ORIGINAL ARTICLE

TJG
The Turkish Journal of Gastroenterology

# Ornidazole-induced autoimmune hepatitis

Galip ERSÖZ[1], Rukiye VARDAR[1], Ulus Salih AKARCA[1], Fatih TEKİN[1], Funda YILMAZ[2], Fulya GÜNŞAR[1], Zeki KARASU[1]

*Departments of [1]Gastroenterology and [2]Pathology, Ege University, School of Medicine, İzmir*

***Background/aims:*** *Certain drugs including oxyphenisatin, methyldopa, nitrofurantoin, diclofenac, interferon, infliximab, pemoline, minocycline, atorvastatin, and rosuvastatin can induce hepatocellular injury that mimics autoimmune hepatitis. Whether drugs and herbs unmask or induce autoimmune hepatitis or simply cause a drug-induced hepatitis with accompanying autoimmune features is unclear. We describe the clinicopathologic details of eight cases with ornidazole-induced hepatitis with autoimmune features.* ***Material and Methods:*** *Patients who presented with acute hepatitis between February 2001 and March 2009 were re-evaluated for the etiology of liver disease. Patients with acute viral hepatitis, metabolic liver disease, vascular liver disease such as Budd-Chiari syndrome, biliary obstruction, or alcohol consumption were excluded. The autoimmune hepatitis scores, which were calculated at the time of diagnosis according to the criteria of the International Autoimmune Hepatitis Group, were recorded. In addition, the simplified criteria of the same group were applied retrospectively to each patient. Patients with ornidazole-induced toxic hepatitis with autoimmune hepatitis were included to constitute the study group of this report. All patients underwent initial liver biopsy, and one patient underwent liver biopsy three years later. All biopsies were scored according to the hepatitis scoring system by Ishak et al. (10).* ***Results:*** *Overall, eight patients (all female) were diagnosed as drug-induced autoimmune hepatitis. With the exception of one patient, all were treated with prednisolone 30 mg/day + azathioprine 50 mg/day. The prednisolone dose was tapered according to the decrease in the level of transaminases. A two-year treatment program was planned for all patients.* ***Conclusions:*** *Ornidazole may cause drug-induced autoimmune hepatitis. Withdrawal of the drug may not provide the recovery despite a rather long wait. Thus, immunosuppressive therapy may be suggested in these cases.*

**Key words:** Drugs, autoimmune hepatitis, ornidazole

## Ornidazolun tetiklediği otoimmun hepatit

***Amaç:*** *Bazı ilaçlar otoimmun hepatitite benzer hepatosellüler hasar yapabilirler. İlaçların ve şifalı bitkilerin ortaya çıkardığı ya da tetiklediği otoimmun hepatit mi veya basitçe ilacın tetiklediği hepatite eşlik eden otoimmun hepatit mi olduğu açık değildir. Biz otoimmun özelliği olan ornidazolun tetiklediği 8 hepatit olgusunun klinikopatolojik detaylarını tanımladık.* ***Yöntem:*** *Şubat 2001 ve Mart 2009 tarihleri arasında akut hepatit ile başvuran karaciğer hastalığı etyolojilerini gözden geçirdik. Akut viral hepatit, metabolik karaciğer hastalığı, Budd-Chiari sendromu gibi vasküler karaciğer hastalığı, biliyer obstrüksiyon ve alkol kullanımı olan olgular dışlandı. Tanı anında "International Autoimmune Hepatitis Group"un kriterlerine göre otoimmun hepatit skoru hesaplandı. Ek olarak, aynı grubun basitleştirilmiş kriterleri retrospektif olarak her bir hasta için uygulandı. Otoimmun hepatit ile birlikte olan ornidazolun tetiklediği toksik hepatit olguları çalışma grubunu oluşturdu. Olguların tümüne başlangıçta ve 1 olguya 3 yıl sonra karaciğer biyopsileri yapıldı. Biyopsilerin tümü Ishak ve ark.larının hepatit skorlama sistemine göre skorlandı.* ***Bulgular:*** *Tümü kadın 8 olgu ilacın tetiklediği otoimmun hepatit tanısı aldı. Bir olgu dışındaki tüm olgular prednisolone 30 mg/gün + azathioprine 50 mg/gün ile tedavi edildi. Prednisolone dozu transaminaz düzeylerindeki düşmeye göre azaltıldı. Tüm olgulara 2 yıllık tedavi planlandı.* ***Sonuç:*** *Ornidazol ilacın tetiklediği otoimmun hepatite neden olabilir. İlacın kesilmesi sonrasında uzun süre beklemeye karşın iyileşme olmayabilir. Böyle olgulara immunosüpresif tedavi önerilebilir.*

