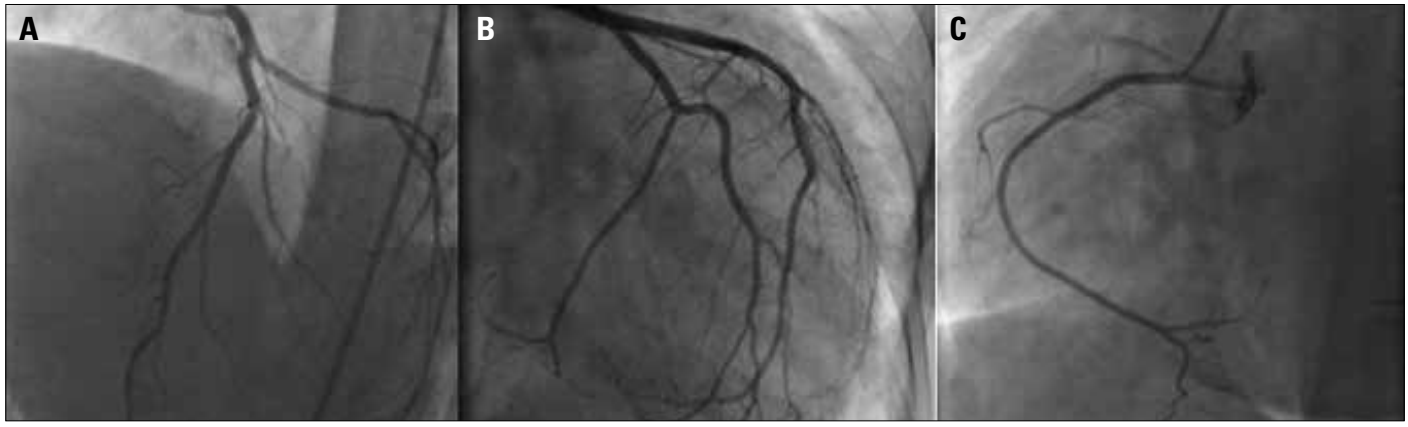

Figure 2. A-C. Coronary angiography showing normal coronary arteries

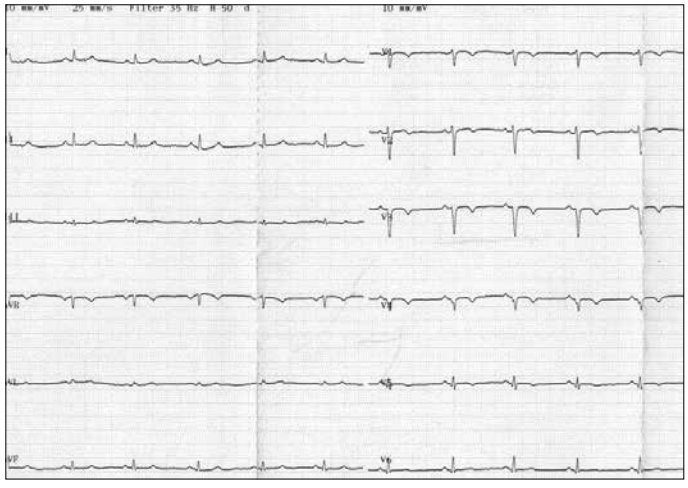

Figure 3. 12-lead ECG showing symmetrical T wave inversions in V_{1-4}, and loss of R waves in V_{1-4} consistent with anterior myocardial infarction

missense mutation leading to high homocysteine levels and mildly increased risk of thrombosis (8).

Conclusion

Our cases support the hypothesis that inherited thrombophilias increase the risk of arterial thrombosis in young individuals with hypercoagulable states as in pregnancy (9-10). Although there is no evidence for routine screening of hereditary thrombophilia in pregnancy, high risk gravidas should be in close follow-up for development of thromboembolic events including MI.

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Cardiac tamponade in a patient treated by sunitinib for metastatic renal cell carcinoma

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Introduction

Sunitinib is an oral, multi-targeted receptor tyrosine kinase inhibitor (TKI). Based on current data, sunitinib is now one of the preferred drugs

for first-line treatment of metastatic renal cell carcinoma (RCC). However, sunitinib may cause various cardiotoxic side effects. Herein, we report a case of cardiac tamponade in a RCC patient treated by sunitinib and discuss the cardiovascular toxicity of sunitinib.

