Hepatitis C- and Human Immunodeficiency Virus-Induced Hypersensitivity Vasculitis

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Case presentation

A 49-year-old Caucasian man with a history of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) was evaluated for fevers, rash, and arthritis. The patient's medical history was notable for HIV (diagnosed in 1994; last CD4 count of 500 and viral load >10,000). He was not on anti-retroviral therapy for the last year due to liver function abnormalities but had no history of opportunistic

infections, he was infected with HCV (viral load greater than 3.5 million, untreated), and also carried diagnoses of hypertension, insulin-dependent diabetes mellitus, paroxysmal atrial fibrillation (not on anticoagulation), depression, and a recent negative purified protein derivative test. He had no known drug allergies. His home medications included detemir, atenolol, humulin, and lisinopril. He had a 90-pack year smoking history, as well as previous alcohol and heroin abuse (which he quit in 1999). He was living with his girlfriend, and on disability.

Five months prior to this evaluation the patient was hospitalized for gross hematuria, fevers to 39°C, and non-bloody diarrhea. During the hospitalization, he developed asymmetric arthritis and a petechial rash. On physical examination, his blood pressure was 170/80 mmHg, he had synovitis of both wrists, proximal interphalangeal (PIP) joints bilaterally, and the left ankle. The rash was flat, non-blanching, purpuric, and worst over his extremities, flank, and shawl area, sparing his palms and soles. His work-up was negative for cryoglobulins; rheumatoid factor (RF); antimyeloperoxidase; and antiproteinase 3 antibodies, anti-Ro (SSA) and anti-La (SSB) antibodies, anti-nuclear antibody (ANA), and anti-double-stranded DNA antibody (dsDNA; Table 1). Complement levels were normal. Hepatitis B serologies were negative. Computerized axial tomography scan (CT scan) of the abdomen and pelvis (without contrast) showed hepatosplenomegaly. Renal ultrasound was negative for hydronephrosis. He was treated with intravenous (IV) Solumedrol 60 mg every 8 h and IV fluids, with resolution of his fever, rash, and arthritis as well as return of his creatinine to his baseline level. A renal biopsy was scheduled but the patient eloped from the hospital before the renal biopsy could be performed. The patient was seen in nephrology clinic 1 month after discharge; repeat cryoglobulins were positive with 2% precipitate and he had 4 g of proteinuria on a spot urine protein to creatinine ratio.

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Each author certifies that his or her institution has approved the reporting of this case, that all investigations were conducted in conformity with ethical principles of research.

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Table 1 Initial significant laboratory tests

Laboratory test	Admission 1	Admission 2	Normal values
White blood cell	9.2	4.9	$4.0\text{--}10.0 \times 10^9/\text{L}$
Differential	N—81%/L—12%	Normal	N—40–74%, L—19–48%
Hemoglobin	13.4	9.5	12–16 g/dl
Platelets	181	310	$150\text{--}350 \times 10^9/\text{L}$
Sodium	143	N/A	135–145 mEq/L
Potassium	4.1	N/A	3.5–5.1 mEq/L
BUN	28	14	7–19 mg/dL
Creatinine	3.9 ^a	2	0.6–1.2 mg/dL
Glucose	279	N/A	70–105 mg/dL
Total protein	7.2	N/A	6.0–8.3 g/dL
Albumin	2.4	2.4	3.7–5.1 g/dL
Total bilirubin	0.9	N/A	0.2–1.5 g/dL
AST	60	Normal	3–50 U/L
ALT	58	Normal	3–60 U/L
Alkaline phosphatase	91	N/A	20–125 U/L
Urine protein	>300	>300	Negative
Urine blood	Large	Large	Negative
Urine RBC	>50	N/A	Negative
Urine sediment	No RBC or WBC casts	RBC casts, no WBC casts	N/A
Urine spot protein/creatinine ratio	2.3 g	0.3 g	0–0.2 g

^a A rise in creatinine from 1.4 to 3.9 over a 1 month period

Five months later, the patient presented with new psoriasiform rash, joint pains, intermittent fevers to 38°C, and weight loss of 30 lb over the previous several months. His review of systems was negative for headaches, visual changes, diplopia, sinus pain, aphthous ulcers, shortness of breath, hemoptysis, chest pain, Raynaud's phenomenon, and dysphagia.

