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Case report

Myocardial infarction in a premenopausal woman with a decreased serum estrogen level due to leuprorelin acetate

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Summary A 45-year-old premenopausal woman was admitted with acute myocardial infarction. Her serum estrogen level was decreased because of leuprorelin acetate administration, 3 months prior to admission for the treatment of uterine myoma. Emergency coronary angiography revealed diffuse narrowing of the distal half of the left anterior descending artery (LAD). The second coronary angiography after anti-anginal medication revealed significant improvement in LAD narrowing, which suggested prolonged coronary vasospasm. She had no coronary risk factors except for a positive family history. This case suggests that a decreased serum estrogen level could cause ischemic heart disease even in premenopausal women.

1. Introduction

It is well known that premenopausal women show a low incidence of ischemic heart disease [1]. To explain this, it has been suggested that estrogens have cardioprotective effects. Leuprorelin acetate, a gonadotropin-releasing hormone, acts as a potent inhibitor of gonadotropin secretion when therapeutic doses are given continuously. It results in decreased levels of luteinizing hormone (LH) as well as follicle-stimulating hormone (FSH), and subsequently suppresses gonadal sex steroid production. Therefore, it is used to treat uterine myoma, endometriosis, prostate cancer, and breast cancer. In premenopausal women treated with leuprorelin acetate, estrogens are reduced to postmenopausal levels.

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It is known that leuprorelin acetate is associated with angina in men, but few cases of ischemic heart disease in women undergoing treatment with leuprorelin acetate have been reported [2]. In this paper, we describe a case of acute myocardial infarction in a premenopausal woman with a decreased serum level of estrogen due to treatment with leuprorelin acetate.

2. Case report

A 45-year-old premenopausal woman, who had never been pregnant, was admitted to our hospital with continuous anterior chest pain for 2 h at rest after work-related emotional stress. She had been diagnosed with uterine myoma at the age of 35 years. She showed a normal menstrual cycle (almost once a month) and suffered from dysmenorrhea with myoma uterus. So, she had been treated with leuprorelin acetate intramuscularly, once every 4 weeks at a dose of 3.75 mg, for 3 months prior to admission at the age of 45 years. She had no history of anginal attack before treatment with leuprorelin acetate. She was a nonsmoker and had no prior history of cardiovascular disease, Kawasaki disease, aortitis, or collagen diseases. She had never taken a contraceptive drug. Her family history was found to be positive for ischemic heart disease; her grandmother and two uncles had ischemic heart disease. However, none of her family had a history of diabetes, hypertension, or hyperlipidemia.

When she visited her family doctor with anterior chest pain, 12-lead electrocardiogram (ECG) showed ST elevation in leads II, III, aVF, and V_2 through V_6 (Fig. 1A). She was referred to our hospital for further evaluation. At the time of admission, no physical abnormality was observed. However blood chemistry revealed a slight increase in the level of creatinine-phosphokinase and positive serum troponin-T. Sublingual administration of nitroglycerin tablets reduced her chest pain, and 12-lead ECG showed an improvement in ST elevation (Fig. 1B). Transthoracic echocardiography revealed mild hypokinesis of the anterior apical portion of the left ventricle. Immediately, continuous drip-infusion of isosorbide dinitrate (ISDN) was started and emergency cardiac catheterization was performed. It revealed 90% narrowing only in the distal half of the left anterior descending artery (LAD) (Fig. 2B and C) but no significant stenosis in the right coronary artery (RCA) (Fig. 2A) or left circumflex artery (LCX) (Fig. 2B). Additional intracoronary injection of ISDN (3 mg) and nicorandil (6 mg) did not improve the stenosis. Despite severe stenosis of the LAD, Thrombolysis In Myocardial Infarction (TIMI) 3 flow was observed and her symptoms were significantly reduced. Therefore, percutaneous coronary intervention was not performed.

She was treated with the continuous intravenous administration of heparin sodium and ISDN. Additionally, she was orally administered diltiazem (200 mg/day), aspirin (100 mg/day), nicorandil (15 mg/day), and isosorbide mononitrate (40 mg/day). Laboratory tests revealed an increased level of creatinine-phosphokinase (708 IU/l) 5 h after admission. On the second hospital day, 12-lead ECG showed negative T waves in II, III, aVF, and V_3 through V_6 leads (Fig. 1C). Her clinical course was uneventful. Treadmill exercise stress testing performed 2 weeks later showed a negative result for ischemia. Three weeks after admission, cardiac catheterization performed using the same medications as above revealed significant improvement of the narrowed lumen of the LAD (Fig. 2D). We did not perform a coronary vasospasm provocation test based on the patient's wishes.

