

AUTOIMMUNE LIVER DISEASE IN A SICILIAN WOMAN

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[Malattia epatica autoimmune in una donna siciliana]

ABSTRACT

Autoimmune hepatitis (AIH) is a chronic liver disease characterized by clinical features analogue to viral and non-autoimmune liver disorders, but with distinct sero-autoimmunologic properties. The disease results from a network of complex interactions involving genetic predisposition, triggering factors, autoantigens and immunoregulatory system. Diagnosis of AIH relies on positive autoantibodies determination and on liver core biopsy histological appearance. Corticosteroid and immunosuppressive drugs are generally useful in the treatment of disease. However, when inflammation cannot be controlled, progression from chronic hepatitis to cirrhosis is often observed and hepatocellular carcinoma may appear at the end stage. Here we reported a case of a woman, affected with AIH. The patient presented features of chronic liver disease of neither viral nor alcoholic aetiology. Serum evidence of hypertransaminasemia, hypergammaglobulinemia and specific autoantibodies were the leading points to final diagnosis, which was validated by liver biopsy. The patient was, finally, successfully treated with steroids.

Key words: autoimmune hepatitis; autoantibodies; corticosteroids.

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Introduction

Liver diseases ranked as the 8th most common cause of death. Autoimmune liver diseases are chronic liver diseases characterized by similar clinical features to viral and non-autoimmune liver disorders, but with distinct sero-autoimmunologic properties. The main kinds of autoimmune liver diseases are autoimmune hepatitis (AIH), primary biliary cirrhosis and primary sclerosing cholangitis. However, secondary autoimmune liver diseases have been associated with several underlying illness, i.e. infections, medications, autoimmune diseases and malignancies (the so-called "overlap syndromes")^(1,2).

AIH was one of the first liver diseases which an effective treatment was developed to and the benefit demonstrated by randomized controlled trials. Nevertheless, both the diagnosis and the treatment of this disease presented full of challenges. Clinical spectrum is very wide, ranging from sub-

clinical and non-progressive disease to fulminant, lethal hepatic failure. Diagnostic criteria, based on IgG raising, demonstration of characteristic autoantibodies, and histological features of hepatitis, in the absence of viral disease, are very helpful.

Adequately high steroid doses are the mainstay of remission induction treatment, while remission maintenance is best achieved by azathioprine.

Therapeutic alternatives are required in a small group of patients, who don't adequately respond to these drugs or are intolerant to their side effects. Here we reported the case of a woman affected with AIH, successfully treated with corticosteroids and immunosuppressive drugs⁽³⁾.

Case report

A 65-years-old sicilian woman was admitted in November 2010 to our Medical Department, due to hypertransaminasemia associated with increased cholestasis indices.

She also suffered of high blood pressure, hypercholesterolemia, gastroesophageal reflux disease (GERD), osteoporosis, and anxious-depressive syndrome, pharmacologically treated with benefit. No history of alcohol intake or other chronic liver diseases risk factors. Few days before admission, she underwent a routine serological examination, which pointed-out hypertransaminasemia (about 30 times reference values) and increased cholestasis indices (about 3 times reference values of serum gamma-glutamyltransferase, γ -GT, alkaline phosphatase, and total and direct bilirubin) but no symptom was referred. Physical examination revealed only mild hepatomegaly, and no cutaneous or mucosal jaundice was detected. Blood samples, performed during hospitalization, showed increased transaminases values (ALT 936 IU/L, AST 593 IU/L), as well as cholestasis indices rising (γ -GT 564 U/L, alkaline phosphatase 215 U/L, hyperbilirubinemia, especially conjugated fraction) and hypergammaglobulinemia. Inflammatory markers (i.e. erythrocyte sedimentation rate, ESR and C-reactive protein, CRP) were within the reference limits, except for a slight increase in ferritinemia. Abdominal ultrasonography did not show any pathological abnormality.

