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A 42-year-old woman with polyarthritis

A 42-YEAR-OLD mother of two children presents to her internist for evaluation of persistent pain in her arms, feet, legs, and hands that developed 5 months previously. The pain started in both wrists and was followed by persistent mild wrist swelling. Over-the-counter ibuprofen initially afforded relief. She describes a dryness of her mouth that coincided with the onset of her symptoms. She has had no rashes, dysesthesias, abdominal pain, diarrhea, weight loss, history of jaundice, mouth ulcers, photosensitivity, Raynaud phenomena, or alopecia. She does not smoke. She drinks wine occasionally.

Physical examination

The skin appears normal. Range of motion in both shoulders is limited because of pain. Both wrists are swollen and tender, as are the second and third metacarpal-phalangeal joints bilaterally. Multiple metatarsal-phalangeal joints are tender to palpation. Grip strength is markedly decreased in both hands. The physical examination is otherwise normal.

Laboratory data

Chemistry studies done on two previous occasions showed slightly elevated alkaline phosphatase levels and normal aminotransferase levels. Results of current studies are:

- Complete blood count: normal
- Erythrocyte sedimentation rate (ESR): 76 mm/hour (normal ≤ 30)
- Creatine kinase level: normal
- Speckled antinuclear antibody (ANA) titer: positive at 1:320 (normal < 1:40)
- Rheumatoid factor (RF): positive at 247 IU/mL (normal < 20)
- Anti-DNA antibody titer: negative.

DIFFERENTIAL DIAGNOSIS OF POLYARTHRITIS

1 In which of the following conditions does chronic symmetrical polyarthritis occur?

- ❑ Rheumatoid arthritis
- ❑ Psoriatic arthritis
- ❑ Systemic lupus erythematosus (SLE)
- ❑ Parvovirus-associated arthritis
- ❑ All the above

This patient presented with a seropositive symmetrical polyarthritis that is consistent with **rheumatoid arthritis**. However, before making this diagnosis, the following mimics must be excluded:

Rheumatoid arthritis has many mimics

Psoriatic arthritis can present as symmetrical arthritis. The absence of psoriasis and the high rheumatoid factor titer make this diagnosis less likely in this case. However, joint disease can precede cutaneous psoriasis in 10% of cases. Involvement of distal phalangeal joints, asymmetric joint involvement, or a "sausage" digit (as opposed to isolated fusiform joint swelling) would suggest psoriatic arthritis, but these findings are not always present.

SLE can present with symmetrical small-joint arthritis. In the absence of nephritis, skin lesions, hematologic manifestations, or other features of SLE, however, it is not possible to make this diagnosis on the basis of polyarthritis and antinuclear antibody alone. Antinuclear antibody is not specific for SLE; it can be found in 22% of patients with hepatitis C virus infection and in more than 5% of patients with rheumatoid arthritis. Low-titer or moderate-titer

antinuclear antibody positivity is common in patients with autoimmune thyroid disease and even in healthy relatives of patients with SLE or other systemic autoimmune disorders.

Parvovirus infection can be associated with acute polyarthritis in a pattern that is similar to that seen in rheumatoid arthritis. The characteristic rash and fever, which are common in children (fifth disease), may not develop in adults. The clinical course of parvovirus-related arthritis is quite variable, ranging from mild evanescent synovitis to a more severe, although nonerosive, polyarthritis that lasts for months. Rheumatoid factor may be present. An elevated IgM anti-parvovirus antibody titer helps in diagnosing acute parvovirus infection.

The decision to test for parvovirus infection is controversial. We test for acute infection in patients with acute moderate or severe polyarthritis when we are considering the early use of disease-modifying therapies such as methotrexate, leflunamide, or tumor necrosis factor antagonists. We would withhold such therapy in the case of presumably self-limited viral-induced arthritis.

Enteropathic arthritis, some forms of **systemic vasculitis,** and **chronic crystal disease** can also mimic rheumatoid arthritis, and should also be considered.

Consider the total presentation, not isolated lab values

LABORATORY TESTS THAT HELP DISTINGUISH AMONG TYPES OF ARTHRITIS

2 Which of the following tests is highly specific in distinguishing among inflammatory causes of arthritis?

- ❑ Rheumatoid factor (for rheumatoid arthritis)
- ❑ Elevated erythrocyte sedimentation rate (for infectious arthritis)
- ❑ Antinuclear antibody (for SLE)
- ❑ None of the above

None of the above tests is particularly specific. An "abnormal autoimmune" serology must always be interpreted in the context of the patient's total presentation, not as an isolated laboratory finding.

