a gastroenterologist. Monitoring of liver function test for at least 3 months is recommended in such patients (11). Acitretin should be discontinued, in the case of toxic hepatic injury during treatment and further examination should be considered (8).

Hepatotoxicity as a proved adverse effect of acitretin has been reviewed in some studies. In the United State clinical trials, 2:525 patients who received acitretin, had sustained clinical jaundice in association with elevated serum bilirubin and transaminases, but these values returned to normal after discontinuation of the drug. In European clinical trials 2:1289 patients had developed pathologically confirmed toxic hepatitis and based on the second biopsy, fibrotic nodular architecture, suggestive of cirrhosis, was seen in one of these patients. In a Canadian clinical trial, 1:63 patients developed hepatotoxicity (3-fold increase in transaminases) and pathological evaluation showed slight lobular disarrangement, multifocal loss of hepatocytes, and mild inflammation of portal tracts consistent with acute hepatitis. Serum level of liver enzymes in this patient returned to normal values 2 months after discontinuation of acitretin. The potential hepatotoxicity after acitretin therapy was prospectively evaluated based on pre- and post treatment liver biopsies. 58%, 25%, and 17% of the patients had no change, improvement, and aggravation in the grades of liver biopsy, respectively. No relationship was found between the abnormality of liver function test and the changes in liver biopsies (8). The histopathological changes after constant use of acitretin are central vein sclerosis, perisinusoidal fibrosis, focal congestion, and marked fatty changes (9,10).

CONCLUSION

Due to the rare serious adverse effects of acitretin, it could be prescribed for patients with good compliance and unsuccessful topical treatment for psoriasis. During treatment, regular visits and laboratory monitoring of the patients are necessary. Positive history of liver disease in the first degree family, might be considered as a warning sign of susceptibility to hepatic injury among acitretin users.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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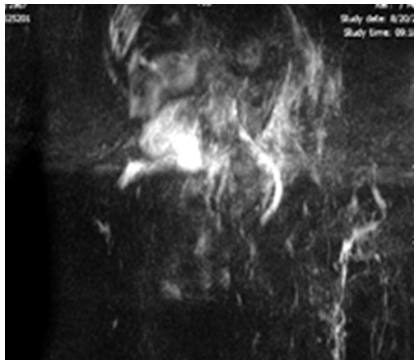

Fig.1: Periportal and pericholecystic edema were found. The diameter of intrahepatic bile ducts was less than normal and pruned that could be due to paranchymal hepatic edema.

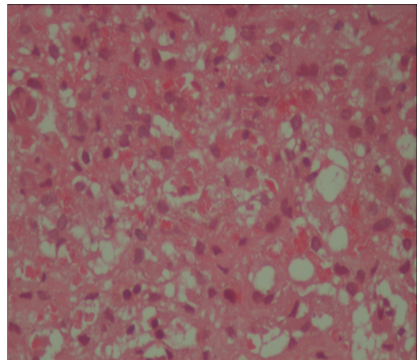

Fig.2: Hydropic changes and single cell necrosis of hepatocytes as well as infiltration of mixed inflammatory cells (H and E staining X400).

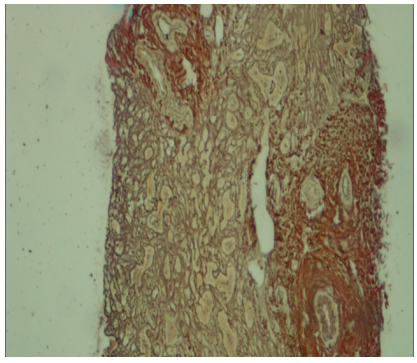

Fig.3: (Reticulin staining X100)

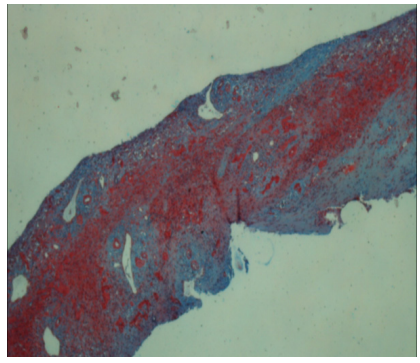

Fig.4: (Trichrome staining X40)

Collapse of reticulin network associated with portal fibrosis

cell necrosis of hepatocytes as well as infiltration of mixed inflammatory cells were shown in hematoxylin, and eosin staining (figure 2). Collapse of reticulin network associated with psuedolobule formation as well as portal fibrosis were shown in reticulin and Masson-trichrome staining (figures 3,4). Overall findings were in favour of an acute/subacute liver injury according to Modified HAI score grade: 14/18, stage: 3/6.

