

Selective Estrogen Receptor Modulator Raloxifene-Associated Aggravation of Nonalcoholic Steatohepatitis

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Abstract

A 53-year-old postmenopausal woman, who had a family history of cryptogenic liver cirrhosis, was diagnosed with osteoporosis, and started on the selective estrogen receptor modulator (SERM) raloxifene 60 mg/day orally. She developed marked liver dysfunction. Her body mass index (BMI) was 26.5. Her blood chemistry indicated AST 342 IU/L, ALT 356 IU/L, and hyaluronic acid 255 ng/mL. An oral glucose tolerance test showed impaired glucose tolerance with marked insulin resistance. Histologically, we diagnosed this case as having pre-cirrhotic nonalcoholic steatohepatitis (NASH). This is the first histologically confirmed case of NASH that was aggravated by raloxifene.

Key words: estrogen, estrogen receptor modulators, fatty liver, nonalcoholic steatohepatitis, osteoporosis, postmenopausal

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Selective estrogen receptor modulators (SERMs) are designed to produce not only beneficial estrogenic actions for certain tissues, such as the bone and liver, during postmenopausal hormone therapy, but also anti-estrogenic actions in tissues, such as the breast and endometrium, where estrogenic actions can be carcinogenic (1). With use of the SERM tamoxifen for treating breast cancer, studies have occasionally reported nonalcoholic steatohepatitis (NASH) (2, 3). However, because other SERMs had not been recognized as a cause of NASH, it was not clear whether NASH is a class side effect of SERMs or a tamoxifen-specific effect. Here, we report the first case of NASH triggered by raloxifene, which was used to treat osteoporosis.

A 53-year-old postmenopausal woman was admitted to our hospital to examine her liver function. Her father and mother had suffered from nonviral liver cirrhosis with hepatocellular carcinoma. Her sister and brother had hypertension. She did not drink alcohol. Minor liver dysfunction and a fatty liver were first noticed on a health examination in 1998 at age 47 years. When an orthopedic surgeon examined her regarding left knee arthralgia in 2002, her liver data were AST 50 IU/L, ALT 82 IU/L, ALP 199 IU/L, and γ -GTP 23 IU/L. She was diagnosed with rheumatoid arthritis

and osteoporosis, and treated with antirheumatic drugs, non-steroidal anti-inflammatory drugs, and vitamin D (Fig. 1). Since that time, her liver function fluctuated, with AST 70-132 IU/L, ALT 110-179 IU/L, ALP 184-206 IU/L, and γ -GTP 33-45 IU/L. She started an oral SERM, raloxifene 60 mg/day on September 13, 2004 to treat her osteoporosis. Subsequently, her liver dysfunction worsened remarkably (Fig. 1), and she was hospitalized in early December 2004. She had gained 3-4 kg in weight within 1 year.

On admission, her body mass index (BMI) was 26.5 and waist circumference was 84 cm. Neither icterus nor vascular spiders were recognized, and her blood pressure was normal. Her blood chemistry was AST 342 IU/L, ALT 356 IU/L, ALP 414 IU/L, γ -GTP 224 IU/L, γ -globulin 0.92 g/dl, HbA_{1c} 5.2%, TC 194 mg/dL, TG 97 mg/dL, and hyaluronic acid 255 ng/mL (normal <50). An oral glucose tolerance test showed impaired glucose tolerance and marked insulin resistance (peak insulin level 200 μ U/mL, HOMA-R 1.78).

She suffered from osteoarthritis in her knee. Since her antinuclear, anti-SS-A, and anti-SS-B antibodies were all positive and she had dry eyes, we diagnosed her with Sjögren's syndrome. Computed tomography and magnetic resonance

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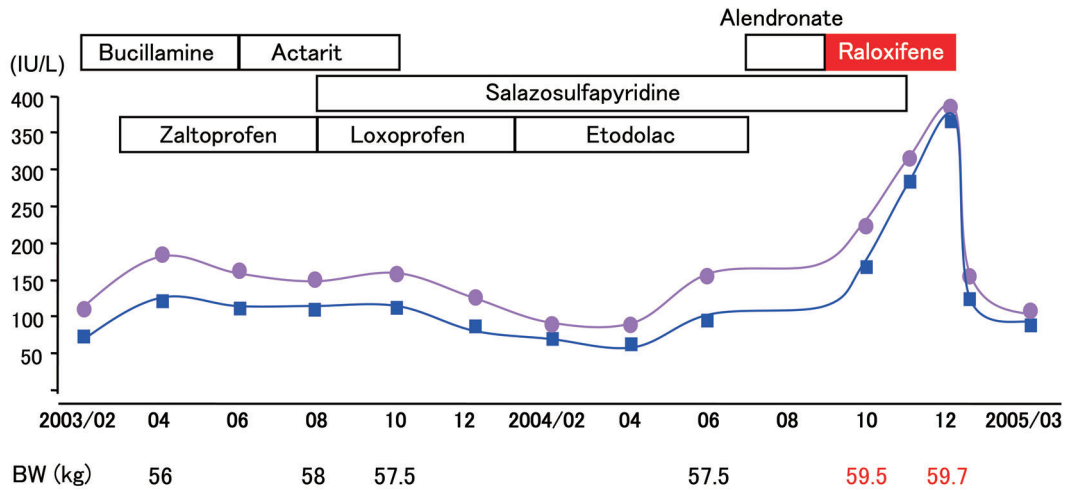


Figure 1. Clinical course. Relationship of raloxifene administration, the levels of alanine aminotransferase (circles) and aspartate aminotransferase (squares), and body weight (BW) in our patient is illustrated.

