CASE STUDY

Wilson's disease with anti-CCP positive rheumatoid arthritis: A rare co-existence

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Abstract

Wilson's disease, a rare autosomal recessive disorder, is characterized by the excessive accumulation of copper in the brain, liver, and other tissues. The present case study deals with a rare co-occurrence of anti-CCP positive RA and Wilson's disease.

Keywords: arthritis, anti-CCP, RA, Wilson's disease

Introduction

Wilson's disease (WD), an autosomal recessive disorder caused due to mutation in the *ATP7B* gene, has an estimated prevalence of one in 30,000 worldwide.[1] The accumulation of copper primarily in the liver and subsequently in the brain causes serious neuropsychiatric and hepatic manifestations. However, musculoskeletal presentations are relatively uncommon. The present study reports a very rare case of co-existence of rheumatoid arthritis (RA) with anti-CCP positivity and WD.

Case report

A 27-year-old male patient presented to the clinic with a 4-month history of arthritis, predominantly involving knees, ankles, wrists, and other joints of hands. He had recurrent fever on alternate days and a previous consultation had found him to be positive for Mantoux test. The patient was prescribed with four anti-tubercular drugs. However, the patient remained symptomatic with fever. Current laboratory work-up reported that the patient was positive for rheumatoid factor and anti-CCP. Moreover, the elevated ESR and CRP levels confirmed the diagnosis as RA. He was prescribed with methotrexate (7 mg/week), hydroxychloroquine (200 mg/week) for one month and short course of steroids. Though the patient had demonstrated symptomatic improvement within four weeks, his SGOT and SGPT were slightly increased. Increase in levels of conjugated bilirubin and alkaline phosphatase were also observed. He was prescribed to continue the same medications. But the fever recurred and he had loss of appetite. Subsequent evaluation of liver function test revealed abnormal increase in total bilirubin, direct bilirubin, SGOT, SPGT, alkaline phosphatase and gamma-glutamyl transpeptidase, indicative of hepatitis. His ultrasound confirmed moderately enlarged spleen and liver. Work-up for viral hepatitis (A, B, C, and E) was negative. The patient was asked to stop all the medications and the hepatitis settled clinically and serologically within a period of 6 weeks. However, persistent transaminitis was observed, but not more than 3 times the upper normal limit. This finding was suggestive of an underlying pathology other than RA.

Assessment of family history had revealed that the patient's sister succumbed to hepatic failure at the age of 23. Negative immunofluorescence tests (anti-neutrophil cytoplasmic antibody, anti-mitochondrial antibody, liver-kidney microsome antibody) ruled out the probability of autoimmune hepatitis. Further evaluation also revealed increase in the ceruloplasmin and copper levels. Biopsy of the liver specimens also confirmed deposition of copper. Based on the aforementioned evidence and findings, the patient was finally diagnosed as having Wilson's disease along with RA. Since RA symptoms were persisting, the patient was prescribed with hydroxychloroquine and sulfasalazine along with close monitoring of liver functions.

The patient had a strong history of hepatic disease along with increased urinary copper and low ceruloplasmin levels. Kayser-Fleischer ring was not observed on slit lamp examination, however biopsy of the liver showed

Table 1: Results of clinical and lab investigations conducted during first and second follow-up

Parameters evaluated	Results	
	First follow-up	Second follow-up
Serum glutamic oxaloacetic transaminase (SGOT, IU/L)	61.49	1002
Serum glutamic pyruvic transaminase (SGPT, IU/L)	52.05	1300
Rheumatoid factor (IU/ml)	134.0	
ESR (mm)	110	
C-reactive protein (mg/L)	121	34
Total bilirubin (mg/dL)	*8*	
Direct bilirubin (mg/dL)	6	
Alkaline phosphatase (IU/L)	330	
Gamma-glutamyl transpeptidase (IU/L)	34	
Hepatitis A Antibody	Negative	
HBsAG	Negative	
HCV	Negative	
Hepatitis B core antibody	Negative	
Anti-neutrophil cytoplasmic antibody	Negative	
Anti-mitochondrial antibody	Negative	
Liver-kidney microsome antibody	Negative	
Copper (µg/dL)	94.9	
Biopsy (dry-wt)	121 µmol/g	310 9 mcg/g

increased levels of copper (Table 1). He was treated with d-penicillamine 250 mg bd and zinc. The drug dosages were monitored by a gastroenterologist, based on the 24-hr urine and serum copper levels.

The patient is currently receiving hydroxychloroquine 200 mg, sulfasalazine 1000 mg, and folic acid 5 mg daily. He has demonstrated a good control of arthritis. Although genetic testing was recommended, the patient refused to do the same.

Discussion

The clinical features of RA were clearly evident in the current case. At the same time, presence of low ceruloplasmin levels and liver biopsy findings were strongly suggestive of WD.

Prolonged use of hepatotoxic drugs such as methotrexate has been reported to cause impairment in liver functions. Methotrexate is known to cause serum aminotransferase elevations and long-term therapy has been linked to cause of cirrhosis, liver disease, and fibrosis.[2] However, in the present case the drug-induced hepatotoxicity due to methotrexate is unlikely, since in most cases only long-term treatment with the drug is linked to hepatic dysfunctions. Moreover, the occurrence of disproportionate transaminitis is more indicative of a primary liver disease than drug-related toxicity.

Kayser-Fleischer ring is a common clinical sign noted in WD patients. The occurrence of deep green pigmentation of the cornea is caused due to the deposition of copper in the descemet membrane. However, it is no longer considered a valid pathognomonic sign, unless associated with neurologic manifestations, as the rings are also commonly noted in patients with chronic cholestatic diseases.

The present case fits into the criteria proposed by Roberts and Schilsky for establishing Wilson's disease. As per the criteria, absence of KF ring, CPN<20 mg/dL, 24-h urine Cu

>40 mcg and Cu quantification of liver biopsy >250 mcg/g dry weight are indicative of Wilson's disease.[1]

To the best of our knowledge, this is the first case report on the co-existence of WD with RA. There are case studies describing the co-occurrence of WD with coincidental sarcoidosis, neurofibromatosis and autoimmune hepatitis.[3-5] Dara et al. reporting the simultaneous presentation of WD and autoimmune hepatitis has highlighted the need to maintain a high level of awareness on such rare co-existence.[5] Marianthi et al. have reported the co-existence of WD and sarcoidosis in a 35-year-old female patient. The study has concluded on the necessity to evaluate the underlying cause of signs and symptoms that are not compatible with the already diagnosed rare disease.[3]

The literature evidence indicates that mutations in *ATP7B* located on chromosome *13q14.3* are associated with the development of WD. However, the secondary role of these mutations in developing non-Wilsonian diseases and WD-related arthropathic presentations has not been clearly elucidated.[6] Genetic testing was not conducted in the present case, since the diagnosis of WD was evident from liver biopsy.

In the current case, the co-existence of RA with WD raises the possibility of a potential link between these two diseases. A possible hypothesis that would explain the co-occurrence is that excessive copper accumulation due to WD could have functioned as an intrinsic factor eliciting immune response in an immunologically predisposed patient.

Patients with such rare co-occurrence of distinct diseases with completely different pathophysiologies need close monitoring and regular follow-up to prevent serious disease-related manifestations.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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