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Unusual Draining Nodules in a Patient with Rheumatoid Nodulosis and Hepatitis C Virus Infection

To the Editor:

Rheumatoid nodulosis is an uncommon condition with a combination of multiple rheumatoid nodules, recurrent joint symptoms, but without erosions, and usually positive tests for rheumatoid factor (RF). We describe a case of rheumatoid nodulosis with followup exceeding 10 years. The nodules first developed during treatment for hepatitis C virus (HCV) infection with interferon (IFN). A nodule biopsy confirmed the presence of a

rheumatoid nodule. This association of draining nodules, rheumatoid nodulosis, and HCV is rare and raises the possibility that it might have been precipitated by the IFN therapy.

A 53-year-old man presented with an 11-year history of hepatitis C and a 10-year history of poorly characterized asymmetrical arthritis and nodules. In February 1999, he was diagnosed elsewhere with hepatitis C based on laboratory tests and started therapy with ribavirin/ α -IFN. After 1 year, he stopped ribavirin/ α -IFN due to absence of effect on the viral load and did not follow up with his hepatologist.

In August 1999, multiple subcutaneous nodules developed on his fin-



Figure 1. A. Nodular lesions on the dorsal aspect of both hands. B. Lesion on the left hand shows spontaneously drained brown or white particulate material (arrowhead). C. Brown and white particulate material from the nodule.

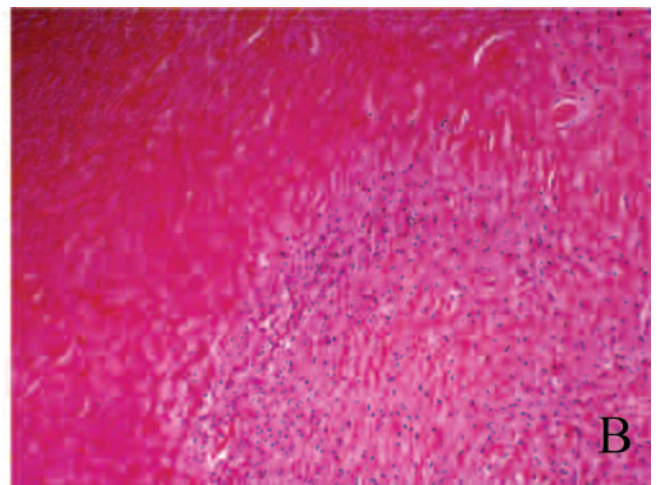
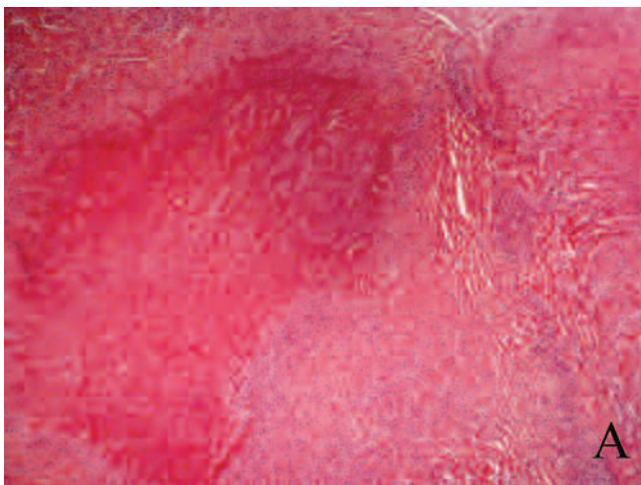


Figure 2. A. Histopathology of a nodule showing palisaded granulomatous inflammation (H&E stains). B. Higher magnification of histopathology showing the fibrinoid necrosis surrounded by palisaded histiocytes, mononuclear cells, and dilated capillaries.

