

Cyclosporine rescue therapy in autoimmune liver cirrhosis: A case report

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Autoimmune hepatitis is an inflammatory condition of the liver that can lead to significant morbidity and mortality. Corticosteroids with or without azathioprine have been shown to improve outcome and are the current standard of care in autoimmune hepatitis patients. However, long-term use of corticosteroids and use of azathioprine could be associated with significant adverse effects that prevent their continued use at optimal dosages or may even require complete cessation. We present a patient with autoimmune liver cirrhosis who was intolerant of corticosteroid and azathioprine, who was successfully treated with cyclosporine. To our knowledge, cyclosporine use has not been reported previously in autoimmune cirrhosis, although it has been used in autoimmune hepatitis patients with reported success and good tolerability. We conclude that cyclosporine seems to be an effective alternative to azathioprine as a steroid-sparing agent in both non-cirrhotic and cirrhotic autoimmune hepatitis.

Key words: Autoimmune liver cirrhosis, autoimmune hepatitis, rescue therapy, cyclosporine, steroid intolerance, azathioprine intolerance

Otoimmün karaciğer sirozunda siklosporin kurtarma tedavisi: Olgu sunumu

Otoimmün hepatit, karaciğerde önemli düzeyde morbidite ve mortaliteye neden olabilen iltihabi bir durumdur. Otoimmün hepatit hastalarında, azatioprinle birlikte veya yalnız başına kullanılan kortikosteroidler sonuçları iyileştirerek şimdiki standart tedaviyi oluşturmaktadır. Ancak kortikosteroidler ve azatioprin'in uzun dönem kullanılması, optimal dozda devamlı kullanılmasını engelleyen ve hatta tamamen kesilmesini gerektiren ciddi yan etkilere neden olabilmektedir. Kortikosteroid ve azatioprin intoleransı olan ve siklosporinle başarılı şekilde tedavi edilen otoimmün karaciğer sirozlu bir hastayı sunuyoruz. Otoimmün hepatitli hastalarda siklosporinin başarıyla ve iyi tolerabilite ile kullanımı bildirilmiş olsa da, bildiğimiz kadarıyla otoimmün sirozda kullanılması daha önce rapor edilmemiştir. Sonuçta, sirotik ve sirotik olmayan otoimmün hepatitli hastalarda siklosporin, azatioprin etkin bir alternatif "steroid sparing" ajan olarak görünmektedir.

Anahtar kelimeler: Otoimmün karaciğer sirozu, otoimmün hepatit, kurtarma tedavisi, siklosporin, steroid intoleransı, azatioprin intoleransı

INTRODUCTION

Autoimmune hepatitis is an inflammatory condition of the liver diagnosed based on a constellation of supportive clinical, laboratory and histopathological findings in the presence of characteristic auto-antibodies and with exclusion of other potential causes of chronic hepatitis (1). Untreated, it can be associated with significant morbidity and mortality (2, 3). Corticosteroids with or without azathioprine have been shown to improve outcome (3-5) and are the current standard of care in autoimmune hepatitis patients (6). However, long-term use of corticosteroids and use of azathioprine could be associated with significant adverse effects that prevent their continued use at optimal dosages or

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may even require complete cessation (6). Recent reports have suggested that cyclosporine may be effective in autoimmune hepatitis patients (7-14). We present a case of successful cyclosporine use in a patient with autoimmune cirrhosis who was intolerant of azathioprine.

