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## Can Hepatitis B Infection be a Risk Factor for Complex Regional Pain Syndrome Type 1?

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### ABSTRACT

**Background:** Complex regional pain syndrome (CRPS) has been described as a painful condition with the appearance of trophic, vasomotor, and sudomotor changes. Most of the predisposing factors causing CRPS are classified. However, the definite cause of this syndrome is yet to be clearly specified in some cases. In this report, we presented a case with hand edema along with severe pain, diagnosed as CRPS type 1, coexisting with hepatitis B infection.

**Case Report:** This study presents a case of a 65-year-old man who had hand edema, severe pain, and decreased range of motion of the wrist without any constitutional symptoms and no history of trauma. He was diagnosed as CRPS type 1 after a detailed physical examination and diagnostic procedures. Ruling out other causes related to CRPS type 1, it is suggested that coexisting hepatitis B infection might be a possible triggering factor for this syndrome.

**Conclusion:** Hepatitis B infection may be a possible causative factor for CRPS type 1.

**Keywords:** Complex regional pain syndrome, edema, hand, hepatitis B, pain

### INTRODUCTION

Complex regional pain syndrome (CRPS) is described as a chronic painful condition characterized by inflammatory and autonomic features (1). Manifestations of this disabling syndrome include not only disproportionate pain but also vasomotor (temperature, skin color changes), sudomotor (edema, sweating changes), and trophic changes (hair, nail, skin) and motor dysfunction (2). It generally affects elderly patients aged between 50 and 70 years old (1, 3). Pathophysiological mechanisms of this syndrome are complex and multifactorial (4).

CRPS can be divided into two subgroups according to whether there is a peripheral nerve injury (CRPS type 2) or not (CRPS type 1). The most commonly reported predisposing factor of CRPS type 1 is trauma (1, 2). Infectious diseases such as hepatitis C, herpes zoster, and leprosy are also known to cause CRPS type 1 (5–7). Although some CRPS type 1 cases have been associated with hepatitis B vaccination, there is no clear evidence on the relationship between CRPS type 1 and hepatitis B infection (8).

In this report, we presented a case with CRPS type 1 on the left hand associated with hepatitis B infection. Possible link between these two entities and differential diagnosis were discussed.

### CASE REPORT

A 65-year-old man was admitted to the Department of Physical Medicine and Rehabilitation Clinic with pain and swelling on his left hand that began almost 2 months ago. On admission, he had been suffering from arthralgia, and he was unable to move his left hand. However, he did not report any constitutional symptoms including fever, malaise, weight loss as well as the rash, arthralgia or arthritis of other joints, inflammatory back pain, dactylitis, uveitis, enthesitis, and any family medical history of rheumatologic diseases. In addition, he had no history of trauma.

On medical history, he reported chronic liver disease due to chronic hepatitis B infection; thus, he had used tenofovir as an antiviral agent for 2 years. Patient had mild hypertension, but he had not been using any medication. No previous history of malignancy or tuberculosis were reported. The patient smoked cigarette for 50 pack-years; he neither used alcohol nor used drugs or herbs. He lives in a rural area.

On physical examination, body temperature of the patient was 36.4°C, blood pressure was 130/85 mmHg, pulse rate was 84 beats per minute, and respiratory rate was 16 breaths per minute. He had normal breath sounds, cardiac sounds, and regular heart rate as well as cardiac rhythm. No hepatosplenomegaly and abnormal lymph nodes were detected. There was a marked tenderness on the wrist second and third metacarpophal-

