Presentation of Case

Dr. Lauren R. Zeitels (Medicine): A 20-year-old man was seen in an outpatient clinic of this hospital because of pain and swelling of the left calf and a purpuric rash.

The patient had been well until 3 weeks before presentation to this hospital, when sore throat, nonproductive cough, rhinorrhea, and chills developed. He noted areas of crusting and occasional bleeding in both nares (Fig. 1). His brother had reportedly received a recent diagnosis of streptococcal pharyngitis.

Two weeks before presentation to this hospital, the patient had traveled by airplane to the northwestern United States for a wilderness backpacking trip. Shortly after he arrived, cramping pain developed in his left calf. Over the next 2 days, the pain worsened in severity and was associated with swelling of the calf. He presented to another clinic for evaluation. Noninvasive ultrasonography of the lower leg was performed, and the results were reportedly normal. Ibuprofen was recommended for pain control, and azithromycin was prescribed for suspected upper respiratory infection. Despite the administration of ibuprofen, the pain in the left calf worsened and limited the patient’s ability to bear weight. The swelling progressed from the calf to the foot, and an erythematous rash developed on the dorsum of both feet.

One week before presentation to this hospital, the patient was evaluated in the emergency department of another hospital. He had a history of Crohn’s disease, which had been diagnosed when he was 10 years of age and had resulted in prolonged glucocorticoid use. During the previous 3 years, weekly treatment with adalimumab led to clinical improvement in his Crohn’s disease and he had a considerable growth spurt, in which he gained several inches in height. During the previous several years, the patient had had multiple self-limited episodes of sore throat, nonproductive cough, rhinorrhea, and nasal crusting with associated bleeding. He occasionally used ibuprofen at home but took no other over-the-counter or herbal medications. He was a college student and resided in the central United States. He drank alcohol occasionally and did not smoke tobacco or use illicit drugs. He had a sibling with Crohn’s disease.
On examination at the other hospital, the temperature was 36.2°C, the blood pressure 118/70 mm Hg, the pulse 70 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. He did not appear ill but was in mild distress because of the pain in the left lower leg. The nasal crusting and the swelling of nasal mucous membranes had markedly improved during the previous 2 weeks. The nasal septum was intact, and no nasal polyps or blood were present. Examination of the neck, heart, lungs, and abdomen was normal. There was tenderness on palpation and swelling in the left lower leg from the calf to the dorsal aspect of the foot, without erythema, warmth, or pitting (Fig. 2A). Synovitis of the left ankle was present. Peripheral pulses were normal. Nontender purpuric lesions, including some that were faintly palpable, were present on both lower legs but were more numerous on the left leg (Fig. 2B). Two tender nodules (each 1 cm in diameter) with overlying erythema were present above the right medial malleolus (Fig. 2C) and were similar to lesions the patient had had transiently in the past. Blood levels of electrolytes, glucose, creatine kinase, C3, and C4 were normal, as were results of renal- and liver-function tests, the complete blood count, and the differential count. Assays for antinuclear antibodies and antineutrophil cytoplasmic antibodies (ANCAs) were negative.

Tests for hepatitis B virus surface antigen, hepatitis B virus surface antibodies, hepatitis C virus antibodies, human immunodeficiency virus (HIV) type 1 p24 antigen, and HIV type 1 and type 2 antibodies were negative. Blood cultures showed no growth. Urinalysis revealed clear, yellow urine, with a specific gravity of 1.014 and a pH of 5.5 and with no glucose, ketones, bilirubin, protein, blood, or nitrates by dipstick; examination of the sediment revealed no red cells, white cells, bacteria, or casts. The blood C-reactive protein level was 2.0 mg per deciliter (reference range, 0 to 0.9), the erythrocyte sedimentation rate 30 mm per hour (reference range, <10), and an antistreptolysin O titer 400 IU per milliliter (reference range, 0 to 200).
Radiography of the chest revealed a normal cardiac silhouette and no consolidations or pleural effusions. Computed tomography of the tibia, fibula, and foot, performed after the administration of intravenous contrast material, revealed normal osseous structures without fractures or cortical erosions, as well as diffuse nonspecific edema of the soft tissues of the ankle and proximal dorsal foot without abscesses or deep fascial thickening.

The patient was admitted to the other hospital, and diagnostic tests were performed. He then traveled to New England to visit family and was referred to this hospital for further treatment.