Several serum tests were then performed:

1) serology for major and minor hepatotropic viruses (hepatitis A virus [HAV], hepatitis B virus [HBV]), hepatitis C virus [HCV], Epstein Barr virus [EBV], cytomegalic virus [CMV], herpes simplex virus [HSV] 1 and 2) which was proved negative, except for a weak anti-HCV antibodies positivity, later disproved;

2) serum cryoglobulins determination was negative;

3) thyroid hormones showed mild abnormalities, with a slight reduction in thyroid stimulating hormone (TSH) levels, and a mild increase in free thyroid hormone fractions (about twice), as subclinical hyperthyroidism expression. Abdominal ultrasonography, negative at first, was repeated after few days, and showed "mild liver enlargement, with homogenous echotexture and regular margins, gallbladder with thickened walls, and slight increase in the common bile duct diameter (0.7 cm)". A third abdominal ultrasonography, performed some days later, showed no variations.

Further investigation was upper abdomen computerized tomography (CT) with contrast, that

pointed out no differences respect to ultrasound framework. According to differential diagnosis approach for unknown origin liver diseases, serological tests for detection of main autoantibodies were performed, and they were all negative, with the exception of anti-nuclear antibodies (ANA) and atypical peri-nuclear antineutrophil cytoplasmic antibodies (p-ANCA), both positive at high titers. Nevertheless, she underwent to liver biopsy, which showed a framework of autoimmune liver disease (grading 3/3; staging 1/4; histological scoring 3 +1 +1). During hospitalization, patient had no abdominal or systemic symptoms that could suggest a liver disease.

According to the histological diagnosis the patient underwent high dosage parenteral corticosteroid therapy, with substantial benefit. She was then discharged, advising to practice oral corticosteroid therapy, with gradual dosage reduction. After about three months, she was readmitted to our Department for clinical and laboratory control: transaminases and cholestasis indexes appeared to be reduced by at least 1/3 compared to baseline. After one year of treatment, all aforesaid serological parameters reduced so steroid drugs was administered at maintenance dose (prednisone 7.5 mg/die).

Discussion

AIH occurs in all races and geographical areas. As it is a relatively rare disease, only few epidemiological data are reported in literature. These suggest a prevalence of at least 1:10,000. In developed countries, i.e. USA, AIH accounts for about 20% of all liver transplantations. In Italy, the main agent associated with chronic hepatitis is hepatitis C virus, whereas AIH is almost rare (prevalence of 0.9% in a survey of 2610 chronic hepatitis patients), and affects about 50.000-100.000 individuals. There are no data about prevalence of autoimmune liver diseases in Sicily, even though there are some reports about the presence of AIH in our geographic area^(4,5).

Although women are still more affected than men, lately the percentage of the latter had recently increased, compared with that in previous studies. AIH onset age varies greatly, from as early as the first year of life up until the eighties. However, as in many other autoimmune diseases, both the median and the mean age of initial disease manifestation are in the forties.

According to previous data, AIH should be considered in the differential diagnosis of any patient with laboratory evidence of liver disease⁽⁶⁾.

AIH carries all features of an autoimmune disease: genetic predisposition, association with other autoimmune diseases (i.e. Hashimoto thyroiditis, type 1 diabetes mellitus, celiac disease, systemic lupus erythematosus, and idiopathic thrombocytopenic purpura), spontaneous disease activity fluctuations, autoantibodies, autoreactive T-cells and inflammatory infiltrate evidence, and a good response to steroids and immunosuppression. As in other autoimmune diseases, neither the aetiology of the disease, nor the triggering factors, nor those that may lead, in some patients, to spontaneous remissions are known. A genetic predisposition can be presumed, according to HLA association. Various other genetic associations have been described (i.e. genetic polymorphisms of immune response genes), but most of these have only been studied in relatively small groups of patients, and often have not been confirmed by other studies⁽⁷⁾.

The clinical manifestations of AIH are highly variable. Almost a third of the patients come to physician attention with an acute icteric hepatitis, occasionally even with fulminant, lethal hepatic failure. However most of the patients have milder and, some, even subclinical disease. They present with non-specific symptoms, such as generalized fatigue. At least a third of patients have already cirrhosis at onset of clinical presentation, suggesting that the disease may be unrecognized for a considerable period of time prior to diagnosis. However, the frequency of patients with jaundice and/or liver cirrhosis, at first physician examination, is finally decreased compared with previous reports one.