At this presentation the physical examination was significant for a temperature of 38°C, cachexia, a prominent psoriasiform rash (worst over the scalp, cheeks, nose, digits, and groin), and nail pitting. On musculoskeletal examination, he had asymmetric polyarticular arthritis involving the right shoulder, bilateral elbows, wrists, right knee, and bilateral ankles. He also had arthritis of the right thumb; fourth and fifth PIP and distal interphalangeal (DIP) joints; and left second and third metacarpophalangeal, PIP, and DIP joints. His digits had a fusiform appearance, consistent with dactylitis. His abdominal examination was notable for hepatomegaly. Laboratory values at this time of second admission are shown in Table 1. His CD4 count was 182 with a HIV viral load of 5,344,000. Cryoglobulins were negative and serum complement levels were normal. Erythrocyte sedimentation rate (ESR) and C-reactive protein were elevated at 115 and 2.1, respectively. A spot urine protein to creatinine ratio was 0.3 g. Prednisone 40 mg daily and sulfasalazine 500 mg daily were started with marked improvement in joint symptoms and rash. Anti-retroviral agents were not started in the acute setting. An infectious work-up was unrevealing, and the patient remained afebrile while in the hospital. A renal biopsy was performed.

Pathologic findings

The submitted renal biopsy contains adequate renal cortical tissue with over 30 glomeruli. There is fairly extensive active and chronic tubulo-interstitial inflammation of moderate

intensity, affecting greater than 70%, with areas of active tubulitis and features of tubular injury. The inflammatory infiltrate is composed of activated lymphocytes with prominent eosinophils, focally admixed with plasma cells and histiocytes (Fig. 1). This is out of proportion to the glomerular disease and is suggestive of a hypersensitivity reaction.

The glomeruli show mild to moderate mesangial hypercellularity, which may be seen in both the settings of HIV and/or HCV infections. In addition, several glomeruli display small fibrocellular crescents in the Bowman space, some with segmental adhesions (Fig. 2). These findings are indicative of a healing phase of severe segmental glomerular injury such as small vessel vasculitis. This appears to be of pauci-immune type, as direct immunofluorescence studies, using anti-human antibodies to immunoglobulins

Fig. 1. Renal biopsy specimen demonstrating areas of diffuse interstitial inflammation with prominent eosinophils (as seen in red). The number of eosinophils here is out of proportion to other active inflammatory cells, consistent with a hypersensitivity type of reaction

Fig. 2. High power view of a healing fibrocellular crescent is indicated with the *oval*. This crescent surrounds and is compressing a glomerulus that shows mesangial hypercellularity and proliferation

and complement components, were negative. This excludes the possibility of immune-complex-mediated glomerular lesions, secondary to infections or other auto-immune diseases.

Several ultrastructural features including conspicuously thickened glomerular capillary basement membranes (Fig. 3), significant foot process effacement and reactive changes in the podocytes, though non-specific, are observed, that can be associated with HIV nephropathy and sometimes with HCV infection. No electron dense deposits to suggest immune complex glomerular deposits were identified.

In summary, the renal biopsy findings are suggestive of mild HIV/HCV-associated changes with a hypersensitivity interstitial inflammatory reaction and a recent healing episode of pauci-immune small vessel vasculitis. Changes of mild diabetic nephropathy were also noted.

Clinical discussion

This is a 49-year-old Caucasian man with untreated HIV and HCV infections presenting with fevers, petechial and psoriasiform rash, polyarticular arthritis, acute renal failure with proteinuria, and transiently positive cryoglobulins that responded to corticosteroid therapy.

