



Letter to the Editor

Kounis syndrome in a patient with ovarian cancer and allergy to iodinated contrast media: Report of a case

Vasospastic angina induced by chemotherapy

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Abstract

We report the case of a 71-year-old woman with previous coronary angioplasty, ovarian cancer with multiple metastases and allergy to iodinated contrast media, who developed vasospastic angina after several treatments with cisplatin and cyclophosphamide, so that we considered this as a case of “allergic angina” or Kounis syndrome (type II variant). The patient underwent standard anti-ischemic therapy with nitrates, calcium blocking agents and enoxaparin so having an uneventful outcome.

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1. Introduction

The syndrome of “allergic angina” was reported in 1991 by Kounis and Zavras as the occurrence of chest pain and allergic reaction caused by inflammatory mediators such as histamine or leukotrienes released during allergic insult [1–3]. Cancer patients have an increased propensity to develop acute hypersensitivity reactions to various chemotherapeutic agents, some of which can induce vasospastic angina and allergic myocardial infarction [4]. We report the case of a 71-year-old woman with previous coronary angioplasty and affected by ovarian cancer with multiple metastases and allergy to iodinated contrast media, who developed severe vasospastic angina after several treatments with cisplatin and cyclophosphamide. She was administered standard anti-ischemic

therapy with nitrates, calcium-blockers and low molecular weight heparin so obtaining an uneventful outcome.

2. Case report

A 71-year-old-woman was admitted to our Hospital for scheduled chemotherapy with cisplatin and cyclophosphamide. Her medical history was consistent with lung tuberculosis treated with artificial pneumothorax, chronic obstructive pulmonary disease, systemic hypertension and previous ST elevation (STEMI) inferior myocardial infarction treated with primary coronary angioplasty without residual Q waves on the electrocardiogram. On this occasion she was also found affected by allergy to iodinated contrast media. Twelve years before admission to the hospital she had been found affected by bilateral ovarian adenocarcinoma infiltrating the uterine wall, with peritoneal metastases. She had therefore been operated on of hysterectomy with bilateral oophorectomy and submitted to six cycles of chemotherapy with cisplatin and carboplatin.

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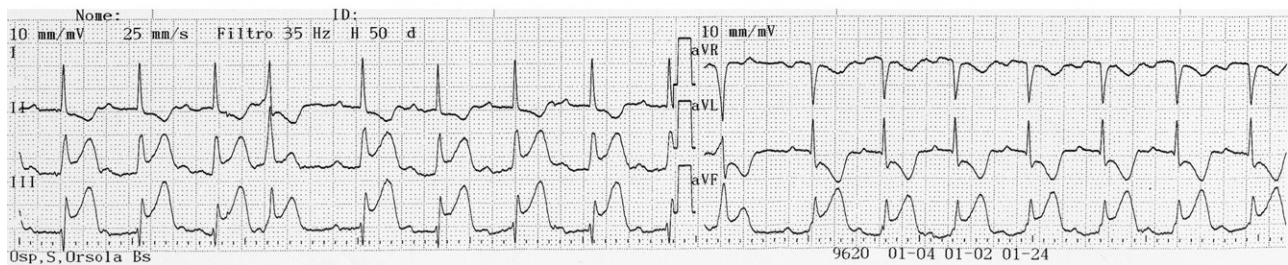


Fig. 1. Spasm related ST elevation in the inferior electrocardiographic leads.

Owing to recurrent manifestations of the disease, in the year 2002 she underwent eight more cycles of chemotherapy with taxol and carboplatin, followed by laparotomy which showed infiltration of the rectum, bladder and vagina. In the year 2004 she underwent seven more cycles of therapy with taxol and carboplatin but this drug had to be withdrawn for allergic reaction. In the year 2005 left colectomy with colostomy was performed for tumoral infiltration of the colon wall by the ovarian cancer. In the year 2007 the patient was treated with topotecan. In the following months she developed a small pericardial effusion without tamponade. Some months later she was again admitted to the outpatient clinic to undergo chemotherapy with cisplatin and cyclophosphamide. After the second administration of these drugs she developed intense chest pain with clammy skin, hypotension and tachycardia. The electrocardiogram showed ST elevation in the inferior leads with premature beats (Fig. 1). The patient was therefore transferred to our coronary care unit and treated with intravenous infusion of nitrates, calcium channel blockers by oral route and subcutaneous enoxaparin, under heart rate and blood pressure monitoring. Rapid regression of symptoms and of ST elevation were observed. The serum cardiac T-troponin was repeatedly controlled every six hours for the first day and three times a day for the following two days, always resulting in the normal range.

