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## Case records of the Massachusetts General Hospital. Case 37-2009. A 46-year-old woman with chronic renal failure, leg swelling, and skin changes.

Daniela Kroshinsky  
*Harvard University*

*Et al.*

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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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## Case 37-2009: A 46-Year-Old Woman with Chronic Renal Failure, Leg Swelling, and Skin Changes

Daniela Kroshinsky, M.D., Jonathan Kay, M.D., and Rosalynn M. Nazarian, M.D.

### PRESENTATION OF CASE

From the Departments of Dermatology (D.K.) and Pathology (R.M.N.), and the Division of Rheumatology, Allergy, and Immunology, Department of Medicine (J.K.), Massachusetts General Hospital; and the Departments of Dermatology (D.K.), Medicine (J.K.), and Pathology (R.M.N.), Harvard Medical School.

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A 46-year-old woman was referred to a rheumatologist at this hospital because of swelling of the legs and skin changes.

The patient had been in her usual state of health until approximately 2 years earlier, when she was admitted to another hospital because of painful swelling of the left leg. She had been using oral contraceptives for 6 months for control of menorrhagia. She had chronic kidney disease caused by congenital ureteral reflux, which had not required dialysis; she was seen regularly by a nephrologist. Magnetic resonance imaging (MRI) with angiography revealed thrombosis of the left common iliac, internal and external iliac, and common femoral veins. MRI of the chest with angiography showed no evidence of pulmonary embolism. Laboratory evaluation showed no evidence of hypothyroidism, no abnormalities of coagulation factor II or V, and normal levels of protein C, protein S, and antithrombin 3; tests for anticardiolipin antibodies and lupus anticoagulant were negative. Oral contraceptives were discontinued, and anticoagulation was begun with heparin, followed by warfarin.

Approximately 7 weeks later, swelling of the left leg increased, associated with a pruritic rash on the left medial thigh. Imaging studies reportedly showed recanalization of the proximal superficial femoral vein and were otherwise unchanged. Doxycycline and azithromycin were administered but discontinued after testing for Lyme disease was negative. Antinuclear-antibody titers were negative, and the level of D-dimer was normal. She saw a dermatologist, and punch-biopsy specimens of the skin of the left thigh and calf were reported to show numerous eosinophils, a feature consistent with a hypersensitivity reaction.

Swelling of the left leg persisted. On examination 6 months after the onset of symptoms, there was pitting edema (1+) of the left leg. The right calf was 32 cm in circumference and the left 35 cm. The skin had a bluish discoloration, and peripheral pulses were normal. Noninvasive vascular studies showed no evidence of deep venous thrombosis. Warfarin was discontinued after approximately 8 months of anticoagulation. One month later, swelling of the left leg worsened. On examination, there was mild edema extending from the left ankle to the mid-thigh, with erythematous discoloration of the skin in a reticular pattern, with atrophic blanche

at the edges. Noninvasive vascular studies disclosed recurrent deep venous thromboses in the left popliteal and calf veins, and anticoagulation with enoxaparin and warfarin was begun. Swelling of the left leg and reticular erythema of the skin persisted.

Approximately 7 months before evaluation at this hospital, the patient noted a sensation of tightness in both legs after prolonged exercise, followed by thickening of the skin of the left upper thigh that progressed to involve the calf. On examination 6 weeks later, there was diffuse erythema and thickening of the skin of the left leg, extending from the lower calf to the thigh; the skin of the right calf was thickened, without erythema. The hematocrit was 34%; the remainder of the complete blood count was normal, as were the erythrocyte sedimentation rate, the creatine kinase level, and testing for antinuclear antibodies. Pathological examination of a specimen from a deep-wedge biopsy of the left thigh revealed septal panniculitis with fibrosis and an inflammatory infiltrate including lymphocytes, eosinophils, and histiocytes with occasional giant cells, features thought to be consistent with erythema nodosum, a hypersensitivity reaction, or eosinophilic fasciitis. Treatment with prednisone (60 mg daily) was begun, and the patient reported decreased erythema and discomfort. Four months later, hemodialysis was initiated because of metabolic acidosis. Administration of mycophenolate mofetil (1000 mg daily) was begun, and prednisone was tapered to 10 mg daily. She was referred to a rheumatologist at this hospital.

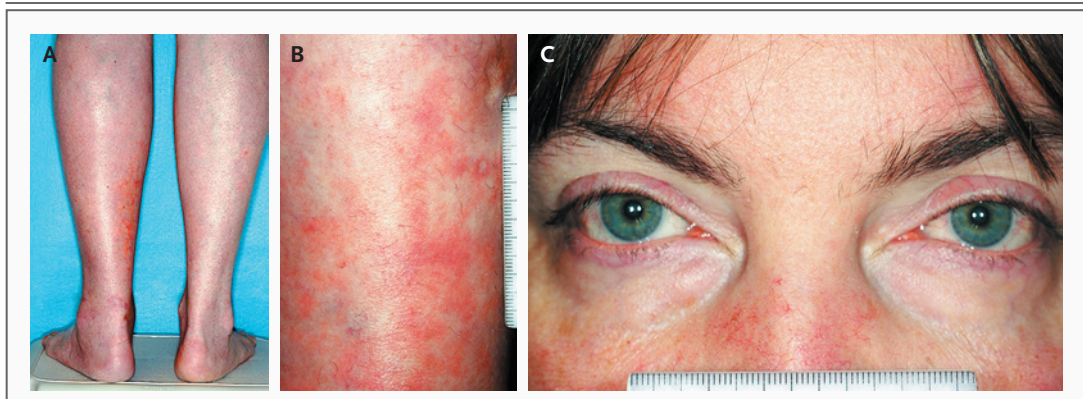
She reported occasional spasms of her fingers during dialysis, mild joint pain, and fatigue but no joint stiffness, morning stiffness, hyperpigmentation, or woody changes of the skin. She reported difficulty walking, bending to the floor, getting in and out of an automobile, and fatigue after walking 2 miles. She had chronic obstructive nephropathy due to congenital bilateral ureteral reflux, with tubular acidosis and secondary hyperparathyroidism. A neobladder had been constructed 20 years earlier. She had had a cholecystectomy and a cesarean section. She did not recall having been exposed to gadolinium. She had been adopted as a child. Her biologic mother had died in her 50s of vulvar carcinoma; a biologic uncle had died of colon cancer, and maternal grandparents had lived into their 80s. There was no known family history of hematologic, renal,

or rheumatic diseases. She lived with her husband and son and worked in an office. She drank alcohol rarely and did not smoke. She was allergic to penicillin, sulfa, nitrofurantoin, and vancomycin. Medications included warfarin, levothyroxine, sodium bicarbonate, calcitriol, calcium carbonate, prednisone, mycophenolate mofetil, and weekly darbepoetin alfa injections.