**Anahtar kelimeler:** İlaçlar, otoimmun hepatit, ornidazol

## INTRODUCTION

Autoimmune hepatitis is a chronic hepatitis of unknown cause that occurs in children and adults of all ages. Diagnosis is based on histologic abnormalities, characteristic clinical and biochemical

**Address for correspondence:** Rukiye VARDAR
Department of Gastroenterology,
Ege University, School of Medicine, İzmir, Turkey
Phone: + 90 232 339 14 48
E-mail: rukiyevardar@gmail.com

**Manuscript received:** 03.09.2010 **Accepted:** 03.01.2011

*Turk J Gastroenterol 2011; 22 (5): 494-499*
*doi: 10.4318/tjg.2011.0245*

*Presented at the 7th National Hepatology Congress, June 10-14, 2009 İzmir*

findings, and presence of autoantibodies. The pathogenesis of autoimmune hepatitis postulates an environmental agent that triggers a cascade of T-cell-mediated events directed at liver antigens in a host genetically predisposed to this disease, leading to a progressive necroinflammatory and fibrotic process and ultimately cirrhosis in the liver. Environmental agents assumed to induce autoimmune hepatitis have not been delineated, but viruses, certain drugs and herbal agents may lead to autoimmune hepatitis.

Certain drugs, including oxyphenisatin, methyldopa, nitrofurantoin, diclofenac, interferon, infliximab, pemoline, minocycline, atorvastatin, and rosuvastatin can induce hepatocellular injury that mimics autoimmune hepatitis (1-5). It has also been suggested that herbal agents such as Dai-saiko-to and black cohosh might trigger autoimmune hepatitis (6). Whether drugs and herbs unmask or induce autoimmune hepatitis or simply cause a drug-induced hepatitis with accompanying autoimmune features is unclear.

We describe the clinicopathologic details of eight cases with ornidazole-induced hepatitis with autoimmune features.

## MATERIALS AND METHODS

Patients who presented with acute hepatitis between February 2001 and March 2009 were re-evaluated for the etiology of liver disease. Acute hepatitis was defined as a biochemical abnormality of hepatocellular pattern of damage (alanine aminotransferase [ALT] >3 times the upper limit) within three months after the withdrawal of the drug in patients without a chronic liver disease history (7).

All available data for the tests that were performed at the time of diagnosis, including viral hepatitis markers (antihepatitis A virus (HAV) IgM, hepatitis B surface antigen (HBsAg), anti-hepatitis B core antigen, anti-hepatitis B surface antigen, hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR), anti-hepatitis C virus (HCV), HCV RNA, anti-hepatitis E virus (HEV), anti-cytomegalovirus (CMV) IgM, anti-CMV IgG, monospot test, and Paul Bunnell test), auto-antibodies (antinuclear antibodies (ANA), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA) and anti-liver-kidney microsomal (LKM1) antibody) and laboratory investigations to exclude metabolic liver disease (alpha1-antitrypsin, ferritin, ceruloplasmin and serum/urinary copper, detailed history) were retrospectively evaluated.

Patients with acute viral hepatitis, metabolic liver disease, vascular liver disease such as Budd-Chiari syndrome, biliary obstruction, or alcohol consumption were excluded. Doppler ultrasonography and magnetic resonance cholangiopancreatography were used to investigate the biliary system and vascular pathology, if present.

The autoimmune hepatitis scores, which were calculated at the time of diagnosis according to the criteria of the International Autoimmune Hepatitis Group, were recorded (8). In addition, the simplified criteria of the same group were applied retrospectively to each patient (9).

