CASE REPORT AND LITERATURE REVIEW

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A CASE REPORT: CERTOLIZUMAB-INDUCED KOUNIS SYNDROME

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Abstract

Kounis syndrome (KS) is an important condition to consider in patients who present with acute coronary syndrome and have a history of allergies or anaphylaxis. It is caused by an inflammatory response to an allergen or anaphylactic trigger that can lead to the narrowing or spasm of the coronary arteries and can result in myocardial infarction or angina. The case you presented is interesting because it suggests that tumor necrosis factor-alpha (TNF-α) inhibitors such as certolizumab can also trigger an allergic or anaphylactic reaction that can lead to KS. It highlights the importance of monitoring patients for potential allergic reactions to these medications and considering KS in patients who present with acute coronary syndrome after receiving these drugs. Further research is needed to better understand the link between TNF-α inhibitors and KS and to develop strategies to prevent and manage to this potentially life-threatening condition. In the meantime, it is important for healthcare providers to be aware of the potential risk and to take appropriate precautions when prescribing TNF-α inhibitors to patients with a history of allergies or anaphylaxis.

Keywords: Allergy, certolizumab, Kounis syndrome, percutaneous coronary angiography

INTRODUCTION

Kounis syndrome (KS) is defined as acute coronary syndrome or angina associated with inflammatory cells triggered by allergic or anaphylactic conditions. It is a life-threatening condition that can be triggered by any substance, including drugs, food, or environmental agents such as insect bites. KS is often overlooked and patients cannon get a diagnosis because it is a rare cause of acute coronary syndrome, although it is not a rare topic of medical literacy. TNF-α inhibitors are also a group of drugs that can cause an allergic reaction; thus, patients receiving these drugs should be monitored closely for the development of symptoms that may indicate KS (1,2). We present a case not previously described in the literature who presented to the emergency department with anaphylactoid symptoms after taking certolizumab and was diagnosed with acute coronary syndrome.

CASE REPORT

While being followed up for rheumatoid arthritis (RA), a 39-year-old female patient experienced mild redness in the application area after the first dose of 400 mg certolizumab was administered subcutaneously to the abdomen for therapeutic purposes. The patient left the hospital after being kept under observation for a while. On returning home, about an hour and a half after the application, the patient developed itching, dyspnea, and syncope. She then applied to the emergency room. Among the risk factors of the patient were drug allergy and a history of RA. Previously an allergic reaction in the form of urticaria was observed against methotrexate and leflunomide, and skin rash, sore throat, shortness of breath, and hypotension developed with tocilizumab. Although the patient did not experience any reactions with prednisolone, hydroxychloroquine, diclofenac

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sodium, flurbiprofen, and 500 mg paracetamol, she had a history of urticaria with 1000 mg paracetamol. During the emergency follow-up, chest pain developed in the form of pressure radiating to the left arm, blood pressure was 70/40 mmHg at this time. Normal sinus rhythm and negative t waves in leads V1-V2 were observed in the 12-lead electrocardiogram (ECG). Arrival troponin I was 2.8 (0-15.6). Considering systemic allergic reaction and anaphylactic shock, the patient was administered 80 mg methylprednisolone 45.5 mg pheniramine with intravenous fluid support and intramuscular adrenaline. Troponin I levels were 46.3 at the third-hour control and 95.3 at the six-hour follow-up. KS was considered, and it was deemed appropriate to continue the follow-up under intensive care conditions. Since there was no room in our center, the patient was transferred to another center that could meet her intensive care needs. In the ECG taken at the center to which she was referred, ST elevations of 0.5 mm in D1 and 1 mm in aVL, as well as ST depressions in D2, D3, and aVF have been observed (Figure 1). After local anesthesia, a needle was used to puncture the patient's right femoral artery, and an introducer sheath was placed. The right and left coronary arteries were visualized at appropriate projection angles using appropriate diagnostic catheters. The left main coronary artery (LMCA) was found to be normal, but plaques that did not cause significant stenosis were observed in the proximal left anterior descending artery (LAD) after the procedure. Thereafter, it was suspected that the patient had developed drug-induced type I KS. During the subsequent clinical follow-up, negative T waves were observed in V1-V3, and non-specific ST changes were observed in V4-V6 in the ECG. This state was considered as pseudonormalization and it supports the ischemia that occurred when the patient presented with chest pain to our clinic, and thus the diagnosis of KS as well (Figure 2).