The patient was referred to liver transplantation clinic with the diagnosis of acitretin induced cirrhosis. After one week admission course the patient was discharged with relative symptom relief and was requested for monthly follow-up. Five months later in the monthly follow-up visit, the following data were obtained: AST=31 U/L (12-38 U/L), ALT=30 U/L (7-41 U/L), ALP=200 U/L (80-306 U/L), total Bili=1 mg/dL (0.3-1.3 mg/dL), direct Bili=0.2 mg/dL (0.1-0.4 mg/dL), and albumin=3 mg/dL.

Liver fibroscan (Fibroscan model 502 touch, Echosence France, Paris) was done 5 months later, which showed fibrosis score of F3 (10.1 kPa) based on metavir histological index, and steatosis score of 332 (dB/m), S3 stage which was equal to 80% steatosis.

We followed up the patient for 9 months without any change in general clinical condition and liver function tests.

DISCUSSION

The American Academy of Dermatology suggests a protocol for monitoring of these patients as follows: CBC and renal function tests (baseline and then every 12 weeks), lipid profile and blood sugar in diabetic patients (baseline and then every 1-2 weeks for the first 4-8 weeks), and also liver function test must be evaluated (every 2 weeks for the first 8 weeks, then every 6-12 weeks((8). If abnormal results were reported, adjustment of acitretin dose and weekly measurement of liver function test should be considered. In this context, discontinuation of acitretin after three fold increase in transaminases is mandatory, and patients with alanine aminotransferase and bilirubin values more than 200 IU/L and 50 mmol/L, respectively should be referred to

Table 1: Lab findings of the patient during follow up

Lab test	Normal values	Lab data at admission	Two months Later	Five months later	Nine months later
AST(U/L)	12-38	1406	42 U/L	31	30
ALT(U/L)	7-41	1062	41 U/L	30	29
ALP(U/L)	80-306	525	484 U/L	200	189
T.Bili (mg/dL)	0.3-1.3	36.6	5.92	1	1
D.Bili (mg/dL)	0.1-0.4	17.1	4.7	0.2	0.2
Alb (g/dL)	3.5-5.3	2.8	2.8	3	3.2
Total protein (g/dL)	6-8.3	5.9	6	6.1	6.5
PT(sec)	12.7-15.4	18	14	13	13
INR	1-1.35	1.52	1.1	1	1
PTT (sec)	26.3-39.4	38	32	32	28
Gama GT (U/L)	9-58	158	62	35	32
LDH (U/mL)	200-450	834	368	250	280
Platelet (micro/mL)	150,000-450,000	170,000	165,000	160,000	168,000

Alb: albumin, ALP: Alkaline Phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, D.Bili: Direct Bilirubin, Gama GT: Gama Glutamyl Transferase, INR: International Normalized Ratio, PT: Prothrombin Time, PTT: Partial Thromboplastin Time, T.Bili: Total Bilirubin

the case of toxic hepatic injury during treatment and further evaluation should be considered (8). Hepatic cell injuries are more prevalent among diabetic, alcoholic, and obese persons, therefore more frequent evaluation of liver function test is recommended in these groups (2). Etretinate could be detected in serum for up to 3 years after treatment, probably due to accumulation of the drug in the adipose tissue (8).

CASE REPORT

A 48-year-old man was admitted to Rasoul-e-Akram Hospital with the complaint of weakness, pruritus, nausea, vomiting, and icter, since two weeks earlier. He was a known case of postural psoriasis and had received acitretin 25mg daily during the last 4 months. Liver function test was normal before the drug prescription. On the first physical examination he looked icteric with dry mucosa of the mouth and scratching of the skin due to pruritus. He was a 10 pack/year smoker. His medical history was unremarkable. He had positive family history of liver disease in his father. The drug was discontinued and the patient received supportive care for acute liver failure. Lab findings of the patient during follow up was demonstrated in table 1.