Patients with ornidazole-induced toxic hepatitis with autoimmune hepatitis were included to constitute the study group of this report.

When no biochemical and clinical recovery was achieved despite a rather long waiting time (32-90 days) despite the N-acetyl cysteine therapy, liver biopsy was performed in all patients. The second biopsy was done in one of these patients after three years. The available liver biopsies were systematically reviewed with special attention to the presence of interface hepatitis, the composition of the portal infiltrate (predominantly lymphoplasmacytic vs mixed vs lymphocytic infiltrate, presence of eosinophils), rosetting of liver cells, biliary changes, perivenular confluent necrosis and inflammation (peri-venulitis), acute lobular hepatitis with apoptotic bodies, hepatocyte ballooning, Kupffer cell hyperplasia, other histopathological findings, and fibrosis. All biopsies were scored according to the hepatitis scoring system by Ishak et al. (10).

The treatment charts and follow-up data were recorded for each patient.

## RESULTS

Three hundred and ten patients presented with acute hepatitis between February 2001 and March 2009. Toxic hepatitis due to various drugs was diagnosed in 128 patients. Among them, a history of ornidazole treatment was detected in 13 patients; 5 of them recovered spontaneously after the withdrawal of the drug.

Overall, 8 patients (all female) were diagnosed as ornidazole-induced autoimmune hepatitis. Demographic data and initial liver function tests of

the patients are summarized in Table 1. With the exception of one patient, all were treated with prednisolone 30 mg/day + azathioprine 50 mg/day. The prednisolone dose was tapered according to the decrease in the level of transaminases. Although four patients were diagnosed with diabetes mellitus, a two-year treatment program was planned and performed in all patients because diagnoses in these patients according to liver biopsy were autoimmune hepatitis.

In three patients diagnosed to have diabetes mellitus type 2 at admittance, insulin was started concurrently with prednisolone. Insulin was stopped at the end of one year in all three patients after the tapering of prednisolone. One patient, who was diagnosed as diabetes mellitus type 2 before admittance and who was on metformin 1000 mg/day for about two years, was put on the same insulin treatment scheme as the above-mentioned three patients. We did not consider the possibility of metformin-related acute hepatitis in view of the history of its use for an extended period.

Two patients had previously been diagnosed to have autoimmune (Hashimoto) thyroiditis and one patient had been diagnosed as Sjögren's syndrome.

According to the International Autoimmune Hepatitis Group (8) criteria, patients were classified as: definite autoimmune hepatitis (n=1) or probable autoimmune hepatitis (n=7). The histopathological data of all patients are summarized in Table 2.

A pattern of liver injury with hepatitic features was observed in all eight patients who had liver biopsy. The appearances were those of interface hepatitis (6/8), portal inflammation with predominantly lymphoplasmacytic infiltrate (7/8), peri-venulitis with nonspecific inflammatory cells (4/8) and peri-venulitis with predominantly plasma cells (4/8), acute lobular hepatitis (5/8), prominent eosinophils in portal tracts (7/8), rosetting of liver cells (1/9), canalicular cholestasis and cholestatic rosettes (2/8), giant cell formation of hepatocytes (4/8), bridging necrosis and subcapsular multiacinar necrosis (collapse) (1/8), and ductular reaction (3/8). The histopathological features were compatible with the diagnosis of autoimmune hepatitis in all patients except for Case 2 (Table 2) (Figures 1, 2). Case 2 had two biopsies. The first was performed during the initial attack of acute hepatitis and showed predominantly acute lobular hepatitis associated with peri-venulitis with nonspecific inflammatory cells, eosinophils in portal tracts, cana-