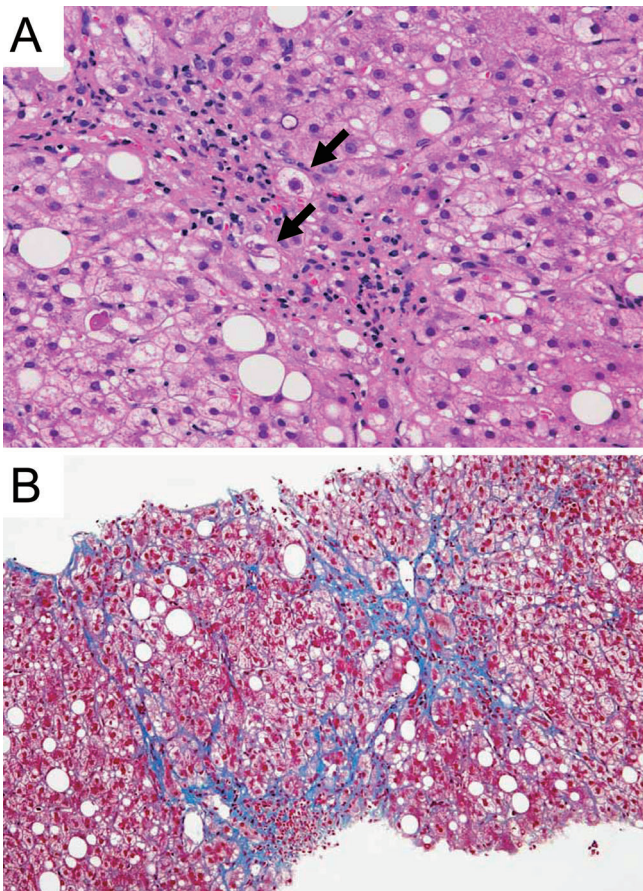


Figure 2. Histological findings of the liver biopsy. A, Hematoxylin & eosin-stained section of the liver. Some hepatocytes around the central veins were swollen with intracytoplasmic acidophilic aggregates (arrows). B, Azan-stained section of the liver. Magnification: A, $\times 200$; B, $\times 100$.

December 14. Histologically, the lobular architecture was moderately distorted with bridging and pericellular fibrosis (Fig. 2A, B). Macrovesicular steatosis was observed in about 30% of hepatocytes, mainly in the centrilobular area (Fig. 2A). Some hepatocytes around the central veins showed marked swelling (ballooning). Some of the ballooned hepatocytes also contained acidophilic aggregates in the cytoplasm, although they were not typical Mallory's bodies (Fig. 2A). Inflammatory cells consisted mainly of lymphocytes and neutrophils infiltrating the hepatic parenchyma (Fig. 2A). Accordingly, we diagnosed this case with pre-cirrhotic NASH (steatosis 1/3, grade 3/3, stage 3/4; non-alcoholic fatty liver disease (NAFLD) classification class 4).

After stopping the raloxifene, her liver dysfunction rapidly improved to baseline, with an AST of 99 IU/L and ALT of 118 IU/L 3 months later. In this patient, raloxifene promoted the pathology of NASH, with insulin resistance and estrogen deficiency on a background of menopause. Estrogen may prevent fibrosis and carcinogenesis of the liver through its antioxidant and antifibrosis actions (4). Raloxifene acts as a partial agonist in bone, but does not stimulate endometrial proliferation in postmenopausal women, presumably due to some combination of the differential expression of transcription factors in the two tissues and the effect of this SERM on estrogen receptor (ER) conformation (1). Tamoxifen, another SERM, is used to treat breast cancer by binding competitively to estrogen receptors in the breast cancer. It was reported that 24 of 66 patients administered tamoxifen developed NASH (2). A recent prospective, randomized, double-blind, placebo-controlled trial revealed that 34 of 2,700 patients treated with tamoxifen and 16 of 2,708 patients given placebo were suspected of having NAFLD (hazard ratio=2.0, $P=0.04$) (3). It also suggested that tamoxifen is associated with a higher risk of developing NASH only in overweight and obese women with features of metabolic syndrome (3). From this perspective,

imaging showed mild swelling of the liver and spleen, and fatty change of the liver. A liver biopsy was performed on

the present patient was also predisposed to NASH, as she was overweight, menopausal, and had a family history of cryptogenic liver cirrhosis and insulin resistance. Unfortunately, since the liver histology was not examined before administering raloxifene, we cannot rule out the possibility that our patient was already predisposed to liver damage. Only one study has reported a case of raloxifene-associated acute hepatitis with jaundice and a raised eosinophil count, which was probably due to an immune mechanism, and was distinct from NASH (5). The histological features of liver injury in this case corresponded to NASH, and differed from the typical features of drug-induced injury of the hepatic

type. At this time, however, we cannot completely eliminate the possibility of superimposed drug-induced hepatitis on preexisting NASH. The accumulation of similar cases is required to confirm that NASH is a class side effect of SERMs. Whether SERM has a positive or negative effect on estrogenic action on the liver to accelerate the development of NASH should be elucidated to better understand the role of estrogen in linking fat to inflammation in the liver. Postmenopausal obese women with osteoporosis, when treated with raloxifene, should have their liver function monitored carefully to prevent the development of NASH.

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