DIFFERENTIAL DIAGNOSIS

Dr. Eli M. Miloslavsky: This 20-year-old man who had a history of Crohn’s disease and was receiving treatment with adalimumab presented with palpable purpura, monoarticular arthritis with prominent swelling, nodular skin lesions, and nasal crusting in the context of a recent upper respiratory illness. These findings are all relatively uncommon in a young man, and in developing a differential diagnosis, focusing on these uncommon features can help to narrow the list of possible causes. Because this patient has had nasal crusting and nodular lesions previously, I will first focus my differential diagnosis on the new manifestations of palpable purpura and monoarticular arthritis.

PURPURA AND ARTHRITIS

Purpuric lesions are generally caused by extravasation of blood from damaged blood vessels. Nonpalpable purpura may be due to thrombocytopenia, systemic illness (e.g., amyloidosis), infection, a hypercoagulable state, nutritional deficiency (e.g., scurvy), sun exposure (e.g., solar purpura), and idiopathic cutaneous conditions (e.g., Schamberg’s disease). However, palpable purpura that involves dependent areas of the body, as was seen in this patient, is strongly suggestive of a small-vessel vasculitis. The presence of inflammatory arthritis in this patient is additional evidence that a vasculitic process is causing the purpura; arthritis is commonly seen in patients with vasculitis but would be uncommon in patients with other causes of purpura.

VASCULITIS

In evaluating a patient with vasculitis, I first attempt to determine whether the involved vessels are small, medium, or large. This categorization of systemic vasculitis offers a useful diagnostic framework, because each vessel size is associated with characteristic clinical features (Table 1). For example, large-vessel vasculitis typically affects the aorta and its branches and does not cause the type of purpuric skin lesions seen in this patient. Because medium-sized arteries supply a larger area of the skin than do small arteries, medium-vessel vasculitis leads to skin ulcers, nodules, and livedo racemosa, whereas small-vessel vasculitis typically causes petechiae and purpura. This patient’s predominant skin manifestation is palpable purpura, which suggests that he has a vasculitis affecting the small arteries.

After assessing the size of the affected vessels, I ascertain the extent of other organ involvement, which determines the urgency of the evaluation and the severity of the disease process. This patient has no proteinuria or hematuria that would suggest glomerulonephritis, and he has no hemoptysis or parenchymal infiltrates that would suggest diffuse alveolar hemorrhage. In addition, he has no neuropathic symptoms that would suggest a vasculitic neuropathy and no abdominal symptoms that would raise concern about vasculitis involving the mesenteric vessels.

SMALL-VESSEL VASCULITIS

Small-vessel vasculitides share common clinical features. For example, constitutional symptoms, inflammatory arthritis, palpable purpura, glomerulonephritis, diffuse alveolar hemorrhage, and vasculitic neuropathy can occur in nearly all small-vessel vasculitides. To evaluate potential causes of a small-vessel vasculitis, I focus on clinical features that can help to differentiate among the vasculitides (Table 1).

Secondary Vasculitis

One of the most prominent features of this patient’s presentation is the finding of skin lesions. Cutaneous vasculitis may occur as a manifestation of cancer, infection, or an inflammatory condition. Before considering the various primary systemic vasculitides, it is important to
determine whether the vasculitis in this patient may be due to one of these other processes. Cancer is unlikely in this young patient who does not have constitutional symptoms, lymphadenopathy, or a testicular mass.

Because this patient is receiving a tumor necrosis factor α (TNF-α) inhibitor, he is at increased risk for infection. In addition, his recent camping trip to the northwestern United States may have put him at risk for a tickborne disease, such as Rocky Mountain spotted fever. However, infections that cause purpura and petechiae, such as Rocky Mountain spotted fever and disseminated meningococcemia, are typically severe and of sudden onset, and these features do not fit with this patient’s presentation. Infections such as subacute bacterial endocarditis can cause cutaneous vasculitis through the formation of antigen–antibody complexes. However, this usually occurs with a gradual time course, and the normal white-cell count and the absence of constitutional symptoms and of risk factors for endocarditis in this patient make this diagnosis unlikely.

