Uveitis in autoimmune hepatitis: A case report

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Abstract

In this case report we describe for the first time an association between autoimmune hepatitis (AIH) and uveitis, without any doubts about other possible etiologies, such as HCV, since all the old reports describe the association of AIH with iridocyclitis before tests for HCV-related hepatitis could be available. A 38-year-old businessman with abnormal liver function tests and hyperemia of the bulbar conjunctiva was admitted to the hospital. Six years before admission, the patient presented with persistent fever, arthralgias, conjunctival hyperemia, leukocytosis and increased ESR, referred to acute rheumatic fever. The presence of systemic diseases, most commonly associated with uveitis, was investigated without results and the patient was then treated with topical corticosteroids. His symptoms resolved. A test for anti-nuclear antibodies was positive, at a titre of 1:320, with a speckled and nucleolar staining pattern. Anti-smooth muscle antibody test was also positive (1:160), while anti-LKM antibodies were negative. Ophthalmologic examination revealed inflammatory cells and proteinaceous flare in the anterior chamber of the left eye, and a stromal lesion in the cornea. He was maintained on immunosuppressive therapy (5 mg prednisone plus topical antibiotic therapy for two weeks) and then discharged. A complete remission of the symptoms was registered on follow-up. At present (July 2005), the patient is on prednisone (5 mg) and has no symptoms. Liver function tests are also within the normal range.

Keywords: Autoimmune hepatitis; Uveitis

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CASE REPORT

A 38-year-old businessman was admitted to the Azienda Ospedaliero-Universitaria Careggi (Florence, Italy) on May 4th 2000, because of abnormal liver function tests and hyperemia of the bulbar conjunctiva.

The patient had no history of liver disease or jaundice, receipt of blood products, intravenous drug abuse, and exposure to alcohol or hepatotoxic drugs, seafood ingestion, any abdominal pain, excessive fatigue, rashes, or foreign travels. All his children were healthy. Family history of gastrointestinal or liver diseases was negative. His mother was affected by goitre and diabetes mellitus.

Six years before admission, the patient presented with persistent fever, arthralgias, conjunctival hyperemia, leukocytosis and increased ESR, which were referred to acute rheumatic fever, despite no evidence of recent group A streptococcal infection, since throat cultures were negative and streptococcal antibody test was normal. The patient was given salicylic acid up to 4 g for 2 mo. and prophylaxis with intramuscular benzathine penicillin G (1.2 g/mo. for 5 years). In 1998, conjunctival hyperemia recurred and iridocyclitis was diagnosed. The presence of systemic dis-
cases, most commonly associated with anterior uveitis, was investigated without results and the patient was treated with topical corticosteroids. His symptoms resolved. At admission for further studies on systemic alterations other than uveitis, the temperature was 36.6 °C, the pulse was 84 bpm, and the respiration rate was 18/min. Blood pressure was 105/70 mmHg. At physical examination, the head, neck and the extremities were normal. Auscultation of the heart and both lungs were normal. The abdomen was not distended; there was no evidence of edema, bleeding diathesis, or spider angiomata.

Main initial laboratory findings were as follows: hematocrit 48.2%, leukocytes 5,400/μL (39.5% neutrophils, 39.7% lymphocytes, 18.2% monocytes, 0.6% basophils, 2.0% eosinophils), platelets 157,000/μL, reticulocyte count 1.35%, glucose 0.83 mg/dL, BUN 0.25 mg/dL, creatinine 1.0 mg/dL, proteins 72 g/L, albumin 42.3 g/L, globulins 29.7 g/L, IgG 1590 mg/dL, IgA 224 mg/dL, IgM 83 mg/dL, AST 960 IU/L, ALT 1510 IU/L, γ-glutamyltranspeptidase 112 IU/L, alkaline phosphatase 249 IU/L, total bilirubin 1.57 mg/dL, conjugated bilirubin 0.4 mg/dL, total cholesterol 116 mg/dL, serum calcium 8.4 mg/dL, serum phosphorus 2.6 mg/dL, serum iron concentration 276 μg/dL, serum ferritin 3,020 μg/mL, and haptoglobin 54 mg/dL. Liver ultrasound showed mild hepatomegaly with an increased ecostructure of the liver. Percutaneous liver biopsy was performed under ultrasound assistance. Liver biopsy showed necroinflammation over the portal, periportal and lobular areas, fibrotic portal tracts, with perportal fibrosis and occasional portal-to-portal bridgings, but intact hepatic architecture. Some hepatocytes showed barely discernible granules of hemosiderin in the lobular area. Bile ductules were without any significant morphological alterations. METAVIR score resulted A2-F3, according to the modified HAI grading and fibrosis staging as proposed by Ishak et al[1]. No stainable iron or copper deposits were found.