The transthoracic echocardiography performed on the second day showed normokinesia of all wall segments and a normal ejection fraction. Since the patient was doing well with standard therapy, after extensive discussion it was decided that a coronary arteriography should not be performed, for the reported previous allergic reaction to contrast media. Six months after this episode the patient is always doing well without any recurrent chest pain.

3. Discussion

In 1991 Kounis and Zavras described the “syndrome of allergic angina” as the coincidental occurrence of chest pain and allergic reactions caused by the release during allergic insults of inflammatory mediators such as histamine or leukotrienes acting on coronary vascular smooth muscle [1]. Allergic angina can progress to acute myocardial infarction which was named “allergic myocardial infarction” [2,3]. Today both allergic angina and infarction are referred as “Kounis syndrome” two variants of which are recognized.

Type I includes patients with normal coronary arteries in whom allergic mediators induce either coronary spasm with normal troponin level, or coronary spasm progressing to acute myocardial infarction. Type II coronary spasm occurs in patients with pre-existing atheromatous disease in whom allergy can induce plaque erosion or rupture manifesting as an acute myocardial infarction [3,5]. It is almost certain that the majority of cases of unstable angina and acute infarction are the result of combined coronary artery spasm and atheromatous plaque erosion or rupture followed by thrombus formation [3].

Elevated plasma levels of histamine concentration were found by Sakata in patients with variant angina [6], and it was demonstrated that patients with acute coronary syndromes of non-allergic etiology have more than twice the blood concentration of histamine than normal subjects [7]. Moreover, in a clinical study 40% of patients with spontaneous angina developed chest pain with ST elevation after infusion of histamine [8]. Also, arachidonic acid metabolites such as thromboxane and leukotrienes have been found significantly higher in the acute stage of non-allergic myocardial infarction than in normal controls [9]. There is evidence that inflammatory cells infiltrate lesions before erosion or rupture occurs and are not part of inflammatory response to rupture initiated by another process [3], so that an “allergic” mechanism can perhaps be hypothesized also in normal subjects, the mechanism being more pronounced in those who have an allergic substrate. Indeed, susceptible individuals expressing a magnified mast cell degranulation effect may be per se more vulnerable to coronary artery spasm and plaque erosion or rupture [4]. This topic is an important one since patients affected by ischemic heart disease receiving stent implantation can be prone to hypersensitivity reactions from five potential antigens, namely nickel strut, polymer coating, eluted drug, clopidogrel and aspirin [10]. Some hypersensitivity cases have indeed been associated with implantation of drug eluting coronary stents [11–13] and between them a case of intra-stent thrombosis in a subject with allergy to larvae of fly *carvaria* [14].

On the other hand Kounis syndrome has also been associated with tako-tsubo syndrome [15,16] and with many other anecdotal clinical conditions such as viper bite or hymenoptera sting [17–20], administration of some drugs like penicillin [4,21], amoxicillin [22], diclofenac sodium

[23], rocuronium [24], mesalamine [25], proton pump inhibitors like lansoprazole [26], and even aspirin [27].

Cancer chemotherapy has also been associated with vasospastic angina [28–33]. Indeed our patient, who had previously been reported allergic to iodinated contrast media, developed allergic angina and coronary vasospasm after therapy with cisplatin and cyclophosphamide. In this patient overt allergic reaction was not evident during her recent admission. However, intracoronary mast cell activation induced by the antineoplastic medication might have released histamine, arachidonic acid metabolites, as well as a variety of cytokines, chemokines, and platelet-activating factor leading to local coronary artery spasm. In her case the clinical outcome was favourable with administration of nitrates, calcium blockers and subcutaneous low molecular weight heparin, without administration of anti-allergic drugs. Indeed, even though inhibition of leukotriene pathway by corticosteroids or mast cell membrane stabilizing agents could be considered as a potential therapeutic strategy [34], no definite guidelines still exist, so that we preferred a classical therapy scheme.

Some conclusions can be drawn from the present case: the first is that patients with allergy to contrast media could be prone to coronary vasospasm as consequence of their allergic substrate at least in some occasions. Secondly, vasospastic angina on an allergic basis can be successfully treated with conventional anti-ischemic drugs, at least until new therapeutic strategies are developed. Therefore, if the response to intensive pharmacological treatment is prompt and efficacious, it is possible to avoid a repeat and urgent coronary angiography and the administration of potentially dangerous iodinated contrast media in such allergic patients.

4. Conclusion

Vasospastic angina can be an ominous consequence of predisposition to allergic reactions in some patients. Owing to the actual more prolonged survival to cancer and the widespread use of chemotherapy regimens that can imply allergy, this possibility should be borne in mind for patients with a history of both cardiac and neoplastic disease. Conventional anti-ischemic therapy in these patients can presently still be considered enough satisfactory and efficacious.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [35].

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