Remission with ursodeoxycholic acid of type 1 autoimmune hepatitis resistant to azathioprine and steroids.

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COMPLETE REMISSION WITH URSODEOXYCHOLIC ACID OF TYPE 1 AUTOIMMUNE HEPATITIS RESISTANT TO AZATHIOPRINE AND STEROIDS

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Autoimmune hepatitis, intolerance to steroids and azathioprine, ursodeoxycholic acid, complete remission

Abstract

Combination therapy with steroids and azathioprine is the reference treatment for autoimmune hepatitis, but potential adverse effects are numerous and intolerance can occur. We report a patient with a well-documented type 1 autoimmune hepatitis intolerant to corticosteroids and azathioprine therapy, in whom eight years of ursodeoxycholic acid monotherapy was associated with complete biochemical and histological remission.

Autoimmune hepatitis (AIH) is a liver disease of unknown etiology often affecting young females. It is a chronic hepatitis characterized by hypergammaglobulinemia and serum autoantibodies, and is unrelated to viral infection, hepatotoxic drugs or hereditary disorders. The natural outcome is generally poor, with cirrhosis at presentation in 50 to 90 % of patients (1).

The preferred treatment consists of corticosteroids and azathioprine (1). Remission is achieved in over 70% of cases and long-term treatment with azathioprine, with or without prednisolone, can prevent relapse (2,3). However, the potential complications of this therapy include cosmetic changes, osteoporosis, diabetes, cataract, arterial hypertension, veno-occlusive disease and bone marrow suppression (3-5). Severe adverse effects occur in about 10% of patients treated with combination therapy, and in 44% of patients treated with high dose prednisone monotherapy (5). For patients with drug toxicity or intolerance, a dose reduction or drug discontinuation may be necessary. Numerous second-line agents which have been used include cyclosporine, 6-mercaptopurine and tacrolimus (6-10).

Ursodeoxycholic acid (UDCA) is the 7b-hydroxy epimer of chenodeoxycholic acid and has been reported to yield. Improvements in liver dysfunction due to cholestatic liver diseases, with few if any adverse effects, UDCA is now the reference therapy for primary biliary cirrhosis (PBC) (11,12).

UDCA has rarely been tested in autoimmune hepatitis, although preliminary reports suggest that it may be effective (13-16).

We report a case of well-documented typical type 1 autoimmune hepatitis in a patient intolerant to corticosteroid and azathioprine combination therapy, in whom long-term complete remission was obtained with UDCA monotherapy.

Case Report

In September 1992, a 37-year-old woman weighing 60 kg was admitted for asthenia associated with elevated serum alanine aminotransferase (ALT) activity (25 times the upper limit of normal (ULN)). Serum alkaline phosphatase and gamma-glutamyl transpeptidase levels were normal. Type 1 AIH was diagnosed on the basis of: (1) hypergammaglobulinaemia at 30 g/L, (2) anti-smooth muscle antibodies (1:1000 by immunofluorescence on unfixed 4mm cryostat sections of rat liver, stomach and kidney), (3) periportal necroinflammatory lesions with lymphoplasmocytic infiltrate and mild portal fibrosis (Figure 1) and 4) no other cause of liver disease. She denied alcohol and drug consumption, and had no markers of hepatitis A, B or C, cytomegalovirus or Epstein-Barr virus infection, Wilson's disease, α1-antitrypsin deficiency, or hemochromatosis. Serum antimitochondrial antibodies were not detected. Histologically, the interlobular and septal bile ducts were normal, and there was neither steatosis nor iron overload. Her HLA phenotype was A2/32B27Bw4Cw2/w7 and DR4/4. Immunosuppressive therapy with corticosteroids (30 mg per day) and azathioprine (100 mg per day) was administered. Steroids were gradually reduced to a dose of 3 mg per day and were stopped in March 1994. One month later, despited continued azathioprine therapy, a relapse occurred with a flare-up of serum ALT (3 ULN); steroids (30 mg per day) were promptly reintroduced, leading to rapid recovery; the dose was gradually reduced to 2.5 mg per day and then stopped in December 1994 (Figure 2).

Because of intolerance (nausea and rash), azathioprine was stopped in April 1995. In June 1995, a new flare-up of autoimmune hepatitis occurred (serum ALT 7.3 ULN), and she refused corticosteroids. She was prescribed ursodeoxycholic acid 800 mg daily. A significant improvement in clinical and biochemical parameters was noted in September 1995, and the serum ALT level returned to normal in November 1995 (Figure 2).

