrical, velvety, papillomatous, gray-brown to black thickening of the skin that can be classified as benign and malignant, depending on the associated systemic disease. Associated findings include acrochordrons (skin tags), increased skin fold markings, and papillomas at the affected sites.[1]

The most common sites of involvement are the base of the neck, axillae, groin, and antecubital fossae. There have been reports of acanthosis nigricans affecting the dorsum of the hand, elbow, periumbilical skin, mucous membranes, vermilion border of the lips, and eyelids.[2-5] Mucosal involvement is more commonly found in the malignant form.[3]

Benign acanthosis nigricans has been associated with multiple endocrinopathies (eg, insulin-resistant diabetes, Addison disease, polycystic ovarian disease, pituitary tumors, and pinealoma); medication use (eg, oral contraceptives, nicotinic acid, corticosteroids, and diethylstibestrol); and polycystic ovaries and hirsutism in a well-defined triad.[2,5,6]

Malignant acanthosis nigricans is predominantly associated with intra-abdominal adenocarcinoma and with gastric adenocarcinoma in particular (45%-61%).[2-4] Acanthosis nigricans associated with cancers at other sites is much less common. It is common for malignant acanthosis nigricans to regress after the tumor is excised; acanthosis nigricans may sometimes recur with metastatic disease.[2] Malignant acanthosis nigricans is usually associated with a sudden onset, rapid progression, pruritus, and a diffuse keratoderma of the palms and soles (eg, tripe palms and tylosis) and can even be generalized.[2,7] It has been proposed that peptide production by the carcinoma may be a factor in the pathogenesis of malignant acanthosis nigricans.[3]

Microscopically, the lesions demonstrate hyperkeratosis and papillomatosis but only slight, irregular acanthosis and occasional hyperpigmentation.[1] Hypertrophy of the dermal papillae with formation of fingerlike projections may be seen.[8] An increase in melanin production is occasionally seen in the stratum corneum, and there is no inflammatory infiltrate.[2] The microscopic findings seen in acanthosis nigricans may be indistinguishable from those seen in the confluent and reticulated papillomatosis of Gougerot and Carteaud.[1]

The unusual location of our patient's acanthosis nigricans and the abrupt onset coinciding with breast cancer point to the malignant subtype of acanthosis nigricans despite the confounding history of type 2 diabetes mellitus and obesity. Breast cancer is not commonly associated with acanthosis nigricans. The most recent review of the literature revealed that among 247 cases of carcinoma associated with acanthosis nigricans, there were 112 gastric, 20 lung, 18 liver, 18 uterine, 11 breast, and 9 ovarian cancers.[4] The appearance of acanthosis nigricans may precede other symptoms or signs of internal malignancy, occur at the same time, or present after the malignancy is noted.

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Diffuse and Progressive Papules and Nodules

Diagnosis: Acute myelogenous leukemia presenting in the skin (leukemia cutis).

MICROSCOPIC FINDINGS, LABORATORY FINDINGS, AND CLINICAL COURSE

Microscopic examination revealed a dense dermal infiltrate consisting of moderately sized atypical monocytoid cells exhibiting pleomorphism, necrosis, and mitotic figures, features characteristic of leukemia cutis. The white blood cell count was higher than 90×10^9/L (reference range, 5.0-10.0 $\times 10^9$/L). A peripheral blood smear obtained at the time of presentation (**Figure 4**) contained numerous blast cells. A bone marrow biopsy specimen demonstrated well-differentiated promonocytes and monocytes as the predominant white cells. Flow cytometric studies revealed CD13, CD14, and CD33 positivity, suggesting a myeloid/monocytic lineage. Histochemical analysis demonstrated strong positive staining for α-naphthyl acetate esterase. Based on the results of these studies, the patient was diagnosed as having acute myelogenous leukemia, class M5b.

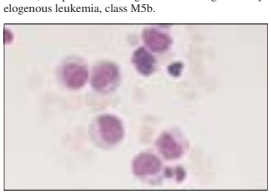

Figure 4.

The patient began induction chemotherapy for bone marrow transplantation with cytarabine. He developed marked gingival hyperplasia and failure of multiple organ systems during chemotherapy. He died 2 weeks after presentation.

DISCUSSION

Leukemia cutis is infiltration of the skin with leukemic cells.[1] It is regarded as dissemination of aggressive systemic leukemia to the skin.[1] Leukemia cutis occurs in the setting of acute myelogenous leukemia (AML), acute lymphocytic leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia.[1] It has been reported to occur in 13% of patients with AML.[2,3] Acute myelogenous (myeloid) leukemias are commonly divided into 7 classes based on the various differentiation stages of the myeloid leukemic cells.[4] Patients with AML-M4 and AML-M5 who develop leukemia cutis tend to have lesions that are large and "plum colored," with a propensity toward being more florid than those seen in other types of leukemia.[5-7] Gingival hyperplasia is also a striking feature in these patients.[5,8]

Microscopic examination of lesions of leukemia cutis from AML-M5, such as those seen in our patient, typically reveals a dense monomorphous infiltrate mostly confined to the upper dermis and consisting of atypical monocytoid cells of varying sizes.[5] Flow cytometry and immunophenotypic analysis show positivity for CD13, CD14, and CD33.[2] The diagnosis of AML-M5 is confirmed by positive histochemical staining with α-naphthyl acetate esterase.[2] Acute myelogenous leukemia, class M5, can be further subtyped based on the degree of differentiation. If most cells are poorly differentiated, the leukemia is subtype M5a. If the majority of the cells are well differentiated, the leukemia is subtype M5b. Thus, this patient's AML was classified as AML-M5b.

Treatment options for AML consist of consolidation chemotherapy, irradiation, and bone marrow transplantation.[5,9] The prognosis, however, is poor. Most patients die within months of diagnosis.[5,10]

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Submissions

Clinicians, local and regional societies, and residents and fellows in dermatology are invited to submit quiz cases to this section. Cases should follow the established pattern and be submitted double-spaced. Photomicrographs and illustrations must be clear and submitted as positive color transparencies. Material should be accompanied by the required copyright transfer statement, as noted in "Instructions for Authors." Material for this section should be submitted to Michael E. Ming, MD, Dermatopathology Section, University of California, San Francisco, 1701 Divisadero St, Suite 334, San Francisco, CA 94115. Reprints are not available.