Severe Thrombocytopenia Caused by Digitoxin Intoxication in a Patient With Heart Failure Associated With Sjögren’s Syndrome

Takashi Haro, MD; Eimei Shimoeke, MD; Takahiko Horiuchi, MD; Toru Maruyama, MD; Yoshiyuki Niho, MD

Congestive heart failure (CHF) related to Sjögren’s syndrome is extremely rare. This report concerns a patient who presented with CHF and severe thrombocytopenia (5,000/μl). Serum concentrations of K, Mg and digoxin were 3.2 mmol/L, 1.4 mg/L and 57.2 ng/ml, respectively. Digitoxin intoxication was evident, seemingly evoked by hypokalemia, hypomagnesemia, hepatorenal dysfunction and hypothyroidism. The severe thrombocytopenia was considered to have been caused by this intoxication, as it disappeared soon after the digitoxin was discontinued and potassium was supplemented. (Jpn Circ J 2000; 64: 309–311)

Key Words: Digitoxin; Electrolytes; Heart failure; Sjögren’s syndrome; Thrombocytopenia

Cardiac dysfunction observed in patients with Sjögren’s syndrome (SS) has generally attracted little attention, only being reported for the first time recently! We experienced a case in which SS was thought to have led to congestive heart failure (CHF). The patient presented with severe thrombocytopenia, which was considered to have arisen from intoxication by the digitoxin that had been administered for the treatment of CHF. To our knowledge, several cases of thrombocytopenia induced by digitoxin intoxication have been reported. We report the current case, because this case clearly demonstrated that cardiac dysfunction was associated with SS, and that digitoxin intoxication occurred due to the underlying combination of hepatorenal dysfunction and electrolyte imbalance, such as hypokalemia and hypomagnesemia, as well as hypothyroidism induced by total thyroidectomy, with the resulting thrombocytopenia being the most severe case to be published yet.

Case Report

A 46-year-old female visited the Outpatient Clinic of the First Department of Internal Medicine of Kyushu University Hospital in 1995. She had been suffering from dry eyes and xerostomia. A gum test revealed a salivary flow of 3 ml/10 min (normal >10 ml/10 min) and Schirmer test indicated suppressed bilateral tear secretion of 6 mm (normal >10 mm). A Rose–Bengal test was also strongly positive. Moreover, the results of sialography and lip biopsy conducted in that year were compatible with those of SS (ie, cherry blossom pattern in the former, which was compatible with stage II in the classification postulated by Rubin and Holt, and diffuse ascinar as well as periductal lymphocytic infiltration in the latter examination). The presence of autoantibodies to Ro(SS-A (x64) and La(SS-B (x2) antigens was noted. Therefore, she was diagnosed as typical SS and methylprednisolone (6–12 mg) was prescribed. Prednisolone had been previously administered for the treatment of Vogt-Koyanagi-Harada syndrome. The patient had had a thyroidectomy because of papillary adenocarcinoma in 1996 and thyroid hormone replacement therapy was given thereafter. Combined digitoxin (0.0125 mg) and furosemide (20 mg) therapy was started at the beginning of 1999 for the treatment of suspected CHF. In the echocardiographic investigation conducted in March 1999 in the Outpatient Clinic, left ventricular (LV) dysfunction and enlargement were diagnosed, based on LV end-diastolic and end-systolic dimensions of 5.40 and 4.25 cm, and on an LV ejection fraction of 51% and fractional shortening of 21%. The cardiothoracic ratio (CTR) calculated from the chest X-ray was 49.0%. In May 1999, she complained of general fatigue due to the CHF, which was relieved by an increase in the dose of digitoxin (from 0.0125 to 0.025 mg) and furosemide (from 20 to 40 mg). In June 1999, in the Outpatient Clinic, she complained of even greater fatigue than ever and thrombocytopenia was detected (50,000/μl). She was therefore admitted to the First Department of Internal Medicine in Kyushu University Hospital for investigation and treatment of the thrombocytopenia. Purpura was present in the lower extremities. Bleeding time was 10.0 min. When she was admitted, the dosages of digitoxin, levothyroxine and methylprednisolone were 0.025 mg, 100 μg and 12 mg, respectively. Platelet count was 5,000/μl at admission. Bone marrow tap showed normocellular findings with 43/μl megakaryocytes. Direct Coombs test was negative. Serum titers for various viral antibodies were not investigated. Hepatorenal dysfunction was present at admission: aspartate aminotransferase, 27 U/L; alanine aminotransferase, 46 U/L; lactate dehydrogenase, 693 U/L; creatinine, 12 mg/dl; and creatinine clearance, 37.4 ml/min. Serum potassium and magnesium concentrations were 3.2 mmol/L and 1.4 mg/L (normal, 1.8–2.7 mg/L), respectively. Thyroid
function tests revealed mild primary hypothyroidism. Autoantibodies such as antinuclear antibody (ANA), ds-DNA and RNP were negative. Because the ECG demonstrated first degree atrioventricular block and ST depression, the serum concentration of digitoxin was measured and found to be 57.2 ng/ml, which is markedly above the therapeutic concentration of 15–25 ng/ml. After ceasing the digitoxin, platelet-rich plasma was transfused and prednisolone (50 mg) as well as K supplementation (32 mmol) were started the day after admission. The platelet count recovered immediately to the normal range without requiring specific antibodies or their Fab fragments for digitoxin. The PR interval on the ECG gradually returned to the normal range (Table 1). Her general fatigue was attenuated despite the discontinuation of digitoxin, which did not exacerbate the CHF. Cardiac catheterization with myocardial biopsy was not performed. The patient is now being followed in the Outpatient Clinic of the University Hospital.