A second liver biopsy was performed in September 1997, 15 months after the outset of UDCA monotherapy. Histological examination showed a marked improvement of the portal inflammatory infiltrate (Figure 3). Ursodeoxycholic acid was stopped. In March 1998 a new increase in serum ALT occurred (2.5 ULN). Prescription of 1000 mg/d UDCA rapidly led to normalization of serum ALT values. In March 1999, the UDCA dose was reduced to 600 mg daily. A sub sequent slight increase in serum ALT (1.6 ULN) was controlled by increasing the UDCA regimen to 800 mg daily. Moreover, gamma-globulin levels were found to be within the normal range. From this date until now (December 2003) Liver tests remained normal (Figure 3). The patient denied any additional liver biopsy. However, several non invasive markers of liver fibrosis ie: apoliprotein A1 1.3 g/L (1.2-1.7), hyaluronic acid 40 μg/L (<75 μg/L), α-2 macroglobulin 2 g/L (1.6-4), prothrombin time 80 % and platelet count 180 000/mm3were within normal range (17).

Discussion

We describe a complete biochemical and histological remission of type 1 autoimmune hepatitis in a middle-aged woman during UDCA therapy. The diagnosis of type 1 autoimmune hepatitis in this patient was unequivocal. Concomitant primary biliary cirrhosis or overlap syndrome was ruled out by liver test results (elevated serum ALT and normal serum alkaline phosphatase and gammaglutamyltranspeptidase at diagnosis), serum antimitochondrial and anti-gp210 antibody negativity and the absence of bile duct injury or ductopenia on histological examination of the liver (19). The effect of UDCA on this patient's autoimmune hepatitis appeared to be dose-dependent, as strongly suggested by the following observations: 1) successful control of relapse following steroid withdrawal, 2) successful control of a post-UDCA relapse by UDCA reintroduction, and 3) successful control of a relapse following a reduction in the UDCA regimen by a slight dose increment.

Ursodeoxycholic acid therapy has led to improvements in many liver diseases, particularly PBC (11,12, 21-23). In chronic viral hepatitis, UDCA is beneficial at low doses (14). Data on UDCA in autoimmune hepatitis are controversial: in a Japanese study of eight patients, levels of serum transaminases and immunological markers (serum IgG, g-globulin, anti-smooth muscle antibodies) fell during UDCA therapy at doses of 11.5-11.8 mg/kg (17). Moreover, in 4 patients who underwent liver biopsy after one year on therapy, there was an improvement in necroinflammatory lesions but not in fibrosis. Interestingly, in one patient, serum ALT again increased after UDCA withdrawal. All eight patients had mild type autoimmune hepatitis with few

symptoms (17). In a recent study by Czaja *et al.* of a small cohort of patients, short term UDCA therapy improved serum aspartate aminotransferase (AST) levels but did not improve the liver histology or facilitate steroid tapering or withdrawal (23). One explanation for these discrepancies may be differences in HLA-DR haplotypes. In the Japanese study, UDCA induced a strong response in patients with the HLA-DR4 phenotype. This was also our patient's phenotype. In Czaja's study a high proportion of patients were HLA-DR17, which is associated with poorer outcome (23-25).

The pathogenesis of autoimmune hepatitis probably involves cellular immune-mediated cytotoxicity. A virus, drug or environmental toxin may be the triggering factor, or the disease may occur spontaneously with the emergence or the persistence of "forbidden clones" and loss of self-tolerance. The trigger may induce high levels of cytokines, which may regulate peptide presentation via MHC class I molecules and induce MHC class II molecule expression on hepatocytes (26). The well-documented beneficial effect of UDCA in PBC involves direct cytoprotection. However, UDCA also has other effects, such as protection of mitochondrial function, hypercholeresis and immunomodulation. In autoimmune hepatitis, UDCA may reduce MHC class I antigen expression on hepatocytes, thereby inhibiting the immune-mediated liver cell damage by suppressing the interaction between antigen-presenting cells and T helper lymphocytes, and the subsequent activation of cytotoxic T lymphocytes (27). In the case we report, and in the series of Nakamura et al., the histological recovery observed during UDCA therapy was most marked when liver damage was initially mild (absence of septal fibrosis). To our knowledge, UDCA has never been reported to improve severe autoimmune hepatitis. Another factor favoring response to UDCA is the HLA-DR4 haplotype.

In conclusion, the case reported here confirms that UDCA can significantly improve autoimmune hepatitis, UDCA may be particularly useful in case of resistance or intolerance to conventional therapies, or as first-line treatment of mild to moderate liver injury due to autoimmune hepatitis in patients with the HLA-DR4 haplotype. Its possible efficacy in combination with steroids and/or azathioprine remains to be determined. The factors influencing the response to UDCA in autoimmune hepatitis need to be clearly identified.

