normal, the clinical picture suggested the presence of serum sickness. Arthritis that is clinically similar to that of patients with PMC has been described in the arthritides of inflammatory bowel disease, post–intestinal bypass, and hepatitis B infection, as well as in Reiter's syndrome and the reactive arthritis seen with infectious diarrhea that is secondary to *Shigella flexneri*, *Yersinia entercolitica*, *Salmonella*, and *Campylobacter jejuni*. In some of these arthritides, for example, hepatitis-associated arthritis and bowel bypass arthritis, immune complexes appear to be the initiators of joint inflammation (5,6). In Reiter's syndrome and *Yersinia* arthritis, it appears that genetic predisposition plays a role in host susceptibility (7,8). A humoral mechanism was thought to be involved in the patient with PMC arthritis decribed by Fairweather et al (3). Circulating antibody to *C difficile* toxin was demonstrated in that patient, whereas 11 other patients with PMC-positive fecal toxin, but without arthritis, did not have circulating antibody to *C difficile* toxin (3).

Since pseudomembranous colitis and arthritis may occur without prior use of antibiotics, as seen in our patient, we recommend flexible sigmoidoscopy and fecal evaluation for *C difficile* toxin in all patients with persistent gastrointestinal symptoms and arthritis, to exclude a diagnosis of pseudomembranous colitis.

John G. Paty, MD
Robert E. Nichols, MD
Chattanooga, TN

1. Rollin DE, Moeller D: Acute migratory polyarthritis associated with antibiotic-induced pseudomembranous colitis. Am J Gastroenterol 65:353–356, 1976
2. Lofgren RP, Tadlock LM, Soltis RD: Acute oligoarthritis associated with Clostridium difficile pseudomembranous colitis. Arch Intern Med 144:617–619, 1984
3. Fairweather SD, George RH, Keighley MRB, Youngs D, Burdon DW: Arthritis in pseudomembranous colitis associated with an antibody to Clostridium difficile toxin. J R Soc Med 73:524, 1980
4. Bolton RP, Wood GM, Losowsky MS: Acute arthritis associated with Clostridium difficile colitis. Br Med J 284:1023–1024, 1981
5. Wands JR, Mann E, Alpert E, Isselbacher KJ: The pathogenesis of arthritis associated with acute hepatitis-B surface antigen-positive hepatitis. J Clin Invest 55:930–936, 1975
6. Good AE, Utsinger PD: Enteropathic arthritis, Textbook of Rheumatology. Second edition. Edited by WN Kelley, ED Harris Jr, S Ruddy, CB Sledge. Philadelphia, WB Saunders, 1985, pp 1031–1041
7. Calin A: Reiter's syndrome, Textbook of Rheumatology. Second edition. Edited by WN Kelley, ED Harris Jr, S Ruddy, CB Sledge. Philadelphia, WB Saunders, 1985, pp 1007–1020
8. Laitinen O, Leirisalo M, Skylv G: Relation between HLA-B27 and clinical features in patients with Yersinia arthritis. Arthritis Rheum 20:1121–1124, 1977

Nitrofurantoin-induced antinuclear antibodies and panniculitis

To the Editor:

The causes of nodular, nonsuppurative panniculitis are diverse and include drugs, connective tissue disease, hyperlipidemia, α_1-antitrypsin deficiency, diabetes mellitus, glomerular nephritis, bacterial infections, sepsis, rheumatic fever, tuberculosis, erythema nodosum, and intestinal bypass surgery (1). There are few recent reports of drug-induced panniculitis, although the older literature describes it in association with administration of bromides and iodides. Lupus panniculitis, or lupus profundus, is a well documented, but uncommon, manifestation of systemic lupus erythematosus (SLE). Drug-induced lupus frequently presents as a rash; however, there are no case reports of associated panniculitis (2,3). We describe a patient who had nitrofurantoin-induced panniculitis with associated serologic abnormalities of positive antinuclear antibody (ANA) and leukopenia.

The patient, a 73-year-old white woman, presented with a 6-month history of tender subcutaneous nodules located on her buttocks, lateral thighs, and the lateral aspects of her upper arms. The lesions progressively enlarged, became confluent, and produced a violaceous discoloration of the skin. Resolution of the lesions left her skin dimpled, and there was a depressed area. She denied having any fever, fatigue, or weight loss. There was no history of recent travel or exposure to tuberculosis, toxins, or unusual animals. She denied having symptoms of pleuritic chest pain, Raynaud's phenomenon, malar rash, photosensitivity, or mouth ulcers. Her medical history included mild hypertension of recent onset, costochondritis, asymptomatic carotid bruits, and depression. She was given prazosin, ibuprofen, isorbide dinitrate, and amitriptyline for these problems, and she continued taking the drugs throughout her current illness. She had a history of frequent episodes of cystitis, and 2 years before her current illness, she was successfully treated prophylactically with nitrofurantoin macrocrystals (50 mg/day).

