Case report

Arterial stiffness, endothelial dysfunction and recurrent angina post-chemotherapy

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Learning Point for Clinicians

This case highlights the mechanisms of predicted angina pectoris several days after multi-drug chemotherapeutic regimen for relapsed multiple myeloma. Physicians should recognize that cumulative chemotherapy could exacerbate both arterial stiffness and endothelial dysfunction and result in transiently frequent coronary vasospasm even with clinically permissible doses of vincristine–adriamycin–dexamethasone chemotherapy or thalidomide.

Case history

In April 2006, a 61-year-old male without coronary risks was referred to our cardiology department because of severe chest oppression 7 days after vincristine–adriamycin–dexamethasone chemotherapy (VAD) for relapsed multiple myeloma. In July 2003, he was diagnosed with multiple myeloma IgA lambda (Durie-Salmon stage IIIA), and received three monthly cycles of VAD, stem cell mobilization with cyclophosphamide and melphalan-based autologous peripheral blood stem cell transplantation. In June 2005, he started thalidomide 200–300 mg daily for a relapse of myeloma. Afterwards, he experienced resting chest discomfort lasting several minutes in July 2005, and severe chest squeezing and syncope in November 2005. After withdrawing thalidomide, his symptoms disappeared. In April 2006, he was re-admitted to our hospital and resumed the fourth cycle of VAD because of re-elevated serum levels of IgA.

Physical examination was unremarkable except for severe perspiration. Electrocardiogram showed transient remarkable ST-segment elevation (6 mm) in leads of I, aVL and V3–6, which persisted for several minutes and rapidly disappeared with sublingual administration of nitroglycerin. Cardiac troponin T was normal. Echocardiography was normal, and iodine-123-beta-methyl iodophenyl-pentadecanoic acid imaging demonstrated a decreased uptake in the middle inferior wall compared to thallium-201 myocardial perfusion imaging. Coronary arteriogram revealed no significant organic stenoses; however, acetylcholine provocation test revealed diffuse subtotal occlusion in proximal left anterior descending and circumflex arteries with ST-T changes and chest oppression (Figure 1). We therefore diagnosed with multivessel coronary vasospasm. The diagnostic criteria for Crow-Fukase/polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes syndrome, sometimes reported with ischemic heart disease, were not fulfilled. He reattempted with the fifth cycle of VAD. On days 5–10, he developed similar symptoms more frequently and earlier than previous cycles. Severe attacks accompanied by transient ST-segment elevation in various leads concentrated on days 6–8. During the sixth cycle of VAD, chest symptoms reappeared extensively on days 6–9 even after...
Figure 1. Coronary angiography revealing significant diffuse stenosis of left coronary artery after 100μg of intracoronary acetylcholine infusion. (A) Control and (B) Ach 100μg.

Figure 2. (A) Changes in baPWV during VAD chemotherapy. The halftone area demonstrates the continuous infusion periods of ISDN 0.25 mg/h because of frequent heart attacks. (B) Serum levels of circulating cytokines on day 1 (before chemotherapy), 4, 8 and 11. (a) NOx, (b) thrombomodulin, (c) high molecule adiponectin, (d) soluble ICAM-1 (e) nitrotyrosine and (f) TGF-β.
administration of benidipine, atorvastatin, ethyl icosa-
sapentate and aspirin.

**Discussion**

Chemotherapy-mediated ischemic syndromes are rarely reported, caused by fluorouracil, capecitabine, cisplatin, carboplatin, interferone-alpha, taxanes, bevacizumab, vinca alkaloids, sorafenib and erlotinib. Vincristine-induced ischaemia is possibly caused by coronary spasm. To elucidate the mechanisms of coronary vasospasm, we investigated the time course of changes in brachial-ankle pulse wave velocity (baPWV) and serum levels of circulating cytokines to compare with chest symptoms (Figure 2). The arterial stiffness measured by baPWV was gradually elevated after VAD and temporarily decreased during continuous infusion of isosorbide dinitrate on days 6–9 because of frequent vasospasm, whose dynamics was consistent with the frequency of symptom. Cytokine survey showed that the lowest NOx, the highest thrombomodulin as a marker of endothelial damage, the lowest high-molecule adiponectin and the lowest ICAM-1 known to reflect endothelial function on day 8 when frequent vasospasm occurred. Serum levels of nitrotyrosine, a product associated with reactive oxygen species (ROS), gradually elevated and peaked on days 8 and 11. Serum levels of TGF-β, a suppressor of endothelial proliferation, transiently elevated on day 4 just after VAD, and returned to baseline on days 8 and 11. Finally, he had a more favorable clinical course after receiving bortezomib, a first-in-class proteasome inhibitor.

We speculated the reasons why frequent vasospasm regularly occurred on days 6–8 after fourth to sixth cycles of VAD were as followed: cumulative chemotherapy-induced endothelial damage had already existed, endothelium-dependent vasodilation was attenuated by inactivation of endogenous NOx, ROS derived from chemotherapy made the endothelial cell integrity open and directly injured endothelium gradually and the influence on cell cycle led repair of endothelium to delay. Not only VAD but thalidomide was thought to have the similar mechanism in chest symptoms.

**Acknowledgement**

We thank Dr Masafumi Kitakaze with regard to selection of cytokines in this case.

**Conflict of interest:** None declared.

**References**