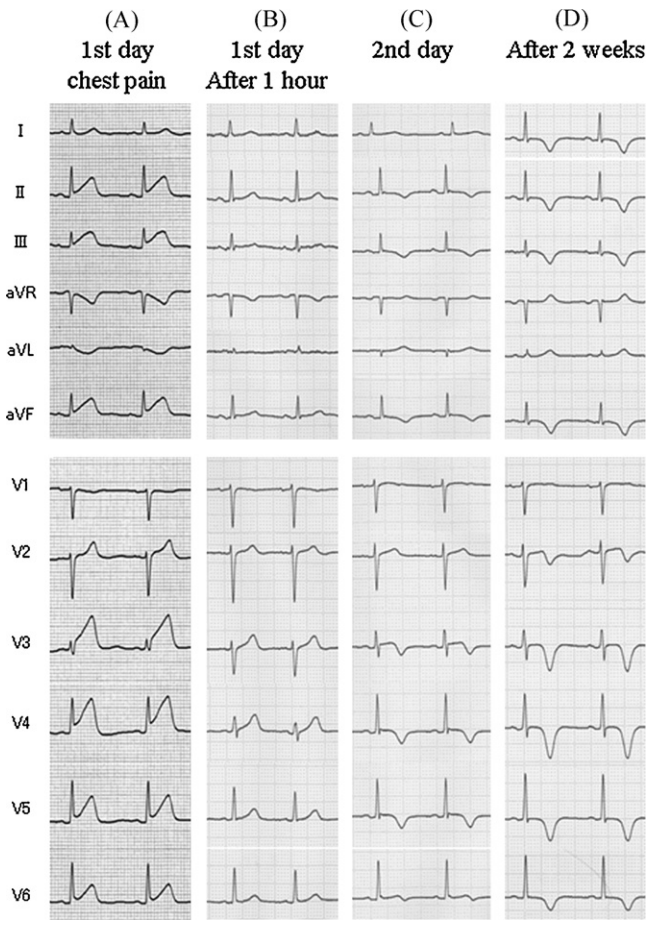

Figure 1 The 12-lead electrocardiograms in the present case. During chest pain, it revealed ST segment elevation in leads II, III, aVF and V_2 through V_6 (A). Nitroglycerin reduced chest pain and improved ST segment elevation (B). On the 2nd day (C) and after 2 weeks (D), negative T waves increased.

Further evaluations of coronary risk factors were performed. Computed tomography of the chest revealed no evidence of vasculitis including aortitis. The results of laboratory tests are shown in Table 1. Two weeks after admission, plasma glucose levels after a 75 g oral glucose load were 86 mg/dl on fasting (insulin level was 11.8 μU/ml), 104 mg/dl at 60 min, and 125 mg/dl at 120 min (insulin level was 56.9 μU/ml), and homeostasis model assessment for insulin resistance (HOMA-IR) was 2.5, which indicated a normal glucose tolerance with insulin resistance. No evidence of collagen diseases including vasculitis or a deficiency of coagulation factor was noted. The serum level of estrogen was decreased because of the use of leuprorelin acetate (Table 1). She stopped using leuprorelin acetate, and, 3 months later, regained recovery of the menstrual cycle. Seven months later, her serum estrogen level was 35 pg/ml