The first presentation included systemic symptoms with evidence of single organ involvement. Prior to having the renal biopsy results, differentials included hyperglobulinemic, cryoglobulinemic, and hypersensitivity vasculitis; postinfectious glomerulonephritis; hemolytic uremic syndrome; and Henoch–Schönlein purpura (HSP). Hyperglobulinemic vasculitis (in this case gamma globulin levels were 4.8 g/dL) usually occurs in association with Waldenström's macroglobulinemia but also can be seen with systemic lupus erythematosus and Sjögren syndrome. The lesions are those of non-palpable purpura such as in this case. Less commonly immune complex deposition in the kidney and renal vasculitis can occur. However, the absence

of a monoclonal gammopathy, anti-SSA, and anti-SSB auto-antibodies, along with a negative ANA test made this less likely. Post-infectious glomerulonephritis was another consideration, especially with a febrile presentation, hematuria, and diarrhea. Glomerulonephritis is more commonly seen post-infection with streptococcal pharyngitis or rash. Additionally, due to the absence of hypocomplementemia and red blood cell casts, this was also less likely. HSP was less likely given the age of the patient, and the absence of IgA deposition on renal biopsy. Polyarteritis nodosa can cause cutaneous leukocytoclastic vasculitis on exception, yet is less likely as this usually affects medium-sized vessels, and is characterized by a focal necrotizing glomerulonephritis on renal biopsy. Based on the initial presentation, in conjunction with the interstitial nephritis on the biopsy, history of untreated HCV, and positive cryoglobulins, the two most likely diagnoses were cryoglobulinemic and hypersensitivity vasculitis.

The second presentation is of severe psoriatic arthritis in a patient with HIV. The interstitial nephritis on the biopsy at this point might also suggest the diffuse infiltrative lymphocytosis syndrome; however, the majority of these patients have parotid enlargement and/or sicca symptoms, which this patient did not have.

Cryoglobulins are immunoglobulins or immunoglobulin-containing complexes that spontaneously precipitate and form a gel at low temperatures. They become soluble again when the temperature rises. A possible causative role of hepatotropic viruses in mixed cryoglobulinemia (particularly hepatitis C) has been hypothesized, suggested by the presence of chronic hepatitis in almost two-thirds of patients. Mixed cryoglobulins consist of a monoclonal IgM antibody with RF specificity that interacts with a broad polyclonal spectrum of IgG molecules. Mixed cryoglobulins activate and consume complement acting like an immune complex. The exact circumstances predisposing HCV-infected patients to develop cryoglobulinemic vasculitis remains unclear. Cryoglobulinemic vasculitis is typically associated with advanced age, longer duration of HCV

Fig. 3. Electron microscopy shows a thickened capillary basement membrane (*arrows*), with effaced foot processes, indicating podocytic injury related to HIV infection

infection, type II mixed cryoglobulinemia (MC), a higher MC serum level, and clonal B cell expansions in both the blood and liver that produce the monoclonal RF [1, 2]. Patients present with cutaneous manifestations, including palpable purpura, Raynaud's phenomenon, and digital ulceration/necrosis. Other manifestations include arthralgias/arthritis, neuropathy, and renal disease (most commonly membranoproliferative glomerulonephritis). In addition to immunoglobulins found in the cryoprecipitate, serum complement levels are almost always low and the test for RF is usually positive, although the monoclonal RF of mixed cryoglobulinemia differs from the type of RF found in rheumatoid arthritis. In our patient, the transiently positive cryoglobulins, history of untreated HCV, skin and joint manifestations, and renal disease made cryoglobulinemia a diagnostic consideration. Our patient had normal complement levels and negative RF, however, and the renal biopsy did not show any immune-complex-mediated lesions to suggest membranoproliferative glomerulonephritis. Thus, cryoglobulinemic vasculitis was excluded.

Of note, there are several treatment options for patients with HCV-related cryoglobulinemic vasculitis. Serious visceral involvement calls for treatment with glucocorticoids and cytotoxic agents. Plasmapheresis has also been used with some success. At present, the drug of choice for treating patients with mixed cryoglobulinemia is interferon-alpha (IFN-alpha). However, it has been associated with a poor response and high relapse rate in patients with systemic vasculitis [3–5]. Combination therapy with IFN-alpha plus ribavirin provides much better short- and long-term results [6, 7]. Recently, a PEGylated IFN alpha-2b (PEG-IFN alpha-2b) has become available, with promising results. A single-center study done in 2006 compared patients treated with IFN alpha-2b plus ribavirin to those receiving PEG-IFN alpha-2b plus ribavirin. Patients receiving the latter had a higher sustained clinical, virologic, and immunologic response rate, regardless of HCV genotype, and viral load [8].