On examination, she was cushingoid. Vital signs were normal. There was mild erythema over the cheeks. The conjunctivae and sclera were normal. There were no oral or nasal ulcerations. There was slight erythema over an area of swelling on the left lower leg but no hyperpigmentation, tethering of the skin to the underlying fascia, peau d'orange change, or hair loss. A dialysis catheter was present in a right upper intercostal space, and an arteriovenous fistula was present in the left antecubital fossa. There was full motion of all joints, without inflammation or deformity. The remainder of the examination was normal. She was advised to continue immunosuppressive therapy and to avoid radiologic studies with gadolinium. She was placed on a waiting list for a renal transplant. The next month, mycophenolate mofetil was discontinued because of thrombocytopenia. During the next year, the skin lesions were unchanged.

Approximately 14 months after presentation, difficulty swallowing (first solid foods, then liquids) developed, and she noted increasing tightness in both legs. On examination by a dermatologist, there was induration of the left leg, extending to the mid-thigh, without brawny discoloration, and prominent telangiectasias over the cheeks. At this time, review of her records disclosed that the patient had received gadolinium contrast material for MRI studies in the past on three occasions; the patient was informed of this. One month later, she returned to the rheumatology clinic.

She had recently noted hyperpigmentation of the skin of the left thigh, both lower legs, and left forearm and reported morning stiffness and increased difficulty walking. On examination, there was hyperpigmentation of the skin of both legs (Fig. 1A and 1B) and the left forearm, tethering of the skin to the underlying fascia, and no peau d'orange change. There were bilateral nasal and temporal yellow scleral plaques (Fig. 1C). There were no joint contractures. The remainder of the physical and neurologic examinations was normal. A diagnostic procedure was performed.



**Figure 1.** Clinical Photographs of the Patient at the Second Rheumatology Visit.

Thickening and discoloration of the skin of the legs are seen, more on the left than on the right (Panel A). Irregular erythema of the skin of the left leg is evident (Panel B). There are yellow scleral plaques on both eyes and telangiectasias on the face (Panel C).

#### DIFFERENTIAL DIAGNOSIS

*Dr. Daniela Kroshinsky:* This patient presented with swelling of the leg, followed by cutaneous, ocular, and systemic findings, including progressive hardening or induration of the skin with hyperpigmentation and telangiectasias, yellow scleral plaques, and difficulty walking, bending, and swallowing. I will approach this case by considering the differential diagnosis first of progressive induration of the skin and then of the cutaneous manifestations of renal disease.

#### PROGRESSIVE INDURATION OF THE SKIN

Progressive induration of the skin may be caused by immunologic or inflammatory disorders, metabolic disorders, depositional disorders, or exposures to toxins. Immunologic or inflammatory causes include eosinophilic fasciitis, graft-versus-host disease, lichen sclerosus et atrophicus, systemic lupus erythematosus, dermatomyositis, and scleroderma. Metabolic conditions include porphyria cutanea tarda, myxedema of hypothyroidism, and phenylketonuria. There are several disorders in which abnormal deposits are associated with skin induration, including scleromyxedema, amyloidosis, nephrogenic systemic fibrosis, scleredema, and lipodermatosclerosis. Finally, exposure to certain toxins such as L-tryptophan or toxic oils can cause induration of the skin.

In view of the patient's history and clinical appearance (no history of transplantation or direct exposure to toxins; localization to the arms

and legs; lack of blistering, scarring, hypertrichosis, or multiorgan dysfunction; and onset in adulthood), we can eliminate graft-versus-host disease, lichen sclerosus et atrophicus, porphyria cutanea tarda, amyloidosis, and phenylketonuria. Assuming her laboratory values are correct, we can also eliminate systemic lupus erythematosus, dermatomyositis, and myxedema, leaving us with a differential diagnosis that includes eosinophilic fasciitis, lipodermatosclerosis, nephrogenic systemic fibrosis, scleredema, scleroderma, and scleromyxedema.

#### CUTANEOUS MANIFESTATIONS OF RENAL DISEASE

Cutaneous manifestations of renal disease include bullous disease of hemodialysis, metastatic calcification, nephrogenic systemic fibrosis, perforating disorders, pseudoporphyria, and prurigo nodularis, the prurigo nodularis often resulting from uremic pruritus. This patient has no vesicles or bullae to suggest bullous disease of hemodialysis or pseudoporphyria. There are no nodules, crusted lesions, excoriations, or reports of pruritus to suggest a perforating disorder, prurigo nodularis, or uremic pruritus. The diagnoses that remain are scleroderma, eosinophilic fasciitis, scleredema, scleromyxedema, lipodermatosclerosis, metastatic calcification, and nephrogenic systemic fibrosis.