Use of illicit drugs, such as cocaine (particularly in combination with levamisole, a common
adulterant of cocaine), may cause vasculitis. However, this patient reports no history of cocaine use, and his lesions are not typical of levamisole-induced vasculitis, which tends to involve the ears.9

Vasculitis can also result from inflammatory conditions, such as systemic lupus erythematosus and Sjögren’s syndrome. This patient has no symptoms that would suggest the presence of these conditions, and the negative test for anti-nuclear antibodies makes both of these diagnoses unlikely. Crohn’s disease has a number of extraintestinal manifestations, and on rare occasions, concomitant vasculitis has been reported. However, the majority of such reported cases are of primary vasculitides in association with Crohn’s disease.10 I cannot rule out the possibility of vasculitis related to Crohn’s disease, but given its rarity, I would consider primary systemic vasculitis to be a more likely cause of this patient’s illness.

Primary Systemic Vasculitis

Small-vessel vasculitides can be divided into two categories: ANCA-associated vasculitis and immune complex–mediated vasculitis. The three types of ANCA-associated vasculitis are eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis, and granulomatosis with polyangiitis. In this patient, the absence of peripheral eosinophilia rules out eosinophilic granulomatosis with polyangiitis. The negative testing for ANCA combined with the absence of renal and pulmonary disease makes microscopic polyangiitis unlikely. However, granulomatosis with polyangiitis should be considered, because it can cause arthritis, cutaneous vasculitis, and granulomatous inflammatory lesions in the nose, sinuses, lungs, and airways.2 Nasal crusting is a common manifestation of granulomatosis with polyangiitis with sinonasal involvement, and it is an important feature that distinguishes granulomatosis with polyangiitis from viral or bacterial sinusitis, which does not typically cause crusting. In patients who have granulomatosis with polyangiitis, the sensitivity of testing for ANCA is more than 90% among those who have renal involvement but is approximately 60% among those who do not have renal involvement.2,3 Although a negative test for ANCA does not rule out granulomatosis with polyangiitis in this case, I would expect nasal crusting due to granulomatosis with polyangiitis to persist rather than resolve spontaneously. In the absence of persistent granulomatous manifestations, a negative test for ANCA is reassuring and makes granulomatosis with polyangiitis an unlikely diagnosis.

Immune Complex–Mediated Vasculitis

Other than vasculitis associated with drug reactions, the most common types of immune complex–mediated vasculitis are cryoglobulinemic vasculitis and IgA vasculitis (formerly Henoch–Schönlein purpura). Cryoglobulinemic vasculitis can be idiopathic but is typically seen in association with hepatitis C virus infection and is less commonly seen with systemic lupus erythematosus, Sjögren’s syndrome, or hepatitis B virus infection.11 Cryoglobulinemic vasculitis is the result of immune complex deposition in vessel walls, which leads to activation of the classical complement pathway. As a result, the blood C4 level is low in the majority of affected patients. Although the cryoglobulin levels were not checked in this patient, the negative testing for hepatitis C virus and the normal complement levels make cryoglobulinemic vasculitis an unlikely diagnosis.

The presence of palpable purpura in this patient warrants consideration of IgA vasculitis because, in contrast to other vasculitides, IgA vasculitis is associated with the onset of cutaneous lesions before or shortly after the onset of extracutaneous manifestations in most cases.12 Although IgA vasculitis occurs more frequently in children than adults, it is a common vasculitis in adults, with a higher incidence than that of granulomatosis with polyangiitis.13,14 This patient had neither gastrointestinal nor renal involvement, both of which are commonly seen in patients with IgA vasculitis. However, approximately one third of patients with IgA vasculitis do not have renal or gastrointestinal involvement.12,15 Although articular manifestations of IgA vasculitis can involve any joint, they tend to involve the large joints of the legs. Prominent leg swelling has been reported with IgA vasculitis.16 In summary, the combination of palpable purpura and arthritis with prominent leg swelling that was seen in this patient is consistent with a diagnosis of IgA vasculitis.

IgA vasculitis is unique among vasculitides because it is frequently triggered by infection or medication use and is often self-limited.13 A number of potential triggers are present in this patient, including a recent upper respiratory in-
Infection and use of a TNF-α inhibitor. It is unclear whether the upper respiratory infection that preceded the small-vessel vasculitis in this patient was caused by group A streptococcus, which the patient's brother reportedly had had recently. A single moderately elevated antistreptolysin O titer could reflect an infection that occurred in the remote past, whereas evidence of a rising streptolysin O titer would be more suggestive of a recent infection. Nevertheless, a broad range of infections, including streptococcal and nonstreptococcal infections, have been implicated in the development of IgA vasculitis. In addition, this patient was receiving a TNF-α inhibitor, and some reports raise the possibility that this class of medications can lead to the development of IgA vasculitis.