gers. The nodules would gradually enlarge, discharge necrotic-appearing material, and then develop a central crater and at that time became painful. In January 2001, aspiration of one of the nodules was negative for crystals. A large finger nodule mass with dimensions $3.0 \times 2.5 \times 1.0$ cm was excised for biopsy. Some individual nodules were injected with intralesional depot methylprednisolone, with complete resolution, but he continued to develop new nodules. Nonsteroidal antiinflammatory drugs (NSAID) helped his occasional pain from draining nodules, but did not change the shape or size of the nodules. Accompanying the nodules, he experienced intermittent joint pain and swelling that involved proximal interphalangeal joints, wrists, shoulders, and elbows. The joint pain improved under treatment with hydroxychloroquine but the nodules persisted. Due to anxiety over side effects he stopped hydroxychloroquine after 6 months. Since then, he followed up with his rheumatologist intermittently. In August 2009, he was next treated with etanercept, which also reportedly helped the joints, but the nodules persisted. He discontinued the etanercept after 1 year since it was not helping the nodules. His joint pains diminished but he reported morning stiffness for 10 minutes in his fingers and shoulders. Now, he takes NSAID infrequently to alleviate the pain of the nodules.

There was no family history of rheumatic disease or nodules. He had a history of remote drug abuse. There was no history of trauma to the fingers. There were no symptoms in the respiratory, cardiovascular, gastrointestinal, and genitourinary systems.

Examination in January 2010 showed definite palpable, visible, dome-like subcutaneous nodules (Figure 1A, 1B). These were solid, with no adherence to deep surfaces, with some located at the distal end of the fingers. These lesions sometimes spontaneously drained brown or white particulate material that he brought to the clinic (Figure 1C). The thickness of skin overlying the nondraining lesions was normal.

Laboratory tests in August 2009 showed the following: hemogram and urinalysis were normal, erythrocyte sedimentation rate, C-reactive protein, and liver and kidney function tests were normal. Tests for cryoglobulin were negative. Serology for hepatitis A, hepatitis B surface antigen and antibody were negative, hepatitis B core antibody was positive, hepatitis C antibody was positive. Viral load of hepatitis C was more than 3 million. Immunologic studies including C3 and C4 components of complement, anti-SSA, anti-SSB, anti-SM, anti-RNP, anti-Jo1, anti-Scl70, anti-dsDNA, C-ANCA, P-ANCA, PR-3, MPO, antimitochondrial antibody, and HLA-B27 were normal or negative. RF was 265 IU/ml (normal < 20). Antibody to cyclic citrullinated peptide (anti-CCP) was strongly positive, > 250 units (normal < 19). The immunofluorescence assay for antinuclear antibodies was positive in a titer of 1/320 U/l (normal < 1/80 U/l), with a homogeneous pattern. Radiographs of the affected joints showed no erosions. Magnetic resonance imaging examination of the hands and feet also showed no erosions or geodes.

The mass lesion that was excised and examined histopathologically in January 2001 revealed a granulomatous lesion appearing as a nodule, with fibrinoid necrosis and necrotic cells in the center, surrounded with palisading histiocytic cells, mononuclear cells, and dilated capillaries. This was considered characteristic of a rheumatoid nodule (Figure 2A, 2B). Immunohistochemistry showed that the irregular central area of necrotic tissue was surrounded by a layer of CD68-positive epithelioid macrophages of variable thickness. In the tissue adjacent to the nodule, we observed small clusters and some small areas containing diffuse CD20-positive B lymphocytes and CD3-positive T lymphocytes, as well as more CD68-positive cells.

A diagnosis of HCV infection and rheumatoid nodulosis was based on the cutaneous, articular, and systemic manifestations and the immunological abnormalities together with the medical history. Nodules and joint pains persist, and the patient is taking only NSAID.

Rheumatoid nodulosis is considered a relatively benign variant of rheumatoid arthritis (RA), characterized by the presence of subcutaneous rheumatoid nodules with recurrent articular symptoms but with no marked synovitis. This was first described by Bywaters in 1949 and emphasized by Ginsberg in 1975. Diagnostic criteria were proposed by Kaye, *et al* in

1984¹. Four criteria are required: histologically documented subcutaneous rheumatoid nodules, recurrent flares of arthritis often presenting as palindromic rheumatism, absence or mildness of systemic symptoms, and benign course despite the presence of RF. Our patient fulfilled all the clinical and morphological criteria for the diagnosis of rheumatoid nodulosis. The subcutaneous nodules are the predominant clinical sign, accompanied by moderate joint involvement and positive serum RF.