#### *Scleroderma*

The presence of skin induration and dysphagia in a 46-year-old woman raises the possibility of scler-

rodema, which is an autoimmune disease that is most often seen in women aged 30 to 50 years and can affect the skin, blood vessels, and internal organs.<sup>1</sup> The diffuse form often involves both distal and proximal limbs, the face and trunk,<sup>1,2</sup> and internal organs and has an increased associated mortality rate as compared with the limited form.<sup>1</sup> The limited form tends to involve the distal limbs and face and has a lower risk of internal-organ involvement. For the diagnosis of scleroderma, the American College of Rheumatology requires one major criterion (symmetric sclerosis proximal to the metacarpophalangeal or metatarsophalangeal joints) or two minor criteria; the minor criteria are sclerodactyly, digital pitting scars or loss of substance from the finger pad, and bibasilar pulmonary fibrosis.<sup>1</sup> This patient had involvement of the proximal and distal limbs but sparing of the face and trunk, and she had no skin changes to the digits or pulmonary problems. Cutaneous scleroderma may be preceded by an edematous phase that may include digital pitting edema but not the diffuse leg edema that this patient had.<sup>1</sup> Features of cutaneous scleroderma are cutaneous induration and dyspigmentation (e.g., diffuse hyperpigmentation accentuated over areas of pressure, leukoderma with perifollicular sparing, telangiectasias on the lips and palms, prominent nail-fold capillary loops alternating with areas in which the nail-fold capillaries are not visible, calcinosis cutis near joints or over distal digits, and hypohidrosis) and Raynaud's phenomenon,<sup>1</sup> which this patient did not have. Laboratory abnormalities in scleroderma include positive tests for antinuclear antibody, antineutrophil cytoplasmic antibody, and antitopoisomerase (Scl-70); this patient was tested only for antinuclear antibodies, which were absent. Of the systemic symptoms that can accompany scleroderma, this patient reported only dysphagia, and the renal findings were attributable to congenital renal disease.

#### *Eosinophilic Fasciitis*

Eosinophilic fasciitis is characterized by symmetric, rapidly progressive swelling and thickening of the skin of the limbs and sometimes the trunk.<sup>1,2</sup> It classically spares the epidermis, causing it to appear wrinkled on examination.<sup>3</sup> It is not clear from the history whether this finding was elicited on examination of our patient's skin. Eosinophilic fasciitis has been reported to occur after vigorous exertion, which our patient reported, or

after exposure to a toxin such as L-tryptophan or rapeseed oil.<sup>3,4</sup> Dimpling or a peau d'orange texture can be seen on the skin and is caused by focal dermal tethering to the underlying fascia by sclerotic bands; this patient lacked these signs.<sup>2,4</sup> Patients may have an elevated erythrocyte sedimentation rate, eosinophilia, or both, but our patient did not.<sup>2-4</sup> Eosinophilic fasciitis can have associated systemic findings such as synovitis or arthritis, joint contractures, restrictive lung disease, pleural effusions, monoclonal gammopathies, and multiple myeloma.<sup>2-4</sup> She had no physical findings or symptoms to suggest these conditions, and she had not been evaluated for a monoclonal gammopathy.

#### *Scleredema*

Scleredema presents as a diffuse hardening of the skin of the upper body due to increased production of mucin and collagen without an increased number of fibroblasts. Types I and II are characterized by induration of cervicofacial skin that can progress to involve the trunk, proximal upper arms, and face,<sup>3</sup> often resulting in masklike facies associated with difficulty opening the mouth. Type I is most often seen in women and children after an upper respiratory infection, especially of streptococcal origin, and resolves spontaneously over a period of months, whereas type II is idiopathic, is slower in onset and resolution, and can be associated with a monoclonal gammopathy.<sup>1,3</sup> Type III (scleredema diabeticorum) presents as hardening and erythema of the skin of the posterior neck and upper back in middle-aged men with diabetes; it results from irreversible glycosylation of collagen fibers that reduces their collagenase-mediated degradation.<sup>1,3</sup> All types can have systemic involvement, with dysphagia, dysarthria, serositis, and myositis, as well as cardiac and ocular changes.<sup>1,3</sup> Other than dysphagia, these findings do not fit this patient's clinical scenario.

#### *Scleromyxedema*

Scleromyxedema is characterized by monomorphic small papules that may be edematous, indurated, erythematous, or hyperpigmented; they occur in a symmetric and commonly linear distribution over the hands, forearms, head, neck, upper trunk, and thighs and are surrounded by shiny, indurated skin.<sup>1,3</sup> Scleromyxedema is a disorder of increased fibroblast proliferation and deposition of mucin and collagen. Involvement of the glabella produces



classic linear furrows, whereas thickening of the skin over the proximal interphalangeal joints produces the “doughnut sign,” a central depression with an elevated, firm rim of skin when these joints are extended.<sup>1,3</sup> The cutaneous findings in our patient do not support this diagnosis. It can be associated with several systemic findings, including dysphagia, as our patient had, proximal muscle weakness, peripheral neuropathy, arthropathy, lung and renal disease, and monoclonal gammopathy.<sup>1,3</sup> Although the patient’s difficulty getting into or out of a chair could be due to proximal muscle weakness, it appears to be related more to skin hardening over her joints, since she also reported difficulty bending and walking.

#### *Lipodermatosclerosis*

Long-standing venous insufficiency can induce a panniculitis that heals with sclerosis and induration of the skin of the medial leg, a condition known as lipodermatosclerosis. It traditionally affects the area just above the malleolus.<sup>5,6</sup> This condition is most often seen in women over 40 years of age and can occur in any dependent site. In its acute phase, lipodermatosclerosis presents with pain, warmth, erythema, and induration of the affected areas.<sup>6</sup> As this condition progresses to dermal and subcutaneous sclerosis in the chronic phase, a sharply demarcated area of induration develops, with hyperpigmentation due to hemosiderin deposition.<sup>5,6</sup> When the condition is pronounced, the lower legs can resemble an “inverted champagne bottle.”<sup>5</sup> Lipodermatosclerosis is usually not progressive and would not account for this patient’s arm involvement or dysphagia.

#### *Metastatic Calcification*

Two forms of cutaneous calcium deposition can occur in patients with renal disease: benign nodular calcification and calciphylaxis. Both are caused by the precipitation of calcium and phosphate salts that is due to abnormal absorption, mobilization, or excretion of these ions, either alone or in combination. In benign nodular calcification, large deposits accumulate in the skin and subcutis, particularly in periarticular locations.<sup>1</sup> The process in our patient was more diffuse than would be expected with benign nodular calcification. Calciphylaxis is a process of ischemic necrosis of the skin and soft tissues due to increased vascular

calcification,<sup>1,7</sup> which manifests clinically as reticulated, violaceous patches that can progress to bullae, necrosis, and ulceration.<sup>7</sup> The lesions are exquisitely tender, unlike this patient’s lesions.