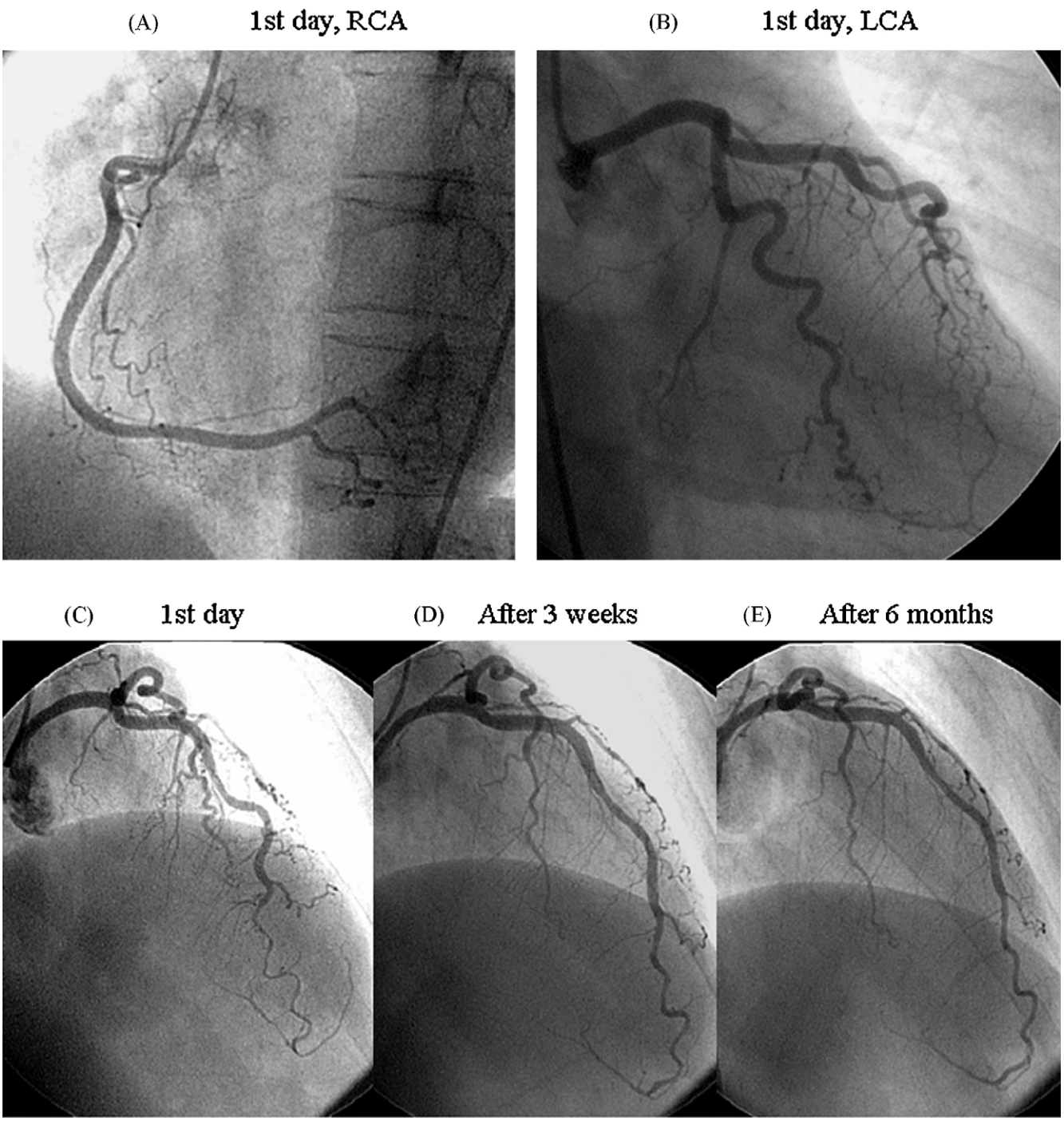

Figure 2 Emergency coronary angiograms on the first hospital day showed no stenosis in the right coronary artery (RCA) (A) or left circumflex coronary artery (LCA) (B), but revealed narrowing in the distal half of the left anterior descending artery (B). On the first hospital day, emergency coronary angiogram showed narrowing at the distal half of the left anterior descending artery (C). Gradual improvement in stenosis was observed after 3 weeks (D) and 6 months (E).

and improved to that of premenopausal women. Her coronary angiography also revealed a normal appearance of the LAD (Fig. 2E). Now, 3 years after stopping treatment with leuprorelin acetate, the estrogen (E2) level is 33 pg/ml, the FSH level is 21.64 μIU/ml and the LH level is 3.74 μIU/ml. She shows a normal menstrual cycle (almost once a month), and suffers from dysmenorrhea with myoma uterus.

3. Discussion

This case was diagnosed as acute myocardial infarction based on the positive findings of typical chest pain, changes in electrograms, an elevated level of creatine-phosphokinase, and positive troponin-T. The 12-lead ECG showed ST elevation not only in leads V_2 through V_6 but also in inferior leads (Fig. 1A), because the apical area of the left

Table 1 The results of laboratory tests on patient admission.