Case Report

A 55-year-old male patient was admitted to Istanbul University, Institute of Oncology outpatient clinic due to macroscopic hematuria and loin pain. He had no history of hypertension, ischemic heart disease or diabetes. Ultrasound imaging detected bilateral renal masses and, left radical nephrectomy and surrenalectomie with right partial nephrectomy was performed. Pathological evaluation revealed bilateral RCC. Six months after the operation, multiple lung metastases were developed and interferon alfa 3 times per week was initiated. Patient was followed up with stabile response. One year afterwards, computed tomography (CT) examination demonstrated both progression of lung metastases, local recurrence in left retroperitoneal area and solitary brain metastasis in supratentorial area with prominent edema. Total cranial radiotherapy was administered 30 Gy in 10 daily fractions, after switching to sunitinib (37.5 mg/day) treatment. Pulmonary metastases and local soft tissue lesion were followed up with partial response under sunitinib treatment for about 1 year. During this period, serum creatinine level remained within 1.2-1.5 mg/dL limits and hypothyroidism was not detected.

While the patient was still receiving sunitinib treatment, he was admitted to emergency department with deteriorating exertional dyspnea and bilateral pretibial edema. Physical examination revealed tachycardia and pulsus paradoxus. Myocardial infarction was excluded by cardiac enzyme testing and electrocardiogram displayed reduced QRS voltages on both precordial and extremity leads. Two-dimensional echocardiography revealed a coexisting massive pericardial effusion with right atrial and ventricular diastolic collapse and pericardial tamponade. Ejection fraction was within normal limits. The patient underwent subxiphoid pericardiocentesis and a total of 2700 mL serous pericardial effusion was drained. Cytologic analysis of pericardial fluid demonstrated reactive mesothelial cells; Gram and Ziehl-Nielsen stains and cultures were negative. Although cardiac tamponade related with sunitinib was not reported in the literature before, for a patient without any history of cardiovascular disease and hypothyroidism, after exclusion of other metabolic and infectious etiologies leading to this clinical situation, drug effect was the only explanation. Besides, after cessation of sunitinib, the patient's symptoms improved with a decrease in exertional dyspnea. Echocardiography was performed 1.5 months later and mild to moderate pericardial effusion was determined. Since then, sunitinib was initiated again with a reduced dose of 25 mg/day and three weeks later, patient was again admitted with complaint of dyspnea. Echocardiography was repeated and, signs of recurrent cardiac tamponade were determined. A total of 2200 cc serous effusion was drained with pericardiocentesis and pericardial biopsy was performed which did not demonstrate any sign of malignancy. We concluded that cardiac tamponade was associated with sunitinib treatment; therefore the drug was discontinued.

Discussion

Increased understanding of RCC biology has led to the development of targeted agents that block proliferative, activated tumor pathways and changed the RCC treatment paradigm in the past 5 years (1, 2). The efficacy of sunitinib on metastatic RCC has been confirmed in randomized trials, where it was shown to improve the median progression free survival, yield a higher objective response rate (3, 4). However, cardiotoxic side effects of sunitinib such as heart failure, left ventricular dysfunction, conduction abnormalities, QT prolongation, acute coronary syndromes, myocardial injury and hypertension are not very rare (5, 6).

The pathogenic mechanism of sunitinib-induced cardiovascular toxicity remains poorly understood. One possible explanation may be due to hypoxia-inducible factor (HIF) which plays an important role in renal carcinogenesis. HIF-1-related gene products are also physiologic mediators of myocardial response to acute or chronic ischemia and myocardial remodeling. As HIF-1 levels are diminished upon tyrosine kinase inhibition, it is rational to assume that TKI-associated cardiotoxicity become more prominent (7, 8). In addition, loss of pericytes around microvessels in sunitinib-treated hearts has been demonstrated in vascular beds that lead to pericardial fluid accumulation via increased vascular permeability (9). Sunitinib also inhibits multiple receptor tyrosine kinases including platelet derived growth factor B (PDGFR B) which has a special function in angiogenesis and maintenance of tissue interstitial fluid pressure. Thus, inhibition of PDGFR B by sunitinib may contribute to increased risk of pericardial effusion (10). Besides, hypersensitivity or immune-mediated reaction to sunitinib rather than fluid reaction, as seen in other TKI-treated cases may be the reason of pericardial effusion (6).

Conclusion

Phase III trials regarding TKI efficiency have not pursued cardiac end points and the identification of cardiac adverse effects was predominantly based on the occurrence of clinical symptoms. So, cardiac damage from TKI treatment is largely underestimated and careful cardiovascular monitoring of these patients is necessary.

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