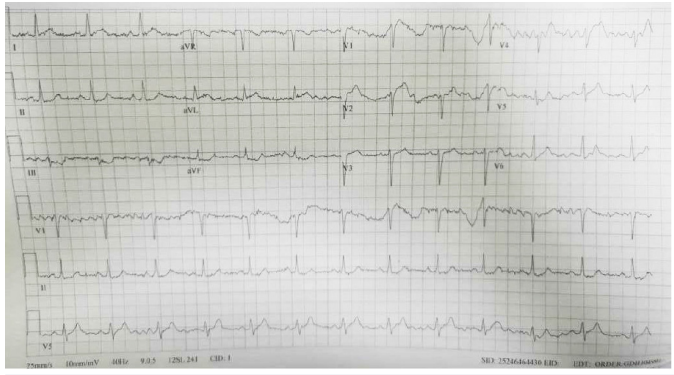

Figure 1. ECG showed ST elevations of 0.5 mm in D1 and 1 mm in aVL, as well as ST depressions in D2, D3, and aVF
ECG: Electrocardiogram

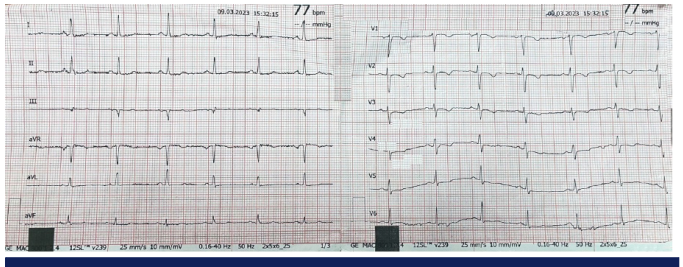

Figure 2. Negative T waves were observed in V1-V3, and non-specific ST changes were observed in V4-V6 in the ECG
ECG: Electrocardiogram

DISCUSSION

TNF-α inhibitors are used for treating rheumatological diseases such as RA, ankylosing spondylitis, and psoriatic arthritis, and the efficacy and safety of certolizumab for treating these diseases have been demonstrated. Certolizumab is a TNF-α inhibitor agent that does not contain the pegol Fc domain but instead contains polyethylene glycol, and it is approved for adult patients with moderately to severely active RA. To our knowledge, KS with certolizumab and other TNF-α inhibitors agents except infliximab has not been reported, whereas there have been rare reports of anaphylactic reactions to certolizumab (3). In an article prepared in the form of a letter to the editor in 2014, KS was suspected in 3 patients who were given follow-up infliximab for inflammatory bowel disease, but this has not been proven (4). Here we present our case, which we think is the first report of type I KS caused by certolizumab. Our patient was followed up with moderate RA and certolizumab treatment was started because an allergic reaction developed with conventional synthetic disease-modifying antirheumatic drugs that had been previously started. She applied to the emergency department with complaints that started an hour and a half after the first dose of the drug. Type I KS caused by certolizumab was considered due to the pressure-like angina lasting longer than 30 min and the observation of plaques that did not cause significant stenosis in the proximal LAD by percutaneous coronary angiography (PCAG) performed upon the significant gradual increases in troponin I during follow-up in the emergency department. Mast cell granules contain various mediators, particularly heparin and histamine, and also tryptase, chymase, carboxypeptidase, cathepsin C and G (5). KS is an acute coronary syndrome characterized by coronary artery spasm caused by these inflammatory mediators released into the environment as a result of endothelial dysfunction or mast cell degranulation with microvascular manifestation. This allergic angina syndrome caused by allergic reactions was first described in 1991 (6). Most cases (80%) occur within 1 h of exposure to the trigger. KS should be suspected in patients presenting with chest pain, shortness of breath, wheezing, and erythema. Three variants of KS have been described, the most common type I KS