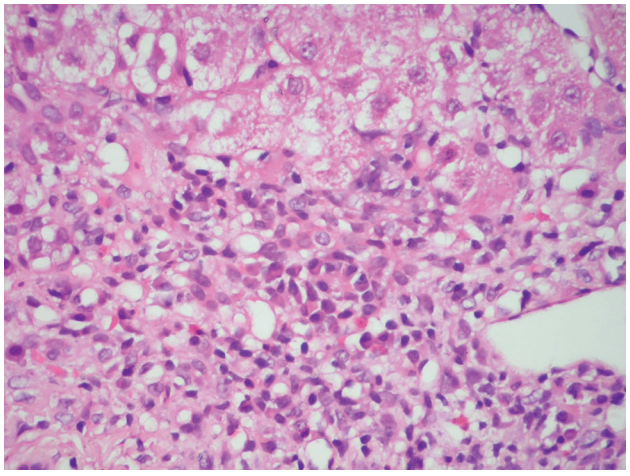

**Figure 1.** Prominent interface hepatitis associated with portal inflammation predominantly of lymphoplasmacytic nature. Hepatocytes in the nearby parenchyma showing hepatocyte ballooning (Hematoxylin-eosin, x400).

**Table 1.** Demographic data and initial laboratory tests of the patients

| Patient no | Age | Sex | Other disease(s) | ALT (IU/L) | AST (IU/L) | ALP (IU/L) | GGT (IU/L) | Globulin (g/dl) | Auto-antibodies |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 34 | F | None | 681 | 754 | 335 | 190 | 4.1 | ANA: 1/160 |
| 2 | 41 | F | DM, AIT | 209 | 244 | 110 | 45 | 4 | ANA: 1/1280, ASMA: 1/80 |
| 3 | 38 | F | None | 305 | 242 | 195 | 82 | 4.9 | ANA: 1/160, AMA: 1/1280 |
| 4 | 49 | F | AIT | 1305 | 668 | 99 | 226 | 3.6 | ANA: 1/80 |
| 5 | 32 | F | None | 715 | 694 | 83 | 79 | 3.1 | - |
| 6 | 49 | F | None | 1207 | 1310 | 162 | 57 | 2.6 | - |
| 7 | 25 | F | None | 1153 | 702 | 111 | 109 | 3.5 | ANA: 1/80 |
| 8 | 57 | F | SS | 455 | 202 | 172 | 207 | 3.7 | ANA: 1/80 |

F: Female. DM: Diabetes mellitus type 2. AIT: Autoimmune thyroiditis. SS: Sjögren's syndrome. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. ALP: Alkaline phosphatase. GGT: Gamma glutamyl transpeptidase. ANA: Antinuclear antibodies. ASMA: Anti-smooth muscle antibody. AMA: Anti-mitochondrial antibody.

**Table 2.** Liver biopsy findings

| Patient no | 1 | 2/2a* | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Interface hepatitis | (+) | 0/(+) | (+) | (+) | (+) | 0 | (+) | (+) |
| Predominantly lymphoplasmacytic portal inflammation | (+) | 0/0 | (+) | (+) | (+) | (+) | (+) | (+) |
| Peri-venulitis with NIC or PPC | NIC | NIC /0 | NIC | PPC | NIC | PPC | PPC | PPC |
| Acute lobular hepatitis | 0 | (+)/0 | (+) | (+) | 0 | (+) | (+) | 0 |
| Eosinophils in portal tracts, more than usual | 0 | (+)/0 | (+) | (+) | (+) | (+) | (+) | (+) |
| Rosetting of liver cells | (+) | 0/0 | 0 | 0 | 0 | 0 | (+) | 0 |
| Canalicular cholestasis and cholestatic rosettes | 0 | (+)/0 | 0 | 0 | 0 | 0 | 0 | (+) |
| Giant cell hepatocytes | 0 | (+)/0 | 0 | 0 | (+) | (+) | (+) | 0 |
| Other | | | bridging and subcapsular multiacinar necrosis (collapse) | | DR | DR | DR | |
| ISHAK SCORE** | 2/2/1/2/0 | 0/2/2/0/1 and 1/0/0/2/1 | 3/4/2/3/3 | 1/5/4/4/0 | 2/5/2/3/0 | 0/5/4/4/0 | 1/1/3/3/3 | 1/3/2/3/4 |
| Grade | 7 | 4 | 12 | 14 | 12 | 13 | 8 | 9 |
| Stage | 0 | 1 | 3 | 0 | 0 | 0 | 3 | 4 |