Rheumatoid factor is an autoantibody directed against the Fc portion of IgG. It is present in up to 80% of patients with rheumatoid arthritis, and is associated with a worse prognosis.

However, rheumatoid factor can also be found in the sera of patients with various other acute and chronic inflammatory diseases and in some apparently healthy people. For example, it can be present in some viral infections (parvovirus, hepatitis), chronic bacterial infections, sarcoidosis, SLE, Wegener granulomatosis, and Sjögren syndrome. Of note, it can be found in up to 71% of patients with hepatitis C virus infection,[1] frequently in high titers.

Thus, diagnosing rheumatoid arthritis solely on the basis of rheumatoid factor can be misleading because it can be present in other diseases that are associated with polyarthritis.

The ESR is nonspecific and is not useful in distinguishing among various inflammatory diseases, as it can be accelerated in patients with infections, malignancies, paraproteins, chronic renal insufficiency, significant hyperlipidemia, pregnancy, and tissue necrosis. The principal mechanism responsible for the accelerated ESR is the tendency of red blood cells to form larger rouleaux in the presence of elevated fibrinogen, alpha and gamma globulins, and cholesterol levels.

Conversely, some patients may have active inflammation and a normal ESR.

Antinuclear antibodies can be detected in a minority of healthy people (usually in low titers) and in patients with a variety of infectious, inflammatory, and neoplastic diseases. They can also be present in up to 22% of patients with hepatitis C virus infection.[1] Because the antibodies are present in virtually all patients with SLE, the test is very sensitive but not specific when used to diagnose this particular condition.

Case continued

Further blood testing in our patient revealed positive anti-hepatitis C virus antibodies with negative hepatitis B and HIV studies. She had 4 million copies/mL of circulating hepatitis C virus RNA.

DIAGNOSING HEPATITIS C ARTHRITIS

3 Which of the following statements about hepatitis C arthritis is false?

- ❑ Many patients with hepatitis C arthritis fulfill the criteria for the diagnosis of rheumatoid arthritis
- ❑ Hepatitis C arthritis can affect small as well as large joints
- ❑ If "liver tests" are normal, a diagnosis of hepatitis C arthritis can be ruled out

Many patients with hepatitis C infection and concomitant arthritis fulfill the American College of Rheumatology criteria for the diagnosis of rheumatoid arthritis. Therefore, testing for hepatitis C antibodies is justified early in the evaluation of patients who present with possible rheumatoid arthritis. In this way, the viral infection can be diagnosed and treated, and potentially hepatotoxic medications such as methotrexate or nonsteroidal anti-inflammatory drugs can be appropriately monitored or avoided.

The oligoarticular and polyarticular arthritis caused by hepatitis C virus infection can affect small and large joints. The joints affected, in order of frequency, are the metacarpal-phalangeal joints, wrists, proximal interphalangeal joints, ankles, metatarsal-phalangeal joints, shoulders, knees, neck, and elbows—a pattern similar to that seen in patients with rheumatoid arthritis.[2] Swelling, tenderness, and redness may develop in the joints, but synovial hypertrophy is often not as prominent as in rheumatoid arthritis.[3] Other rheumatic manifestations of hepatitis C include chronic fatigue, myalgias, sicca syndrome, carpal tunnel syndrome, and palmar tenosynovitis.

Hepatitis-related arthritis is usually radiographically nondestructive and nonerosive.

Abnormal aminotransferase levels may suggest viral hepatitis, although some patients with chronic hepatitis C virus infection have normal liver enzyme levels. Also, alkaline phosphatase can be elevated in patients with rheumatoid arthritis or sarcoidosis. Patients with myositis may have elevated aminotransferase levels of muscle origin. Patients with hepatitis C virus infection may never be jaundiced, in fact, only 25% of adult patients with hepatitis C ever develop jaundice.

