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Case Report

Leuprolide induced Myocardial Infarction

Vikas Mishra, Rajendra Kumar Bansal, Chandra Mohan Verma, Ramesh Thakur, Umeshwar Pandey, Santosh Kumar Sinha, Mohamadulla Razi, Mohammad Ahmad, Raj Pratap Singh Bharadwaj

Department of Cardiology, LPS Institute of cardiology, GSVM Medical College, Kanpur, UP, INDIA.

ABSTRACT

A 36-year-old premenopausal woman was admitted with acute myocardial infarction. The lady was being administered leuprolide, a GnRH agonist which suppresses FSH and LH which in turn decreases blood estrogen level for the treatment of uterine fibroid. Patient was initially thrombolysed with streptokinase and later treated with anticoagulants and antianginals. Check coronary angiography performed on the fourth day revealed mid left anterior descending artery (LAD) 99% stenosis. Apart from mild hypertension which was controlled by lifestyle modifications there were no other coronary risk factors. It was concluded that decreased serum estrogen level caused by leuprolide could cause ischemic heart disease even in premenopausal women and caution to be exercised while using this drug.

Key words: Myocardial infarction, Coronary vasospasm, Anti-estrogen, Leuprolide, Uterine fibroid.

Correspondence:

Dr. Vikas Mishra , MD

Department of Cardiology LPS Institute of cardiology GSVM Medical College, Kanpur, UP, India.

Email- dr.vikasmishra@gmail.com

Ph- 07052768771

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INTRODUCTION

It is a well known fact that premenopausal women show a low incidence of ischemic heart disease.[1] It has been suggested that estrogens have cardioprotective effects. Leuprolide, 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 leuprolide, estrogens are reduced to postmenopausal levels. It is known that leuprolide is associated with angina in men, but very few cases of ischemic heart disease have been reported in women undergoing treatment with leuprolide.[2] In this report, we describe a premenopausal woman on leuprolide therapy who presented with ST segment elevation (STE) myocardial infarction.

CASE REPORT

A 36-year-old premenopausal woman, on treatment with leuprolide for uterine myoma, was admitted to our hospital with continuous chest pain radiating to left upper limb since ten hours. She initially consulted her family doctor with anterior chest pain. A 12-lead electrocardiogram (ECG) showed ST elevation in leads V_2 through V_6 with q RBBB pattern (Figure 1). She was referred to our hospital for further management after receiving a loading dose of aspirin 325 mg, clopidogrel 300 mg and atorvastatin 80 mg. She was on therapy with leuprolide, once every month planned for 3 months at a dose of 3.75 mg subcutaneously. Patient had received the second dose six days prior to this episode. She had prior history of hypertension diagnosed six months back which was controlled on salt restricted diet and lifestyle modification. There was no history of any cardiovascular symptoms and her blood pressures were normal during the leuprolide therapy as was reported from her gynecological case notes. She was a non-smoker and had no prior history of cardiovascular disease or collagen diseases. She had never taken a contraceptive drug. There was no family history of ischemic heart disease. However, both her parents were hypertensive and well controlled on antihypertensives.

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. Transthoracic echocardiography revealed mild hypokinesis of the anterior apical portion of the left ventricle. Patient was offered percutaneus coronary intervention but she opted for medical management. Immediately, patient was thrombolysed with streptokinase. Later conservative treatment with continuous drip-infusion of nitroglycerine and enoxaparin 60 mg subcutaneously was started. Additionally, she was administered oral metoprolol (100 mg/day), aspirin (150 mg/day), clopidogrel 75 mg, atorvastatin 80 mg, ramipril 5 mg, furosemide+spironolactone (20 mg+50 mg) and isosorbide mononitrate (40 mg/day). Patient was asymptomatic after two days.

On the fourth day of admission, prior to discharge, cardiac catheterization was performed. It revealed 95% narrowing in the mid of the left anterior descending artery (LAD) (Figure. 2). Percutaneous coronary intervention was not performed as the patient refused to undergo stent implantation. Her clinical course was uneventful. Treadmill exercise stress testing performed 2 weeks later showed a negative result for ischemia. The results of laboratory tests are shown in Table 1. No evidence of collagen diseases including vasculitis or a deficiency of coagulation factor was noted. Hence leuprolide causing decreased serum level of estrogen was postulated as the causative factor (Table 1). Leuprolide was stopped, and three months later, her serum estrogen level improved to that of premenopausal women (35 pg/ml) along with some other tests. (Table 1)

DISCUSSION

Several studies have reported that young adults with acute myocardial infarction often angiographically show normal coronary arteries,[3] coronary vasospasm[4] or artherosclerosis in LAD.[5] To our knowledge, only 4 cases of cardiovascular disease secondary to leuprolide use have been reported in women[6-9] and this being the first case reported in Indian population. In this case, the first coronary angiography revealed near-total 99% stenosis in mid LAD unlike previous cases reported in literature where diffuse narrowing in the distal half of the LAD or coronary vaso-

Table 1. Laboratory tests on patient admission.

