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Case 10-2013: A 30-Year-Old Man with Fever, Myalgias, Arthritis, and Rash

John H. Stone, M.D., M.P.H., and Mandakolathur R. Murali, M.D.

PRESENTATION OF CASE

Dr. Sheila F. Mitsuma (Medicine): A 30-year-old man with a history of intravenous drug use was admitted to this hospital because of fever, myalgias, arthritis, and rash.

The patient was in his usual state of health until 12 days before admission, when 2 days after discharge from a detoxification clinic, he reportedly self-administered heroin intravenously. Two days later, fever, chills, cough, myalgias, anorexia, and malaise occurred and were associated with the gradual onset of joint swelling and pain, an erythematous and nonpruritic rash, and episodes of severe diaphoresis. The joint symptoms first developed in the ankles, and during the 3 days before admission, they affected his knees, hands, and elbows and were accompanied by weakness of the arms and legs.

Two days before admission, the patient went to the emergency department of another hospital. On examination, the temperature was 38.3°C. The white-cell count was reportedly normal, the blood alanine aminotransferase level was 110 U per liter, and the aspartate aminotransferase level was 73 U per liter; the remainder of the complete blood count and metabolic panel was normal. A chest radiograph, electrocardiogram, and transesophageal echocardiogram were also reportedly normal. Cultures of the blood were obtained. A diagnosis of a viral syndrome was made, and he returned home. Fevers resolved, but the pain increased and became more severe in the arms than in the legs; the patient rated it at 10 on a scale of 0 to 10, with 10 indicating the most severe pain. He walked gingerly and in small steps because of his joint symptoms and was unable to raise his arms above his head or grasp a cup of coffee. He came to the emergency department of this hospital.

The patient reported redness of the eyes and pain in the neck region. However, he reported no headaches, sore throat, rhinorrhea, sinusitis, tinnitus, loss of weight, impairment of his senses (smell, vision, hearing, and taste), or changes in bowel and urinary function. One month before admission, wheezing, dyspnea at rest, lightheadedness, and a dry cough developed, without fever or chills. The patient had used intravenous drugs for 10 years, participated intermittently in needle-exchange programs, and had enrolled in detoxification programs 15 times. Three days after the onset of symptoms, methadone therapy was begun. He also had migraines, long-standing Raynaud's phenomenon, and recurrent epistaxis after repair of facial and nasal-bridge fractures. He had a history of a fractured wrist and, after intra-

From the Department of Medicine, Massachusetts General Hospital, and the Department of Medicine, Harvard Medical School — both in Boston.

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venous drug use, an abscess in his left arm. He suspected that he had hepatitis C virus (HCV) infection, acquired after a remote exposure to a known carrier. Testing for human immunodeficiency virus (HIV) 6 months earlier had reportedly been negative. He had taken ibuprofen for muscle pain and had no known allergies. He was unemployed and lived with his mother. He was sexually active and monogamous with his girlfriend and did not use barrier protection. He smoked cigarettes. His father had coronary artery disease and had had his first myocardial infarction when he was in his 30s; his mother, sister, and multiple maternal relatives had diabetes mellitus; a sister had systemic lupus erythematosus; another sister had eczema; and a nephew had Kawasaki's disease.

On examination, the temperature was 37.2°C, the blood pressure 138/88 mm Hg, the pulse 106 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 96% while the patient was breathing ambient air. The conjunctivae were injected, and dentition was poor. Breath sounds were coarse, with mild wheezing, and there was a tender, palpable liver tip 2 cm below the costal margin. On the extremities and anterior trunk, there was a fine, erythematous, blanching, reticular, macular rash. The joints of the hands, elbows, knees, and ankles were diffusely swollen and warm. There were also effusions in the wrists, metacarpal-phalangeal joints, and knees. Active movement of the large joints caused severe pain; passive range of motion was full, including that of the cervical spine. There was diffuse muscle tenderness (especially in the quadriceps and calves) and 1+ edema in the extremities, decreased muscle strength (4 out of 5) with extension and flexion of the arms and hands, and 3+ deep-tendon reflexes of the brachioradialis and patellar tendons. The gait involved small steps and a wide stance; the remainder of the examination was normal.

The hematocrit, hemoglobin, and red-cell indexes were normal, as were blood levels of electrolytes, calcium, phosphorus, magnesium, creatine kinase, total and direct bilirubin, total protein, albumin, globulin, and alkaline phosphatase and the results of renal-function tests; other test results are shown in Table 1. Testing of a specimen of blood for rheumatoid factor and antibodies to cyclic citrullinated peptide and

double-stranded DNA was negative. Testing for antibodies against HIV type 1 (HIV-1) and HIV type 2 (HIV-2) was nonreactive, and HIV-1 RNA was not detected. Testing of blood for cryoprotein was also negative. A test for syphilis, with the use of rapid plasma reagin, was negative. Urinalysis revealed trace urobilinogen and was otherwise normal. Cultures of the blood drawn earlier remained sterile. A chest radiograph was normal. A combination of acetaminophen and oxycodone was administered.

Diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. John H. Stone: This 30-year-old man presented with fever, myalgias, arthritis, and a rash. Two critical pieces of information will frame my differential diagnosis. First, this patient was an injection-drug user, and therefore we must consider all the perils associated with this behavior. Second, this patient presented with polyarthritis, a condition that is distinctly different from having joint pains or arthralgias.

INJECTION-DRUG USE

The use of injection drugs is associated with many potential causes of this patient's symptoms. The patient attributed the onset of his symptoms to the self-injection of heroin 12 days earlier. I will therefore focus my differential diagnosis on potential explanations associated with the use of heroin itself, on the effects of adulterants used to "cut" street drugs, and on the effect of infectious agents associated with either bloodborne pathogens contracted through needle sharing or failure to clean the skin adequately before injection of drugs. The final diagnosis must be one that can lead to a true polyarthritis, not just polyarthralgia.

HEROIN

Heroin has been associated with rhabdomyolysis, which may result from either the direct effects of the drug or unrelieved pressure on body parts that occurs in association with coma.¹ Rhabdomyolysis might account for the elevated aminotransferase levels, assuming that their source is skeletal muscle rather than the liver, but in this patient the levels were too low for florid rhabdomyolysis. Moreover, the alanine aminotransferase level was higher than the aspartate aminotrans-

ferase level, implicating a hepatic origin. Similarly, the blood creatine kinase level was normal, making rhabdomyolysis unlikely. Rhabdomyolysis also does not explain two key features of the patient's presentation — the inflammatory arthritis and rash. I suspect that the “weakness” was discomfort associated with moving tender joints and painful muscles, rather than true deficits of muscle power.

ADULTERANTS

Adulterants are compounds added to street drugs to increase profits for the seller. In the 1970s, a mini-epidemic of severe musculoskeletal problems resulted from an unidentified adulterant in brown heroin, so-called because of its color, which contrasted with the usual white of street heroin.² Fever, paraspinal myalgias, polyarthralgia, and marked tenderness localized to periarticular structures, such as tendon insertions (enthesopathy), developed and resolved within days of discontinuation of the drug. The joint problems were most consistent with peri-arthritis. It seems unlikely that this patient injected brown heroin, because he presented with polyarthrititis rather than peri-arthritis and, to my knowledge, the adulterant that made brown heroin brown — which was never definitively identified — is no longer used.

Levamisole, a veterinary antihelminthic agent once used to treat rheumatoid arthritis, colon cancer, and the nephrotic syndrome, has become the most common adulterant of cocaine.³ The prevalence of levamisole in samples of cocaine sold on the street is estimated to be as high as 70%.⁴ Levamisole can lead to a dramatic vasculopathy and even vasculitis of small and medium-size blood vessels. The syndrome of levamisole-induced vascular injury and tissue damage is characterized by thrombosis, leukocytoclasia, and necrotizing lesions in blood vessels.⁵ This syndrome is accompanied by a confusing array of autoantibodies, including high titers of antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid antibodies, and antibodies to double-stranded DNA. The cutaneous vasculopathy induced by levamisole has a predilection for fatty tissues, often leading to large ulcerative and necrotic lesions of the breasts, thighs, and flanks that mimic warfarin-induced necrosis. Necrosis of the earlobe is a common and distinctive find-

Table 1. Laboratory Data.

Variable	Reference Range, Adults*	On Admission
White-cell count (per mm ³)	4500–11,000	8400
Differential count (%)		
Neutrophils	40–70	75
Lymphocytes	22–44	17
Monocytes	4–11	5
Eosinophils	0–8	2
Basophils	0–3	1
Platelet count (per mm ³)	150,000–350,000	386,000
Erythrocyte sedimentation rate (mm/hr)	0–17	22
Glucose (mg/dl)†	70–110	125
Aspartate aminotransferase (U/liter)	10–40	133
Alanine aminotransferase (U/liter)	10–55	190
Antinuclear antibody	Negative at 1:40 and 1:160 dilutions	Positive at 1:40 and 1:160 dilutions, speckled pattern
Complement (mg/dl)		
C3	86–184	119
C4	20–58	28

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

† To convert the values for glucose to millimoles per liter, multiply by 0.05551.

ing associated with levamisole-induced vasculopathy and vasculitis.^{5–7} This patient's fine, erythematous, blanching, reticular, macular rash bears little resemblance to a levamisole-induced lesion.