TABLE 1

Clues that suggest polyarthritis might be due to hepatitis C virus infection

History
- Intravenous drug abuse
- Transfusion history
- Profound fatigue

Physical findings
- Jaundice
- Hepatomegaly
- Sicca syndrome (negative anti-Ro)
- Features of cryoglobulinemia (purpura, neuropathy)

Laboratory findings
- Elevated aminotransferase levels
- Elevated alkaline phosphatase level
- Cryoglobulinemia
- High-titer rheumatoid factor

Radiographic findings
- Chronic (> 1 year) inflammatory polyarthritis without erosions

In short, patients with hepatitis C virus infection may initially present with rheumatologic complaints that are indistinguishable from those of a systemic autoimmune disease. Patients presenting with oligoarthritis or polyarthritis should be asked if they have a history of jaundice, intravenous drug abuse, blood transfusion, rash or leg ulcers, or sicca and neuropathy symptoms, especially if the onset of the arthritis was acute. However, even in the absence of a history suggesting hepatitis C virus exposure (TABLE 1), patients with polyarthritis or any of these clinical features should be screened for hepatitis C and B infection. At most, 60% of patients infected with hepatitis C virus have identified risk factors for infection.

Test for hepatitis C early in patients with possible rheumatoid arthritis

EXTRAHEPATIC MANIFESTATIONS OF HEPATITIS C

4 Hepatitis C virus infection has been associated with all of the following conditions except which one?

- ❑ Mixed cryoglobulinemia syndrome
- ❑ Lymphocytic sialadenitis
- ❑ Lichen planus

TABLE 2

Extrahepatic manifestations of hepatitis C

Arthralgia
Arthritis
Autoantibodies
Autoimmune thyroiditis
B-cell lymphoma
Lichen planus
Membranoproliferative glomerulonephritis
Mixed cryoglobulinemia and vasculitis
Mooren corneal ulcer
Peripheral neuropathy
Porphyria cutanea tarda
Sialadenitis

ADAPTED FROM REFERENCES 1, 3, AND 4

TABLE 3

Prevalence of antibodies in hepatitis C

ANTIBODY	PREVALENCE
Rheumatoid factor	71%
Antinuclear antibody	22%
Anti-smooth muscle antibodies	22%
Antithyroid antibodies*	8%

*Antithyroglobulin, antithyroid microsomal antibodies

DATA FROM PAWLOTSKY JM, ROUDOT-THORAVAL F, SIMMONDS P, ET AL. EXTRAHEPATIC IMMUNOLOGIC MANIFESTATIONS IN CHRONIC HEPATITIS C AND HEPATITIS C VIRUS SEROTYPES. ANN INTERN MED 1995; 122:169–173.

- ❑ Low-grade B-cell lymphoma
- ❑ Spondylitis
- ❑ Hepatocellular carcinoma

Hepatitis C infection may affect not only the liver but various nonhepatic tissues as well (TABLE 2).[4]

Hepatitis C is the major cause of what was formerly known as "essential" mixed cryoglobulinemia: its RNA has been detected in 90% of patients with "essential" mixed cryoglobulinemia, and cryoglobulins have been found in 30% to 50% of patients with chronic hepatitis C virus infection.[5,6] However, symptoms of mixed cryoglobulinemia are present in less than 10% of patients with hepatitis C virus infection.

Hepatitis C virus infection has also been associated with:

- Lymphocytic sialadenitis, which has been found in 57% of patients with hepatitis C[7]
- Membranoproliferative or membranous glomerulonephritis
- Autoimmune thyroiditis
- Lichen planus
- Mooren corneal ulcers
- Idiopathic pulmonary fibrosis
- Uveitis
- Sicca syndrome (xerostomia or xerophthalmia), which is a common clinical finding in elderly patients
- Low-grade B-cell lymphomas, which occur in patients with chronic hepatitis C virus infection at a higher rate than those without it
- Hepatocellular carcinoma.

In addition, multiple different autoantibodies occur in patients with hepatitis C virus infection, although anti-DNA antibodies are generally absent (TABLE 3). The arthritis of hepatitis C does not include spondylitis.

