

CASE REPORT

Acute myocardial infarction associated with clomiphene citrate in a young woman

Genç bir kadında klomifen sitrat ile ilişkili akut miyokart enfarktüsü

Şahin Avşar, M.D.,¹ Ahmet Öz, M.D.,² Aydan Köken Avşar, M.D.,³
Adnan Kaya, M.D.,⁴ Edibe Betül Börklü, M.D.⁵

¹Department of Cardiology, Urla State Hospital, İzmir, Turkey

²Department of Cardiology, Sultan Abdülhamid Han Training and Research Hospital, İstanbul, Turkey

³Department of Internal Medicine, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

⁴Department of Cardiology, Düzce University Faculty of Medicine, Düzce, Turkey

⁵Department of Cardiology, Dr. Siyami Ersek Cardiovascular and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Summary– Clomiphene citrate is a drug that stimulates ovulation and is commonly used in cases of female infertility. Generally, it is recognized as a safe agent for ovulation induction, but rarely, it is associated with life-threatening conditions. A 36-year-old woman who had been prescribed clomiphene citrate for infertility was admitted to the emergency department for chest pain lasting for 2 hours. She had no history of smoking, and she did not have any cardiac risk factor for myocardial infarction (MI). An electrocardiogram performed on admission revealed ST-elevation in the precordial leads. She was taken to the catheter laboratory for ST-elevation myocardial infarction, and the coronary angiography revealed total occlusion of the midportion of the left anterior descending artery (LAD) with a heavy thrombus burden. The circumflex and right coronary arteries were normal. After balloon dilatation, a 2.75x15-mm drug eluting stent was implanted in the mid part of the LAD. The patient had an uncomplicated recovery. Before discharge, echocardiography revealed apical akinesis; anterior and lateral hypokinesis; and an ejection fraction of 45% with mild mitral regurgitation. Although clomiphene citrate is a relatively safe drug for ovarian stimulation, it has been associated with serious side effects, such as MI. Physicians should be aware of the potential risks of clomiphene citrate, especially in patients with risk factors for coronary artery disease.

Özet– Klomifen sitrat ovülasyonu uyarmak için kadınlarda kısırlıkta yaygın olarak kullanılan bir ilaçtır. Genellikle, klomifen sitrat ovülasyonun uyarılması için güvenli bir madde olarak kabul edilir ancak nadiren yaşamı tehdit eden koşullarla ilişkili olabilir. Kısırlık için klomifen sitrat reçete edilen 36 yaşında kadın hasta iki saattir olan göğüs ağrısı nedeni ile acil servise başvurdu. Sigara içme öyküsü yoktu ve miyokart enfarktüsü (ME) için herhangi bir kardiyak risk faktörü mevcut değildi. Başvuru elektrokardiyografisinde prekordiyal derivasyonlarda ST yükselmesi saptandı. ST yükselmeli ME tanısıyla kateter laboratuvarına alındı ve koroner anjiyografide tromboz yükü fazla olan sol ön inen arterin (LAD) orta bölümünün tamamen tıkanmış olduğu görüldü. Sirkümfleks ve sağ koroner arterler normaldi. Balon dilatasyonundan sonra 2.75x15 mm ilaç salınımlı stent (DES) LAD'nin orta bölümüne yerleştirildi. Hasta komplikasyonsuz olarak iyileşti. Taburculuktan önceki ekokardiyografi apikal akinezi, anterior, lateral hipokinezi ve hafif mitral yetersizliği ile %45 ejeksiyon fraksiyonu saptandı. Klomifen sitrat yumurtalık uyarılması için nispeten güvenli bir ilaç olmasına rağmen, ME gibi ciddi yan etkilere neden olabilir. Hekimler özellikle koroner arter hastalığı için risk faktörü taşıyan hastalarda klomifen sitratın potansiyel riskinin farkında olmalıdır.