CASE REPORT

A 50-year-old female patient, of Chinese ethnicity, presented two years ago to this institution with a one-week duration of lethargy, abdominal distension and bilateral leg swelling. She had been menopausal for one year, did not have any significant medical history, and denied any alcohol consumption. Physical examination at presentation revealed mild pallor, gross ascites and bilateral pedal edema. She had no other stigmata of chronic liver disease. A summary of relevant investigations at her initial presentation is as follows:

Blood profile

- Hemoglobin (Hb) 8.0 g/dl, white blood cell (WBC) $5.3 \times 10^9/L$, platelets $210 \times 10^9/L$
- International normalized ratio (INR) 1.1
- Total protein 62 g/L, albumin 23 g/L, globulin 39 g/L, total bilirubin 17 $\mu\text{mol/L}$, conjugated bilirubin 12 $\mu\text{mol/L}$, alkaline phosphatase (ALP) 169 IU/L, alanine aminotransferase (ALT) 118 IU/L, aspartate aminotransferase (AST) 126 IU/L, and gamma glutamyltransferase (GGT) 145 IU/L
- Hepatitis B s antigen not detected, anti-hepatitis C antibody not detected

Autoimmune profile

- Immunoglobulin G (IgG) 1750 mg/dl, IgA 543 mg/dl, IgM 303 mg/dl
- C3 112 mg/dl, C4 25 mg/dl
- Anti-nuclear factor positive (titer 1:320, nucleolar/centromere pattern), anti-double-stranded DNA negative, anti-smooth muscle negative, anti-mitochondrial antibody positive

Imaging/Endoscopy

- Contrast-enhanced computed tomography (CT) scan of the chest, abdomen and pelvis showed a shrunken liver with gross ascites and bilateral pleural effusion.
- Esophagogastroduodenoscopy (EGDS) revealed three columns of grade I esophageal varices with portal gastropathy.

An ultrasound-guided liver biopsy was subsequently performed and histopathological examination of the liver biopsy sample showed cirrhosis associated with ongoing chronic active hepatitis (modified Histologic Activity Index score 12, stage 4). A diagnosis of liver cirrhosis Child-Pugh Grade B secondary to autoimmune hepatitis was made.

Initial therapy with oral prednisolone resulted in a significant improvement in her liver function tests (LFTs) and a reduction in diuretic therapy for ascites. As the prednisolone dosage was reduced to 20 mg daily, there was a rebound of her ALT to 122 IU/L. As she was becoming increasingly cushingoid, she was commenced on oral azathioprine 50 mg daily. As her LFTs improved, the azathioprine dosage was increased to 75 mg daily and prednisolone was successfully tapered off. Six months into treatment with azathioprine, she complained of increasing lethargy and was noted to have marked pallor. There was neither history nor clinical evidence of gastrointestinal (GI) bleeding. Preliminary hematological investigations revealed the following:

- Hb 5.4 g/dl, WBC $3.7 \times 10^9/L$, platelets $135 \times 10^9/L$
- Serum iron 17.7 $\mu\text{mol/L}$, serum ferritin 50.9 $\mu\text{g/L}$, serum folate 31.2 nmol/L, serum vitamin B₁₂ 345 pmol/L

Endoscopy of the upper and lower GI tract was performed to exclude any GI bleeding. Four columns of grade I esophageal varices and portal gastropathy were identified in the upper GI tract, while the colon and the small bowel (examined by CT enterography) were normal. She was transfused with four units of red cell concentrate and started on iron supplementation, and the dose of azathioprine was reduced to 50 mg. Four months later, she developed symptomatic anemia again (Hb 7.2 g/dl), and a peripheral blood film revealed red cell anisopoikilocytosis with normochromic normocytic cells, irregularly contracted forms, tear drop poikilocytes, macrocytes, and fragmented forms. A bone marrow aspirate and trephine biopsy were performed and revealed a hypocellular marrow (Figure 1) with adequate tri-lineage hemopoiesis and moderate dyserythropoiesis (Figure 2). No abnormal infiltrates or significant hemophagocytosis was noted in the marrow. Serum thiopurine methyltransferase (TPMT) level was checked at this stage and found to be normal at 14.1 U/ml.