LEGENDS TO FIGURES

Figure 1: HES X 200 Histological features at diagnosis: Portal tracts are enlarged with a lymphoplasmocytic inflammatory infiltrate (A). Portal tract fibrosis is present without bridging fibrosis. In the lobular tract, a moderate chronic interface and lobular hepatitis is present (B).

Figure 2: Changes in biochemical liver test results, immunological parameters and histological features during UDCA therapy

SMA: anti-smooth muscle antibodies. ULN: upper limit of normal.

UDCA: ursodeoxycholic acid.

Figure 3: HES X 200 Histological features after two years of UDCA monotherapy. Note the improvement of the inflammatory infiltrate in the portal tract (A); a mild to moderate chronic (interface and lobular) hepatitis persists (B).

REFERENCES

1. Czaja AJ. Autoimmune liver disease. In: Zakim and Boyer, eds. Hepatology. A textbook of liver disease. Vol II, 1259-1292.
2. Krawitt EL. Autoimmune hepatitis. N Engl J Med 1996; 334 : 897-9.
3. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in auto-immune hepatitis. N Engl J Med 1995 ; 333 : 958-963.
4. Summerskill WHJ, Korman MG, Ammon HV, et al. Prednisone for chronic active liver disease: dose titration, standard dose, and combination with azathioprine compared. Gut 1975; 16: 876-883.
5. Czaja AJ. Diagnosis, prognosis, and treatment of classical autoimmune chronic active hepatitis. In: Krawitt EL, Wiesner RH, eds . Autoimmune liver disease. New York: Raven Press, 1991: 143-66.
6. Alvarez F, Ciocca M, Canero-Velasco C, et al. Short term cyclosporine induces a remission of autoimmune hepatitis in children. J Hepatol 1999 ; 30 : 222-7.
7. Pratt DS, Flavin DP, Kaplan MM. The successful treatment of autoimmune hepatitis with 6-mercaptopurine after failure with azathioprine. Gastroenterology 1996; 110 : 271-274.
8. Richardson PD, James PD, Ryder SD. Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis resistant to or intolerant of azathioprine. J Hepatol 2000 ; 33 : 371-375.
9. Van Thiel DH, Wright H, Caroll P, et al. Tacrolimus: a potential treatment for autoimmune chronic active hepatitis: results of an open-label preliminary trial. Am J Gastroenterol 1995; 90: 771-6.

10. Poupon RE, Poupon R, Balkau B, et al. Ursodiol for the long-term treatment of primary biliary cirrhosis. N Engl J Med 1994; 330: 1342-1347.
11. Poupon RE, Bonnand AM, Chretien Y, et al. Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. Hepatology 1999; 29: 1668-1671.
12. Nakamura K, Yoneda M, Yokohama S, et al. Efficacy of ursodeoxycholic acid in Japanese patients with type 1 autoimmune hepatitis. J Gastroenterol Hepatol 1998; 13: 490-495.
13. Crosignani A, Battezzati PM, Setchell KD, et al. Effects of ursodeoxycholic acid on serum liver enzymes and bile acid metabolism in chronic active hepatitis: A dose-response study. Hepatology 1991; 13: 339-344.
14. Czaja AJ. Autoimmune hepatitis. Current therapeutic concepts. Clin Immunother. 1994; 1: 413-429.
15. Mima S, Sekiya C, Kanagawa H, et al. Ursodeoxycholic acid (UDCA) therapy for autoimmune hepatitis. Int Hepatol Commun 1994; 2: 207-212.
16. Nakamura K, Yoneda M, Yokohama S, et al. Effocacy of ursodeoxycholic acid in Japanese patients with type 1 autoimmune hepatitis. J Gastroenterol Hepatol 1998; 13: 490-495.
17. Cadranel JF, Mathurin P. Prothrombin index decrease: a useful and reliable marker of of extensive fibrosis. Eur J Gastroenterol Hepatol 2002; 14: 1057-1059.
18. Czaja AJ. Frequency and nature of the variant syndromes of autoimmune liver disease. Hepatology 1998; 28: 360-5.

