Low-Dose Oral Contraceptives and Spontaneous Coronary Artery Dissection With Heavy Clot Burden in a Nonpregnant Woman

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Abstract
Spontaneous coronary artery dissection (SCAD) is an infrequent cause of acute coronary syndrome (ACS) caused by a nontraumatic tear in the coronary artery wall. The true incidence is thought to be underestimated owing to its diagnostic difficulty as coronary angiography is insensitive in assessing the arterial wall structure, thereby warranting additional diagnostic modalities such as intravascular ultrasound. We report a case of a young woman who had been taking oral contraceptives, and presented with acute non-ST segment elevation myocardial infarction due to SCAD with superimposed thrombosis.

Keywords
spontaneous coronary artery dissection, oral contraceptives, non-ST segment elevation myocardial infarction

Background
Spontaneous coronary artery dissection (SCAD) is an uncommon cause of acute coronary syndrome (ACS) caused by a nontraumatic tear in the coronary artery wall. The incidence of SCAD varies across the literature as it is often misdiagnosed; however, it is reported to be responsible for 24% of acute myocardial infarctions (AMI) in women below 50 years of age. Several predisposing risk factors for SCAD have been identified, including fibromuscular dysplasia, pregnancy, and hormonal therapy. Although oral contraceptives or hormone replacement therapy have been associated with an increased risk of SCAD, and coronary thrombosis. The simultaneous occurrence of SCAD with intraluminal thrombosis has been scarcely reported. Hereby, we report a case of a young female who presented with an acute non-ST segment elevation myocardial infarction (NSTEMI) due to SCAD and intraluminal thrombosis.

Case Presentation
A 30-year-old female with hypertension and major depressive disorder (MDD) presented with progressive substernal pain for 4 hours. The pain was described as sharp, severe, and associated with diaphoresis and radiation to the left arm. For the past 6 months, home medications included labetalol, bupropion, and low-dose oral contraceptives (norethindrone acetate 1 mg and ethinyl estradiol 0.01 mg). She did not smoke and denied the use of nasal decongestants, workout supplements, or the use of any illicit drugs. There was no family history of cardiac or thromboembolic disease. Vitals were remarkable for a heart rate of 103 beats per minute and a blood pressure of 135/82 mm Hg. She was morbidly obese with a body mass index of 56.51 kg/m². The physical examination was unremarkable. A 12-lead electrocardiogram (EKG) demonstrated sinus tachycardia (Figure 1). High-sensitivity troponin-T was elevated and increased from 147.1 to 573 ng/L. The urinary drug screen was negative.

A diagnosis of NSTEMI was made. Coronary angiography was performed and a thrombus was noted in the proximal left anterior descending artery (LAD), extending from...
the ostium to just before the first diagonal branch (Figure 2A). After reviewing the images, a decision was made to proceed with intravascular ultrasound (IVUS) of the LAD. Intravascular ultrasound confirmed an intra-coronary thrombus extending from the ostial LAD to just prior to the first diagonal artery. It was also noted that there was an intimal flap at the proximal part of the LAD just a few millimeters distal to the ostium of the vessel (Figures 3A and 3B). Tirofiban was administered, and aspiration thrombectomy was performed, and a repeat angiogram and IVUS were done, which confirmed removal of most of the thrombus with minimal clot burden noted (Figures 2B and 3C). There were no atherosclerotic lesions in the affected vessel or in the other coronary arteries. After thrombectomy, the tirofiban infusion was continued for 18 hours. She was successfully discharged on dual antiplatelet therapy 2 days later.

**Discussion**

Although the risk of venous thromboembolism associated with oral contraceptives is well-recognized, the correlation between low-dose oral contraceptives and arterial thrombosis is less certain. According to data from a large meta-analysis, combined oral contraceptives were associated with a 1.6-fold increase in the risk of AMI or ischemic stroke, independent of the progestogen preparation. A dose-dependent effect was observed between ethinyl estradiol and the risk of AMI. The lowest dose of ethinyl estradiol included in the analysis was 0.02 mg, which was twice the dose our patient was taking.