Clomiphene citrate is a selective estrogen receptor modulator agent; it is the most widely prescribed agent for ovulation induction.^[1] Clomiphene

citrate leads to the depletion of estrogen receptors at the level of the pituitary and the hypothalamus, interrupting the negative feedback normally produced

Received: June 04, 2017 Accepted: November 03, 2017

Correspondence: Dr. Ahmet Öz. Sultan Abdülhamid Han Eğitim ve Araştırma Hastanesi, Kardiyoloji Anabilim Dalı, İstanbul, Turkey.

Tel: +90 216 - 542 20 20 e-mail: drozahmet@gmail.com

© 2018 Turkish Society of Cardiology



by estrogen. As a result, gonadotropin-releasing hormone secretion is increased, which stimulates pituitary production of the follicle-stimulating hormone (FSH). FSH is associated with follicular growth and maturation upon the emergence of 1 or more dominant follicles.^[2]

Clomiphene citrate is considered a first-line treatment for ovulatory dysfunction because it is low cost, easily applicable, and has minimal side effects. The most frequent cardiovascular side effect is vasomotor flushes, which is observed in 10% of patients. Uncommon cardiovascular side effects are arrhythmias, chest pain, pulmonary edema, hypertension, palpitations, pulmonary embolism, shortness of breath, and thrombophlebitis.^[3]

The manufacturer has reported chest pain as a possible side effect, but there is no information about myocardial infarction (MI). Presently described is a case of acute ST-elevation myocardial infarction (STEMI) in a young woman who had been treated with clomiphene citrate for infertility.

CASE REPORT

A 36-year-old woman was admitted to the emergency department of Siyami Ersek Hospital for chest pain ongoing for 2 hours. She had no previous history of chest pain, no history of recent emotional or physical stress. She had never smoked, she did not have any cardiac

Abbreviations:

ACS	Acute coronary syndrome
DES	Drug-eluting stent
FSH	Follicle-stimulating hormone
LAD	Left anterior descending artery
MI	Myocardial infarction
SCAD	Spontaneous coronary artery dissection
STEMI	ST-elevation myocardial infarction

risk factor, and there was no family history of coronary artery disease. Treatment of ovulatory dysfunction with clomiphene citrate (50 mg once a day) had been initiated 5 days prior. On arrival to the emergency department, her blood pressure was 110/72 mm Hg and her heart rate was 87 bpm. A physical examination revealed normal jugular venous pressure and normal heart sounds, with no gallops or murmur. An electrocardiogram performed on admission indicated ST-elevation in the precordial leads (Fig. 1). The patient was taken to the catheter laboratory and coronary angiography revealed total occlusion of the midportion of the left anterior descending artery (LAD) with a heavy thrombus burden but there was no dissection of the LAD (Video 1*). The circumflex and right coronary arteries were normal. After balloon dilatation, a 2.75x15 mm drug-eluting stent (DES) was implanted in the mid part of the LAD (Video 2*) and the patient was taken to the coronary care unit. She was immediately treated with aspirin, unfractionated heparin, tirofiban, clopidogrel, metoprolol, ramipril, and atorvastatin. The patient had an uncomplicated recovery with no recurrence of chest pain. The maximal value of troponin was 50 ng/mL and was 347 U/mL for creatinine-kinase MB. Other laboratory results were within normal limits and a serum beta human chorionic gonadotropin test was negative. Serum tests for connective tissue diseases, systemic vasculitis, and hypercoagulable states were negative. Before discharge, echocardiography revealed apical akinesis; anterior, lateral hypokinesis; and an ejection fraction of 45% with mild mitral regurgitation. Clomiphene citrate was discontinued and she was discharged with aspirin, clopidogrel, metoprolol, atorvastatin, and ramipril treatment.