#### *Nephrogenic Systemic Fibrosis*

Nephrogenic systemic fibrosis is a relatively recently recognized rapidly progressive fibrosing disorder of skin and internal organs that is seen in patients with kidney disease (estimated glomerular filtration rate, <30) who receive gadolinium-containing contrast agents for MRI or magnetic resonance angiography.<sup>7-12</sup> Almost all reported patients have received hemodialysis, peritoneal dialysis, or both, with peritoneal dialysis thought to confer a greater risk of the disorder than hemodialysis.<sup>9,11,13</sup> The condition is also associated with a history of thrombosis or coagulopathy, a vascular procedure or vascular injury, metabolic acidosis, and erythropoietin use, although the role of these factors, if any, is unclear.<sup>3,7-12</sup> Our patient had all these risk factors, although she was initially unaware of having been exposed to gadolinium.

Nephrogenic systemic fibrosis is characterized by swelling and symmetric, woody induration of the skin on the distal limbs that progresses proximally and can also involve the trunk.<sup>3,7,9,11,13</sup> As seen in this patient, the lesions are poorly demarcated, thickened plaques that range from erythematous to hyperpigmented and have an irregular leading edge that has been called “amoeboid.”<sup>7,9,11-13</sup> Patients may note an itchy or painful quality to the affected skin.<sup>3,7,11</sup> The surface may have a cobblestone or peau d’orange texture.<sup>3,11,12</sup> Extracutaneous findings include scleral telangiectasias early and yellow scleral plaques later, as well as joint inflexibility and contractures that result in decreased mobility and difficulty lifting or bending the legs.<sup>7,9,12,13</sup> Systemic fibrosis can affect the heart, lungs, skeletal muscle, and other organs.<sup>3,10,11</sup> Our patient ultimately displayed many of these features.

It is believed that renal failure and metabolic acidosis increase the half-life of gadolinium in the body, allowing chelated gadolinium to dissociate from its ligand and deposit in the skin and other tissues.<sup>3,8-11</sup> Gadolinium triggers recruitment of circulating fibrocytes to the skin and internal organs, resulting in fibrosis.<sup>8,10-13</sup> Circu-

lating fibrocytes are bone marrow–derived cells that are normally recruited to sites of tissue injury to aid in wound healing.

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SUMMARY

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In summary, this patient with a history of renal failure, metabolic acidosis, recurrent thromboses, dialysis, erythropoietin use, and gadolinium exposure presented with progressive leg swelling, hardening and hyperpigmentation of the skin of the legs and arms, and yellow scleral plaques. The differential diagnosis can be narrowed to eosinophilic fasciitis and nephrogenic systemic fibrosis. In light of disease progression despite prednisone and time and the lack of peripheral-blood eosinophilia, I believe the diagnosis is nephrogenic systemic fibrosis.

There are no specific laboratory tests useful in diagnosing nephrogenic systemic fibrosis.<sup>9,13</sup> I would review previous skin-biopsy specimens with a dermatopathologist, including a complete discussion of the clinical features and a review of clinical photos if available. If these biopsy specimens are nondiagnostic, I would repeat the deep-wedge biopsy of the skin. I would also repeat the complete blood count, thyroid-function tests, and coagulopathy testing and would order serum and urine protein electrophoresis and tests for Scl-70 and anticentromere antibody to help rule out other diagnoses.

*Dr. Nancy Lee Harris (Pathology):* Dr. Kay, what was your thinking when you saw this patient?

*Dr. Jonathan Kay:* When I first saw the patient in rheumatologic consultation, her clinical presentation and improvement after treatment with prednisone, as well as the pathologist's interpretation of the wedge-biopsy specimen from her left thigh, led me to a diagnosis of eosinophilic fasciitis. I recommended that she taper the prednisone dose, keep her left leg mobile to prevent recurrence of deep venous thrombosis, and avoid excessive exercise, which has been thought to elicit eosinophilic fasciitis disease activity.

Fifteen months later, she sought reevaluation because of hyperpigmentation and induration of the skin of her left forearm, left thigh, and both lower legs. At that time, she told me that she had learned that she had received gadodiamide, a gadolinium-containing contrast agent, at the

time of MRI examinations on three occasions in the past.

On examination, the skin changes and scleral plaques were typical of nephrogenic systemic fibrosis, which had clearly progressed since her first consultation with me. The previous skin-biopsy specimen was reevaluated by the pathologist.

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CLINICAL DIAGNOSIS

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Nephrogenic systemic fibrosis.

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DR. DANIELA KROSHINSKY'S  
DIAGNOSIS

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Nephrogenic systemic fibrosis.