Hypersensitivity vasculitis is a small vessel vasculitis. It can be secondary to infections, drug reactions, or malignancies. Infectious causes include chronic viremias (such as Hepatitis B or C virus and HIV), bacteremias (such as gonococcemia), and Lyme disease. Many medications can cause hypersensitivity vasculitis. The penicillins, cephalosporins, sulfonamides (including most loop and thiazide-type diuretics), phenytoin, and allopurinol are a few of the drugs that have been implicated. In some patients, hypersensitivity vasculitis occurs during the course of or prior to malignancies, most often hematologic (such as myelodysplastic syndrome or lymphoid malignancies) rather than solid tumors [9]. Although the disorder is usually acute, chronic disease has been reported in those with Hepatitis C virus infection [10]. Clinical findings include skin lesions (palpable purpura and/or petechiae), fever, arthralgias, and an elevated ESR. Systemic manifestations include fever, pericarditis, arthritis, headaches, nephritis, and retinal vasculitis in advanced cases. Renal involvement may manifest as hematuria, proteinuria, and cellular casts, and usually has a worse prognosis.

Skin biopsy in a patient with hypersensitivity vasculitis may show neutrophils around an arteriole or venule; however, biopsy alone is usually not diagnostic and usually shows nonspecific vascular inflammation [11]. According to the American College of Rheumatology Diagnostic Criteria (Table 2), our patient technically met two of five criteria for hypersensitivity vasculitis, based on age (>16) and history of palpable purpura (of note, the presence of three or more of these criteria has a sensitivity and specificity of 71% and 84%, respectively [12]). It is possible that his vasculitic illness was medication-related, although no specific medication could be identified in temporal relation to his symptoms. While our patient's biopsy did not show neutrophils around an arteriole or venule, it did show diffuse inflammation with prominent eosinophils. Advanced HIV and HCV infection may influence aspects of the host response during hypersensitivity vasculitis. These biopsy findings, in the setting of untreated HIV and HCV, along with his systemic manifestations, made the diagnosis of hypersensitivity vasculitis more likely.

There are several non-vasculitic disease processes which can closely mimic the presentation of vasculitis. In the work-up of patients with presumed vasculitis of any etiology, infectious and autoimmune work-up should be done to rule out these mimickers. For our patient, it was particularly important to rule out infectious processes (such as endocarditis and sepsis), given both his degree of immunodeficiency and history of intravenous drug abuse. Patients with untreated HCV can also present with numerous extrahepatic clinical and biologic manifestations. Clinical manifestations can involve the joints and skin, as in our patient. Biologic abnormalities can include antinuclear antibodies and anti-smooth muscle antibodies [13]. Without the findings from the renal biopsy, it would have been difficult to determine whether our patient's systemic manifestations were a result of a vasculitic process or due to extrahepatic manifestations of his HCV.

Treatment for hypersensitivity vasculitis should be aimed at stopping any identifiable offending agent, as well as at underlying infections, such as acute retroviral agents for HIV and interferon to those with Hepatitis C, as in our patient. Acute therapy may include steroids and/or immunosuppressive agents; however, these latter therapies should be used with caution in a patient with either of these viral infections.

Our patient (with no prior history of psoriasis or psoriatic arthritis) then developed an acute psoriasiform

Table 2 The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis [12]

Age >16
Use of a possible offending drug in temporal relation to the symptoms
Palpable purpura
Maculopapular rash
Biopsy of a skin lesion showing neutrophils around an arteriole or venule

The presence of three or more of these criteria has a sensitivity and specificity of 71% and 84%, respectively

eruption during the second admission. This new rash was associated with onychodystrophy and a different pattern of joint involvement, including DIP arthritis and dactylitis, the latter indicative of enthesitis. This begs the question of what trigger(s) could have led to such a phenomenon. We can speculate that this patient, with untreated HIV and HCV, was exposed to an array of pathogens and had a marked degree of immune activation including elevated levels of cytokines and chemokines and extensive immune dysregulation, which likely contributed to the arthrocuteaneous disorder. Whether or not there is a direct correlation between the hypersensitivity vasculitis and psoriasiform eruption is unclear. Interestingly, there are reports of medication-induced psoriasiform eruptions, including paroxetine [14], quinidine [15], and even anti-tumor necrosis-alpha (TNF-alpha) therapies [16, 17], none of which our patient received.

