Clinical Oncology: Case Reports

Case Report

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Carboplatin-Induced Allergic Coronary Vasospastic Reaction (Kounis Syndrome)

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Abstract

We describe a case of carboplatin-induced allergic coronary vasospastic reaction manifesting as ST-elevation myocardial infarction (Kounis syndrome) in a 67-year old male with lung adenocarcinoma and underlying ischemic heart disease. Shortly after commencing his 2nd carboplatin cycle, the patient presented with acute bronchospasm and hemodynamic collapse, anterolateral ST-elevations, elevated cardiac biomarkers and apical akinesia. Following initial management with high-dose steroids, a coronary angiography was performed demonstrating obstructive lesion in his left anterior descending artery which was treated with percutaneous coronary intervention and stent placement. The patient demonstrated significant clinical improvement. This case highlights the diagnostic work-up and management of patients with chemotherapy-induced Kounis syndrome which should be included in the differential diagnosis of patients with chemotherapy-induced chest pain or ACS.

Keywords

Kounis syndrome; Carboplatin; Myocardial infarction; Anaphylaxis

Abbreviation

ACS: Acute Coronary Syndrome; hs-cTnT: High Sensitive Troponin T; NT pro-BNP: N-terminal Pro-Brain Natriuretic Peptide; PCI: Percutaneous Coronary Intervention; RCA: Right Coronary Artery; TTE: Trans-thoracic echocardiogram

Case Presentation

A 67-year-old male, past smoker, was diagnosed in January 2018 with metastatic lung adenocarcinoma. Past medical history was significant for ischemic heart disease and Percutaneous Coronary Intervention (PCI) to the Right Coronary Artery (RCA) in 2010 and bladder transitional cell cancer in 2008 with complete remission after local surgical management. For his stage IV non-small cell lung cancer, he was first treated with carboplatin/pemetrexed and bevacizumab for four cycles with partial response, followed by consolidation radiotherapy to the right thorax and mediastinum as his disease was considered oligo-metastatic. Owing to disease progression, the patient was treated with immunotherapy as 2nd line (pembrolizumab) and an investigational 3rd line Her2 kinase inhibitor (poziotinib) within a clinical trial. In September 2020, due to disease progression in the form of adrenal and retroperitoneal metastases, he was re-challenged with carboplatin and pemetrexed, which he had previously received uneventfully with good oncologic outcome.

On September 23rd 2020, the patient was admitted to the Oncology Ambulatory Care Unit to receive his second treatment cycle of carboplatin. Several minutes after commencing the drug infusion, the patient presented with acute respiratory distress which has rapidly deteriorated to apnea with hemodynamic collapse (non-invasive blood pressure measurement 70/40 mmHg). Telemetry monitoring demonstrated sinus tachycardia of 150 beats/minutes. On physical examination, lung auscultation revealed diffused bilateral wheezing, yet cutaneous rash was not evident. As the leading working diagnosis was chemotherapy-induced anaphylaxis, carboplatin infusion was terminated and 300 mg intravenous hydrocortisone was administrated along with advanced cardiac life support protocol. Remarkedly, and before the administration of adrenaline, the patient had rapidly stabilized with full respiratory and hemodynamic recovery. Regaining consciousness, the patient complained of new-onset crushing chest pain. A 12-lead electrocardiogram revealed anterior (V2-V6) ST-segment elevation with evidence of old inferior myocardial infarction (Figure 1A). A bedside Trans-Thoracic Echocardiography (TTE) exam demonstrated a segmental anterolateral hypokinesis with moderately-reduced left ventricular global function (in contrast to his baseline TTE study which was significant only for mild LV systolic dysfunction with inferior regional hypokinesis). Main differential diagnosis at this point was Type 1 or Type 2 acute myocardial infarction (either due to carboplatin-induced coronary vasospasm or hypotensive supply-demand mismatch) versus Takotsubo's cardiomyopathy. The patient was emergently taken to the cardiac catheterization laboratory and was found to have an obstructive lesion in his middle left anterior descending artery along with a significant stenosis of the left-main artery (Figure 1B). He was treated with PCI to both coronaries with a good angiographic result, followed by symptomatic and electrocardiographic resolution. Treatment with dual anti-platelet therapy was initiated. Initial laboratory evaluation demonstrated