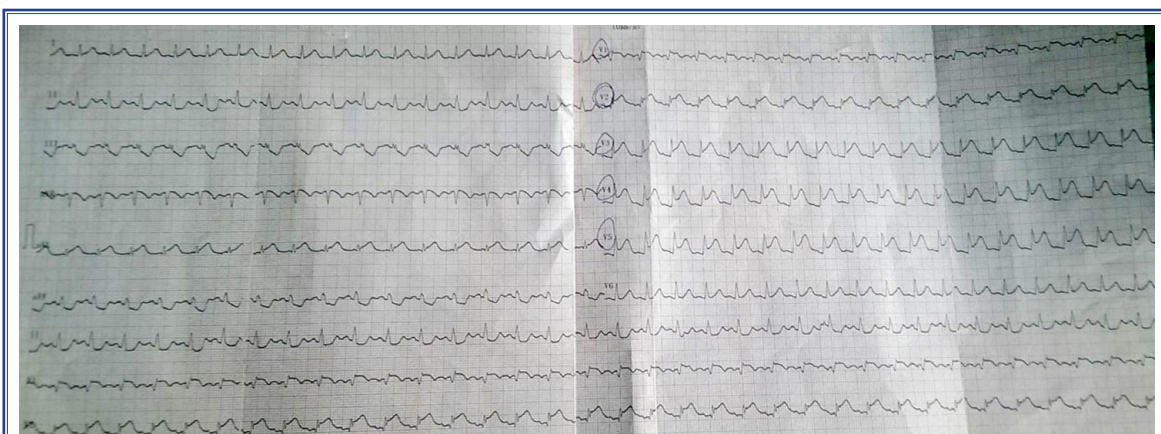


Figure 1. Admission electrocardiogram indicated acute anterior myocardial infarction.

DISCUSSION

STEMI in a young, healthy woman without significant traditional risk factors is very rare.^[4] However, STEMI has a significant rate of morbidity and mortality, and includes psychological effects and financial constraints for the patient and relatives, especially in young men and women. The causes of MI among patients younger than 45 years of age can be divided into 4 groups: atheromatous coronary artery disease, non-atheromatous coronary artery disease, hypercoagulable states, and MI related to drugs or substances.^[4]

The etiology of atheromatous coronary heart disease is linked to conventional (older age, family history of coronary heart disease, race) and modifiable (hypercholesterolemia, hypertension, diabetes mellitus, smoking, obesity, and mental stress) risk factors in adults.^[5] In this case, no conventional risk factors for MI were determined. Moreover, the coronary angiography didn't show any sign of atheromatous coronary artery disease.

Non-atheromatous coronary artery abnormalities include congenital coronary artery anomalies, myocardial bridging, and spontaneous coronary artery dissection (SCAD),^[5] but in this case, angiography did not reveal any coronary artery abnormalities or myocardial bridging. SCAD is defined as a tear in the coronary arterial wall that is not related to trauma or medical instrumentation. It is an important cause of acute coronary syndrome (ACS) in young women, responsible for up to 25% of all ACS cases in women under 50 years of age.^[6] The most commonly identified predisposing risk factors for SCAD are giving birth, fibromuscular dysplasia, and hormonal therapy.^[7] Although the clinical presentation in this case was similar to SCAD, there was no sign of coronary artery dissection on the coronary angiography. However, in some cases, further detailed imaging of the arterial wall with optical coherence tomography or intravascular ultrasound is required for a definitive diagnosis. Due to the emergency conditions in this case, these tests were not performed and therefore, SCAD was not completely excluded.

Another condition that must be taken into consideration is Kounis syndrome, which is characterized by a group of symptoms that manifest as unstable

vasospastic or non-vasospastic angina secondary to a hypersensitivity reaction.^[8] The mechanism of Kounis syndrome involves a release of inflammatory cytokines through mast cell activation, which leads to coronary artery vasospasm and atheromatous plaque rupture.^[9] Diagnosis of Kounis syndrome is based on clinical symptoms and signs as well as on laboratory, electrocardiographic, echocardiographic, and angiographic evidence. A variety of these findings might accompany allergic symptomatology.^[10] In the present case there were no systemic allergic reactions that would lead to a diagnosis of Kounis syndrome. Beta mimetic agents can cause coronary vasospasm in Kounis syndrome, but in our case, metoprolol was used safely and Kounis syndrome was excluded in our diagnostic schema.