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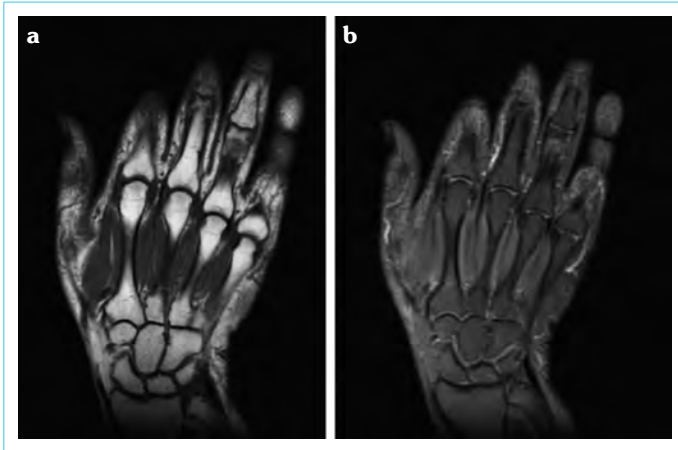
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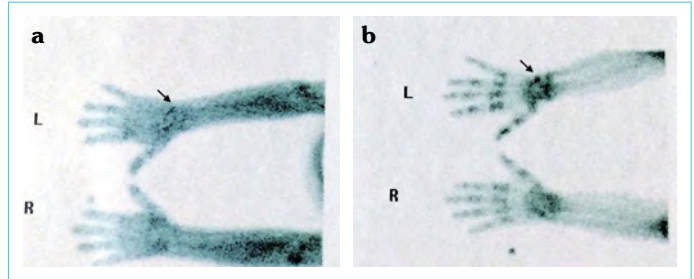
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**Figure 1. Magnetic resonance imaging of the left hand and wrist demonstrating soft tissue swelling but no other pathology. (a) T1 sequence (b) T2 fat pad sequence**

langeal joints of the left hand. In addition, a diffuse swelling and warmth were noted on the dorsum of the left hand. There was no erythematous rash, but sudomotor changes were suspected. Range of motion of the left wrist and second and third metacarpophalangeal joints were minimally limited with a clear allodynia. Grip strength of the left hand was diminished. Hypoesthesia or anesthesia were not determined.

Blood levels of electrolytes, total protein, albumin, folate, vitamin B12, thyroid function tests, renal function tests, liver function tests were normal. Complete blood count was normal as well. Fasting glucose and HbA1c levels were noted as normal. Erythrocyte sedimentation rate and C-reactive protein levels were also within normal limits. Examination of peripheral blood smear revealed increased red cells, which were normal in size, and no abnormal cells were observed on the smear. Protein electrophoresis was also normal. Blood tests for hepatitis B including hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), hepatitis B viral capsid protein (HBcAg), and HBV-DNA were positive. Moreover, hepatitis B tests antibody was negative. Results of hepatitis tests were compatible with acute or chronic hepatitis B. The department of gastroenterology recommended a close follow-up along with the



**Figure 2. Three-phase bone scan images following injection of technetium-99m methylene diphosphonate indicating (a) minimal increased blood flow of the left wrist in flow phase and (b) focal increased uptake of the left wrist in bone phase**

maintenance therapy of antiviral treatment that the patient used. Liver biopsy was not recommended for the patient at the time of consultation. Serological and rheumatological tests including rheumatoid factor, anti-nuclear antibody (ANA), anti-ds DNA, anti-citrullinated peptide antibody (ACPA), anti-centromere antibody, anti-scl 70 antibody, anti-Jo-1 antibody, and Brucella and Salmonella antibodies were all found to be negative.

Ultrasound imaging with power Doppler technique revealed no detectable synovitis. In addition, magnetic resonance imaging of the left hand demonstrated no signs of synovitis as well (Fig. 1).

The patient was screened in terms of tuberculosis to rule out dactylitis or arthritis associated with mycobacterial infection. Sputum smear and culture were negative. Also, computed tomography of the thorax was normal. Electromyography (EMG) was performed in order to elicit potential peripheral nerve damage, but nerve compression syndromes such as carpal tunnel syndrome were not verified via electrophysiological examination. Three-phase bone scan of the patient showed minimal increased blood flow in flow phase and focal increased uptake in bone phase on the left hand, which is compatible with CRPS type 1 (Fig. 2). With all these above-mentioned physical findings, laboratory results revealed the diagnosis of CRPS type 1 (Table 1). The diagnosis was based on specific diagnostic criteria, which was adopted from the International Association for the Study of Pain in 2012 (1).