Ophthalmologic examination, performed to rule out Wilson’s disease, revealed no diminished visual activity in both eyes; eye movements were normal, without diplopia; the globes were intrinsically normal, so as papillary light reflexes. The fundus oculi was normal, without signs of vasculitis. Biomicroscopy of the anterior segment of the eye was negative for iridocyclitis. No Kayser-Fleischer rings were noted.

Considering the clinical presentation, together with increased serum aminotransferase levels, absence of viral markers for hepatitis B, C, and other hepatotropic viruses, evidence on liver biopsy of chronic hepatitis with mild-
to-moderate fibrosis, the patients was diagnosed to have autoimmune hepatitis (AIH) with mild activity and discrete fibrosis. Patient was discharged on prednisone 25 mg and entered clinical and biochemical remission, further confirming diagnosis. After the discharge the patient continued to have treatment with corticosteroids as an outpatient at a dose of 5 mg.

On January 2002 the patient was readmitted to the hospital because of fever (39 °C), occurring especially in the evening. He also complained photophobia, and blurred vision in both eyes. The blood pressure was 110/65 mmHg, the pulse rate was 87 bpm, and the respirations were 18/minute. Physical findings were unmodified in respect to the previous readmission.

Laboratory investigations showed the following data: hematocrit 39.7%, leukocytes 9,690/µL (65% neutrophils, 19.3% lymphocytes, 14.5% monocytes, 0% basophils, 1.2% eosinophils), platelets 497,000/µL, reticulocyte count 1.35%, glucose 1.22 mg/dL, BUN 0.24 mg/dL, creatinine 1.2 mg/dL, proteins 84 g/L, albumin 33.9 g/L, globulins 26 IU/L, AST 14 IU/L, ALT 16 IU/L, γ-glutamyltranspeptidase 26 IU/L, alkaline phosphatase 52 IU/L, total bilirubin 0.14 mg/dL, conjugated bilirubin 0.14 mg/dL, total cholesterol 96 mg/dL, serum calcium 9.1 mg/dL, serum phosphorus 2.4 mg/dL, serum iron concentration 82 µg/dL, serum ferritin 263 ng/mL, haptoglobin 120 mg/dL, international normalized ratio for prothrombin time 1.0, and the activated partial thromboplastin time 26.1 s. Flogosis indexes (ESR, C-reactive protein, fibrinogen) were elevated. TSH was 1.57 mU/L. Urinanalysis was normal. Direct and indirect Coombs tests were both negative. Serum circulating immune complexes were within the normal range; C5 was 196 mg/dL, C4 43 mg/dL, and serum immunoelectrophoresis showed increased IgG. A test for anti-nuclear antibodies was positive, at a titre of 1:320, with a speckled and nuclear staining pattern. Test for anti-smooth muscle antibodies was also positive (1:160), anti-LKM antibodies were negative. Titres of antithyroid peroxidase autoantibodies and anti-thyroglobulin autoantibodies were 420 and 85.6 IU/mL, respectively.

Serologic markers of viral infection (toxoplasma, EBV, mycobacterium sp, CMV, HAV, HBV, HCV and neurotropic viruses) were all negative. Antistreptococcal and anti-staphylococcal antibodies were undetectable (Table 1).

Ultrasound of the liver was normal. Ophthalmologic examination revealed inflammatory cells and proteinaceous flare in the anterior chamber of the left eye (Tyndall + -), and a stromal lesion in the cornea. The right eye was unaffected.

He was maintained on immunosuppressive therapy (5 mg prednisone) plus topical antibiotic treatment for two weeks and then discharged. A complete remission of the symptoms was registered on follow-up. At present (July 2005), the patient is on prednisone (5 mg) and has no symptoms. Liver function tests are also within the normal range.