Findings of the physical examination were normal, except for mild obesity and numerous skin changes. There were nodular subcutaneous swellings that were slightly tender to palpation. The nodules were located in confluent patches, in a symmetric pattern, over the lateral aspects of her upper arms, thighs, and across her buttocks. The skin overlying the nodules showed a hyperemic violaceous discoloration.

A biopsy of the right arm lesion had been performed 6 weeks after the onset of her illness. The specimen contained an ovoid, encapsulated, homogeneous, fatty, 1-cm mass. Microscopic examination of sections of the mass revealed the presence of fibrous and adipose tissue, with a small amount of peripheral nerve. There was an intense angiocentric infiltrate of lymphocytes, histiocytes, and numerous plasma cells (Figure 1). There was marked endothelial swelling, with focal fibrinoid changes of the vessel wall and extension of the infiltrate into the surrounding lobule. Focally, there were granulomas, with lipid-laden macrophages and an occasional multinucleated giant cell. There was slight thickening of the fibrous septae, but no involvement by the inflammatory infiltrate (Figure 1). Alcian blue staining of the specimen demonstrated a slight increase in mucin content in the perivascular areas. Mucicarmine staining was negative.

The patient's illness progressed over a 6-month period, at which time she was thought to have a nitrofurantoin-induced panniculitis. The nitrofurantoin therapy was discontinued; she continued taking her other medications. Within 5 days after the nitrofurantoin treatment was stopped, the skin

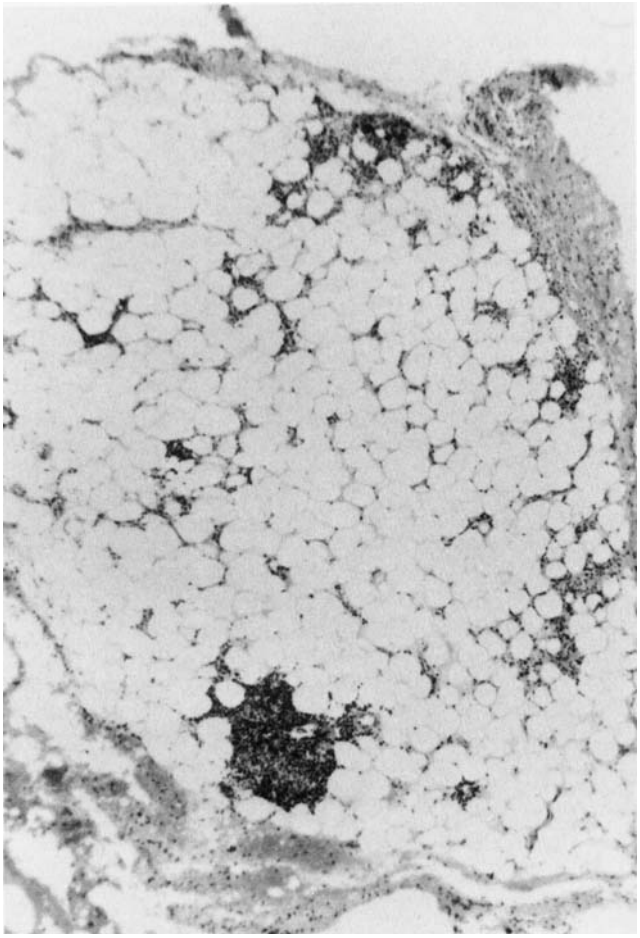

Figure 1. Photomicrograph of biopsy specimen of the right arm lesion, taken 6 weeks after the onset of illness. There is a moderate lobular and angiocentric infiltrate of lymphocytes and histiocytes (hematoxylin and eosin stained, original magnification × 63).

lesions improved. One month after the drug was stopped, lesions resolved, although she had atrophy of the superficial skin at the sites of previous lesions. Examination of the patient 5 years later revealed no recurrent skin rashes, symptoms of SLE, or other medical illnesses.

