DIFFERENTIATION OF RHEUMATOID ARTHRITIS FROM HEPATITIS C-RELATED ARTHROPATHY: CASE REPORT

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DIFFERENTIATION OF RHEUMATOID ARTHRITIS FROM HEPATITIS C-RELATED ARTHROPATHY: CASE REPORT (Abstract): Chronic virus C hepatitis records high prevalence, almost 170 million people worldwide being infected. Systemic involvement is frequent and the implication of the osteoarticular system raises various problems in properly diagnosing and treating it. Rheumatoid arthritis is the most frequent type of inflammatory polyarthritis, with a prevalence of 0.8% in the general population. The rheumatoid factor recorded high values at virus C hepatitis patients (19-80%) even in the absence of articular manifestations, its sensitivity and specificity being reduced for the rheumatoid arthritis diagnosed simultaneous with virus C hepatitis. We report a case of chronic virus C hepatitis patient which, after 30 years of evolution, presents the onset of senile rheumatoid polyarthritis. The authors discuss the usefulness dosage of anti-cyclic citrullinated peptide antibodies for establishing the differential diagnosis between rheumatoid arthritis and hepatitis C-related arthropathy and the particularities of the specific treatment when there is a hepatitis C virus associated infection. Keywords: VIRUS C HEPATITIS, RHEUMATOID ARTHRITIS, HEPATITIS C–RELATED ARTHROPATHY, RHEUMATHOID FACTOR, ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES.

The prevalence of virus C hepatitis (VCH) infection reaches alarming levels, worldwide being recorded almost 170 million cases (1, 2). The prevalence is maximum at the age group of 30–49 years, the infection is chronic at 80% of the patients and the progression rate towards end–stage liver disease is of 10–20%, for a period of 20 years of observation (3). Rheumatoid arthritis (RA) is the most frequent type of inflammatory arthritis, with a prevalence of 0.8% in the general population, 1.3 million adults being diagnosed with RA in the USA. Without treatment, 20 – 30% of the patients diagnosed will evolve towards a major degree of disability in the next 3 years (4, 5). The relationship between the two affections is two-way, as far as epidemiology, pathogenesis and treatment response are concerned; the traditional serological marker for RA, the rheumatoid factor (RF), was detectable at 70 – 80 % of the patients with RA, but it can have higher values also at patients with VCH, in a per-
percent of 19-80%, even in the absence of joint manifestations (6). On the other hand, serum anti–hepatitis C virus (HCV) antibodies were present in RA patient at the following levels: 5.2% and 7.6% (7, 8). We report a case of an elderly patient, which came with polyarthralgias, after more than 30 years of evolution of chronic hepatitis with HCV, at which imaging and immunologic investigations establish the diagnosis of senile RA.

**CASE PRESENTATION**

An 83-year-old women, with antecedents of VCH from the age of 50 and with arterial hypertension associated with left bundle branch block from the age of 58, presents pain, tumefaction and functional incapacity at the level of metacarpophalangeal (MCP) and proximal bilateral interphalangeal (IP) joints, cervicalgia, weight loss and progressive asthenia during the past 3 months. The patient is a former nurse, has not smoked or used alcohol, and from the clinical examination resulted normal body mass index (21.5 kg/m²), the affected joints of both hands being swollen and painful, the limitation of the cervical spine for anterior, posterior and lateral flexion, hepatomegaly with high consistency and 2nd degree splenomegaly.

Hematological and biochemical biological tests were within the normal limits, except for the increase of gamma-glutamyl transferase (γGT) up to the value of 89 U/L (reference range <61U/L) and moderate hepatocytolisis (ALAT 136 U/L, ASAT 134 U/L).

The abdominal ultrasound pointed out the enlargement of the right liver lobe, with micronodular hyperechoic structure and splenomegaly; the abdominal computed tomography excluded the presence of liver tumor formations. From the radiography of the hands results bilateral risarthrosis associated with clips of MCP articulations, proximal and distal IP but also periarticular osteoporosis and erosions, suggestive for the begging of RA (fig. 1). Imaging investigations are completed by cervical spine computed tomography which excludes the presence of osteolytic lesions at this level and articular ultrasound which underlines the erosions from the II and III MCP joints accompanied by inflammatory reaction and synovitis (fig. 2, 3).

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**Fig. 1.** Bilateral radiography of the hands showing periarticular osteoporosis and erosions

**Fig. 2.** Cervical spine computed tomography showing degenerative lesions
The immunological report revealed positive tests for HCV, RF increased at 70.9 UI (normal range < 16 UI), anti-cyclic citrullinated peptide (ACCP) antibodies with pathological values of 34 UI (normal range < 12 UI), cryoglobulins and antinuclear antibodies absent. The treatment was started with hydroxychloroquine in dose of 400mg/day in association with non-steroid anti-inflammatory drugs (NSAID) during hyperalgesic periods. The general state and the painful articular syndrome improved in only 3 weeks.