Hypercoagulable diseases such as antiphospholipid syndrome are associated with recurrent arterial and venous thrombosis. It is often detected in young patients in the third or fourth decades of life. It can be primary or secondary, associated with other autoimmune diseases like systemic lupus erythematosus.^[5] Nephrotic syndrome and factor V Leiden mutation are associated with procoagulation and have been reported to have resulted in MI in young people.^[11] However, serum blood samples for connective tissue disease, systemic vasculitis, and hypercoagulable states were negative and these diagnoses were excluded in our case.

Several drugs and substances can cause chest pain or MI. One review included 130 reports of drug-induced chest pain and 53 reports of drug-induced MI.^[12] In a large trial, Coloma et al.^[13] found 163 drugs to be associated with an increased risk of MI in a preliminary screening, but they found 9 drugs definitely related to MI at the end of the study. Cocaine is the leading substance that can induce ACS through vasoconstriction, atheroma rupture, and dissection.^[14] In our case report, the patient had not used any illegal drugs; therefore this diagnosis was rejected.

No causal relationship between clomiphene citrate and acute MI has been established. Between January 2004 and October 2012, MI in 5 individuals taking clomiphene citrate was reported to the FDA.^[15] The mechanism of MI while using clomiphene citrate is not clear. Like many other hormonal agents, clomiphene citrate can cause hypercoagulation and it can slow the flow of blood. Overproduc-

tion of ovarian hormones and vasoactive substances are considered to be a cause of hypercoagulation. Thromboembolic complications of clomiphene citrate, including MI,^[16] pulmonary embolism,^[17] deep vein thrombosis,^[18] ischemic stroke,^[19] and central vein occlusion^[20] have been reported. Apart from clomiphene citrate, other agents utilized in ovarian stimulation have also been reported to be associated with MI.^[21,22] In the present case, clomiphene citrate use may have predisposed our patient to STEMI, or even precipitated STEMI.

Conclusion

Clomiphene citrate is considered to be safe for ovulation induction and to have minimal side effects. However, acute MI might be an uncommon but life-threatening complication of clomiphene citrate use. Physicians should be aware of the potential risk, especially in patients with associated risk factors for coronary artery disease.

**Supplementary video file associated with this article can be found in the online version of the journal.*

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Authorship contributions: Concept: Ş.A.; Design: A.K.; Supervision: E.B.B.; Materials: A.Ö.; Data collection: A.Ö.; Literature search: A.Ö., A.K.A.; Writing: Ş.A.