(73%) developing coronary artery spasm without an underlying atherosclerosis. It occurs due to plaque erosion or rupture of type II (22%), seen in patients with pre-existing but asymptomatic coronary artery disease. Type III (5%) represents thrombosis due to an allergic reaction to the coronary stent (7). Risk factors include a previous history of allergies, diabetes, hypertension, dyslipidemia, and smoking. In clinically suspected patients, blood biochemical tests such as serum histamine, immunoglobulin E (IgE), eosinophils, tryptase, myocardial enzymes, and ECG and coronary angiography results support the diagnosis of KS. Tryptase, histamine, and IgE levels were not measured in our patient. However, a negative serum histamine level does not exclude the diagnosis of KS because serum histamine has a very short half-life of 8 min (8). In addition, the application of IgE levels in the diagnosis of KS is uncertain, and a normal IgE level does not exclude the diagnosis of KS (8). However, IgE levels may also be elevated in patients with acute coronary syndrome. Clinicians should carefully review the patients medical history, including medication use and allergic reactions critical to the diagnosis of KS. In this study, the diagnosis was suspected mostly based on the history and clinical findings. Treatment management for KS involves the management of allergic reactions and myocardial revascularization. Allergic reaction control with antihistamines and corticosteroids in patients with type I KS may also relieve cardiac symptoms (9). Existing vasospasm can be easily reversed by vasodilators. Fluid resuscitation is important in patients presenting with anaphylactic shock. The use of epinephrine may worsen myocardial ischemia and coronary vasospasm, prolong the QTc interval, and cause arrhythmias. In the type II variant, treatment should be initiated with an acute coronary event protocol in addition to antihistamines and corticosteroids (10). However, morphine, which is widely used in acute coronary syndrome, should be used with caution because of its mast cell degranulation effect and because beta-blockers have unmet alpha-adrenergic effects (7). Treatment management in type II and type III KS includes timely PCAG. In this study, PCAG was performed because of persistent angina, a significant increase in troponin values in repetitive measurements, and ST depression in D1-AVL in ECG. Plaque that did not cause significant stenosis was detected in the proximal LAD; therefore, type I KS is considered. Vasospastic angina occurred one and a half hours after the administration of certolizumab, followed by an increase in troponin levels. No case of KS triggered by either the other TNF-α inhibitors is as etanercept, adalimumab, golimumab, or certolizumab has been reported to date. Regarding another TNF-α inhibitors, infiliximab, there were three suspicious case reports in the form of letters to the editor, but these have not been proven (4). Therefore, our case is important. Allergic reactions can be seen with TNF-α inhibitors, especially infiliximab, and patients may present with various presentations of these reactions. As a result, KS is not very rare but perhaps often overlooked. It is important to perform the necessary tests for diagnosis, especially in patients who present to the emergency department with shortness of breath and angina and who have a history of exposure to environmental agents such as insect bites and drug use before symptoms and KS should be kept in mind in these cases. In these patients, cardiac findings and allergic symptoms should be treated immediately. Therefore, considering the disease first and then confirming the diagnosis and appropriate treatment management can be lifesaving.

Ethics

Informed Consent: Informed consent was obtained from our patient included in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.D.K., B.N.C., R.T.Ö., Y.P., Concept: N.D.K., Design: N.D.K., Data Collection or Processing: N.D.K., R.T.Ö., Analysis or Interpretation: N.D.K., B.N.C., Literature Search: N.D.K., Y.P., Writing: N.D.K., B.N.C.

Conflict of Interest: The authors have no conflicts of interest to declare.

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