Features of this patient's presentation that would be atypical in a patient with IgA vasculitis include the nodular lesions and nasal crusting. The fact that he had had these symptoms intermittently before the onset of this illness suggests that they may be unrelated to the current episode. Although their cause remains uncertain, the patient's underlying Crohn's disease offers a plausible explanation for both symptoms. Common cutaneous manifestations of Crohn's disease include pyoderma gangrenosum, neutrophilic dermatosis, and erythema nodosum. Despite the fact that this patient's intestinal manifestations appear to be well controlled, his nodular lesions could be consistent with erythema nodosum. On rare occasions, nasal crusting has been reported as an extraintestinal manifestation of Crohn's disease, and therefore it may be further evidence of active Crohn's disease, although other causes of nasal crusting are possible, as well.

In summary, in the absence of signs and symptoms of cancer and infection, a primary systemic small-vessel vasculitis is the most likely explanation of the features of this patient's presentation. Given the presence of palpable purpura and arthritis with prominent periarthritis swelling and the absence of features suggestive of other vasculitides, IgA vasculitis is the most likely diagnosis in this patient. The presence of several possible triggers of IgA vasculitis further supports this diagnosis. I suspect the diagnostic test was a skin biopsy. Hematoxylin and eosin staining of a biopsy specimen would reveal a leukocytoclastic vasculitis, which is a typical finding on skin biopsy in a patient with any small-vessel vasculitis and is not specific for IgA vasculitis. In order to distinguish between IgA vasculitis and other causes of leukocytoclastic vasculitis, immunofluorescence staining of a second biopsy specimen would be needed to evaluate for IgA deposition in the vessel walls.

Dr. Meridale V. Baggett (Medicine): Dr. Stone, what was your impression when you evaluated this patient?

Dr. John H. Stone: Evaluation of this patient was confounded by several potential “red herrings,” including the long-standing Crohn's disease, the immunosuppression with a TNF-α inhibitor, the recent travel history, and the illness in a family member. We were convinced, however, that the presence of palpable purpura must represent a small-vessel vasculitis. In view of the patient's age, the presence of an antecedent upper respiratory tract infection, and the presence of a compatible pattern of peripheral-joint arthritis, we thought that IgA vasculitis was the most likely diagnosis. One feature that favored IgA vasculitis over other forms of small-vessel vasculitis was the strikingly asymmetric leg swelling. IgA vasculitis is known to be associated with such edema in a variety of locations, although the precise mechanism of this disease manifestation is not well defined. We suspected that the swelling in this patient resulted from an intense, localized vasculitis in the gastrocnemius muscle. At the other hospital, the diagnostic procedure was a skin biopsy. In order to confirm the diagnosis of IgA vasculitis, we requested tissue that had been obtained during that procedure and reviewed the histopathological findings.

### Clinical Diagnosis

IgA vasculitis and Crohn's disease with erythema nodosum.

### Dr. Eli M. Miloslavsky's Diagnosis

IgA vasculitis.

### Pathological Discussion

Dr. Andrea P. Moy: Microscopic evaluation of a 4-mm punch-biopsy specimen of lesional skin from the left ankle was performed. Hematoxylin and eosin staining revealed a superficial and
mid-dermal perivascular and interstitial inflammatory infiltrate that was composed predominantly of neutrophils. Prominent leukocytoclasis, neutrophil nuclear dust, erythrocyte extravasation, and focal fibrinoid necrosis of the vessel walls were present (Fig. 3). These findings were consistent with a diagnosis of leukocytoclastic vasculitis.

Leukocytoclastic vasculitis represents a vascular reaction pattern in the skin and is not a specific diagnosis. It can be a manifestation of IgA or urticarial vasculitis or may be idiopathic. It may also result from underlying infections, medication use, inflammatory disorders, and cancer.25,26 The pathogenesis involves deposition of circulating immune complex in the walls of small vessels and activation of the complement system. The subsequent influx of neutrophils leads to the release of lysosomal enzymes, which damage the vessel wall, leading to fibrin deposition and extravasation of erythrocytes.27 This is a dynamic process with variation in the amount of immune complex deposition, and the histopathological features observed in a biopsy specimen that is 18 to 24 hours old are most likely to lead to a diagnosis.28 The characteristic histopathological findings of leukocytoclastic vasculitis include a neutrophil-rich infiltrate surrounding postcapillary venules and capillary loops with leukocytoclasia, vascular endothelial swelling, fibrinoid necrosis of the vessel walls, and erythrocyte extravasation.26,28

In order to help narrow the differential diagnosis for leukocytoclastic vasculitis, direct immunofluorescence staining can be performed. Many patients with leukocytoclastic vasculitis have

Figure 3. Skin-Biopsy Specimen from the Left Ankle (Hematoxylin and Eosin).