**Table 1.** The diagnostic approach to a patient with CRPS type 1

Physical examination	Allodynia, swelling, and limited joint mobility of the hand with trophic changes
Laboratory evaluation	Normal complete blood count, liver and kidney function tests, acute-phase reactants, protein electrophoresis Positive HBsAg, HBeAg, HBcAg, and HBV-DNA Negative RF, ANA, Anti-ds DNA, ACPA, anti-centromere antibody, anti-scl 70 antibody, anti-Jo-1 antibody, <i>Brucella</i> and <i>Salmonella</i> antibodies
Microbiologic evaluation	Negative sputum smear and culture
Musculoskeletal ultrasound	No synovitis
Magnetic resonance imaging	No synovitis
Electromyography	No nerve compression
Three-phase bone scan	Minimal increased blood flow in flow phase and focal increased uptake in bone phase*

HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; HBcAg: Hepatitis B viral capsid protein; ANA: Anti-nuclear antibody; ACPA: Anti-citrullinated peptide antibody; \*: Compatible with CRPS type 1

The patient received physical therapy program including fluidotherapy, desensitization massage, and range of motion exercises to all fingers of the left hand for 10 consecutive days. Additionally, 150 mg of pregabalin daily was prescribed to the patient for neuropathic pain. After physical therapy, the patient was discharged due to more than 80% of pain relief. All symptoms were resolved completely at 6 months of follow-up.

## DISCUSSION

CRPS type 1 has been associated with various etiologies excluding nerve injury (1, 2). More common causes of CRPS type 1 include minor trauma and fracture of the distal radius (3). Infectious diseases and inflammatory and autoimmune disorders should also be considered for differential diagnosis (2). Hepatitis C infection, herpes zoster, and leprosy have been identified to be possible causes of CRPS (5–7). Besides, a number of vaccines such as hepatitis B, human papillomavirus, and diphtheria-tetanus have been reported to be potential risk factors for the syndrome (8–10). According to the vaccine adverse event report system in British Columbia, only 4 cases out of the 40,000 children immunized for hepatitis B were reported to have CRPS type 1 after vaccination (8). On the other hand, no data was found concerning hepatitis B infection as a triggering factor for CRPS type 1 in the literature.

The pathophysiology of CRPS remains heterogeneous and controversial. The main hypothesis is that an inflammation arising after trauma to the extremity can initiate the pathway causing CRPS. Many factors including cytokines, vascular endothelial growth factor, catecholamines, and autoantibodies can contribute to the decreasing threshold of the peripheral nociceptors, making the latter more sensitive. Increased nerve sensitivity due to these mediators can result in hyperalgesia and allodynia (4, 11).

Some viral infections including hepatitis C, herpes zoster, leprosy, human immunodeficiency virus, and parvovirus B19 have been associated with CRPS in the literature (5–7, 12, 13). But the exact pathogenesis of how the infection initiates CRPS is yet to be determined. The axonal damage, inflammation, and vascular dysfunction causing unsuitably triggering action potentials and releasing cytokines have been hypothesized as the reason for CRPS in a patient with leprosy. The threshold of the pain receptors is decreased; consequentially, interpretation of pain is changed (7). According to the above-mentioned theory, in our case, hepatitis B infection may emerge as an inflammation discharging cytokines and neuropeptides, which, in turn, may sensitize neurons in the spinal cord. Hereby, this sensitization initiates a snowball effect causing CRPS type 1.

Viral arthritis has been determined as another potential cause of hand swelling and pain. Although the patient had chronic hepatitis B infection since 2016, the main cause of CRPS might be the changing clinical status of chronic hepatitis. Both acute and chronic hepatitis B infection may initiate arthritis, which is often characterized by polyarticular distribution resembling rheumatoid arthritis. When large synovitis and joint damage occur, clinical findings and laboratory outcomes are consistent with arthritis including synovitis, painful joint, higher rheumatoid factor, lower C3, and C4 levels (14). In the current case, inflammatory signs of arthritis were all negative. Additionally, other important causes of severe hand pain and arthritis were excluded in this patient.

In conclusion, physicians should not disregard the infections, especially hepatitis B, when determining the etiology of CRPS type 1. Although the certainty of hepatitis B infection as an initiative factor is not well defined, keep it in mind as a possible cause for the syndrome.

**Informed Consent:** Written informed consent was obtained from the patient who presented in this report.

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