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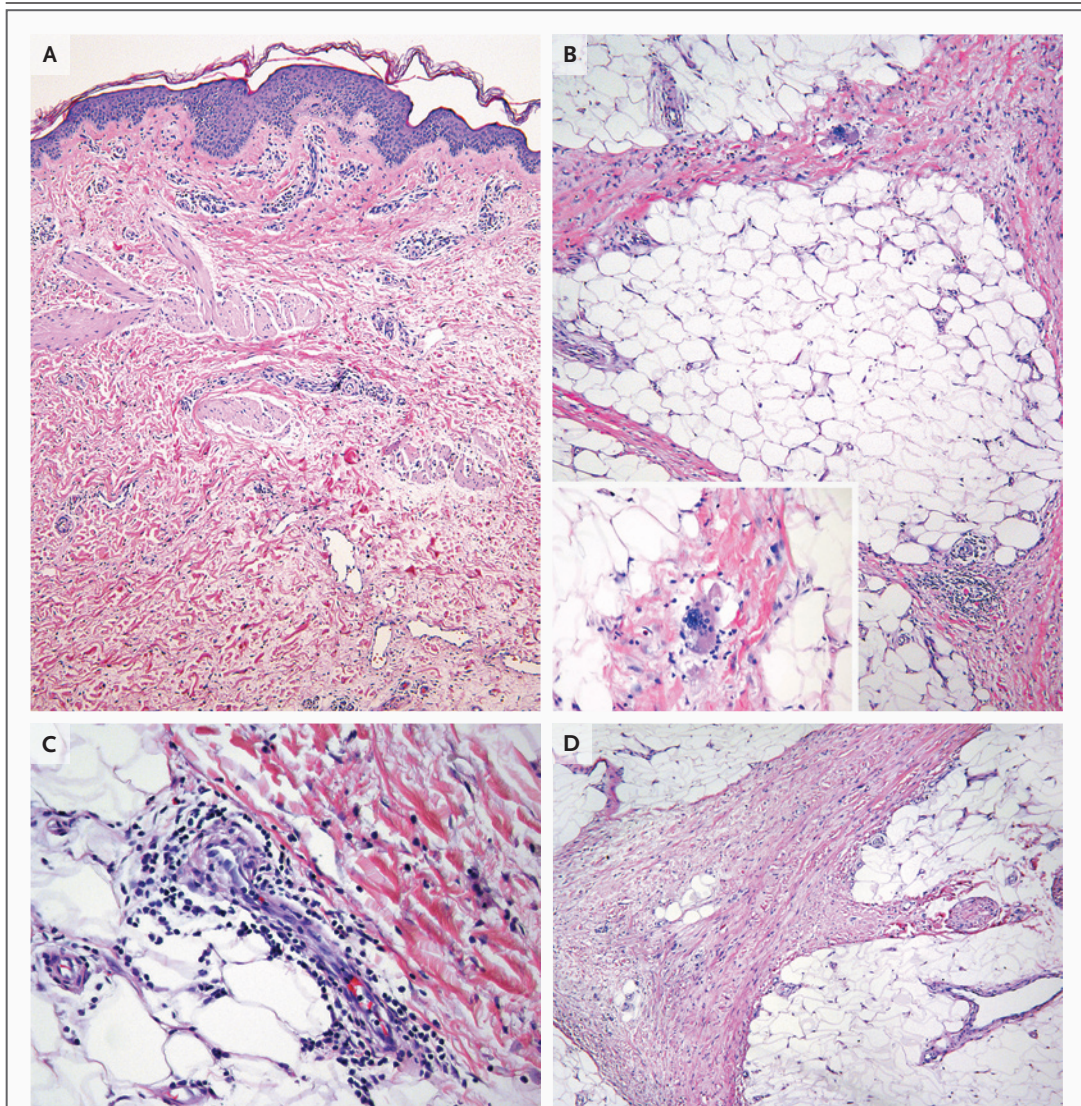
PATHOLOGICAL DISCUSSION

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*Dr. Rosalynn M. Nazarian:* Review of the specimen from the wedge biopsy of skin on the left thigh, performed 7 months before her first evaluation at this hospital, disclosed a superficial perivascular lymphocytic infiltrate, dermal edema, and increased cellularity in the reticular dermis (Fig. 2A). Thickening of the interlobular septa in the subcutaneous fat was seen, with a septal inflammatory infiltrate consisting of histiocytes with occasional multinucleated giant cells, lymphocytes, and eosinophils (Fig. 2B and inset). Focally, the septal infiltrate extended to involve the lobules in a perivascular and lacelike distribution (Fig. 2C). In other areas, there was marked thickening and fibrosis of the interlobular septa without an inflammatory infiltrate (Fig. 2D).

In the context of additional clinical information, the previous slides of the biopsy specimens were reexamined at the patient's second visit to the rheumatologist, with the addition of more stains. Further inspection of the fibrotic areas within the dermis and subcutaneous fat revealed a conspicuous increase in the density of spindle-shaped fibroblasts and thickened collagen bundles with adjacent clefts; both are characteristic features of nephrogenic systemic fibrosis<sup>14,15</sup> (Fig. 3A). The spindle-shaped cells were focally positive on immunohistochemical staining for smooth-muscle actin (Fig. 3B), a feature suggestive of myofibroblastic differentiation, and strongly positive for CD34 (Fig. 3C), a feature consistent with





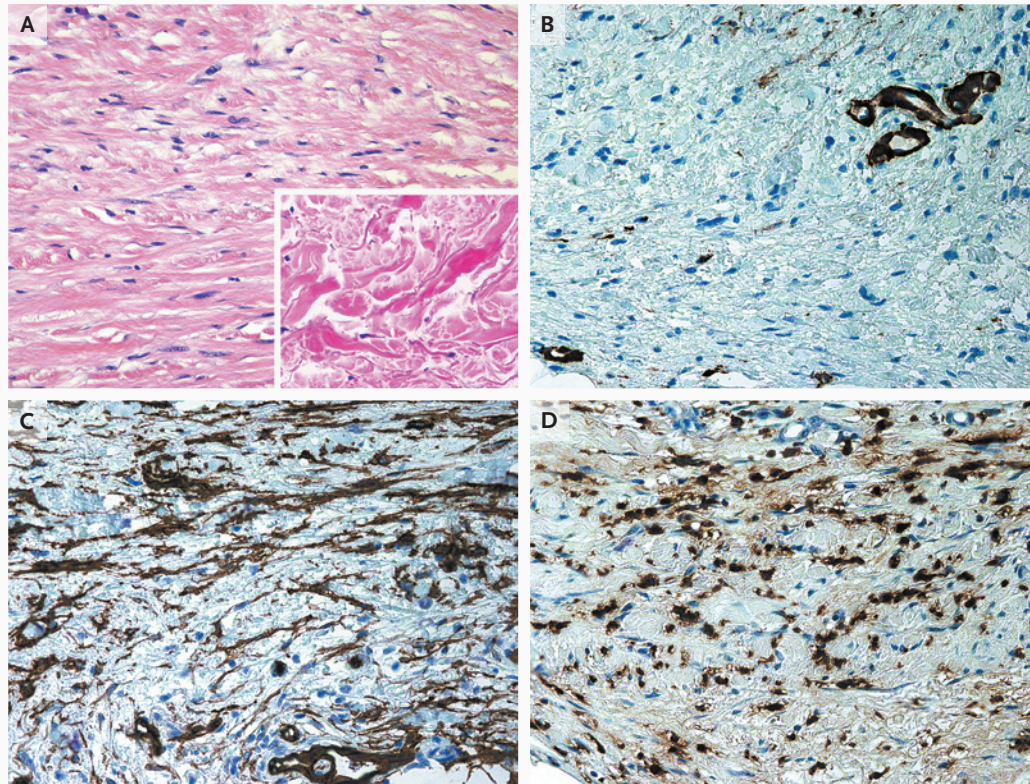
**Figure 2.** Biopsy Specimen of Affected Skin on the Left Thigh, 7 Months before the Initial Evaluation (Hematoxylin and Eosin).