A diagnosis of azathioprine-induced myelosuppression was made and azathioprine was permanently withheld. Although her blood counts impro-

ved following withdrawal of azathioprine, she developed a relapse of her autoimmune hepatitis (serum ALT 166 IU/L, AST 107 IU/L). Prednisolone therapy was re-commenced followed by the initiation of oral cyclosporine 50 mg twice daily. When reviewed one week later, her LFTs had completely normalized and the prednisolone was tapered off successfully. Nine months following commencement of cyclosporine, her LFTs have remained normal, while maintaining a normal renal function and blood pressure. Figures 3 and 4 summarize the trends in the blood results for this patient.

DISCUSSION

Azathioprine is effective as a corticosteroid-sparing agent in various autoimmune disorders inclu-

ding autoimmune hepatitis. The American Association for the Study of Liver Diseases recommends azathioprine in combination with a reduced dose of corticosteroids for autoimmune hepatitis, especially among patients who are more susceptible to corticosteroid-related side effects (6). The combination regimen is associated with a lower occurrence of corticosteroid-related side effects compared to the higher dose corticosteroid-only regimen (10% versus 44%) (15).

However, azathioprine has its own undesirable side effect profile. Severe myelosuppression, sometimes fatal, has been reported with its use (16-21). Our patient was started on azathioprine in view of the need for a relatively high dosage of corticosteroid for maintenance of suppressed disease acti-

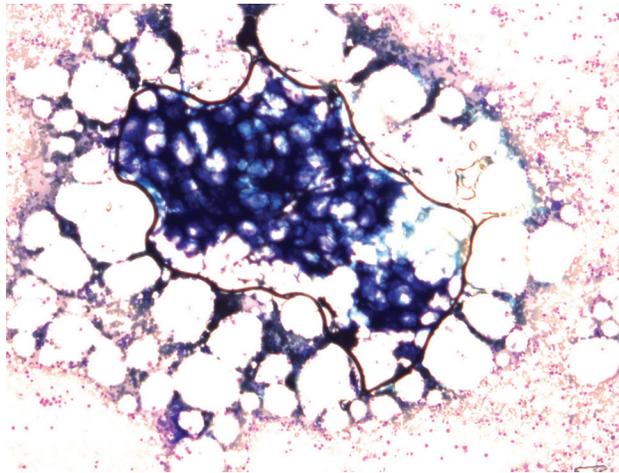


Figure 1. Photograph showing hypocellular bone marrow particles.

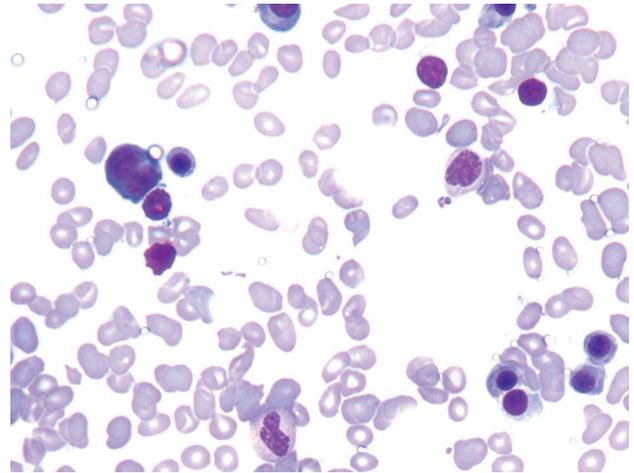


Figure 2. Photograph showing binuclearity, a feature of dyserythropoiesis.

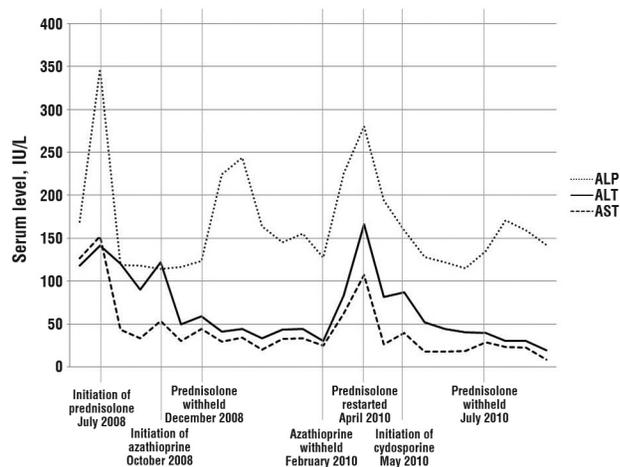


Figure 3. Trend of liver enzymes in relation to commencement and withdrawal of drugs used for the treatment of autoimmune hepatitis in our patient.