TREATMENT OF HEPATITIS C ARTHRITIS

5 Which of the following is (are) part of the standard treatment of hepatitis C arthritis?

- ❑ Interferon alfa
- ❑ Ribavirin
- ❑ Hydroxychloroquine
- ❑ Corticosteroids in low doses
- ❑ Nonsteroidal anti-inflammatory drugs (NSAIDs)
- ❑ Methotrexate
- ❑ Anti-tumor necrosis factor therapy

The optimal treatment of hepatitis C arthritis is not established

The optimal treatment of hepatitis C arthritis is not established, although all of the above drugs have been tried. The goals are to eradicate the virus, limit the infection-associated complications, and prevent end-stage liver disease. Whether suppressing viremia and

TABLE 4

National Institutes of Health guidelines for selection of patients for interferon therapy

Chronic hepatitis C virus infection and any of the following conditions:

- Persistently elevated alanine aminotransferase
- Positive hepatitis C virus RNA
- Liver biopsy with either portal or bridging fibrosis and at least a moderate degree of necrosis and inflammation
- Essential mixed cryoglobulinemia
- Stable HIV disease with good clinical and functional status

NATIONAL INSTITUTES OF HEALTH CONSENSUS DEVELOPMENT CONFERENCE PANEL STATEMENT. MANAGEMENT OF HEPATITIS C. HEPATOLOGY 1997; 26(SUPPL 1):2S-10S.

TABLE 5

Side effects of interferon

"Flulike" symptoms
Myalgias, arthralgias
Weight loss
Bone marrow suppression
Alopecia
Psychiatric effects
  Depression
  Sleep disturbances
  Confusion
  Emotional lability
Seizure
Autoimmune effects
  Diabetes mellitus
Thrombocytopenia
Thyroid disease

reducing inflammation slows the progression of liver disease and prevents hepatocellular carcinoma is not known.

Different types of **interferon alfa** have been approved by the Food and Drug Administration to treat hepatitis C virus infection. Their clinical efficacy is similar, and they have been used in different doses and durations that range from 3 to 6 million units three to five times per week for 6 to 12 months. Patients who were treated for 12 months had a more durable response than those treated for 6 months. Not all patients with hepatitis C are candidates for interferon therapy (TABLE 4),[8] and not all respond.

Treatment with interferon alfa alone leads to a sustained antiviral response (ie, after the treatment is stopped for at least 6 months) in only 10% to 15% of patients. Combination therapy with **ribavirin**, a nucleoside analogue, increases the sustained response rate to 40% to 50% in previously untreated patients. Patients whose disease responds to initial interferon monotherapy but then relapses have a sustained response rate of 47% with combination therapy compared with 5% with interferon retreatment alone.[9] Patients whose disease does not respond initially to interferon are unlikely (< 10%) to have a response to combination therapy.[10] In many cases, treatment is not well tolerated because of interferon-induced myalgias, fevers, depression, and malaise (TABLE 5) and ribavirin-induced hemolytic anemia.

Interferon alfa has been used in the treatment of hepatitis C-associated mixed cryoglobulinemia syndrome with good results, but it has also been reported to exacerbate arthritis in some patients with hepatitis C infection.[11]

Hydroxychloroquine and **low-dose oral corticosteroids** (5 mg/day or less) were used successfully in the treatment of HCV arthritis in 19 patients by Lovey et al[2]; the arthritis improved during a follow-up period of 3 to 48 months. However, corticosteroid use in patients with hepatitis C arthritis is not without theoretical risk. Hepatitis C viral load increased threefold after corticosteroids were given (10 to 60 mg/day for 7 to 12 weeks) and returned to baseline levels when the corticosteroids were withdrawn; clinical hepatitis was not exacerbated. When corticosteroids were withdrawn in six patients, repeat biopsy revealed a marked improvement in one patient, inflammation reduction in three, and no change in two.[12,13]

NSAIDs may be used to control the milder symptoms of HCV arthritis. In one study,[14] patients with interferon-resistant chronic HCV infection received an NSAID (ketoprofen) in combination with interfer-

on. The combination failed to normalize the patients' serum aminotransferase levels, and there was no statistically significant difference in the mean serum alanine aminotransferase and aspartate aminotransferase levels before and after ketoprofen intervention. Although NSAIDs rarely cause clinical hepatotoxicity, they do frequently cause elevated transaminase levels. They should not be used in patients with severe liver failure.

Methotrexate was used to treat one patient with hepatitis C arthropathy with "good" results.[2] Alcohol ingestion increases the risk that hepatitis C virus infection will progress to liver failure. Thus, the use of a potentially hepatotoxic medication such as methotrexate in patients with parenchymal liver disease may also be deleterious.

Anti-tumor necrosis factor therapy. Serum tumor necrosis factor alpha levels were found to be elevated in all patients with chronic hepatitis C virus infection, and soluble tumor necrosis alpha receptors were significantly higher in patients with hepatitis C virus infection with liver cirrhosis and hepatocellular carcinoma than in patients who were chronic asymptomatic carriers of hepatitis C virus.[15,16] Whether anti-tumor necrosis factor therapy will play a role in the treatment of patients with HCV infection is still unknown.

