

# Type I autoimmune hepatitis, inverted psoriasis with psoriatic arthropathy and type 2 diabetes mellitus as complications of a chronic B virus hepatitis treated with interferon - Case report

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**Abstract.** We present the case of a 31 year old male patient, admitted in the 3rd Medical Clinic Cluj-Napoca for asthenia, fatigue, effort hepatalgia, pain located in the legs and small joints of the hands. Patient has been diagnosed a year ago with chronic B viral hepatitis and received Peginterferon alpha 2a treatment. After performing clinical and paraclinical exams we established that patient suffers from type I autoimmune hepatitis, inverted psoriasis with psoriatic arthropathy, recent onset of type II diabetes mellitus. These conditions are likely to appear consecutively to Interferon therapy. The markers for B virus hepatitis (Ag-HBs, IgM-HBc, AgHBe, ADN-HBV) were negative. The evolution was favorable after therapy with immunosuppressants, corticoids, oral antidiabetics and antisecretors.

**Key Words:** autoimmune hepatitis, inverted psoriasis, psoriasis arthritis, type II diabetes mellitus, Interferon, chronic B virus hepatitis.

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## Introduction

Autoimmune hepatitis is a chronic liver inflammatory condition, with possible progressive evolution towards liver cirrhosis, characterized by the presence of liver inflammation, piecemeal liver necrosis and specific serum autoantibodies (Longhi *et al* 2010). The disease may accompany other autoimmune conditions and the main therapeutic resources are glucocorticoids and immunosuppressants. AH could also accompany chronic viral hepatitis among overlap syndromes or could be triggered by these infections or their therapy (Tripathi *et al* 2009). At the moment, the majority of the authors accept 2 types of AH (table 1). Psoriasis is an autoimmune inflammatory disease, characterized by infiltration of epidermis by T-cell lymphocytes that produce cytokines capable of inducing keratinocytes proliferation. Keratinocytes stimulated this way are capable of inducing T-cell stimulation, the result being the development of specific cutaneous lesions in areas subjected to mechanical friction (Pietrzak *et al* 2008). In inverted psoriasis the lesions appear on flexion folds. A group of patients with psoriasis develop psoriatic arthritis, a form of seronegative spondylarthritis with genetic mark of HLA B 27 (Menter *et al* 2010). T1DM is an autoimmune condition resulting consecutively the destruction of  $\beta$  pancreatic islet cells and may be accompanied by various syndromic or non-syndromic autoimmune diseases. In the description of T2DM,

immunologic paradigm, neglected till recently, becomes gradually of some importance (DiPenta *et al* 2007).

**Table 1.** Classification of AH (Czaja 1998, Manns 2010, modified)

AH type*	Autoantibodies	Characteristics
1	ANA, SMA, AA, SLA/LP, AMA, pANCA	Young women
2	LKM** (against P450IID6), ALC1, SLA/LP	No sex or age prevalent

\* Some authors still consider AH type 3 when SLA/LP are present, while others accept type 4 AH, distinguished by LKM 3 and anti HDV antibodies. \*\* LKM types: LKM1 ( type 2 AH), LKM2 (drug induced hepatitis), LKM3 (chronic D virus hepatitis).

## Case report

A 31 years old Caucasian male patient, U. F., came to the Gastroenterology Ambulatory of the 3rd Medical Clinic in Cluj-Napoca, Romania, for investigation and therapy, accusing intense joint pain in his feet, knees and small joints of his hands, asthenia, fatigue, effort hepatalgia. Clinical examination revealed BP = 120/75 mm Hg and HR 80', disseminated onycholysis with onychomadesis of the lower limbs,

tumefaction of distal and proximal interphalangeal joints of both legs, tending to affect the skeleton centripetally, antalgic flexion posture of the knees, psoriasiforme cutaneous lesions of dorsal foot and suprajacent skin of small foot joints, tumefaction of the first interphalangeal joints on right hand, tumefaction of proximal and distal interphalangeal joints in both feet and swelling of both knees, liver at 2 cm under the right rib border, grade 2 splenomegaly, hepatic arrow on the right middle collar bone line measuring 14 cm.

At the same time, the patient presented psoriasiforme cutaneous eruptions of folds with symmetric tumefaction of distal joints of lower limbs so he underwent a dermatological consult which concluded as a diagnosis the inverted psoriasis with psoriatic arthropathy and the dermatologist prescribed a treatment with Sulfasalazine (SALAZOPYRINE- Pfizer, Sweden, 3 g day<sup>-1</sup>), with no clinical result.

The patient has been diagnosed one year ago with chronic B virus hepatitis and as a result of the data obtained from biochemical analyses (AST=475 U l<sup>-1</sup>, ALT=629 U l<sup>-1</sup>), virus analysis (Ag HBs+, AgHBe+, AcHBe-, Ac-HCV-, AcHDV-, ANA-, LKM1-, AMA-, ADN-HBV=2x10<sup>6</sup> copies ml<sup>-1</sup>) and the histological elements provided by the liver biopsy (moderate periportal necrosis, severe portal inflammation, absent fibrosis), therapy with Interferon (Peginterferon alpha 2a- PEGASISR-Roche, UK, 180 mcg 0.5ml<sup>-1</sup>, 1 dose week<sup>-1</sup>, 48 weeks) has been considered the proper choice. The patient's symptoms appeared shortly after the end of the Interferon therapy.