Other problems, particularly cocaine-induced midline destructive lesions, are associated with smoking or inhaling the drug, rather than injecting it.^{8,9} These problems generally remain confined to the upper respiratory tract and tissues of the face and are not associated with a disseminated vasculitis. Although high titers of ANCA result, the antigen specificity is for human neutrophil elastase.^{8,9} Unfortunately, such patients also have ANCA directed against proteinase 3, making the distinction between cocaine-induced midline lesions and granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) difficult. We are not informed of this

patient's ANCA status, but his presentation does not suggest a syndrome related to drug-induced, ANCA-associated vasculitis.

INFECTION

Injection-drug use often causes bacterial infections of the skin, soft tissue, bloodstream, and heart valves. If appropriate antibiotic therapy is lacking, these infections may pose a threat to life. The nature of this patient's joint problems may help us rule out a bacterial process. He had true articular swelling of multiple joints in a symmetric fashion. The arthritis began in his ankles and extended to the knees, hands, and elbows. He walked gingerly, with small steps, and was unable to raise his arms above his head or grasp a cup. His inflammatory joint symptoms, which are reminiscent of untreated rheumatoid arthritis or serum sickness, are not particularly compatible with the joint manifestations that are typical of subacute or acute infective endocarditis.¹⁰ In addition, the patient's rash is not reminiscent of the cutaneous manifestations of a disseminated bacterial infection, such as Osler's nodes, Janeway's lesions, and splinter hemorrhages.¹¹ Thus, a bacterial infection, such as those acquired from injection-drug use, is unlikely.

Finally, we must consider viral pathogens that can be transmitted through injection-drug use and needle sharing. These include HCV, HIV, and hepatitis B virus (HBV). Given the lengthy incubation period of these viruses, infection would most likely have occurred earlier than the 12 days before admission that the patient pinpointed as the onset of his symptoms. HCV is associated with a variety of potential musculoskeletal symptoms that would rarely include a polyarthritis that resembles rheumatoid arthritis.^{12,13} More commonly, infection with HCV leads to joint symptoms that are confused with rheumatoid arthritis, partly because HCV infections are associated with rheumatoid-factor positivity caused by the presence of mixed cryoglobulins.¹⁴ Most patients with type II or type III cryoglobulinemia test positive for rheumatoid factor because the IgM component of the mixed cryoglobulin is directed against the Fc portion of IgG, which is the definition of rheumatoid-factor activity. The nature of this patient's rash was inconsistent with the diagnosis of HCV-associated cryoglobulinemic vasculitis, which would generally be accompanied by purpura

with a predilection for dependent areas, particularly the legs. Thus, the likelihood that HCV was the cause of this patient's presentation is low.

Testing for antibodies against HIV-1 and HIV-2 was nonreactive. Therefore, certain musculoskeletal manifestations of chronic HIV-1 infection can be ruled out, particularly seronegative spondyloarthropathies such as reactive arthritis or psoriatic arthritis, both of which are often more severe among HIV-infected patients.¹⁵ Although acute HIV-1 infection should be considered, the absence of detectable HIV-1 RNA rules out this diagnosis. Furthermore, the presence of arthritis, rather than arthralgia, is inconsistent with primary HIV infection.^{16,17}

In a minority of patients, acute infection with HBV causes a syndrome resembling serum sickness. Robert Graves first described the illness in 1843:

Let me first direct your attention to a train of morbid phenomena sometimes observed co-existing with arthritic inflammation. A person labouring under inflammation of the joints gets an attack of hepatitis, accompanied by jaundice, and this is followed by urticaria . . . [One] gentleman, in consequence of exposure to cold, was attacked with arthritic inflammation and fever. After he had been about ten days ill, he became suddenly jaundiced, and in a day or two afterwards a copious eruption of urticaria appeared over his body and limbs.¹⁸

Graves's description is a nearly classic rendition of the syndrome resembling serum sickness caused by acute HBV infection and perfectly describes this patient's symptoms. Polyarthritis and urticaria almost always occur as part of the prodromal stage of the syndrome, preceding the icteric phase by several days to several weeks. These symptoms are usually abrupt in onset. The polyarthritis is symmetric, with a predilection for small joints of the hands and knees, and may appear in an additive or migratory pattern associated with morning stiffness. A rash occurs at approximately the same time as the arthritis in half of all cases. The rash is most often urticarial, but erythematous macules and papules and petechiae are also reported. The syndrome usually persists for days or weeks, with a mean

duration of approximately 20 days. Patients often have both fatigue and generalized weakness at some point in the course of the illness. The joint and skin manifestations typically resolve completely before or at the onset of the icteric phase of hepatitis. Approximately 40% of patients with the syndrome ultimately become jaundiced.

