Case Report

Severe and prolonged jaundice in a lupus nephritis patient treated with cyclophosphamide

G. Moroni, M. Maccario, S. Fargion and C. Ponticelli

Division of Nephrology and Dialysis and Institute of Internal Medicine and Medical Physiopathology, IRCCS, Ospedale Maggiore, Milano, Italy

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Introduction

Cyclophosphamide is an alkylating agent widely used in oncology, rheumatology, clinical immunology and nephrology. Cyclophosphamide may cause bone marrow toxicity, bladder toxicity, gonadal toxicity, and mutagenic effects [1]. At high doses the drug may also engender cardiac and lung toxicity [2]. In contrast hepatotoxicity is rare and usually mild.

We report here the case of a patient with systemic lupus erythematosus (SLE) who developed severe but reversible jaundice 2 weeks after the beginning of treatment with oral cyclophosphamide.

Case report

A 27-year-old woman was referred to our Unit in October 1991 because of fever, malaise, arthralgias, oedemas, and nephrotic syndrome. She showed elevated anti-DNA antibodies (542 U1/ml; normal value below 100 U1/ml), low serum C3 (17 mg/dl; normal value 55–120 mg/dl), low serum C4 (10 mg/dl; normal value 15-45 mg/dl), normal plasma creatinine (0.7 mg/dl), and proteinuria of 4.5 g/24 h with dysmorphic microhaematuria and cylindruria in the urine sediment. A renal biopsy showed diffuse proliferative lupus nephritis. After diagnosis, she was treated with three intravenous methylprednisolone pulses of 1 g each every 24 h, followed by oral prednisone 0.5 mg/kg per day for 1 month, which was then progressively tapered to 10 mg per day. After 3 months of treatment, proteinuria disappeared, urine sediment normalized and she maintained in complete remission until March 1996 when fever, arthralgias, and nephrotic proteinuria (5 g per day) with active urine sediment reappeared, associated with low C3 levels (23 mg/dl) low C4 levels (12 mg/dl), and raised anti-DNA antibodies (840 U1/ml). She was treated again with a new course of three intravenous methylprednisolone pulses, followed by oral prednisone 0.5 mg/kg per day. A week later, while she was still nephrotic, it was decided to decrease prednisone to 0.3 mg/kg per day because of an elevated intraocular pressure, and oral cyclophosphamide 100 mg per day (2 mg/kg per day) was introduced. At that time liver function tests were normal. A week later, white cell count was 4700/mm$^3$ and cyclophosphamide was reduced to 75 mg per day. At the end of the second week of treatment the patient developed malaise, nausea, vomiting, pruritus, jaundice, and dark urine. She was hospitalized again.

On admission the main laboratory data were: plasma creatinine 0.8 mg/dl, total serum protein 4.9 g/dl, serum albumin 2.6 g/dl, immunoglobulin (Ig) G 1177 mg/dl, IgA 262 mg/dl, IgM 71 mg/dl, white blood cell count 2800/mm$^3$ (with normal differential count), haematocrit 33%, haemoglobin 10.5 g/dl, platelet count 404 000/mm$^3$. Serum C3 and C4 levels and anti-DNA antibodies had returned to normal values and anti-smooth-muscle and antimitochondrial antibodies were negative. Urinalysis showed proteinuria 0.75 g/24 h. In the urinary sediment the isomorphic erythrocytes were too many to count and there were several bilirubin casts. High levels of serum bilirubin (8 mg/dl), alkaline phosphatase (780 U/l), and aspartate aminotransferase (320 U/l) were found (Figure 1). Laboratory tests for viral hepatitis A, B, C, G were negative. Serological tests for cytomegalovirus, herpes virus, and toxoplasma were also negative. Repeated ultrasonography of the liver did not show either cholelithiasis or dilatation of the hepatic ducts. The patient had never received blood products and was not taking any other drug likely to cause liver toxicity. Cyclophosphamide was stopped but jaundice continued to worsen (Figure 1).

During the third week of hospitalization the patient underwent liver biopsy, which revealed severe cholestasis, scanty inflammatory cell infiltration, and very few necrotic hepatocytes, confined to the areas of severe cholestasis. Five weeks after cyclophosphamide was stopped, liver enzymes and bilirubin began to improve spontaneously, and completely normalized within 4 months from the onset of jaundice.

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Fig. 1. Results of liver function tests after cyclophosphamide was withdrawn in a 27-year-old woman with SLE. Bilirubin normal \( \leq 1 \text{ mg/dl} \); AST, aspartate transaminase, normal 0–37 U/l; alkaline phosphatase, normal 98–279 U/l.

**Discussion**

This woman developed a severe and progressive jaundice a few days after starting cyclophosphamide, whereas she had normal liver function before this therapy. No evidence of infection due to viruses known to cause hepatitis (A, B, C, G, CMV, EBV) was found. She did not show any ultrasonographic evidence of cholelithiasis and/or biliary tract disease. The clinical and biochemical signs of SLE were improving when jaundice developed, so that a diagnosis of lupus hepatitis was quite unlikely [3], nor there were signs supporting a diagnosis of another autoimmune hepatitis [4]. Instead there were other signs of cyclophosphamide toxicity such as leukopenia and severe monomorphic haematuria, which might be attributed to bladder toxicity induced by cyclophosphamide. Liver abnormalities resolved completely only some months after cyclophosphamide withdrawn. We concluded therefore that this patient suffered from a severe hepatic toxicity caused by cyclophosphamide.

To the best of our knowledge only 12 cases [5–12] of severe hepatotoxicity caused by cyclophosphamide have been reported in the literature in spite of the wide use of this drug (Table 1). In the previously described cases liver toxicity became clinically evident after 2–40 weeks of oral or intravenous cyclophosphamide therapy. Two patients died of hepatic failure [5,10] while the other patients completely recovered after cyclophosphamide was stopped. When performed, liver biopsy showed different histological pattern: (a) perivenous hepatocyte necrosis [9], (b) diffuse hepatocellular destruction in conjunction with mild fatty infiltration [8], (c) massive hepatic necrosis with only the reticular framework and remaining sinusoids [5] and (d) small hepatic vein damage and fibrosis [13]. Although the hepatotoxic mechanism of cyclophosphamide is not completely clarified it has been hypothesized that an abnormal hepatic conjugation of acrolein (one of the cytotoxic metabolites of cyclophosphamide) was the main responsible for liver dysfunction [14].

In our patient liver biopsy showed severe cholestasis with minimal hepatocellular injury, a picture completely different from the patterns described in patients who developed hepatotoxicity caused by cyclophos-
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
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<th>Cy dosage</th>
<th>Bil. (mg/dl)</th>
<th>AST (U/l)</th>
<th>AF (U/l)</th>
<th>Liver biopsy</th>
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Cy, cyclophosphamide; Bil, bilirubin; AF, alkaline phosphate; AST, aspartate transaminase; F, female; M, male; SLE, systemic lupus erythematosus.

References


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