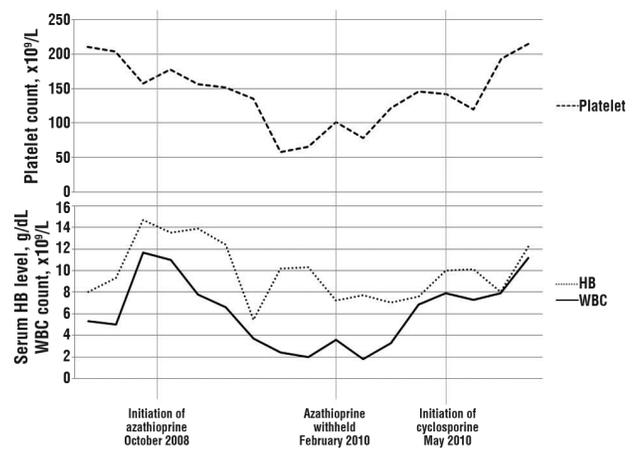


Figure 4. Trend of blood counts in relation to commencement and withdrawal of azathioprine and commencement of cyclosporine in our patient.

vity on the background of development of cushingoid features. Unfortunately, nine months into treatment with azathioprine, she developed pancytopenia with severe anemia requiring transfusion. A diagnosis of azathioprine-induced myelosuppression was made, and her blood counts returned to normal a few months after withdrawal of azathioprine.

Our patient had a normal serum TPMT level. While severe azathioprine-induced myelosuppression has been associated with TPMT deficiency (19), studies have shown that genotyping or phenotyping for TPMT activity does not accurately predict the occurrence of this side effect among patients with autoimmune hepatitis treated with azathioprine (22-24). Heneghan *et al.* (24) found that there was no statistically significant difference in the mean serum TPMT level among autoimmune hepatitis patients who developed azathioprine-related toxicity compared to those who did not. Instead, they found that cirrhosis was more common in those who developed azathioprine-related toxicity than in those who did not.

As our patient could not tolerate corticosteroid and azathioprine, an alternative treatment option was necessary to prevent the otherwise inevitable progression of her autoimmune liver disease. Cyclosporine seemed to be a promising answer. Cyclosporine has been used in pediatric (7-11) and adult (12-14) autoimmune hepatitis patients with

reported success and good tolerability. Malekzadeh *et al.* (12) reported on a series of adult autoimmune hepatitis patients treated with cyclosporine. Of the 19 patients treated with low-dose cyclosporine, 10 either failed corticosteroid or were intolerant of its side effects, while the remaining nine were started on cyclosporine as first-line therapy. Of the 15 patients who completed the 26-week course of cyclosporine, all but one had complete clinical remission. Cyclosporine was well-tolerated and none of the patients required dose adjustment or premature cessation of the drug due to side effects. In fact, patients who were previously on corticosteroids reported a preference for cyclosporine due to its better side effect profile. This suggested that cyclosporine is an effective and well-tolerated alternative treatment for adult autoimmune hepatitis patients. Whether or not cyclosporine is more effective and is better tolerated than corticosteroid as first-line therapy is the subject of an ongoing randomized controlled trial (25).

To our knowledge, cyclosporine use has not been reported before in autoimmune cirrhosis. We conclude that cyclosporine seems to be an effective alternative to azathioprine as a steroid-sparing agent in both non-cirrhotic and cirrhotic autoimmune hepatitis. The use of cyclosporine as a first-line treatment specifically for patients with liver cirrhosis due to autoimmune hepatitis seems reasonable but would require evaluation with further studies.

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