On the basis of his symptoms of polyarthritis, rash, fatigue, and liver-function abnormalities, I believe that this patient had acute HBV infection, acquired from needle sharing in the context of injection-drug use. I suspect the diagnosis was made by HBV serologic testing and the detection of HBV DNA and HBV surface antigen (HBsAg).

DR. JOHN H. STONE'S DIAGNOSIS

Serum sickness associated with acute hepatitis B virus infection.

PATHOLOGICAL DISCUSSION

Dr. Mandakolathur R. Murali: In arriving at the correct pathological diagnosis, we must answer two questions. First, do the laboratory tests support the diagnosis of acute HBV infection? Second, can the syndrome resembling serum sickness be explained in association with acute HBV infection?

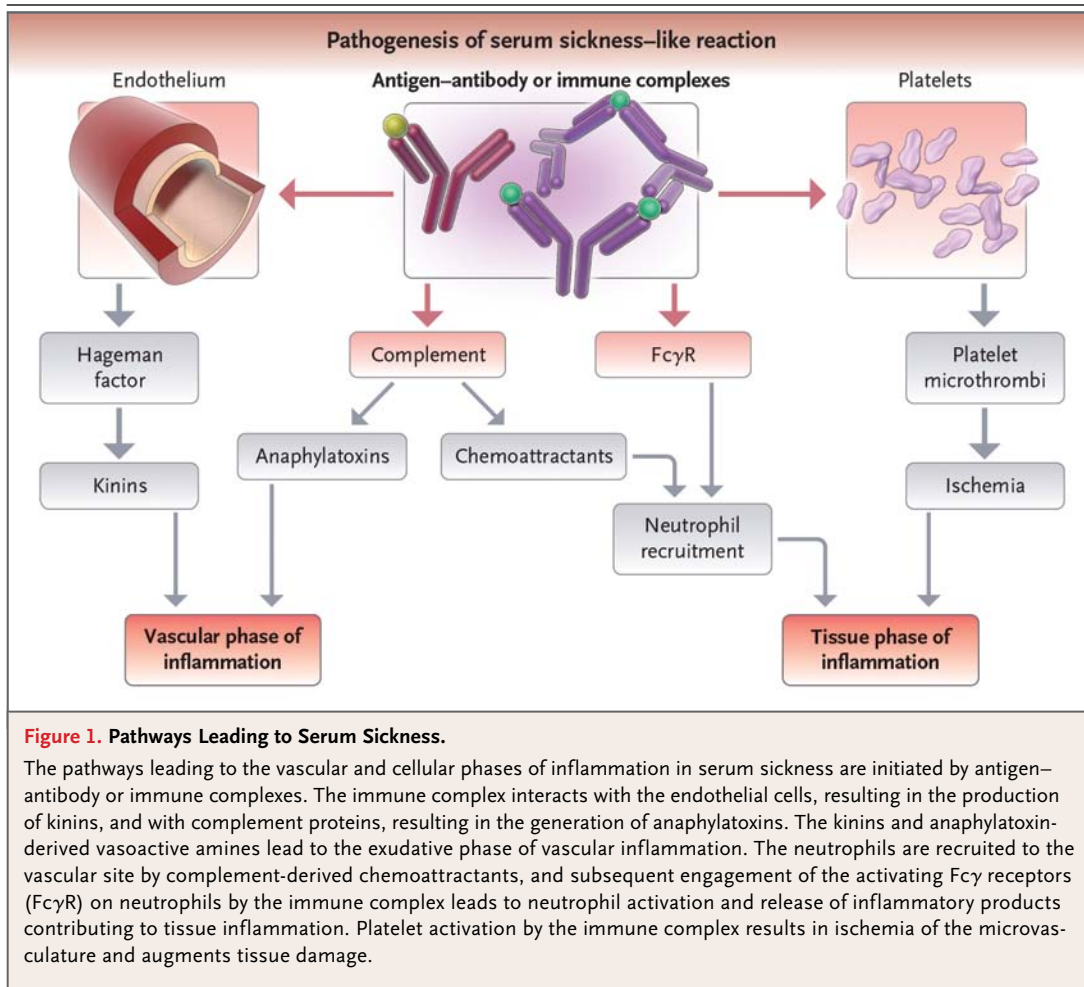
The diagnosis of acute HBV infection is usually suspected after the detection of elevated hepatic aminotransferase levels. In this patient, the aminotransferase levels were mildly elevated at the time of admission (alanine aminotransferase, 190 U per liter; and aspartate aminotransferase, 133 U per liter). During the next 2 weeks, however, the hepatic aminotransferase levels rose dramatically, with the alanine aminotransferase level reaching a peak of 3566 U per liter and aspartate aminotransferase 2022 U per liter on hospital day 16. To determine whether these high levels of aminotransferases were caused by HBV, we examined HBV-specific markers.