WBC	6400/μl
Hb	15.3 g/dl
Plt	19.1×10^4/μl
TP	7.6 g/dl
GOT	22 IU/l
GPT	16 IU/l
CPK	209 IU/l
CK-MB	29 IU/l
LDH	202 IU/l
BUN	9.4 mg/dl
Cr	0.5 mg/dl
UA	3.4 mg/dl
TC	189 mg/d
TG	72 mg/dl
LDL-c	94 mg/dl
HDL-c	65 mg/dl
LP(a)	25.0 mg/dl
BS	123 mg/dl
HbA1c	4.9%
FDP	2.25 μg/ml
D-dimer	0.07 μg/ml
AT III	92%
ProteinC	112%
ProteinS	75%
CRP	<0.01 μg/dl
ANA	<40
RF	4 IU/ml
PR3-ANCA	<3.5 U/ml
MPO-ANCA	<1.3 U/ml
AntiCLAb	<8.0 U/ml
AntiCLβ2Ab	<0.7 U/ml
Testosterone	0.15 ng/ml
Estradiol	<10 pg/ml
Progesterone	<0.2 ng/ml

WBC, white blood cell count; Hb, hemoglobin; Plt, platelet; TP, total protein; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; CPK, creatine-phosphokinase; CK-MB, creatine kinase-MB; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein-cholesterol; HDL-c, high-density lipoprotein-cholesterol; LP(a), lipoprotein(a); BS, blood sugar; HbA1c, hemoglobin A1c; FDP, fibrin degradation products; AT III, antithrombin III; CRP, C-reactive protein; ANA, antinuclear antibody; RF, rheumatoid factor; PR3-ANCA, proteinase-3-antineutrophil cytoplastic antibody; MPO-ANCA, myeloperoxidase-antineutrophil cytoplastic antibody; AntiCLAb, anticardiolipin antibody IgG; AntiCLβ2Ab, anticardiolipin antibody, cardiolipin antibody β2—glycoprotein-1 complex.

ventricle was fed by the culprit lesion of the LAD (Fig. 2B and C) rather than by RCA (Fig. 2A) and LCX (Fig. 2B), which were relatively small.

Previous clinical investigations reported that young adults with acute myocardial infarction often angiographically showed normal coronary arteries [3], frequently related to coronary vasospasm [4]. In this case, the first coronary angiography revealed diffuse narrowing in the distal half of the LAD, but neither coronary dissection nor thrombosis. Although ISDN and nicorandil could not immediately improve the LAD stenosis, after anti-anginal medications, follow-up angiography performed 3 weeks later showed improvement of the stenosis, which could be attributed to prolonged coronary vasospasm.

The prevalence of coronary vasospasm differs among populations, and is higher in Japan than in Western countries, probably due to genetic as well as environmental factors [4]. For example, it is reported that various genetic polymorphisms of the endothelial nitric oxide synthase (e-NOS) gene are significantly associated with coronary vasospasm in Japan. In this case, her family history of ischemic heart disease might imply these genetic backgrounds.

After stopping treatment with leuprorelin acetate, the estrogen level recovered to normal, not high, levels. These data along with the FSH and LH levels indicate that she might be approaching menopause, but she is still a premenopausal woman with a normal menstrual cycle.

We cannot exclude the possibility that the occurrence of acute myocardial infarction was incidental during treatment with leuprorelin acetate, but it is not unlikely for only the family history to account for myocardial infarction like this in premenopausal women. Ordinarily, premenopausal women without coronary risk factors (e.g. smoking, diabetes mellitus, and hypertension) rarely experience ischemic heart disease, because of protection by the anti-atherogenic effects of estrogens. The use of leuprorelin acetate, through the decrease in estrogens, might affect lipid metabolism (e.g. the increase in low-density lipoprotein-cholesterol) and induce ischemic coronary disease. However, in this case, the laboratory data showed no abnormality of the lipid profile.

The beneficial effects of estrogens can account for the improvement in endothelial function as well as alteration of the lipid profile [5]. Experimental studies reported that estrogens, increasing the amount of mRNAs for e-NOS, cause an increase in the production of nitric oxide as an endothelium-derived relaxing factor [6]. In postmenopausal women, it was reported that the administration of estrogen improves endothelium-dependent coronary vasodilator function [7,8].

Clinically, in premenopausal women with coronary vasospasm, decreased serum estrogen levels in the menstrual cycle could be associated with the worsening of ischemia and decreased coronary vasodilator function [9]. Similarly, in postmenopausal women, estrogen levels are associated with the threshold levels of angina with coronary artery disease [10].

Therefore, in this case, decreased levels of estrogens due to the use of leuprorelin acetate, causing the dysfunction of endothelium-dependent coronary vasodilatation, might have resulted in the prolongation of coronary vasospasm. We should be careful about ischemic heart disease in premenopausal women with a decreased serum estrogen level.

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