It is assumed that as the treatment regimens for hepatitis C virus infection continue to evolve, the extrahepatic manifestations also should be better controlled.

CONCLUSION

Hepatitis C infection should be included in the differential diagnosis of patients with polyarthritis, especially if other clues can be elicited from the history and workup (eg, previous blood transfusion, intravenous drug use, history of jaundice, acute onset of symptoms, or elevated transaminase levels). In many patients, the infection is associated with the presence of rheumatoid factor and antinuclear antibodies, which may cause diagnostic confusion.

Treatment of hepatitis C arthritis has not been standardized, and it gives rise to multiple concerns. These include the possibility of increasing the viral load with the use of corticosteroids, exacerbating the arthritis with the use of interferon, and exacerbating hepatotoxicity with the use of methotrexate.

REFERENCES

1. **Pawlotsky JM, Roudot-Thoraval F, Simmonds P, et al.** Extrahepatic immunologic manifestations in chronic hepatitis C and hepatitis C virus serotypes. Ann Intern Med 1995; 122:169–173.
2. **Lovy MR, Starkebaum G, Uberoi S.** Hepatitis C infection presenting with rheumatic manifestations: A mimic of rheumatoid arthritis. J Rheumatol 1996; 23:979–983.
3. **Siegel LB, Cohn L, Nashel D.** Rheumatic manifestations of hepatitis C infection. Semin Arthritis Rheum 1993; 23:149–154.
4. **Cacoub P, Renou C, Rosenthal E, et al.** Extrahepatic manifestations associated with heptaitis C virus infection. Medicine 2000; 79:47–56.
5. **Misiani R, Bellavita P, Fenili D, et al.** Hepatitis C virus infection in patients with essential mixed cryoglobulinemia. Ann Intern Med 1992; 117:573–577.
6. **Lunel F, Musset L, Cacoub P, et al.** Cryoglobulinemia in chronic liver diseases: role of hepatitis C virus and liver damage. Gastroenterology 1994; 106:1291–1300.
7. **Haddad J, Deny P, Munz-Gotheil C, et al.** Lymphocytic sialadenitis of Sjogren's syndrome associated with chronic hepatitis C virus liver disease. Lancet 1992; 339:321–323.
8. **National Institutes of Health Consensus Development Conference Panel Statement.** Management of hepatitis C. Hepatology 1997; 26(Suppl 1):2S-10S.
9. **Gross JB Jr.** Clinician's guide to hepatitis C. Mayo Clin Proc 1998; 73:355–361.
10. **Davis GL, Esteban-Mur R, Rustgi V, et al.** Interferon alfa-2b alone or in combination with ribavarin for the treatment of relapse of chronic hepatitis C. N Engl J Med 1998; 339:1493–1499.
11. **Chung A, Older SA.** Interferon-alfa associated arthritis. J Rheumatol 1997; 24:1844–1845.
12. **Magrin S, Craxi A, Fabiano C, et al.** Hepatitis C viremia in chronic liver disease: Relationship to interferon-alpha or corticosteroid treatment. Hepatology 1994; 19:273–279.
13. **Fong TL, Valinluck B, Govindarajan S, Charboneau F, Adkins RH, Redeker AG.** Short-term prednisone therapy affects aminotransferase activity and hepatitis C virus RNA levels in chronic hepatitis C. Gastroenterology 1994; 107:196–199.
14. **Anderson FH, Zeng L, Yoshida EM, Rock NR.** Failure of ketoprofen and interferon combination therapy to improve interferon-resistant chronic hepatitis C. Can J Gastroenterol 1997; 11:294–297.
15. **Larrea E, Garcia N, Qian C, Civeira M, Prieto J.** Tumor necrosis factor α gene expression and the response to interferon in chronic hepatitis C. Hepatology 1996; 23:210–217.
16. **Kakumu S, Okumura A, Ishikawa T, et al.** Serum levels of IL-10, IL-15 and soluble tumor necrosis factor alfa (TNF-alpha) receptors in type C chronic liver disease. Clin Exp Immunol 1997; 109:458–463.

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Include hepatitis C in the differential diagnosis of polyarthritis