REFERENCES

- Hughes E, Brown J, Collins JJ, Vanderkerchove P. Clomiphene citrate for unexplained subfertility in women. *Cochrane Database Syst Rev* 2010;CD0000057. [CrossRef]
- Ekpo G, Moy I, Pavone ME, Milad MP. The use of clomiphene citrate for ovulation induction: When, why, and how? *Contemporary Ob/Gyn* 2011;56:42-52.
- Product information. Clomid (clomiphene). Hoechst Marison-Roussel Inc, Kansas City, MO.
- Lawal L, Lange R, Schulman S. Acute myocardial infarction in two young women without significant risk factors. *J Invasive Cardiol* 2009;21:E3-5.
- Egred M, Viswanathan G, Davis G. Myocardial infarction in young adults. *Postgrad Med J* 2005;81:741-5. [CrossRef]
- Saw J, Aymong E, Mancini GB, Sedlak T, Starovoytov A, Ricci D. Nonatherosclerotic coronary artery disease in young women. *Can J Cardiol*. 2014;30:814-9. [CrossRef]
- Saw J, Sedlak T, Ganesh SK, Isserow S, Mancini GB. Cardiology patient page. Spontaneous coronary artery dissection (SCAD). *Circulation* 2015;131:e3-5. [CrossRef]
- Kogias JS, Sideris SK, Anifadis SK. Kounis syndrome associated with hypersensitivity to hymenoptera stings. *Int J Cardiol* 2007;114:252-5. [CrossRef]
- Waller BF. Non atherosclerotic coronary heart disease. In: Fuster V, Wane Alexander A, O'Rourke RA, editors. *Hurst's The Heart*, 13th ed. New York: McGraw-Hill; 2010.
- Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med* 2016;54:1545-59. [CrossRef]
- Tanis BC, Bloemenkamp DG, van den Bosch MA, Kemmeren JM, Algra A, van de Graaf Y, et al. Prothrombotic coagulation defects and cardiovascular risk factors in young women with acute myocardial infarction. *Br J Haematol* 2003;122:471-8. [CrossRef]
- Ottvanger JP, Wilson JH, Stricker BH. Drug-induced chest pain and myocardial infarction. Reports to a national centre and review of the literature. *Eur J Clin Pharmacol*. 1997;53:105-10. [CrossRef]
- Coloma PM, Schuemie MJ, Trifirò G, Furlong L, van Mulligen E, Bauer-Mehren A, et al; EU-ADR consortium. Drug-induced acute myocardial infarction: identifying 'prime suspects' from electronic healthcare records-based surveillance system. *PLoS One* 2013;8:e72148. [CrossRef]
- Riezzo I, Fiore C, De Carlo D, Pascale N, Neri M, Turillazzi E, Fineschi V. Side effects of cocaine abuse: multiorgan toxicity and pathological consequences. *Curr Med Chem* 2012;19:5624-46. [CrossRef]
- Study of possible correlation between myocardial infarction and clomiphene citrate. Available at: <http://factmed.com/study-clomiphene%20citrate-causing-myocardial%20infarction.php>. Accessed Apr 24, 2018.
- Duran JR 3rd, Raja ML. Myocardial infarction in pregnancy associated with clomiphene citrate for ovulation induction: a case report. *J Reprod Med* 2007;52:1059-62.
- Chamberlain RA, Cumming DC. Pulmonary embolism during clomiphene therapy for infertility in a male: a case report. *Int J Fertil* 1986;31:198-9.
- Benshushan A, Shushan A, Paltiel O, Mordel N, Laufer N. Ovulation induction with clomiphene citrate complicated by deep vein thrombosis. *Eur J Obstet Gynecol Reprod Biol* 1995;62:261-2. [CrossRef]
- Inbar OJ, Levran D, Mashiach S, Dor J. Ischemic stroke due to induction of ovulation with clomiphene citrate and menotropins without evidence of ovarian hyperstimulation syndrome. *Fertil Steril* 1994;62:1075-6. [CrossRef]
- Lee VY, Liu DT, Li CL, Hoi-Fan, Lam DS. Central retinal vein occlusion associated with clomiphene-induced ovulation. *Fertil Steril* 2008;90:2011.e11-2
- Akdemir R, Uyan C, Emiroglu Y. Acute myocardial infarction secondary thrombosis associated with ovarian hyperstimula-

- tion syndrome. *Int J Cardiol* 2002;83:187–9. [\[CrossRef\]](#)
22. Girolami A, Scandellari R, Tezza F, Paternoster D, Girolami B. Arterial thrombosis in young women after ovarian stimulation: case report and review of the literature. *J Thromb Thrombolysis* 2007;24:169–74. [\[CrossRef\]](#)

Keywords: Acute myocardial infarction; clomiphene citrate; coronary artery; drug induced thrombosis.

Anahtar sözcükler: Akut miyokart enfarktüsü; klomifen sitrat; koroner arter; ilaçla bağlı tromboz.