Fig. 3. Articular ultrasound of MCP and IP joints showing erosions, inflammatory reaction and synovitis (arrow)

**DISCUSSION**

Chronic HCV infection is accompanied by various extrahepatic manifestations which were included by Ferri C et al. in 2007 in the so-called HCV syndrome (9), and the articular modifications are among the most frequent ones. Most studies reported polyarthralgias of variable frequency (20–83%) (1). One of the big prospective studies, which included 1614 patients with chronic hepatitis C, mentioned the prevalence of polyarthralgias of 23% (10). Arthritis are less frequent and they are characterized by symmetric polyarthritis which can be mistaken for RA or by mono or oligoarthritis, intermittent, without erosive–destructive features. Mono or oligo-articular affection is more frequent at large joints and is associated to the presence of cryoglobulins, while symmetric polyarthritis has an evolution similar to that of RA (11-14). HCV-related arthropathy can be clinically similar to RA, many patients experiencing the diagnosis criteria stated by American College of Rheumatology (ACR) (15).

In this patient’s case, the main differential diagnosis reported to senile RA and HCV associated arthropathy. The differentiation consisted in the dosage of the ACCP antibodies, which recorded higher levels and the radiographies of the hand which pointed out periarticular erosions, rare in HCV arthropathy. The comparative immunological studies at patients with chronic hepatitis C virus proved the superiority of ACCP antibodies in RA diagnosis. ACCP antibodies were scarcely positive at patients with HCV and arthralgia (5.7%), absent at the secondary Sjögren syndrome (0%) but they were present at 78% of the patients with RA (1). A previous study used for detecting ACCP antibodies a second generation ELISA kit (cut off = 20U/ml) and reported a prevalence of 6.9% (2/29) in patients with HCV and mixed cryoglobulinemia and 0% (0/50) in patients without cryoglobulinemia (16). In a different group of 39 patients with HCV, 31 of which with associated arthropathy, compared with 30 patients with RA criteria, ACCP antibodies were present in 77% of the patients with RA and in no patients with HCV (13). Classically, 50% of the patients with VCH present mixed cryoglobulines and 24% arthralgia (1). Referring to the primary Sjögren syndrome, the
percentages are small, less than 10% of the patients with primary Sjögren syndrome presenting ACCP antibodies (17).

VCH was associated with many other extrahepatic manifestations as vasculitis, glomerulonephritis, thyroiditis and salivadenitis, but polyarthritis were most cited (10). Fadda et al. examined 302 patients with VCH for arthritis (8% of the patients with cryoglobulinemia presented non-erosive oligoarthritis, 15% of the patients with cryoglobulines experienced polyarthritis and 30% of them presented erosions at radiological investigations) (18). Among the self-antibodies produced by the organism in VCH, RF is one of the most frequent (30%-70%), sometimes present at high levels (12). Unlike RF, ACCP antibodies were not mentioned as autoimmune markers and did not record high levels at patients with VCH, included in the published studies (1, 6, 13, 16, 19–21). Lu et al. (19) also studied the diagnostic role of anti-agalactosil IgG antibodies in differentiating RA from the other similar arthropathies, present in VCH, hepatitis B virus or primary Sjögren syndrome. They pointed out that the anti-agalactosil antibodies’ sensitivity and specificity is lower than that of ACCP antibodies (81% sensitivity and 98.4% specificity), which remain the golden standard in differentiating RA from other arthropathies associated to viral hepatitis and primary Sjögren syndrome. They also investigated the presence of chronic VCH limits the treatment options of the associated RA. Considering the age too, we chose for our patient the hydroxchloroquine treatment associated with NSAID; the improvements were noticeable after the first weeks of treatment. Other authors also mention the possibility of using hydroxchloroquine and sulfasalazine in patients with moderate liver disorders. Cyclosporine, with anti-viral effect as well, but also tumor necrosis
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factor (TNF) inhibitors, rituximab and abatacept were used (3, 24).

CONCLUSIONS
This case as well as the previous reports in the literature emphasized the particularities of the RA in comparison with hepatitis C-related arthropathy and describe the utility of ACCP as laboratory diagnostic tool.

REFERENCES


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**TARGETED ANTIFUNGAL PROPHYLAXIS IN HEART TRANSPLANT RECIPIENTS**

Tissot *et al* conducted a retrospective analysis to identify the risk factors for the development of invasive fungal infection (IFI) after heart transplantation (HTx) and implement a new antifungal prophylaxis policy. For this purpose, clinical characteristics of HTx recipients hospitalized during a seven years period were recorded and risk factors associated with IFI were identified using Cox regression analysis (Period 1). Based on the results of the first analysis, all recipients at high risk for IFI received targeted caspofungin prophylaxis (Period 2 of the study, lasting 3 years). During Period 1, 10% of patients developed IFI after transplantation. The use of posttransplant extracorporeal membrane oxygenation was the strongest predictor for IFI by multivariate analysis, while *Aspergillus* colonization and renal replacement therapy were significant predictors by univariate analysis. Antifungal prophylaxis was administered to 17% of patients at high risk for IFI in period 1 versus 100% in Period 2. Only 4% of the patients developed IFI during Period 2. Antifungal prophylaxis was associated with a reduction in IFI incidence and mortality. Extracorporeal membrane oxygenation is an important risk factor for IFI after transplantation and requires targeted administration of antifungal prophylaxis (Tissot F, Pascual M, Hullin R, *et al*. Impact of Targeted Antifungal Prophylaxis in Heart Transplant Recipients at High Risk for Early Invasive Fungal Infection. *Transplantation*. 2014 Feb 11).

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