Complete blood count (CBC), renal function test, and lipid profile were normal. We found 1+ proteinuria and 3+ bilirubinuria with 2-3 granular casts in urine analysis. We found 80 mg protein in 24-hour urine sample. The chest radiograph was normal. Coarse normal size liver was the only abnormal finding in abdominal ultrasonography. At admission, the patient was assessed for viral markers (Hepatitis B surface Antigen, Anti-Hepatitis B core Antibody as IgG and IgM ,Anti-Hepatitis C Virus Antibody ,Anti- Human Immunodeficiency Virus Antibody I and II, Anti-Herpes Simplex Virus Antibody, Anti- Epstein Barr Virus Antibody, Anti-Varicella Zoster Virus Antibody, Anti-Cytomegalo Virus Antibody) with negative results. Metabolic and immune based liver disease laboratory evaluation (Haemoglobin A1C, Fasting Blood Sugar, Anti-nuclear Antibody, Anti-Smooth Muscle Antibody, Anti-Liver Kidney Microsomal Antibody, serum protein electrophoresis, ferritin, Anti-mitochondrial Antibody, Peripheral Anti-Neutrophil Cytoplasmic Antibody, Anti-Saccharomyces Cytoplasmic Antibody,serum IgG4, TSH, Anti-tissue transglutaminase Antibody as IgG and IgA) was done with normal range results. LDH and liver enzymes decreased during hospital course without any significant change in ALP and bilirubin level.

Upper endoscopy was done with normal results. Magnetic resonance cholangiopancreatography (MRCP) was done, which showed periportal and pericholecystic edema and decreased diameter of intrahepatic bile ducts due to paranchymal hepatic edema. Other parts were normal according to the report. (figure 1)

Finally, liver biopsy was done. The sample was stained with hematoxylin, and eosin, trichrome, and reticulin. Extensive lobular architecture disarray with marked necro-inflammatory changes of parenchyma characterized by obvious hydropic changes and single

Govaresh/ Vol. 22, No.1, Spring 2017;64-67.

Case Report

Severe Hepatotoxic Injury and Cirrhosis Due to Acitretin: A Case Review

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ABSTRACT

A 48-year-old man was found to have elevated liver enzymes and clinical manifestations of icter, itching, nausea, and vomiting. He had developed a severe hepatotoxic reaction, liver fibrosis, and cirrhosis after treatment with acitretin 25 mg daily (oral retinoid, which is the derivative of etretinate). Elevated serum aminotransferase levels, which are usually reversible, have been reported during treatment with acitretin, however; the present study indicates a warning message that severe hepatotoxic injury may follow such a treatment.

Keywords: Acitretin, Hepatictoxicity, Cirrhosis

please cite this paper as:
Ghavam R, Mokhtare M, Zare-mirzaie A, Aziz Ahari AR, Faghihi AH, Hejrati AR. Severe Hepatotoxic Injury and Cirrhosis Due to Acitretin: A Case Review. *Govaresh* 2017;22:64-67.

INTRODUCTION

Acitretin, a synthetic retinoid compound, is the active metabolite of etretinate. It is substituted for etretinate as a systemic second-line treatment in severe psoriasis that doesn't respond to topical drugs. Its mechanism of action in psoriasis is to decrease epidermal proliferation. Its bioavailability is increased when is used with high fat foods. Its use is forbidden in women who are pregnant or are planning to be, due to its serious teratogenic effects. Acitretin binds with albumin and is metabolized in the liver. Finally it is excreted through urine and bile (1).

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Received: 01 Dec. 2016
Edited: 06 Feb. 2017
Accepted: 07 Feb. 2017

Patients who receive acitretin, may experience some adverse effects, however, they generally disappear when the dosage is reduced or the drug is stopped. The most common adverse effects are dry lips and hyperlipidemia that are dose dependent and normally get better during 4-8 weeks after the drug discontinuation (2).

Pseudotumor cerebri is a very rare serious side-effect. Acitretin should be discontinued rapidly if the patient experiences headache, nausea, vomiting, and visual disturbance. The patient should then be referred for neurological assessment (3,4). Moreover, vulvovaginal candidiasis has been reported as another rare side effect (5,6). Increased sensitivity to insulin and hypoglycaemia, are seen in diabetic patients during retinoids utilization (7).

Hepatotoxicity as an adverse effect of acitretin is discussed further here. Temporary and generally reversible elevated liver enzymes (LDH, AST, ALT, and GGT) may happen in up to 15% of patients who receive acitretin (3,5).

Elevated serum alkaline phosphatase (10% to 25%) and direct serum bilirubin (10% to 25%) have also been reported (8). Acitretin should be discontinued, in