Once a patient becomes symptomatic with HBV, the characteristic laboratory features of acute infection include the detection of HBV DNA and HBsAg, the production of IgM antibody against hepatitis B core antigen (HBe), and less often, the presence of hepatitis B e antigen (HBeAg). In this case, testing revealed that all these features were present within the first few days after admission. The level of circulating

HBV DNA was extremely high (>380,000,000 IU per milliliter), a test for HBsAg was positive, a test for antibody against HBsAg (anti-HBs) was negative, HBeAg was reactive, antibody against HBeAg (anti-HBe) was nonreactive, and HBe IgM was reactive. Taken together, these features result in a molecular and serologic profile that is diagnostic of acute HBV infection.

After the diagnosis of acute HBV infection was established, it was noticed that this patient also had classic signs and symptoms of serum sickness, a disorder caused by antigen-antibody or immune complexes formed in the zone of antigen excess. A spectrum of biologically active immune complexes contributes to the inflammation associated with serum sickness. In general, they are small, soluble antigen-antibody complexes that are not removed by the phagocytic macrophages that reside in the liver and spleen. The resultant circulating immune complexes contribute to the vascular and cellular phases of inflammation (Fig. 1). The diverse antigens are composed of epitopes of HBsAg, HBe, and viral DNA. Antibodies to these antigens bind their specific antigens and form immune complexes. Interaction of immune complexes with complement proteins and subsequent activation of Fcγ receptors, complement receptors, or both on phagocytic cells are required for the development of serum sickness.¹⁹⁻²¹ Although we typically expect abnormalities in complement levels in association with serum sickness, the normal C3 and C4 levels noted in this patient on admission do not rule out the diagnosis of HBV-associated, immune complex-mediated serum sickness. In this case, serial monitoring of the levels of C3, C4, and complement hemolytic activity (CH50) was not performed. Consequently, the dynamics of complement activation were not captured in their entirety. Serial measurement of immune complexes containing C1q and C3b would also have been valuable in documenting the development and resolution of serum sickness.

In summary, the diagnosis in this case is acute HBV infection associated with a disease resembling serum sickness, mediated by immune complexes. Correlation of the serologic findings with the patient's clinical manifestations and understanding of the biology of serum sickness are crucial to the understanding of this disease, its diagnosis, and its clinical outcome.



PATHOLOGICAL DIAGNOSIS

Serum sickness associated with acute hepatitis B virus infection.

FOLLOW-UP

Dr. Mitsuma: Until the current era's availability of effective antiviral agents, this patient would not have received any treatment other than supportive care, and he probably would have recovered uneventfully. Because of the magnitude of the viremia, however, he was treated with entecavir. By day 30, the aminotransferase levels had normalized. Paralleling the clinical improvement, the anti-HBs and anti-HBe became positive along with conversion to HBc IgG antibody, signaling the patient's recovery from an acute reaction re-

sembling serum sickness caused by acute HBV infection. By day 65, the HBV DNA level had declined to less than 60 IU, the limit of detection for this assay. Testing for anti-HBs and anti-HBe remained positive; HBsAg and HBeAg were no longer detectable. The patient was asymptomatic, with normal hepatic enzyme levels.

A Physician: Why does serum sickness happen specifically with HBV and not with other diseases?

Dr. Murali: For serum sickness to occur, a prolonged phase of circulating immune complexes is necessary. The prerequisite for that is antigenic persistence, which is best exemplified by chronic and often indolent viral infections, such as HBV and, to a lesser extent, cytomegalovirus and enterovirus, among others. Persistent antigenemia (e.g., as seen in subacute endocarditis and infections associated with shunts or tunneled catheters)

and even the administration of medications such as penicillin and sulfonamides are less common causes of a reaction resembling serum sickness.

A Physician: How do you make the decision to treat a patient with acute HBV?

Dr. Mitsuma: Although I do not know whether antiviral therapy altered the natural history of HBV in this patient, we elected to treat him because of the magnitude of viremia, the disturbance in synthetic function of the liver, and the continued rise in aminotransferase levels.

FINAL DIAGNOSIS

Acute infection with hepatitis B virus.

This case was discussed at the medical case conference.

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