Discussion

The present case was characteristic in that the cardiac dysfunction was probably due to SS per se, whereas the intoxication by the digitoxin that had been administered for the treatment of the CHF occurred in conjunction with the underlying hepatoportal dysfunction, hypokalemia, hypomagnesemia and hypothyroidism, and it was this intoxication that led to the severe thrombocytopenia.

Although cardiac involvement has been reported frequently in other collagen diseases, CHF associated with SS is extremely rare. Recently, however, a case of cardiac dysfunction thought to be due to this syndrome was reported. Because the CHF improved only after corticosteroid therapy, that report concluded that reversible autoimmune myocarditis was probably the cause of CHF. In the present case, methylprednisolone (6–12 mg/day) had been administered for more than 10 years, so the obvious therapeutic effect of corticosteroid on the CHF caused by SS was difficult to confirm by echocardiogram. However, in order to bring about greater improvement in the CHF, additional digitoxin therapy had been initiated several months before the appearance of thrombocytopenia. There are several factors that predispose patients to digitoxin intoxication. Hepatorenal dysfunction retards the excretion of digitoxin. Sarcolemmal Na-K ATPase is a target molecule of the digitoxis compounds and is regulated by various electrolytes and humoral factors. Potassium competitively binds with digitoxis compounds at the Na-K ATPase binding site and, therefore, hypokalemia is a prerequisite for drug intoxication. Deficiency of magnesium, which works as a cofactor of Na-K ATPase, is associated with decreased effectiveness of cardiac glycosides. Thyroid hormone is thought to regulate the sarcolemmal expression of Na-K ATPase and hypothyroidism suppresses Na-K ATPase; hence a low concentration of digitoxin can inhibit Na-K ATPase activity. The clinical background of the present case can therefore be assumed to be the underlying reason for the digitoxin intoxication.

Several cases presenting with thrombocytopenia as the major, albeit not the first, manifestation of digitoxin intoxication have been reported in the literature. The common features of these cases are that they are mainly females and older, relative to the present case. The platelet count of these previously published cases ranged from 25,000 to 49,000/μl (Table 2). Comparatively speaking, the thrombocytopenia in the present case was extremely severe in spite of the fact that the serum digitoxin levels in some of the reported cases were greater than that of the present case. Thrombocytopenia induced by the toxicity of cardiac glycosides is related to an allergic reaction such that one patient developed thrombocytopenia associated with the

<table>
<thead>
<tr>
<th>Reference</th>
<th>Platelet count (x10^9/μl)</th>
<th>Digitoxin concentration (ng/ml)</th>
</tr>
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<tbody>
<tr>
<td>Berger W</td>
<td>70 y.o. F</td>
<td>4.2</td>
</tr>
<tr>
<td>Young WC, et al</td>
<td>55 y.o. M</td>
<td>4.9</td>
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<tr>
<td>Medonica R, et al</td>
<td>76 y.o. F</td>
<td>4.1</td>
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<tr>
<td>Heus A, et al</td>
<td>77 y.o. M</td>
<td>2.6</td>
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<tr>
<td>Schneider AW, et al</td>
<td>80 y.o. F</td>
<td>3.5</td>
</tr>
<tr>
<td>Gleichweiler M, et al</td>
<td>82 y.o. F</td>
<td>2.5</td>
</tr>
<tr>
<td>Krappeweis J, et al</td>
<td>65 y.o. F</td>
<td>4.0</td>
</tr>
<tr>
<td>Dahmen KG, et al</td>
<td>81 y.o. F</td>
<td>2.7</td>
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<tr>
<td>Present case</td>
<td>46 y.o. F</td>
<td>0.5</td>
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NE, not evaluated. *Calculated according to the molecular weight of digitoxin as 765.
administration of digoxin, which has a shorter biological half-time than digitoxin, and another patient developed digoxin-induced vasculitis, which was associated with a positive skin test. It has recently become known that cardiac glycosides modulate the production of various proinflammatory cytokines that are important in the occurrence and progression of CHF. Therefore, this immunomodulatory aspect of digitalis toxicity is probably related to the development of thrombocytopenia in the present case. Although neither serum antibodies to digitoxin nor altered production of various cytokines could be demonstrated, the immunological reaction may have been exaggerated because of SS, and platelet destruction may have been enhanced in the setting of generalized vasculitis, which is commonly observed in various collagen diseases.

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References