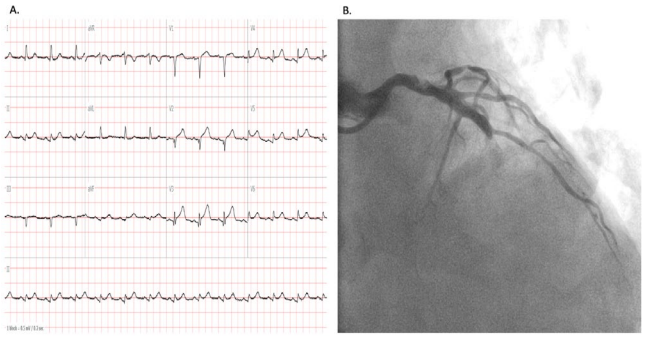

Figure 1: Patient's ECG and coronary angiography on presentation; A) Patient's 12-lead ECG on presentation showing anterior ST-elevation myocardial infarction; B) Coronary angiography demonstrating ostial ulcerated plaque in distal left main, diffuse proximal non-obstructive atherosclerosis in proximal left anterior descending artery and a cut off 100% in middle left anterior descending artery (culprit lesion); Abbreviations: ECG; electrocardiogram.

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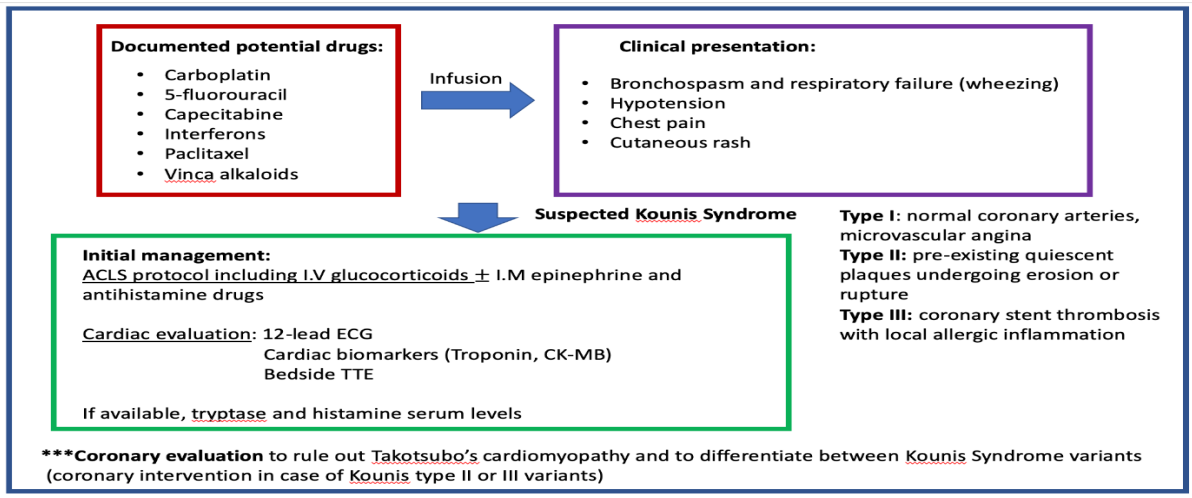

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high-sensitivity cardiac troponin (hs-cTnT) level of 86g/L (normal 0-14 ng/L) and N-terminal pro B-type natriuretic peptide (NT pro-BNP) level of 180pg/ml (normal adjusted for age and sex <249 pg/ml). Peak cardiac biomarkers levels were: hs-cTnT level 4940 ng/L and NT pro-BNP level of 3633 pg/ml.