At low power, dermal edema and a superficial perivascular infiltrate is seen. Increased cellularity of the reticular dermis is also noted (Panel A). The subcutaneous fat deep in the section shown in Panel A reveals thickening of the septum, with a mixed inflammatory infiltrate that is consistent with a septal panniculitis (Panel B). At higher magnification, it is apparent that the septal inflammatory infiltrate is composed of histiocytes with occasional multinucleated giant cells, lymphocytes, and eosinophils (inset). Focally, the septal infiltrate has extended to involve the lobule in a perivascular and lacelike pattern (Panel C). In other areas, thickening and fibrosis of the interlobular septum are marked and reveal increased fibroblast cellularity without an associated inflammatory infiltrate (Panel D).

the characteristic dermal fibroblasts of nephrogenic systemic fibrosis.<sup>14</sup> Factor XIIIa-positive mononuclear cells were present throughout the dermis (Fig. 3D), which is another feature typical of (but not specific for) nephrogenic systemic fibrosis.<sup>14</sup> Definitive diagnosis of nephrogenic sys-

temic fibrosis requires knowledge of the clinical history and examination of a deep punch-biopsy specimen that contains subcutaneous tissue. In addition to the features illustrated here, the dermal fibroblasts in nephrogenic systemic fibrosis are also highlighted by procollagen-I stains, and





**Figure 3. Findings on Reexamination of the Skin-Biopsy Specimen, 14 Months after the Initial Evaluation.**

Examination of a single high-power field of affected skin from the left thigh of this patient (Panel A, hematoxylin and eosin) reveals an increased number of spindle-shaped dermal fibroblasts (>69 fibroblast-cell nuclei per high-power field) and thickened eosinophilic collagen bundles with adjacent clefts, as compared with normal skin from a healthy person (inset). The mean density of dermal fibroblast nuclei in patients with nephrogenic systemic fibrosis in a recent study was 69 nuclei per high-power field, as compared with 14 nuclei per high-power field in normal persons.<sup>15</sup> An immunohistochemical stain for smooth-muscle actin (Panel B) highlights the perivascular smooth muscle (strong, diffuse brown staining) and shows focal positive staining in the spindle-shaped cells, which is suggestive of myofibroblastic differentiation. An immunohistochemical stain for CD34 (Panel C) shows strong diffuse positivity in the spindle-shaped cells and highlights the endothelial cells within normal vascular channels. An immunohistochemical stain for factor XIIIa (Panel D) shows positive staining of mononuclear cells throughout the dermis.

elongated dermal elastic fibers are highlighted by the Verhoeff–van Gieson stain.<sup>14</sup> There may be mucin deposition and calcification, ossification, and osteoclast-like giant cells; giant cells were seen in this case.<sup>16,17</sup>

The histologic differential diagnosis of nephrogenic systemic fibrosis is broad (Table 1). Scleromyxedema and eosinophilic fasciitis are the closest histologic mimics, since they share findings of increased fibroblast cellularity and the presence of factor XIIIa–positive histiocytic cells. Laboratory studies are helpful in differentiating these entities.<sup>20,21</sup> In addition, “pools” of dermal mucin

are often seen in scleromyxedema, whereas when mucin is present in nephrogenic systemic fibrosis, deposition is only focal.<sup>22</sup> Normal skin is also included in the histologic differential diagnosis, since the histologic findings in early nephrogenic systemic fibrosis may be subtle. Differentiating nephrogenic systemic fibrosis from other entities involves consideration of the extent of dermal fibroblast cellularity, dermal mucin deposition, cytologic atypia, and associated inflammatory infiltrate, as well as of the immunohistochemical profile. In addition, knowledge of the clinical history, including renal function, presence or ab-

**Table 1. Differential Diagnosis of Nephrogenic Systemic Fibrosis in the Skin.**

Differential Diagnosis	Fibroblast Hypercellularity	Dermal Mucin	Immunohistochemical Profile	Distinguishing Feature
Nephrogenic systemic fibrosis	Yes	Yes	CD34, factor XIIIa*	Renal disease, high fibroblast count (approximately 69 per high-power field)
Scleromyxedema	Yes	Yes	CD34, factor XIIIa	Paraproteinemia
Systemic sclerosis, morphea, and exposure to toxins	No	Yes		Circulating autoantibodies, exposure to L-tryptophan* or rapeseed oil
Lichen sclerosus et atrophicus	No	No		Circulating autoantibodies, Koebner's phenomenon
Sclerodermatous chronic graft-versus-host disease	No	Yes		Bone marrow transplant†
Eosinophilic fasciitis	Yes	No	Factor XIIIa	Peripheral eosinophilia, hypergammaglobulinemia
Malignant tumors				
Dermatofibrosarcoma protuberans	Yes	No	CD34*	Cytologically malignant
Desmoplastic melanoma	Yes	No	S100	Cytologically malignant
Normal skin	Maybe	Maybe		Low fibroblast count (approximately 14 per high-power field)

\* Data are from Cowper et al.<sup>18</sup>† Data are from Peñas et al.<sup>19</sup>

sence of a history of gadolinium administration, and serologic studies, may be essential.