The patient had been under the care of her local physician, regularly, for years prior to this illness. Results of laboratory tests, including hemograms and liver function studies, before initiation of the nitrofurantoin were normal. Tests performed 6 weeks after the panniculitis started showed a white blood cell (WBC) count of 4,300/mm^3, with a normal differential cell count and no eosinophilia. Her erythrocyte sedimentation rate (ESR) was 32 mm/hour. A test for ANA was positive at a titer of 1:640, and showed a homogeneous pattern. Liver function tests showed mild elevations in levels of serum glutamic pyruric transaminase, to 57 units/liter (normal 0–40), serum glutamic oxaloacetic transaminase, to 50 units/liter (normal 0–40), and lactate dehydrogenase (LDH), to 241 units/liter (normal 60–200).

Repeat laboratory tests just before the nitrofurantoin was discontinued showed a WBC count of 4,650/mm^3. Additional investigative studies were performed, and cryoglobulins were found to be present in low concentrations. All of the following results were normal: C3, total hemolytic complement, VDRL, febrile agglutinins, double-stranded DNA antibody, histone-reconstituted ANA, rheumatoid factor, LE cell preparation, and angiotensin-converting enzyme. A test for purified protein derivative was negative. Results of a chest radiograph and a liver–spleen scan were normal.

Four months after discontinuation of the nitrofurantoin, her ANA titer had declined to 1:160 and her ESR was 23 mm/hour. Results of liver function studies were normal, except for a mild elevation of the LDH level, to 246 units/liter. Results of repeat tests for ANA at 1 year and 5 years after her illness were negative, and her WBC counts remained normal.

Nitrofurantoin as an inducer of panniculitis has not been reported. The company that produces nitrofurantoin has received no report of panniculitis secondary to treatment with this drug. Selroos and Edgren (4) reported that nitrofurantoin induced a lupus-like syndrome in 3 of their patients who had associated pulmonary reactions, positive ANAs, pleurisy, and arthralgias. Leukopenia was not reported in those patients, but it commonly occurs in SLE and in idiopathic SLE with panniculitis (5), and it is one of the manifestations of drug-induced lupus (3).

Panniculitis is a cause of subcutaneous nodules in SLE patients, and it is seen in approximately 2–3% of patients in large series, as well as in a significant portion of people with discoid lupus erythematosus (5). Sánchez et al (6), in a review of 29 cases of lupus panniculitis, suggested that lupus panniculitis is fairly characteristic and can be identified by the presence of lymphocytic panniculitis, hyaline degeneration of fat, hyaline papillary bodies, and the development of lymphoid nodules in the lower dermis and subcutaneous tissue. Those authors noted that, frequently, there were lymphoid nodular structures within the fat lobule, as well as near the fibroseptum, and occasionally, there were collections of granulomas. The pathologic findings in our patient were similar to those described by Sánchez et al, although the apparent characteristic finding of hyaline degeneration of fat was not present. In addition, the inflammatory cell infiltrate was predominantly lobular.

The histologic differentiation of the various panniculitides is difficult because of the significant overlap of the pathologic findings (6). The classic description of nodular nonsuppurative panniculitis, or Weber-Christian disease, is of a degeneration and necrosis of fat cells, associated with infiltration by polymorphonuclear lymphocytes. Changes occur mainly in the fat lobules, and following the inflammatory phase, there is replacement of the fat by necrosis. In contrast, erythema nodosum represents a septal panniculitis that involves the venule of the fibrous septae and is associated with inflammation in the dermal subcutaneous interface. The pathologic findings in our patient showed an inflammatory cell infiltrate that was predominantly lobular.

The physical findings of this case of nitrofurantoin-induced panniculitis are similar to those described in lupus panniculitis, including the subcutaneous atrophy, the slowly

progressive acute and chronic lesions that existed together, and the location on the proximal extremities, trunk, and lower back (5). Our patient had associated serologic abnormalities suggestive of a lupus-like reaction, including positive ANA, leukopenia, and an elevated ESR. No other cause for this condition could be established, and complete resolution of all abnormalities occurred within 8 months of withdrawing the nitrofurantoin. The diagnosis in the patient described here appears to be nitrofurantoin-induced panniculitis with associated positive ANA and leukopenia.