	At presentation	At 3 months	Normal range
WBC	17000/µl	8500/ µl	4000-11000/ µl
Hb	13.3 g/dl	13.5g/dl	13-17g/dl
Plt	18.2 × 104/µl	22.2x 104/µl	15.0-40.0 x104/ µl
TP	6.8 g/dl		4-7g/dl
SGOT	37 IU/l		20-40 IU/l
SGPT	19 IU/l		15-35 IU/l
CPK	488 IU/l		20-200 IU/L
CK-MB	56 ng/mL		0-4 ng/mL
Trop I	12.389 ng/ml		0-0.4 ng/ml
BUN	9.4 mg/dl		6–20 mg/dL
Cr	0.9 mg/dl	1.0mg/dl	0.7-1.3 mg/dl
UA	6.8 mg/dl		3-7 mg/dl
TC	140 mg/dl		130-200 mg/dl
TG	86 mg/dl		50-150mg/dl
LDL-c	74 mg/dl		70-120 mg/dl
HDL-c	48 mg/dl		40-80 mg/dl
VLDL	17.0 mg/dl		2 to 30 mg/dL
RBS	108 mg/dl	110mg/dl	80-140 mg/dl
HbA1c	5.3%		5-6%
CRP	<0.01 µg/dl		< 5 mg/L
ANA	<40IU		<40IU
RF	4 IU/ml		<25 IU/ml
PR3-ANCA	<3.5 U/ml		<20 U/ml
MPO-ANCA	<1.3 U/ml		<5U/ml
AntiCLAb	<8.0 U/ml		<8.0 U/ml
AntiCLβ2Ab	<0.7 U/ml		<0.7 U/ml
Testosterone	1 nmol/L		10-25 nmol/L
Estradiol	18 pg/ml	35 pg/ml	20–400 pg/mL
FSH	3.5mIU/ml	8 mIU/L	5–20 mIU/L
LH	0.41 mIU/ml	7 mIU/L	5–20 mIU/mL

Table: 1- 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; 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.

spasm was seen. During cardiac catheterisation, her LAD did not dilate with intracoronary nitroglycerin administration, which makes coronary vasospasm less likely. No dissection was seen on the catheterisation study. There was LAD territory involvement in our case also as seen in other cases described in literature.

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 in leads V_1 through V_5 (Figure.1).

Women with chest pain syndromes are more likely than men to have nonatherosclerotic coronary arteries with abnormal coronary flow.[10] There are various forms of nonatherosclerotic coronary artery disease (NACAD), including coronary vasospasm, dissection, fibromuscular dysplasia, ectasia, vasculitis, congenital coronary anomaly, and embolism.[10] The most common are vasospasm, dissection and fibromuscular dysplasia

We cannot exclude the possibility that the occurrence of acute myocardial infarction was incidental during treatment with leuprorelin acetate, but it is unlikely for a premenopausal woman that borderline hypertension would account for myocardial infarction like this. Ordinarily, premenopausal women without coronary risk factors (e.g. smoking, diabetes mellitus, and hypertension) rarely experience ischemic heart disease, due to protection by the anti-atherogenic effects of estrogens.

The beneficial effects of estrogens can account for the improvement in endothelial function as well as alteration of the lipid profile.[5] Experimental studies report that estrogens, increasing the amount of mRNAs for e-

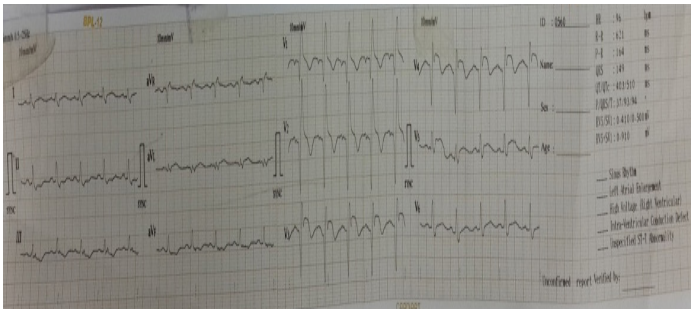

Figure 1: The 12-lead electrocardiograms in the present case. During chest pain, it revealed ST segment elevation in leads V1-V5 with qRBBB patern.

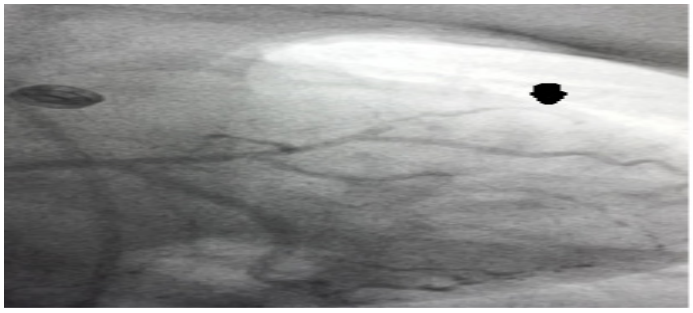

Figure 2: Coronary angiograms revealed near total occlusion of the mid left anterior descending artery

NOS, cause an increase in the production of nitric oxide as an endothelium-derived relaxing factor In postmenopausal women, it was reported that the administration of estrogen improves endothelium-dependent coronary vasodilator function.[6]

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.[10] Similarly, in postmenopausal women, estrogen levels are associated with the threshold levels of angina with coronary artery disease.[10] 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.[11] However, in this case, the laboratory data showed no abnormality of the lipid profile. In our patient, after stopping treatment with leuprorelin acetate, the estrogen level recovered to normal. 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 and hence the ischaemia. The FSH and LH levels indicate that she might be approaching menopause, but she is presently a premenopausal woman with a normal menstrual cycle.

Ischemic heart disease in premenopausal women should therefore be investigated in detail for drug induced decreased serum estrogen levels and corrected accordingly.

CONFLICT OF INTEREST :

None

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