Immunologic discussion

Psoriatic arthritis (PsA) is a distinctive inflammatory arthritis associated with enthesitis, new bone formation, and cutaneous findings of psoriasis. Our patient met the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria for diagnosis based on clinical evidence of psoriasis, nail pitting, a negative RF, and dactylitis (Table 3). These criteria, developed in 2006, have a specificity of 98.7% and sensitivity of 91.4% for diagnosis of PsA [18]. Genetic factors appear to play a role in psoriasis and PsA. Variants in the promoter region of the TNF-alpha gene have been found to be associated with psoriasis and psoriatic arthritis [19]. Further genetic associations involving cytokines have been discovered as well. These are thought to play an important role in the psoriatic inflammatory process, particularly interleukin (IL)-12 and IL-23 [20]. By far the major genetic susceptibility to PsA is associated with certain HLA alleles including HLA B27 [21], B28, B29, DR4 [21], DR7, and cw-0602 [22].

The incidence of PsA appears to be increased in both frequency and severity in HIV patients, which leads us to wonder if PsA pathogenesis is different in a patient with HIV. The current understanding of the psoriasis pathogenesis assigns central importance to an interaction between acquired and innate immunity [23]. At the onset of the disease, as well as during exacerbations in its later course, special dendritic cells in the epidermis and dermis are activated; among other effects, these cells produce the messenger substances TNF-alpha and IL-23, which, in turn, promote the development of certain subclasses of T cells (Th1 and Th17). These T cells secrete mediators that could contribute to the vascular and epidermal changes of psoriasis. The activation of intracellular signal transduction pathways plays an essential role in reinforcing the inflammatory immune reaction [24]. In the setting of the profound immunodeficiency of HIV, as in our patient, CD4 T cell function is lost; however, CD8 T cell and NK cell function persists. The loss of CD4 T cells makes the patient susceptible to more infections and to microbial persistence,

thereby triggering other adaptive and innate immune responses. It is likely the development of PsA in the setting of advanced HIV infection reflects the interaction of elevated level of activating cytokines, enhanced apoptosis of CD4 T cells, and persisting or elevated levels of CD8 and NK cells.

Clinical discussion: long-term follow-up

During a 1-year follow-up period, the patient has had no further hospitalizations. He has been maintained on anti-retroviral medications, which were restarted as an outpatient after hospitalization. He has had no opportunistic infections. He has not had progression of his renal disease with his serum creatinine level stable at 2 mg/dl and urinalysis without sediment or protein. He has however suffered from persistent skin and joint complaints related to his psoriatic arthritis; he has been managed by phototherapy, topical agents, sulfasalazine 2,500 mg daily, and methotrexate 10 mg weekly.

Conclusion

Given our patient's complicated presentation, in conjunction with a history of untreated HIV and HCV, the differential diagnosis was broad and challenging. The systemic nature of his illness as well as the pathology results from his renal biopsy all suggest that the initial illness was a vasculitic process. His subsequent develop-

Table 3 The CASPAR (Classification criteria for Psoriatic Arthritis) criteria

To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or enthesal) with greater than or equal to 3 points from the following 5 categories

Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis
Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist
A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider
A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report
Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination
A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range
Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist
Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot

The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%. Current psoriasis is assigned a score of 2; all other features are assigned a score of 1

ment of a psoriasiform rash and arthritis was typical for psoriatic arthritis. The interplay between these two diseases in one host is unclear. However, it does seem clear that chronic infection with HIV and HCV in this patient was a trigger for immune dysregulation resulting to this autoimmune phenomenon. Further study of vasculitis and PsA in this patient population will aid in our understanding of the pathogenesis of these entities and perhaps the development of targeted therapies for all patient populations with these diseases.

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