DANGEROUS TRIPLET: POLYCYSTIC OVARY SYNDROME, ORAL CONTRACEPTIVES AND KOUNIS SYNDROME

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Abstract

Polycystic ovary syndrome is characterized by ovulatory dysfunction, androgen excess and polycystic ovaries and is associated with hypertension, diabetes, metabolic syndrome and cardiovascular events. Oral contraceptives constitute first-line treatment, particularly when symptomatic hyperandrogenism is present. However, these drugs are associated with cardiovascular events and hypersensitivity reactions that pose problem in differential diagnosis and therapy. We present a 14-year-old female with polycystic ovary syndrome taking oral contraceptive and suffering from recurrent coronary ischemic attacks with increased eosinophils, and troponin levels suggesting Kounis syndrome.

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Key words: Contraceptives; Eosinophils; Kounis syndrome; Polycystic ovary syndrome; Troponin

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a clinical disorder characterized by ovulatory dysfunction, androgen excess and polycystic ovaries. It is the most common endocrine disorder in the females of reproductive age, mostly presented with obesity, glucose intolerance, hyperinsulinemia, dyslipidemia and hypertension. The females with PCOS carry an increased risk of cardiovascular ischemic events independent of the obesity[5-8] with the prevalence of 4%-10%. In addition, the rate of occurrence of cardiovascular events in the 25-34-year-old female group with PCOS has been found to be 2.6%. Furthermore, therapy with combined oral contraceptives has been associated with both deep vein thrombosis and pulmonary embolism[9] as well as hypersensitivity reaction[10] that pose problems in differential diagnosis and treatment. We report a young...
14-year-old female patient with PCOS who was exposed to the above dangerous triplet and suffered from recurrent attacks of chest pain with high troponin levels and increased eosinophils while the coronary arteries were normal.

CASE REPORT

A 14-year-old female [56 kg, 160 cm, body mass index (BMI): 21.87 kg/m$^2$] attended the endocrinology outpatient clinic for PCOS due to hyperandrogenism, oligomenorrhea, and polycystic ovaries. She was referred to our pediatric cardiology clinic for recurrent chest pain attacks and the elevated cardiac enzymes while she was receiving intermittent contraceptive medication.

In her past medical history, the prenatal and perinatal periods were uneventful. There was no consanguinity between her mother and father. There was no cardiovascular disease or any other chronic disease history in her family. Her physical growth and psychomotor development were compatible with her age. However, her thelarche and genital hair growth started at the age of 7.5 years. This was not accompanied by any menstrual bleeding. The family brought her to endocrinology outpatient clinic where laboratory investigation showed high testosterone and cholesterol levels. Additional laboratory investigation for adrenal pathology revealed no abnormality. She was advised not to take any medication up to 14 years of age. At this age endocrinologists decided to put her on oral contraceptive (ethinyl estradiol + 0.03 mg drospirenone 3 mg combination) which resulted in menstrual bleeding. However, she could not use contraceptives regularly due to nausea, headache and loss of appetite. Three months later and while she was receiving intermittently the contraceptive therapy she experienced severe chest discomfort with skin itching lasting for 15 min and she was transferred to the emergency department. Serum creatine kinase muscle was 57 U/L (normal levels: 0-24) and the troponin level was 11.91 ng/mL (normal levels: 0-0.04). Her pulse was 100 beats per minute regular and electrocardiogram showed sinus rhythm, T wave inversion in lead III and flattening of T wave in lead left foot derivation in electrocardiography (Figure 1). Total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol levels were found to be 230 mg/dL, 290 mg/dL, 63 mg/dL, 108 mg/dL and 58 mg/dL, respectively. Eosinophils were also raised to 700/mm$^3$ (normal levels up to 500/mm$^3$). Chest radiography and echocardiography were also normal. Stress test, holter electrocardiogram and coronary computed tomography angiogram revealed no abnormality (Figure 2). The same clinical symptoms appeared while she was taking intermittently the contraceptive treatment and necessitating repeated hospital admissions, in approximately 1 or 2 mo intervals. At every hospitalization, repeated high sensitivity troponin levels and eosinophils were always elevated while the girl was feeling itchy. In view of the above findings we decided to change contraceptives to progesterone 5 mg and spironolactone 50 mg. After cessation of the oral contraceptive treatment, chest pain attacks disappeared despite taking the new medication. Biochemical tests, electrocardiogram (Figure 3), echocardiography, holter and repeated stress tests during the follow-up period of one year were all within normal limits. Cardiac enzymes and troponin returned to normal levels but eosinophils were still high (700/mm$^3$). We did not perform skin prick tests and patch tests to oral contraceptives on ethical grounds. She was characterized as an atopic individual and was advised to refrain the previous contraceptive medication.

DISCUSSION

The diagnosis of PCOS is difficult because of the heterogeneity of the phenotype. The classical phenotype is observed in 75% of PCOS cases and cardiovascular risk factors are most frequently encountered in this group. Because several features of PCOS may be in evolution in adolescents, it was suggested recently that only firm criteria should be used to make a diagnosis of PCOS during adolescence. These criteria include hyperandrogenism,
oligomenorrhea, and polycystic ovaries. Significant associations between PCOS and severity of cardiovascular diseases, family history of myocardial infarction as well as with elevated levels of insulin and triglycerides and lower levels of HDL-C have been reported[7]. Metabolic syndrome, type 2 diabetes, abdominal obesity and hypertension, are frequently observed in young patients with PCOS, which are factors associated with cardiovascular diseases. Our patient has had dyslipidemia with increased cholesterol and triglycerides. Oral contraceptives are used for the treatment of PCOS. Combined oral contraceptives containing drospirenone are preferred especially in the PCOS patients with hirsutism[8]. The risk of myocardial infarction and intracerebral events is 2.5% higher in the patients taking combined oral contraceptives containing low dose estrogen[9].

Our patient had no findings suggesting drug-related venous thromboembolism but she had chest discomfort associated with increased high sensitivity troponin levels and eosinophilia that suggested coronary event. Drug-related Kounis syndrome has been reported on several occasions[10]. In general, Kounis syndrome has an acute onset, but some subclinical cases have been reported[11]. Several mediators such as, cytokines and chemokines including histamine, neutral proteases, arachidonic acid products and platelet activating factor are released during the allergic episode. The same mediators are also involved in the acute coronary syndromes. Several drugs have been accused for triggering this syndrome. However, the only drug our patient took was oral contraceptive consisting of ethinyl estradiol and drospirenone. Allergy to oral contraceptive therapy has been already described on several occasions. Erythema multiforme limited to the oral mucosa was reported in

Figure 2 Normal computed tomography angiogram excluding thrombosis.

Figure 3 Normal electrocardiogram during cessation of contraceptive while the eosinophils were increased.
Patients with polycystic ovary syndrome who have to use oral contraceptives should be evaluated separately in terms of drug related cardiac events and hypersensitivity associated with Kounis syndrome.
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