The patient was discharged home after a 1-week hospitalization. Follow-up TTE study demonstrated apical hypokinesia with moderate left ventricular global dysfunction. Chemotherapy with pemetrexed alone was resumed uneventfully.

Discussion

Although chemotherapy-induced allergic reactions are common, their presentation as Acute Coronary Syndrome (ACS) is infrequent. We describe here a case of carboplatin-induced Type II Kounis syndrome and acute ST-elevation myocardial infarction in a patient with underlying coronary artery disease.

Kounis Syndrome is an ACS caused by an allergic (anaphylactic or anaphylactoid) reaction to drugs or other substances. Three types of Kounis Syndrome have been described [1]: Type I which occurs in patients with normal or nearly-normal coronary arteries and represents a form of microvascular angina with or without elevation of cardiac biomarkers; Type II which manifests in atherosclerotic arteries where the vasospastic reaction damages pre-existing stable quiescent plaques leading to erosion or rupture and thus acute myocardial infarction; Type III which manifest as coronary stent thrombosis with local allergic inflammatory reaction. The pathogenesis of Kounis Syndrome is attributed to the vasospastic effect of mast cell degranulation on the coronary smooth muscle, and the release of various inflammatory mediators such as histamine, neutral proteases, platelet activating factor and arachidonic acid derivatives [1,2].

Platinum-based drugs are frequently prescribed in various cancer-treatment protocols such in the treatment of lung, ovarian, testicular and endometrial cancers. More than 40 specific systemic side-effects including hypersensitivity reactions have been linked to this family of drugs [3,4]. Cardiotoxicity following the administration of platinum-based drugs has been clinically manifested with brady-or tachy-arrhythmias, left ventricular systolic and diastolic dysfunction and coronary ischemia [4,5]. The pathophysiology of platinum-based coronary artery disease is most probably multifactorial and includes promotion of pro-coagulable state and arterial thrombosis and direct endothelial toxic effects [5]. Moreover, over the last two decades, there have been several reports of coronary vasospasm after infusion of platinum-based compounds presenting as Type I Kounis Syndrome [6-10]. We present here a case of a patient with Type II Kounis syndrome manifesting angiographically as ruptured atherosclerotic plaque with an occlusive thrombotic lesion. Other anti-neoplastic drugs which have also been associated with the Kounis syndrome are 5-fluorouracil, capecitabine, interferons, paclitaxel and vinca alkaloids [1].

The diagnosis of the Kounis syndrome is based on the combined clinical picture of systemic allergic reaction accompanied by ACS and its diagnostic findings (Figure 2) in an appropriate drug exposure scenario. Measurement of tryptase and histamine serum levels may be helpful, although practically limited by their very short half-lives [1]. Importantly, being a hypersensitivity reaction, the occurrence of Kounis syndrome is not dose-dependent and may arise at any time during treatment [10]. The management of Kounis syndrome targets both its cardiac and allergic components, while acknowledging potential therapeutic contradictions. Although intravenous corticosteroids and antihistamine drugs are useful in controlling the allergic response, and while calcium channel blockers and nitrates can effectively treat coronary vasospasm, the use of aspirin and beta-blockers are potentially detrimental due to their mechanisms of action that involve cyclooxygenase inhibition and unopposed action of alpha-adrenergic receptors, respectively. Patients with Kounis type II variant should be managed by current ACS guidelines along with the rapid administration of corticosteroids and antihistamines.

Conclusion

In conclusion, a hypersensitivity coronary vasospastic reaction should be included in the differential diagnosis of patients with

chemotherapy-induced chest pain or ACS. Accordingly, a targeted clinical evaluation for systemic hypersensitivity signs and symptoms (such as cutaneous rash and pulmonary wheezing) along with ACS diagnostic protocol should be employed.

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