A characteristic feature in many patients is an acute relapsing course. As a matter of fact, most of them, if not diagnosed or not treated for any other reason, will experience a spontaneous partial recovery, and, sometimes even a complete normalization of liver function tests. However, histological disease activity usually persists, and another acute exacerbation is usually predictable within few months.

Some others progress to a chronic hepatitis, generally characterized by a fluctuating course. On clinical examination, signs of chronic liver disease may be highlighted, i.e. palmar erythema (which may disappear after successful immunosuppressive therapy), and palpable enlarged liver, sometimes swollen and tender. In advanced disease, nodularity

may be palpable⁽⁸⁾. Several patients with AIH present, late, with cirrhosis, at times decompensated. Many of them are diagnosed as having a "cryptogenic cirrhosis", and in the past AIH was the most common cause of cryptogenic cirrhosis⁽⁹⁾.

In 1993 the International Autoimmune Hepatitis Group developed a scoring system to help standardization of patients in scientific publications⁽¹⁰⁾. This scoring system, revised in 1999, has also been applied by some to daily clinical practice, for which it had not been primarily designed nor tested, and found to be very cumbersome⁽¹¹⁾. In 2008 the International Autoimmune Hepatitis Group suggested a simplified scoring system for clinical practice, which is useful in most cases⁽¹²⁾.

However, diagnosis is based on four features: hypergammaglobulinaemia, autoantibodies, histology and absence of viral hepatitis. Hypergammaglobulinaemia is the cheapest of these screening tests, the most characteristic finding being a selective elevation of serum IgG, with serum IgA and IgM normal levels. Autoantibodies are an hallmark of AIH and constitute an important part of the diagnostic work-up. However, both ANA and smooth-muscle antibodies (SMA) are not disease-specific markers. Antibodies versus liver-kidney microsomes type 1 (LKM1) and atypical p-ANCA are not disease-specific markers too, and occur in only a small fraction of patients.

Only SLA/LP autoantibodies are disease-specific markers, and therefore of high diagnostic value, but can only be detected by commercial assays in up to 30% of AIH patients.

Moreover, several studies reported that patients with AIH and histological features of acute hepatitis show lower levels of serum IgG and ANA titers. Histology is considered a necessary prerequisite to AIH diagnosis. The revised scoring system distinguishes "compatible with AIH" histology, scoring as 1 point, from "typical for AIH" histology, scoring as 2 points. Characteristic histological features suggesting typical AIH include interface hepatitis, portal and periportal inflammation, presence of plasma cells, resetting of hepatocytes, and emperipolesis. Most patients with AIH just exhibit complications of chronic inflammation, including fibrosis, and about a third of them are already cirrhotic. Cirrhosis in AIH is often irregular and characterized by macronodular regeneration. Absence of viral hepatitis was generally thought to be a prerequisite to diagnose AIH, but in a few patients viral infection and AIH may co-exist.

This is particularly relevant in countries with viral hepatitis high prevalence, where AIH diagnosis may be entirely overlooked in viral hepatitis infected patients. As a matter of fact, autoimmune phenomena are frequently found in HCV-infected patients. ANA-positive and HCV infected patients generally have a lower probability of AIH diagnosis. The revised simplified scoring system allows AIH diagnosis in these patients, proving high IgG levels and autoantibodies titres, as well as typical histology, which should be reviewed by an expert liver histopathologist^(13,14,15).

Randomized trials unequivocally showed the survival benefit of corticosteroid and immunosuppressant treatment in patients with AIH. The lately published American Association for the Study of Liver Diseases (AASLD) practice guidelines recommend either an onset dose of 30 mg prednisone combined with 1-2 mg azathioprine (AZA) per day, or monotherapy with prednisone at a daily starting dose of 40-60 mg, in adults.

However, as AZA is hepatotoxic, particularly in jaundiced patients with decompensated disease, it is advisable to treat first with steroids high dosages, then add AZA later, just after jaundice has subsided and partial disease control is achieved. It seems that steroids are the mainstay of remission induction treatment, while remission maintenance is best achieved by AZA.