**DISCUSSION**

About 25% of patients with AIH have an acute onset. In most cases, however, the clinical presentation of AIH is characterized by the same signs and symptoms of chronic hepatitis of other aetiology. A specific feature of AIH is the association with extrahepatic immune-mediated syndromes, including autoimmune thyroiditis[2-5], scleroderma, rheumatoid arthritis, Sjögren’s syndrome or diabetes mellitus (Table 2). An old report describes the association of chronic autoimmune hepatitis with iridocyclitis[6], but at that time tests for HCV-related hepatitis were not available[7].

The hallmark of acute anterior uveitis is the presence of inflammatory cells and proteinaceous flare in the anterior chamber of the eye. Symptoms include pain, photophobia, and blurred vision in the involved eye(s). Iridocyclitis may be part of a more generalized autoimmune and endogenous uveitis, such as Reiter's syndrome, more commonly observed in patients with HIV infection. Phacogenic uveitis, sympathetic ophthalma and Vogt-Kaganayi-Harada syndrome can represent ocular autoimmune diseases suitable for a differential diagnosis, even if both phacogenic uveitis and sympathetic ophthalma are post-traumatic granulomatous uveitis. In this patient, however, there is no history of physical or surgical trauma, ruling out the possibility of an involvement of the above disorders in this case. The Vogt-Kaganayi-Harada syndrome is an idiopathic, bilateral, inflammatory syndrome occurring in middle age and characterized by a typical granulomatous intraocular inflammation. The aetiology of this syndrome is unknown and the disorder is assumed to be an autoimmune hypersensitivity response to pigment. Poliosis (i.e. localized depigmentation of the hair) occurs in more than 90 percent of these patients, together with alopecia and vitiligo. Auditory disturbances occur in more than 75% of patients, and many other neurologic findings, including psychosis, have been sometimes reported. However, this disorder is very rare, and most cases have been associated with a previous penetrating ocular injury, which is absent in our patient.

We also considered, for the differential diagnosis, a possible ophthalmic localization of systemic diseases, either infectious or not[6]. Wegener's granulomatosis is characterized by fever, weight loss and other systemic manifestations, together with ocular and oropharyngeal signs. Moreover, ankylosing spondylitis and chronic inflammatory bowel diseases can both be complicated by anterior uveitis. Furthermore, viral infections can cause uveitis: toxoplasmosis is generally the most common cause of infective uveitis, and AIDS is also mostly associated with cryptococ-
cal chorioretinitis or posterior uveitis. A possible cause of uveitis can, finally, be represented by systemic lupus erythematosus, which is typically characterized by arthralgia, fever and ocular involvement, the presence of circulating antinuclear autoantibodies and no substantial remission after corticosteroid therapy.

AIH type I is the most common form of AIH worldwide and is associated with antinuclear antibodies and/or smooth muscle antibodies. This is a disorder characterized by hepatic and extrahepatic involvement; the most frequent extrahepatic associations of AIH are mentioned in the table above (Table 2). In this case report, we have described, for the first time, an association between AIH and uveitis, without any doubts about other possible etiologies, such as HCV infection, which is associated with a better response to therapy and, even if it is usually followed by immunosuppression, cannot be excluded in the differential diagnosis of our patient. Aza-thioprine treatment has been registered associated with antinuclear autoantibodies and no substantial remission after corticosteroid therapy.

The majority of patients affected by AIH require a long-term maintenance therapy, and the milder disease is associated with a better response to therapy. Corticosteroid treatment is the best choice therapy for AIH and, even if it is usually followed by immunosuppression, we preferred a low-dose steroid treatment, registering both remission of hepatitis and absence of any significant side effects. This is well documented in the literature. Moreover, azathioprine has a significant early adverse reaction (EAR) profile, which includes an acute syndrome of constitutional symptoms, fever, rash, and acute pancreatitis and often requires discontinuation of drug. Some Authors report that EAR (early adverse reactions) precludes azathioprine use in patients with Crohn’s disease (CD) and autoimmune hepatitis (AIH). Finally, we skip immunosuppressive treatment since it has been described an increased tumor risk under azathioprine therapy, especially in Vogt-Kaganayi-Harada (VKH) syndrome. Vogt-Kaganayi-Harada (VKH) syndrome was excluded in the differential diagnosis of our patient. Azathioprine treatment has been registered associated with increased risk of malignancies.

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