Robert G. Sanford, MD
Harrisburg, PA
P. Michael Olmstead, MD
Pennsylvania State University
Hershey, PA

1. Case Records of the Massachusetts General Hospital: weekly clinicopathological exercises. Case 17–1982. N Engl J Med 306: 1035–1043, 1982
2. Lee SL, Chase PH: Drug-induced systemic lupus erythematosus. Semin Arthritis Rheum 5:83–103, 1975
3. Weinstein A: Drug-induced lupus erythematosus, Progress in Clinical Immunology. First edition. Edited by R Schwartz. New York, Grune & Stratton, 1980, pp 1–21
4. Selroos O, Edgren J: Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin. Acta Med Scand 197:125–129, 1975
5. Winkelmann RK: Panniculitis in connective tissue disease. Arch Dermatol 119:336–344, 1983
6. Sánchez NP, Peters MS, Winkelmann RK: The histopathology of lupus erythematosus panniculitis. J Am Acad Dermatol 5:673–680, 1981

Pedal gangrene caused by giant cell arteritis

To the Editor:

Giant cell arteritis, also known as temporal, cranial, or granulomatous arteritis, is a vasculitis of unknown etiology that affects medium- and large-sized arteries (1). It typically involves the cranial branches of arteries that originate from the aortic arch (2). Thus, upper extremity involvement is considerably more common than lower extremity disease (1). Leg claudication symptoms have been described in some patients, but there has only been 1 previously documented case of giant cell arteritis involving the distal vasculature of the leg and foot that resulted in ischemic necrosis and gangrene of the foot (3).

A 75-year-old man was admitted to the hospital with a 2-month history of pain and swelling of the right foot. Four years earlier, he had noted pain and stiffness in the hip and shoulder girdle areas, especially upon arising. He did not consult a physician about these symptoms, but he began taking 6.0 gm of aspirin per day in divided doses and had partial relief. He remained well until he developed intense pain in the right foot which, initially, was related to exertion, but soon became constant in nature.

Two weeks prior to admission, he noted an area of ulceration between the fourth and fifth toes on his right foot. The patient never smoked and had no history of hypertension, coronary artery disease, or diabetes. He was admitted to the hospital where, within 1 week, he was noted to have developed gangrenous changes that involved the entire right fourth toe and the distal forefoot.

Pulses were 3+ in his upper extremities and over the femoral and popliteal arteries, but were not palpable distally in either leg. The remainder of the physical examination results were unremarkable. The erythrocyte sedimentation rate (ESR) was 128 mm/hour. A complete blood count and differential count were within normal limits. Urinalysis revealed 2 coarse granular casts per high power field and 4–6 white blood cells and 8–10 red blood cells per high power field. The serum creatinine level was 1.0 mg/dl and the blood urea nitrogen level was 16 mg/dl. An abdominal aortogram with bilateral femoral run-off demonstrated occlusion of the proximal right anterior tibial artery and the left peroneal and posterior tibial arteries. There was no evidence of embolic disease. The aorta, iliac, and femoral and renal arteries showed minimal evidence of atherosclerosis.

The patient underwent amputation below the right knee. Histologic examination of the amputated extremity revealed a necrotizing vasculitis diffusely involving the anterior and posterior tibial and dorsalis pedis arteries. There was marked intimal proliferation, and a predominantly mononuclear inflammatory cell infiltrate was present in the inner portion of the media adjacent to the internal elastic lamina, which showed evidence of disruption and fragmentation. Multinucleated histiocytic giant cells were seen in some sections adjacent to disrupted elastic membrane (Figure 1). It was noteworthy that there were only minimal atherosclerotic changes present within the vessel walls. A temporal artery biopsy specimen showed identical histopathologic changes.

Postoperatively, the patient was started on a regimen of prednisone, 60 mg/day, but refused therapy with cyclophosphamide. There was no further ulcer development in the right lower extremity. Two months later, his urinary abnormalities resolved and his ESR was 10 mm/hour. However, 8 months later, he developed gangrene of the left foot, which required amputation below the knee.

The predilection for involvement of the branches of arteries originating from the arch of the aorta in giant cell arteritis is well recognized. Upper extremity claudication, bruits over large proximal arteries, and decreased or absent pulses in the neck and arms are common manifestations (4). Lower extremity involvement, when it occurs, presents as leg claudication (1).

Finlayson and Robinson (3) described an elderly woman with gangrene of the feet who required amputation; histologic examination revealed the typical features of giant cell arteritis in the tibial and peroneal arteries. Atlas (5) reported the case of a 68-year-old woman with gangrene of the foot, which he attributed to Buerger's disease, but Heptinstall et al, on reviewing the case several years later, believed that the histologic findings were more consistent with giant cell arteritis (6). Of 248 patients with giant cell arteritis observed at the Mayo Clinic, 1 developed severe claudication of the legs that was unresponsive to prednisone and resulted in gangrene of the lower legs and feet (1). However, examination of the leg arteries in the amputated specimens revealed generalized advanced arteriosclerosis obliterans and minimal mononuclear cell infiltration in 1 popliteal artery.