Acute lobular hepatitis: acute lobular hepatitis with apoptotic bodies, striking hepatocyte ballooning and Kupffer cell hyperplasia.
DR: Ductular reaction. NIC: Nonspecific inflammatory cells. PPC: Predominantly plasma cells.
* The data of the first and second biopsy after 3 years, respectively
** Components of Ishak Score: Periportal or periseptal interface hepatitis/ confluent necrosis/ apoptosis and focal inflammation/ portal inflammation/ fibrosis and cirrhosis

licular cholestasis and cholestatic rosettes, and giant cell hepatocytes (Figure 3a). The second biopsy performed three years later showed features of chronic hepatitis with interface hepatitis and portal fibrosis (Figure 3b).

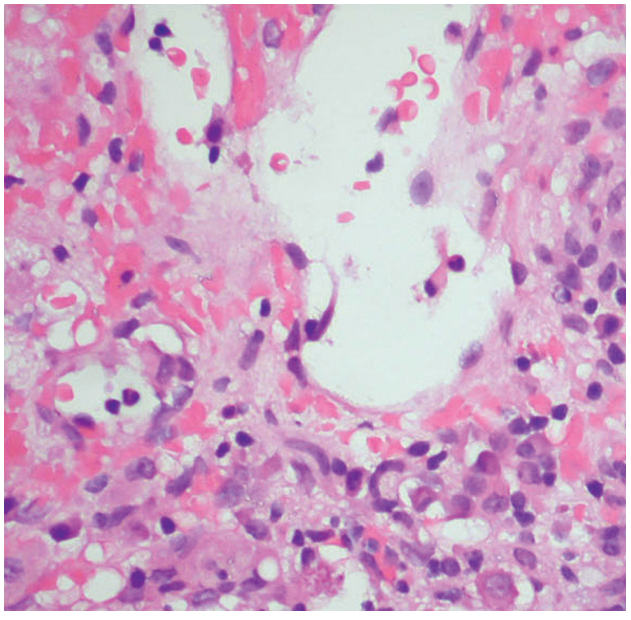

**Figure 2.** Perivenular confluent necrosis and inflammation (peri-venulitis) with predominantly plasma cells (Hematoxylin-eosin, x400).

The duration of the intake and dose of the drug and the time interval between the diagnosis and treatment were different in each patient; these data are summarized in Table 3. In all patients, liver biopsy revealed hepatocellular pattern of damage as described in the criteria of the 'International Consensus Meeting for liver injury' (11). During the time before introducing treatment, transaminase and bilirubin levels were almost unchanged.

Transaminase and bilirubin levels returned to normal levels within 1-6 weeks in all of the 7 patients who were treated with prednisolone 30 mg/day + azathioprine 50 mg/day. In one patient, treatment was discontinued after the two-year treatment protocol was completed, and clinical and biochemical remission was sustained. The other six patients are still under immunosuppressive therapy, and remission is ongoing in all six patients. The first patient in this series (Case 1) did not receive any immunosuppressive treatment and underwent liver transplantation. This patient had a history of ornidazole intake three times with six- and eight- month intervals and developed three attacks of acute hepatitis, during which auto-antibodies were found to be negative. ALT level was consistently found to be >100 IU/L after the

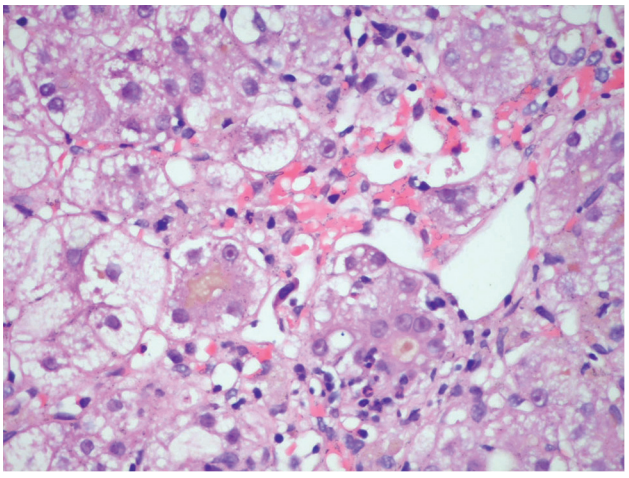

**Figure 3a.** Case 2- First biopsy showing prominently acute lobular hepatitis, hepatocyte ballooning, perivenular confluent necrosis, canalicular cholestasis, and cholestatic rosettes (Hematoxylin-eosin, x400).