19. Heathcote EJ, Cauch-Dudek K, Walker V, et al. The Canadian multicenter double-blind randomized controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1994; 19: 1149-1156.
20. Lindor KD, Dickson ER, Baldus WP, et al. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. Gastroenterology 1994; 106: 1284-1290.
21. Corpechot C, Carrat T, Bonnand AM, et al. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. Hepatology 2000; 32: 1196-1199.
22. Czaja AJ, Carpenter HA, Lindor KD. Ursodeoxycholic acid as adjunctive therapy for problematic type 1 autoimmune hepatitis: a randomized placebo-controlled treatment trial. Hepatology 1999; 30: 1381-1386.
23. Czaja AJ, Strettell MDJ, Thomson LJ, Santrach PJ, Moore SB, Donaldson PT, Williams R. Associations between alleles of the major histocompatibility complex and type 1 autoimmune hepatitis. Hepatology 1997; 25: 317-323.
24. Obermayer-Straub P, Strassburg CP et al. Autoimmune hepatitis. J Hepatol 2000; 32: 181-197.
25. Calmus Y, Gano P, Rougier P, Poupon R. Hepatic expression of class I and class II major histocompatibility complex molecules in primary biliary cirrhosis: effect of ursodeoxycholic acid. Hepatology 1990; 11: 12-15.
26. Hillaire S, Boucher E, Calmus Y, et al. Effects of bile acids and cholestasis on major histocompatibility complex class I in human and rat hepatocytes. Gastroenterology 1994; 107: 781-788.

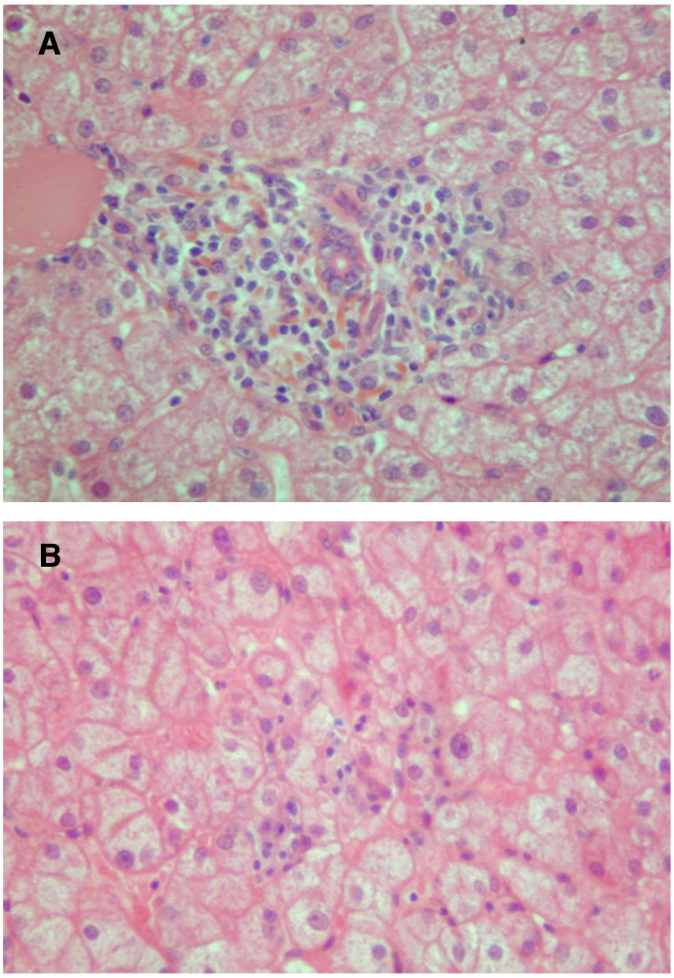

Figure 1

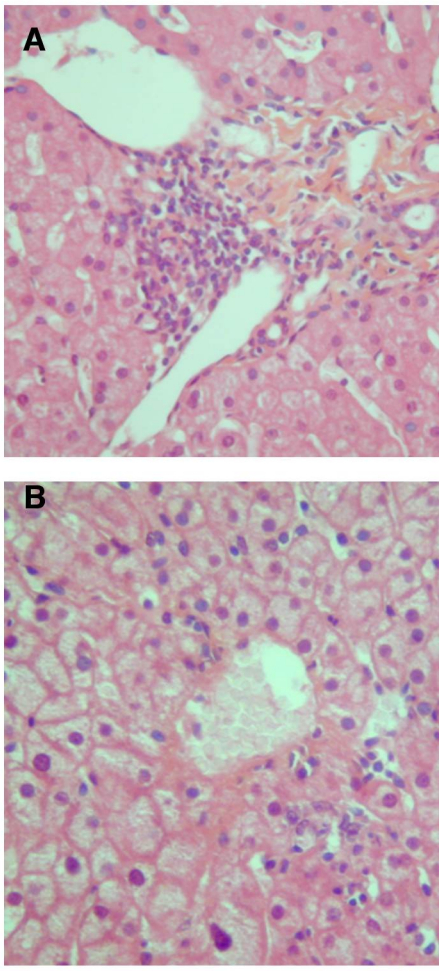

Figure 3

Changes in biochemical liver test results and immunological parameters during UDCA therapy