The most reasonable approach is probably to tailor treatment according to the individual patient characteristics, depending on whether the risk of steroid side-effects is higher than the risk of long-term higher azathioprine doses ones, or vice versa⁽¹⁶⁾. Budesonide is lately receiving considerable attention as an alternative to prednisone in the treatment of AIH, especially in patients in whom steroid side-effects are expected to be a problem⁽¹⁷⁾.

With respect to treatment with ursodeoxycholic acid (UDCA), the number of AIH patients treated with UDCA recently increased compared with that in previous studies. Although the exact UDCA underlying activity mechanisms in AIH have not been clarified, the drug is currently administered to patients affected with "problematic" AIH, in addition to steroids and immunosuppressive drugs⁽¹⁸⁾.

AIH management requires careful follow-up and strict adherence to treatment both by treating physicians and patients. Follow-up biopsies may be particularly helpful in these patients, to guide immunosuppressive therapy⁽¹⁹⁾.

Treatment failure occurs in 20% of AIH patients assuming prednisone and AZA. Few patients show an insufficient response to standard immunosuppression, and some show reactivation during reduction of steroid doses. In these patients stronger immunosuppressive agents appear to be required, and good results have been reported administering cyclosporine, tacrolimus, cyclophosphamide, infliximab and mycophenolate mofetil.

Specific studies on second line treatment, in not responsive patients, are needed, and no comparative data are still available⁽²⁰⁾. It appears that the calcineurin inhibitors, cyclosporine and tacrolimus, are efficient agents, but, like in other autoimmune diseases, they are not immunomodulatory, and therefore tend to require permanent treatment, while real immunomodulatory agents, such as cyclophosphamide or infliximab, may allow reduction of immunosuppression over time⁽²¹⁾.

The TH1/TH2 cytokines production imbalance has been associated with AIH pathogenesis, and researchers reported that TH1 cytokines, as TNF- α , seem to prevail in comparison with TH2 ones in the liver of patients with active AIH. Therefore, theoretically, anti-TNF- α agents (i.e. infliximab) can be one of the options for AIH treatment; however, a case of AIH, suspected of resulting from anti-TNF- α agents, has also been reported. Therefore, cytokines, as TNF- α , role to the pathogenesis of the disease may be complex and the efficacy of anti-TNF- α treatment is still controversial⁽²²⁾.

Treatment with mycophenolate mofetil, salt form of immunosuppressive drug mycophenolic acid, induced response or remission in most of patients with AIH and AZA-intolerance, but it appears to be of very limited efficacy in patients not responding to AZA, even if experience in children is kinder than in adults⁽²³⁾.

Prognosis of treated AIH is usually positive. Some centers report normal life expectancy rates, but there may be a patient selection bias. In particular, some patients with early severe disease progress rapidly, despite immunosuppression, and require liver transplantation. Moreover, patients presenting with already advanced cirrhosis or liver failure may die in the early phase of treatment, due to infectious complications related to immunosuppressive drugs. Liver transplantation is rarely required in patients affected with AIH, but is more common in children, who present fulminant hepatitis more often than adults. Main reasons for liver transplantation are fulminant disease not enough responding to steroid

drugs, disease progression due to patient compliance lack, and long-term progression despite adequate treatment, especially in initially already advanced cirrhosis⁽²⁴⁾.

Due to improvement in the prognosis and aging of AIH patients, malignancies have become important complications. It was long thought that in autoimmune liver diseases the risk of hepatocellular carcinoma (HCC) is negligible. The relative AIH rarity makes it impossible to correctly evaluate the incidence of HCC in AIH cirrhosis, but as several cases of HCC in AIH cirrhosis have been reported from a variety of centers (about 1.3% of patients showed HCC during observation period), it appears reasonable to include AIH cirrhosis among the conditions justifying regular ultrasound screening for the development of neoplastic foci⁽²⁵⁾.

In conclusion, our case emphasizes that physicians should always keep in mind the possibility of AIH in patients who present with features of chronic liver disease, in whom viral studies are negative, and no history of alcohol intake and no obvious etiology is demonstrable. Screening for autoantibody should be considered in the general workup of such patients, together with liver histologic examination.

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