#### DISCUSSION OF MANAGEMENT

*Dr. Kay:* A number of treatments for nephrogenic systemic fibrosis, including topical and oral corticosteroids, selective histamine H<sub>2</sub>-receptor blockers, cyclosporine, other immunosuppressive therapy, and plasmapheresis, have proved to be ineffective.<sup>23,24</sup> Several other treatments have been tried, with variable results. Thalidomide has resulted in improvement in cutaneous changes in several patients with skin disease of recent onset; however, most patients with advanced skin disease did not have a response.<sup>25</sup> Reductions in skin tightness and hardening have been described in patients with nephrogenic systemic fibrosis treated with extracorporeal photopheresis with ultraviolet A light.<sup>26-28</sup> Single case reports have described improvement of skin changes with pentoxifylline<sup>29</sup> and intravenous sodium thiosulfate.<sup>30</sup>

Signaling by means of tyrosine kinase-mediated pathways (transforming growth factor  $\beta$ 1 [TGF $\beta$ 1], Abl, Kit, and platelet-derived growth factor [PDGF] receptor) may be important in the proliferation of fibroblasts and deposition of col-

lagen in tissues in nephrogenic systemic fibrosis.<sup>31-33</sup> Imatinib mesylate selectively inhibits signaling mediated by Abl, Kit, and the PDGF receptor<sup>32,34</sup> and decreases both basal and TGF $\beta$ - and PDGF-induced type I collagen and fibronectin synthesis by dermal fibroblasts.<sup>35</sup> By inhibiting signal transduction through the TGF $\beta$  and PDGF receptors, imatinib mesylate blocks the cellular response to these profibrotic cytokines, even if their tissue levels remain elevated. We observed lessening of skin tethering and joint contractures and reduced dermal and interlobular septal fibrosis and type I procollagen staining in two patients with nephrogenic systemic fibrosis who had been treated with imatinib mesylate for 4 months.<sup>36</sup> There is now an investigator-initiated phase 2, open-label pilot study of imatinib mesylate for the treatment of nephrogenic systemic fibrosis (ClinicalTrials.gov number, NCT00677092, supported by a grant from Novartis and by a grant [1 UL 1 RR025758-01] from the National Center for Research Resources to Harvard Clinical and Translational Science Center), in which patients are treated with imatinib mesylate (400 mg daily) for 4 months and then are observed for 2 months after stopping therapy. The primary outcome is the change in the modified Rodnan skin score (a standard outcome measure for skin disease in

patients with scleroderma that is calculated by summation of skin thickness in 17 body sites) from baseline to 4 months.

When I saw this patient the second time, I suggested that she taper and eventually discontinue prednisone and consider participation in this study, which she elected to do.

*Dr. Harris:* The patient was not able to come today because of complications of her kidney disease, but she sent me some comments that she thought might interest physicians: "First, do not ask a patient if he or she has been exposed to gadolinium. I was asked this and thought that it was either a form of asbestos or disease like tuberculosis. It was not until I was later asked if I had had any tests using contrast material that I made the connection. Second, if someone is not on dialysis, do not assume that he or she will not develop nephrogenic systemic fibrosis. I was not on dialysis until after my last exposure to gadolinium. Finally, if you think a patient's rash is due to Lyme disease and the test is negative multiple times, move on. I was tested about five times for Lyme disease."

Are there any questions?

*A Physician:* What is the current recommendation for the use of gadolinium?

*Dr. Kay:* At this hospital, patients who are on dialysis or have a creatinine clearance of less than 15 ml per minute per 1.73 m<sup>2</sup> of body-surface area (stage 5 chronic kidney disease) do not receive gadolinium-containing contrast agents. Before administering gadolinium, written informed consent is obtained from patients who have a creatinine clearance between 15 and 29 ml per minute (stage 4 chronic kidney disease).

*Dr. Harris:* This is the third case of nephrogenic

systemic fibrosis that we have discussed at one of these exercises,<sup>37,38</sup> and in two cases, the diagnosis was initially missed on examination of skin-biopsy specimens. Although this patient's initial clinical presentation was atypical, the diagnosis of nephrogenic systemic fibrosis was considered by the patient's nephrologist and dermatologist. However, at the time of the biopsy, neither the suspicion of nephrogenic systemic fibrosis nor the history of chronic renal failure was communicated to the pathologist.

*Dr. Lyn M. Duncan (Dermatopathology):* Nephrogenic systemic fibrosis is a diagnosis that relies on good communication between clinicians and pathologists and requires clinicopathological correlation.

*Dr. Harris:* In dermatopathology, and also in other areas of pathology, the clinical history can be essential to establishing a specific pathological diagnosis. Electronic medical records are proving helpful, since we can have the patient's record open on a computer screen in front of us while we are looking at the slides.

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#### ANATOMICAL DIAGNOSIS

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#### Nephrogenic systemic fibrosis.

Presented at the postgraduate course Dermatopathology Update, September 18, 2008, sponsored by the Harvard Medical School Office of Continuing Medical Education.

*Dr. Kay* (now at the Rheumatology Center, UMass Memorial Medical Center, and the Division of Rheumatology, University of Massachusetts Medical School — both in Worcester) reports receiving consulting fees from Amgen, Array BioPharma, Bracco, Centocor, EnzymeRx, Human Genome Sciences, Sanofi-Aventis, Savient, UCB, Roche, and Wyeth; an honorarium from Bristol-Myers Squibb Norway; and grant support from Centocor, Genentech, Novartis, and Pfizer. No other potential conflict of interest relevant to this article was reported.