A superficial and mid‑dermal perivascular inflammatory infiltrate is shown (Panel A). It is composed predominantly of neutrophils, and there is prominent leukocytoclasis and erythrocyte extravasation (Panels B and C). Focal fibrinoid necrosis of the vessel walls is present (Panel D, arrow). These findings are consistent with the diagnosis of leukocytoclastic vasculitis.
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**DISCUSSION OF MANAGEMENT**

Dr. Stone: IgA vasculitis occurs most commonly in children, and the majority of cases prove to be self-limited illnesses that require no specific therapy. The four organ systems that are most commonly affected by the disease are the skin, the joints, the bowel, and the kidneys. When the clinical manifestations in any of these organs are sufficiently severe, treatment must be considered not only for symptomatic relief but also to prevent vasculitis-related damage. In this patient, the cutaneous disease, which was limited to a small portion of the skin and was not associated with cutaneous ulceration, was relatively mild and did not require treatment. The patient had no gastrointestinal symptoms at presentation. Gastrointestinal involvement in IgA vasculitis is usually

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Evidence of perivascular immunoreactivity for IgG, IgM, C3, and fibrinogen on direct immunofluorescence staining.\(^{25,26,29}\) In this case, a second 4-mm punch-biopsy specimen of lesional skin from the left ankle was received in Michel's fixative, and direct immunofluorescence staining revealed positive granular perivascular immunoreactivity for IgA, C3, and fibrin, findings consistent with IgA-associated leukocytoclastic vasculitis (Fig. 4). It is important to note that IgA-associated leukocytoclastic vasculitis is not pathognomonic for IgA vasculitis, since IgA deposition may also be seen in leukocytoclastic vasculitis that is due to cryoglobulinemia or the use of certain medications, including TNF-α inhibitors.\(^{30,31}\) However, in this case, the pathological diagnosis of IgA vasculitis is confirmed when the findings are considered in the context of this patient's clinical presentation.

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**Figure 4. Skin-Biopsy Specimen from the Left Ankle (Direct Immunofluorescence).**

Positive immunoreactivity for IgA (Panels A and B), C3 (Panel C), and fibrin (Panel D) is present in a granular, perivascular pattern. This pattern of staining is consistent with the diagnosis of IgA vasculitis.
characterized by colicky abdominal pain that often occurs before the eruption of palpable purpura on the skin and sometimes leads to exploratory surgery for a presumed acute abdomen. The patient also had no evidence of glomerulonephritis, a complication of IgA vasculitis that is particularly challenging to treat and can develop even during the weeks or months after the initial presentation. However, his musculoskeletal symptoms were severe; he was unable to walk because of his ankle arthritis and the intense tenderness and swelling of his gastrocnemius muscle. On the basis of the severity of his musculoskeletal symptoms, we elected to initiate glucocorticoid therapy.

Glucocorticoids are effective in the treatment of IgA vasculitis. In view of the patient’s long history of glucocorticoid use for the treatment of Crohn’s disease, we thought it was important to use the lowest effective dose. We prescribed a 2-week tapering course of prednisone, with a starting dose of 20 mg per day.

The patient’s purpura resolved quickly and did not recur after treatment with prednisone was complete. The synovitis and muscle tenderness and swelling were slower to resolve, and the possibility of a chronic regional pain syndrome was considered. Fortunately, these symptoms also resolved over a number of additional weeks, and the patient was able to return to college in time for the fall semester. Symptoms of IgA vasculitis have not recurred in this patient.

ANATOMICAL DIAGNOSIS

IgA vasculitis.

This case was presented at the Medical Case Conference.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This case is dedicated to the memory of Massachusetts General Hospital medical residents Lauren Zeitels, M.D., Ph.D., and Victor Fedorov, M.D., Ph.D., who died in an avalanche in March 2017.

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