The estrogen component of combined oral contraceptives is responsible for the increased risk of AMI, especially in combination with other risk factors including smoking,
hypertension, diabetes, and hypercholesterolemia. Several mechanisms have been proposed for this increased risk of AMI, including upregulation of von Willebrand factor through endothelial cell stimulation, enhanced plasma levels of clotting factors and fibrinogen, and decreased protein S levels. Interestingly, data from in vivo studies revealed that chronic administration of low-dose estradiol is associated with a pro-inflammatory state through direct activation of estrogen receptors on macrophages.

Fibromuscular dysplasia, a noninflammatory, nonatherosclerotic arteriopathy, is encountered in more than 40% of patients with SCAD, with the pathophysiology not fully understood. Young females have a predilection for SCAD as the cause of AMI, particularly during pregnancy, which might be explained by a combination of estrogen-mediated arteriopathy and physiological stress. Based on autopsy findings, the aortas of pregnant women are associated with reticulum fiber fragmentation, smooth muscle cell hypertrophy and hyperplasia, and decreased mucopolysaccharides.

Spontaneous coronary artery dissection is frequently underdiagnosed or misdiagnosed with angiography because it only visualizes the vessels along with the lack of physician familiarity with its different angiographic variants. Angiographic evidence of a dissection may not be visible with minimal intramural hematoma as in our patient. On the contrary, IVUS can provide insights into unique morphological features of SCAD such as double lumen morphology, intramural hematoma, and also superimposed thrombus. Initially, due to the angiographic findings of intracoronary thrombosis, SCAD was suspected as the cause of the ACS due to the patient’s age and sex. A definitive diagnosis of SCAD was only made after the application of IVUS.

Several cases have been reported regarding the development of SCAD in otherwise healthy young women taking oral contraceptives. Nevertheless, the co-occurrence of SCAD with a large intraluminal clot burden has been rarely reported. The guidelines for management of SCAD have yet to be established due to the lack of large randomized controlled trials. Conservative treatment is associated with good outcomes in most of the patients, as reported from observational studies. Intervention should be reserved for those with high-risk features including hemodynamic instability, ongoing ischemia, ventricular arrhythmias, or left main involvement as percutaneous coronary intervention is associated with risks of technical failure such as passage of wire into the false lumen and propagation of dissection.

Conclusion
Spontaneous coronary artery dissection is associated with considerable morbidity and mortality, largely due to its diagnostic difficulty. Clinical awareness is imperative to recognize the possibility of SCAD-related ACS. Although high-dose estrogen in oral contraceptives has now been linked with an elevated risk of arterial thrombosis, data regarding the association between low-dose estrogen and SCAD are lacking. Acute coronary syndrome in an otherwise healthy woman without traditional risk factors for coronary heart disease should raise the possibility of a SCAD, especially if the patient is using oral contraceptives.

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Ethics Approval
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Informed Consent
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References
1. Yip A, Saw J. Spontaneous coronary artery dissection—a review. Cardiovasc Diagn Ther. 2015;5(1):37-48.
2. Saw J, Aymong E, Mancini GB, Sedlak T, Starovoytov A, Ricci D. Nonatherosclerotic coronary artery disease in young women. Can J Cardiol. 2014;30(7):814-819.
3. Tweet MS, Hayes SN, Pitta SR, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. Circulation. 2012;126(5):579-588.
4. Zehir R, Karabay CY, Kocabay G. Myocardial infarction and spontaneous dissection of coronary artery due to oral contraceptive. J Cardiovasc Med (Hagerstown). 2011;12(6):448-450.
5. Evangelou D, Letsas KP, Korantzopoulos P, et al. Spontaneous coronary artery dissection associated with oral contraceptive use: a case report and review of the literature. Int J Cardiol. 2006;112(3):380-382.
6. Rahhal A, Khir F, Adam M, et al. Low dose combined oral contraceptives induced thrombotic anterior wall myocardial infarction: a case report. BMC Cardiovasc Disord. 2020;20(1):182.
7. Maleki M, Lange RL. Coronary thrombosis in young women on oral contraceptives: report of two cases and review of the literature. Am Heart J. 1973;85(6):749-754.
8. Morimont L, Haguet H, Dogné JM, Gaspard U, Douxfils J. Combined oral contraceptives and venous thromboembolism: review and perspective to mitigate the risk. Front Endocrinol (Lausanne). 2021;12:769187.
9. Roach RE, Helmerhorst FM, Lijfering WM, et al. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database Syst Rev. 2015;2015(8):CD011054.