Biological analyses revealed accelerated ESR, hepatocytolysis syndrome (AST=214 U l<sup>-1</sup>, ALT=231 U l<sup>-1</sup>), newly discovered hyperglycemia, hyperproteinemia (TSP=9.2g 100 ml<sup>-1</sup>) with hypergammaglobulinemia (2.32 g 100 ml<sup>-1</sup>, 26%) and detectable ANA and SMA levels (the last one having high values 1 320<sup>-1</sup>), altered oral glucose tolerance test (glycaemia a jeunne 340 mg dl<sup>-1</sup> after one hour 340 mg dl<sup>-1</sup>, after 2 hours 360 mg dl<sup>-1</sup>). The markers for B virus hepatitis (Ag-HBs, IgM-HBc, AgHBe, ADN-HBV) were negative.

Abdominal ultrasonography showed a mild hepatomegaly (left lobe=85 mm, right lobe=165 mm) with splenomegaly, the spleen measuring 140 mm.

Personal pathological history of the patient prior to virus B hepatitis infection (possible infection source – from anamnestic date could have been a stomatological maneuver) are not significant. Family history with relevance for the current pathology could be represented by the fact that both patient's parents suffer from type II diabetes mellitus.

Considering patient's symptoms, anamnestic data, elements from the clinical exam, studying the medical papers of the patient and corroborating these data with the results of the para-clinic explorations we decided to begin the treatment with immune suppressors like azathioprine (IMURAN) in doses of 50 mg day<sup>-1</sup> associated with corticotherapy – prednisone (PREDNISON) 20 mg day<sup>-1</sup> (the dose was lowered at 15 mg day<sup>-1</sup> after 2 weeks of treatment). Along with the therapy there

were also administrated proton pump inhibitors – omeprazole (OMERAN) in doses of 20 mg twice a day, in order to prevent potential gastric aggression secondary to corticoids treatment.

To improve the glicoregulation problems and to avoid additional glicoregulation failure due to corticotherapy we also administrated glimepiride (AMARYL) in doses of 1mg per day, then we increased the dose to 1mg twice a day in order to obtain a satisfactory serum glucose levels.

Under this treatment the patient's evolution was very good, with quick improvement of rheumatic symptomatology, significant improvement of posture and walking, resolution of hepatocytolysis syndrome and improvement of general condition.

## Discussion

Occurrence of AH after Interferon administration is more frequent after therapy for C chronic viral hepatitis even after the eradication of the infection (Petropoulou *et al* 2010), some authors presenting even cases of fulminant forms (Coriat *et al* 2008). In many cases Interferon induced AH could be accompanied by other autoimmune conditions (Martins *et al* 2004, Trikudanathan *et al* 2011.). The main causes could be the Interferon's immunogenicity as AH appears in patients that used Interferon for the treatment of other conditions than chronic viral hepatitis (Lebiedz *et al* 2009) as well as molecular mimicry between viral antigens and autoantigens (Bianchi *et al* 2007). Although less frequent than following C viral infection AH may appear after the chronic B hepatitis treated with Interferon (Cianciara *et al* 1995). Usually B viral hepatitis induces a type I AH and C viral hepatitis induces a type II AH (Shantha *et al* 2002). Though less studied, other viral infections with liver tropism may induce AH, even under the form of overlap syndromes (Heurgue *et al* 2009, Tovoda-Akui *et al* 2011). The implications of the immune system seems to have a substantial contribution in T2DM (Musa *et al* 2010) as there are some cases of T2DM associated with autoimmune disorders (Schroner *et al* 2008). Autoimmunity against  $\beta$  islet cells characterizing T1DM may be demonstrated in up to 10-15% of patients with T2DM many of them having GAD and ICA antibodies (Pietropaolo *et al* 2000; Syed *et al* 2002). In T2DM there are elevated levels of various cytokines and acute phase reactants like CRP, SAA, SA, IL6, situation that makes from T2DM a condition with deep immunological implications and these reactants may also concur to the shaping of X metabolic syndrome (Pickup *et al* 1998).

In recent literature there are many cases of autoimmune hepatitis associated with viral hepatitis. Most of them are overlapping cases but exist some individuals in which the autoimmune pathology is triggered by the Interferon treatment administered for the viral hepatitis (Floreani *et al* 2005).

The particularity of our case consists of the possible triggering of a type I autoimmune hepatitis and of a non-typical psoriasis (inverted psoriasis, psoriasis of folds) in a patient with chronic B viral hepatitis treated with Interferon and as well as of the recent discovered type II diabetes mellitus shortly after the debut of these diseases, although usually T1DM accompanies autoimmune pathology. It is possible that we do not have enough

knowledge about every pathway of T2DM and that some autoimmune changes could affect insulin cell targets and consequently induce insulin resistance.

## Abbreviations

AH=autoimmune hepatitis, ANA=antinuclear antibodies, SMA=smooth muscle antibodies, AA=antiactinic antibodies, LKM=liver-kidney microsomal antibodies, SLA/LP= antibodies against soluble liver antigene /liver pancreas antigen, ALC1= anti-liver cytosol I antibodies, pANCA= perinuclear Anti-Neutrophil Cytoplasmic Antibodies, AMA=anti-mitochondrial antibodies, BP=blood pressure, HR=hearth rate, T1DM=type I diabetes mellitus, T2DM=type II diabetes mellitus, ESR=erythrocyte sedimentation rate, GAD=glutamic acid decarboxylase, ICA=islet cell antibodies, CRP=C reactive protein, SAA=serum amiloid A, SA=sialic acid, IL6=interleukin 6,HBV=hepatitis B virus, HCV=hepatitis C virus HDV=hepatitis D virus, TSP=total serum proteins, Ag=antigene,Ac=antibodies, AST= aspartate aminotransferase, ALT=alanine aminotransferase.

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