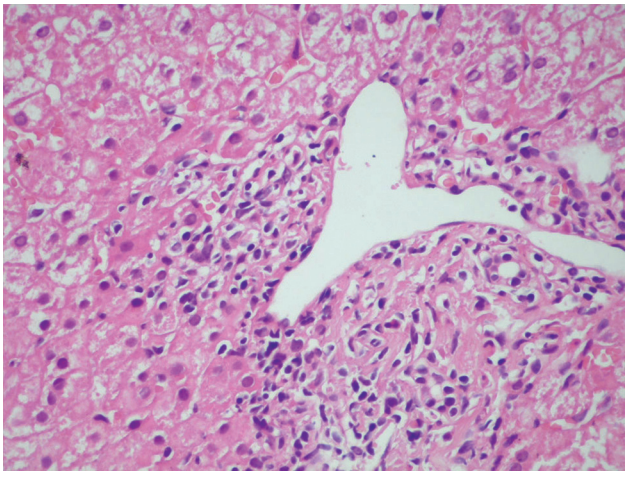

**Figure 3b.** Case 2- Second biopsy three years after the first one showing features of chronic hepatitis with interface hepatitis and portal fibrosis (Hematoxylin-eosin, x200).

last intake of the drug. Decompensated cirrhosis developed after six years, and ANA was found to be positive (1/160) at the time of decompensation. The details of this case were previously reported (12).

Bilirubin levels, transaminases and prothrombin time returned to normal limits after 50 days of prednisolone + azathioprine treatment. Outcomes of the patients are summarized in Table 4.

## DISCUSSION

In this article, we present eight patients with ornidazole-induced autoimmune hepatitis, among whom seven were successfully treated with immunosuppressive therapy. When the patients were scored according to the criteria of the International Autoimmune Hepatitis Group (8), one patient was diagnosed as definite autoimmune hepatitis (score=18) and 7 patients as probable autoimmune hepatitis (scores=12-17). However, because of the low sensitivity and specificity of these criteria, the same group reported new simplified criteria in 2008 (9). A retrospective analysis of the patients according to these simplified criteria revealed that six patients were diagnosed as definite autoimmune hepatitis and 2 patients as probable autoimmune hepatitis. This small study corroborates that the new simplified criteria may be even more valuable since immunosuppressive therapy (prednisolone + azathioprine) was successful in all cases.

Despite the absence of immunosuppressive therapy, a complete clinical, histopathological and biochemical recovery after the drug withdrawal may be achieved in patients with drug- induced autoimmune hepatitis. Thus, the necessity of immunosuppressive therapy for the present patients is a question. However, no biochemical recovery was achieved despite a rather long waiting time (32-90

**Table 3.** Data about the drug use

| Patient no | Dose (mg/day) | Duration (day) | Prodromal time (day) | Waiting interval (day) | Prodromal symptoms |
|---|---|---|---|---|---|
| 1 | 2x500 | 10 | 10 | 22 | Fatigue, nausea, vomiting, fever |
| 2 | 2x500 | 7 | 8 | 38 | Nausea, vomiting |
| 3 | 2x500 | 7 | 12 | 34 | Fatigue, nausea, myalgia |
| 4 | 2x500 | 7 | 10 | 32 | Fatigue, fever, myalgia, arthralgia |
| 5 | 2X500 | 5 | 15 | 30 | Fatigue, nausea, vomiting |
| 6 | 2X500 | 10 | 10 | 20 | Abdominalgia, fatigue, nausea |
| 7 | 2X500 | 7 | 15 | 12 | Abdominalgia, bloating, anorexia |
| 8 | 2X500 | 5 | 10 | 26 | Fatigue, nausea |

Prodromal time: The time between drug use and diagnosis of hepatitis. Waiting interval: The time between the diagnosis and treatment.