Rheumatoid nodules develop in about 20% of patients with RA and in patients with RA are associated with more severe erosive disease². Clinically, they are solitary or multiple, firm, rubbery, nontender, skin-colored, subcutaneous nodules, ranging from 2 mm to > 6 cm, mostly movable, although they can be attached to deeper structures including fascia, periosteum, and tendons. Cutaneous nodules are generally located on extensor surfaces of the forearm and extensor tendons of the hands, particularly at the metacarpophalangeal and proximal interphalangeal joints, occasionally at the occiput, ear auricles, heels, ischial tuberosities, sacrum and sacral prominences, and rarely located in Achilles tendons, penis, vulva and the nasal bridge. Extracutaneous rheumatoid nodules have also been described. Rheumatoid nodules are not entirely specific to RA. They can be seen in a variety of other conditions or in isolation³. Besides RA and rheumatoid nodulosis, rheumatoid nodules have been associated with disorders such as palindromic rheumatism⁴, systemic lupus erythematosus and chronic active hepatitis⁵ with negative RF, and also granuloma annulare⁶, ankylosing spondylitis, mixed connective tissue disease, and dermatomyositis⁵ with reports giving no record of RF.

We have described a patient with primary rheumatoid nodulosis, who had HCV infection and unusual draining nodules. HCV has been increasingly recognized as a cause of rheumatic disease and other autoimmune phenomena, and can be associated with the presence of various autoantibodies⁷. Arthropathies are the most common extrahepatic manifestations of HCV infection. The polyarthritis of HCV-infected patients is symmetrical, may be nondeforming, and involves primarily the small joints. Many patients with HCV-related arthritis and positive RF may be diagnosed mistakenly as having RA and thus may be treated with corticosteroids and cytotoxic drugs, which may worsen HCV viremia⁸. An important clinical characteristic of HCV-related arthropathy is the lack of bone erosions on imaging; therefore, imaging may provide support in differentiating it from RA. The exact mechanism by which HCV infection triggers arthritis has not been determined. HCV is not mentioned as a cause of rheumatoid nodules or nodulosis in the reviews of the subject.

Our patient could fulfill the American College of Rheumatology (ACR) 2010 revised classification criteria for RA⁹. According to these criteria, patients can be classified as having RA based on the confirmed presence of synovitis in at least 1 joint, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in 4 domains: number and site of involved joints, serologic abnormality, elevated acute-phase response, and symptom duration. These criteria, however, require that alternative diagnoses be excluded, and we believe that hepatitis C is a reasonable exclusion. The case, interestingly, does not fulfill the ACR 1987 revised classification criteria for RA¹⁰. An unexpected aspect of our case was the high titer of anti-CCP. Anti-CCP antibodies are characteristic of and can play an important role in early diagnosis of RA, and their presence enables accurate prediction of the development of RA¹¹. Anti-CCP antibodies are not unique to RA. Low titers have been reported in psoriatic arthritis¹² and also even hepatitis C¹³. Our patient is unusual in that he has high-titer anti-CCP, but with no joint damage during 10 years mostly without immunosuppressive therapy. It will be important to learn if other similar cases are seen.

Patients with HCV infection are inevitably a therapeutic challenge. The use of IFN for HCV has increased dramatically since it was first shown to be efficacious¹⁴. Autoimmune diseases can be induced by IFN therapy and do not always improve after the cessation of IFN and may persist for months. Teragawa, *et al* suggested that the immune system, once activated by exogenous IFN, might remain in an active state without further stimulation of exogenous IFN¹⁵. In our case, the features of nodules were rec-

ognized during treatment with ribavirin/IFN, but after cessation of ribavirin/IFN the nodules are continuing to develop. Thus, although we cannot exclude that nodule development was coincidental, we can speculate that IFN may have contributed. That the nodules were very unusual in behavior, with dramatic draining, might possibly be related to the immunological reactions started during IFN therapy.

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