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#### REFERENCES

- Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology*. 2nd ed. St. Louis: Mosby, 2008.
- Bielsa I, Ariza A. Deep morphea. *Semin Cutan Med Surg* 2007;26:90-5.
- Boin F, Hummers LK. Scleroderma-like fibrosing disorders. *Rheum Dis Clin North Am* 2008;34:199-220.
- Bischoff L, Derk CT. Eosinophilic fasciitis: demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. *Int J Dermatol* 2008;47:29-35.
- Barron GS, Jacob SE, Kirsner RS. Dermatologic complications of chronic venous disease: medical management and beyond. *Ann Vasc Surg* 2007;21:652-62.
- Fisher DA. Desideratum dermatologicum: eliminating lipodermatosclerosis; the term and the entities. *Int J Dermatol* 2000;39:490-2.
- Weenig RH, Gibson LE, el-Azhary R. The role of the hospital dermatologist in the diagnosis and treatment of calciphylaxis and nephrogenic systemic fibrosis. *Semin Cutan Med Surg* 2007;26:163-7.
- Grobner T, Prischl FC. Patient characteristics and risk factors for nephrogenic systemic fibrosis following gadolinium exposure. *Semin Dial* 2008;21:135-9.
- Knopp EA, Cowper SE. Nephrogenic systemic fibrosis: early recognition and treatment. *Semin Dial* 2008;21:123-8.
- Perazella MA. Tissue deposition of gadolinium and development of NSF: a convergence of factors. *Semin Dial* 2008; 21:150-4.
- Prasad SR, Jagirdar J. Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy: a primer for radiologists. *J Comput Assist Tomogr* 2008;32:1-3.
- Scheinfeld N. Nephrogenic fibrosing dermopathy: a comprehensive review for the dermatologist. *Am J Clin Dermatol* 2006;7:237-47.
- Introcaso CE, Hivnor C, Cowper S, Werth VP. Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis: a case series of nine patients and review of the literature. *Int J Dermatol* 2007;46:447-52.
- Todd DJ, Kagan A, Chibnik LB, Kay J.



- Cutaneous changes of nephrogenic systemic fibrosis: predictor of early mortality and association with gadolinium exposure. *Arthritis Rheum* 2007;56:3433-41.
15. Nazarian RM, Mandal RV, Kagan A, Kay J, Duncan LM. Quantitative assessment of dermal fibroblasts in nephrogenic systemic fibrosis. *Mod Pathol* 2008; 21:99A. abstract.
16. Abraham JL, Thakral C, Skov L, Rossen K, Marckmann P. Dermal inorganic gadolinium concentrations: evidence for in vivo transmetallation and long-term persistence in nephrogenic systemic fibrosis. *Br J Dermatol* 2008;158:273-80.
17. Deng AC, Bilu Martin D, Sina B, Gaspari A. Localized nephrogenic fibrosing dermatopathy: aberrant dermal repairing? *J Am Acad Dermatol* 2008;58:336-9.
18. Cowper SE, Su LD, Bhawan J, Robin HS, LeBoit PE. Nephrogenic fibrosing dermatopathy. *Am J Dermatopathol* 2001; 23:383-93.
19. Peñas PF, Jones-Caballero M, Aragüés M, Fernández-Herrera J, Fraga J, García-Diez A. Sclerodermatous graft-vs-host disease: clinical and pathological study of 17 patients. *Arch Dermatol* 2002;138:924-34.
20. Doyle JA, Ginsburg WW. Eosinophilic fasciitis. *Med Clin North Am* 1989;73: 1157-66.
21. Kucher C, Xu X, Pasha T, Elenitsas R. Histopathologic comparison of nephrogenic fibrosing dermatopathy and scleromyxedema. *J Cutan Pathol* 2005;32:484-90.
22. Dinneen AM, Dicken CH. Scleromyxedema. *J Am Acad Dermatol* 1995;33:37-43.
23. Baron PW, Cantos K, Hillebrand DJ, et al. Nephrogenic fibrosing dermatopathy after liver transplantation successfully treated with plasmapheresis. *Am J Dermatopathol* 2003;25:204-9.
24. Swartz RD, Crofford LJ, Phan SH, Ike RW, Su LD. Nephrogenic fibrosing dermatopathy: a novel cutaneous fibrosing disorder in patients with renal failure. *Am J Med* 2003;114:563-72.
25. Chou RC, Mackool BT, Strasswimmer JM, Liu V, Moschella SL, Kay J. Thalidomide therapy improves skin thickening and joint contractures in nephrogenic fibrosing dermatopathy. *Arthritis Rheum* 2004;50:Suppl:S635-S636. abstract.
26. Gilliet M, Cozzio A, Burg G, Nestle FO. Successful treatment of three cases of nephrogenic fibrosing dermatopathy with extracorporeal photopheresis. *Br J Dermatol* 2005;152:531-6.
27. Mathur K, Morris S, Deighan C, Green R, Douglas KW. Extracorporeal photopheresis improves nephrogenic fibrosing dermatopathy/nephrogenic systemic fibrosis: three case reports and review of literature. *J Clin Apher* 2008;23:144-50.
28. Richmond H, Zwerner J, Kim Y, Fiorentino D. Nephrogenic systemic fibrosis: relationship to gadolinium and response to photopheresis. *Arch Dermatol* 2007;143:1025-30. [Erratum, *Arch Dermatol* 2007;143:1565.]
29. Grobner T. Gadolinium — a specific trigger for the development of nephrogenic fibrosing dermatopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006;21:1104-8. [Erratum, *Nephrol Dial Transplant* 2006;21:1745.]
30. Yerram P, Saab G, Karuparthi PR, Hayden MR, Khanna R. Nephrogenic systemic fibrosis: a mysterious disease in patients with renal failure — role of gadolinium-based contrast media in causation and the beneficial effect of intravenous sodium thiosulfate. *Clin J Am Soc Nephrol* 2007;2:258-63.
31. Jiménez SA, Artlett CM, Sandorfi N, et al. Dialysis-associated systemic fibrosis (nephrogenic fibrosing dermatopathy): study of inflammatory cells and transforming growth factor beta1 expression in affected skin. *Arthritis Rheum* 2004;50:2660-6.
32. Daniels CE, Wilkes MC, Edens M, et al. Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. *J Clin Invest* 2004;114:1308-16.
33. Wermuth PJ, Del Galdo F, Jiménez SA. Induction of the expression of profibrotic cytokines and growth factors in normal human peripheral blood monocytes by gadolinium contrast agents. *Arthritis Rheum* 2009;60:1508-18.
34. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med* 1996;2:561-6.
35. Distler JH, Jüngel A, Huber LC, et al. Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis. *Arthritis Rheum* 2007;56:311-22.
36. Kay J, High WA. Imatinib mesylate treatment of nephrogenic systemic fibrosis. *Arthritis Rheum* 2008;58:2543-8.
37. Case Records of the Massachusetts General Hospital (Case 35-2004). *N Engl J Med* 2004;351:2219-27.
38. Case Records of the Massachusetts General Hospital (Case 6-2008). *N Engl J Med* 2008;358:827-38.

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