**Table 4.** Score results and outcomes of the patients

| Patient no | Autoimmune hepatitis score | Outcome |
|---|---|---|
| 1 | 14 | Liver transplantation (alive) |
| 2 | 18 | On immunosuppressive therapy for 3 years |
| 3 | 12 | On immunosuppressive therapy for 2 years |
| 4 | 17 | On immunosuppressive therapy for 2 years |
| 5 | 12 | On immunosuppressive therapy for 18 months |
| 6 | 12 | On immunosuppressive therapy for 16 months |
| 7 | 12 | On immunosuppressive therapy for 10 months |
| 8 | 13 | On immunosuppressive therapy for 6 months |

days) without an immunosuppressive therapy. The only patient without an immunosuppressive therapy was finally diagnosed as decompensated cirrhosis. On the other hand, all of the remaining seven patients who had received an immunosuppressive therapy showed a complete recovery.

According to current findings, we may speculate that "simple" drug-induced hepatotoxicity may resolve spontaneously if the immune system is not triggered; however, in cases with immune activation, immunosuppressive therapy is necessary. To differentiate those two scenarios, liver biopsy may help. In this case series, all the drug-induced autoimmune hepatitis developed after the use of ornidazole. This drug is a well-known hepatotoxic drug. Ornidazole is also well-known to cause either hepatocellular or cholestatic pattern of liver damage (13,14). Ornidazole-induced autoimmune hepatitis was also reported in one patient previously (15). Unlike these studies, we used immunosuppressive therapy because we had a negative experience that was previously reported (12). One can speculate that many patients with ornidazole-induced autoimmune hepatitis might not be reported in the English literature.

In conclusion, ornidazole may cause drug-induced autoimmune hepatitis. Withdrawal of the drug may not provide the recovery despite a rather long wait. Thus, immunosuppressive therapy may be suggested in these cases.

## REFERENCES


1. Krawitt EL. Autoimmune hepatitis. N Engl J Med 2006; 354: 54-66.
2. Rosh JR, Dellert SF, Narkewicz M, et al. Four cases of severe hepatotoxicity associated with pemoline: possible autoimmune pathogenesis. Pediatrics 1998; 101: 921-3.
3. Goldstein NS, Bayati N, Silverman AL, et al. Minocycline as a cause of drug-induced autoimmune hepatitis. Report of four cases and comparison with autoimmune hepatitis. Am J Clin Pathol 2000; 114: 591-8.
4. Germano V, Picchianti Diamanti A, Baccano G, et al. Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis. Ann Rheum Dis 2005; 64: 1519-20.
5. Wolters LM, Van Buuren HR. Rosuvastatin-associated hepatitis with autoimmune features. Eur J Gastroenterol Hepatol 2005; 17: 589-90.
6. Kamiyama T, Nouchi T, Kojima S, et al. Autoimmune hepatitis triggered by administration of an herbal medicine. Am J Gastroenterol 1997; 92: 703-4.
7. Andrade RJ, Lucena MI, Kaplowitz N, et al. Outcome of acute idiosyncratic drug-induced liver injury: long-term follow-up in a hepatotoxicity registry. Hepatology 2006; 44: 1581-8.
8. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31: 929-38.
9. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008; 48: 169-76.
10. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995; 22: 696-9.
11. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990; 11: 272–6.
12. Ersöz G, Karasu Z, Akarca US, et al. Nitroimidazole-induced chronic hepatitis. Eur J Gastroenterol Hepatol 2001; 13: 963-6.
13. Tabak F, Özaras R, Erzin Y, et al. Ornidazole-induced liver damage: report of three cases and review of the literature. Liver Int 2003; 23: 351-4.
14. Harputluoğlu MM, Demirel U, Karadağ N, et al. Severe hepatitis with prolonged cholestasis and bile duct injury due the long-term use of ornidazole. Acta Gastroenterol Belg 2007; 70: 293-5.
15. Koşar Y, Saşmaz N, Oğuz P, et al. Ornidazole-induced autoimmune hepatitis. Eur J Gastroenterol Hepatol 2001; 13: 737-9.