The spectrum of 5-fluorouracil cardiotoxicity

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Cardiotoxicity is a rare but serious complication of 5-fluorouracil therapy. Coronary vasospasm and, less frequently, acute myocarditis have been identified as underlying mechanisms. We report a case of severe toxicity in a relatively young and fit male patient being treated for metastatic colonic adenocarcinoma displaying characteristics that cannot be explained by either mechanism alone. ***Anti-Cancer Drugs*** **20:79–80 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Background

5-Fluorouracil (5FU) belongs to the antimetabolite class of chemotherapy agents and is very widely used in the treatment of gastrointestinal, pancreatic, breast, bladder and prostatic cancers. It interrupts the cell cycle by interfering with DNA synthesis through the inhibition of the enzyme thymidylate synthase in cancer cells ultimately causing cell death. Cardiotoxicity is a rare but serious complication of 5FU therapy which was first reported in 1975 [1]. The most frequently described manifestations have been ischaemia related, a phenomenon that is attributed to coronary vasospasm [2]. However, there are growing reports of 5FU-induced nonischaemic cardiomyopathy suggesting that 5FU can also cause myocarditis [3–8]. We report an extremely severe case that we believe is the first to display characteristics indicating that both of these mechanisms of toxicity were involved in the same presentation.

Case report

A 54-year-old man recently diagnosed with colonic adenocarcinoma and liver metastases was admitted for his first course of 5FU, folinic acid and oxaliplatin chemotherapy. He had no significant medical history, no cardiovascular risk factors and had recently completed a half marathon. Twenty hours into the infusion he developed sudden onset, intermittent, crushing central chest pain radiating to his jaw, associated with nausea, sweating and dyspnoea. He was haemodynamically stable and the only abnormality on clinical examination was mild bilateral basal crepitations on auscultation of his lung fields. ECGs during pain revealed lateral ST elevation with reciprocal change alternating with intermittent left bundle branch block. Emergency coronary angiography revealed normal coronary arteries and troponin I was raised at 4.07. Echocardiography revealed a markedly dilated left ventricle (LV) with global systolic dysfunction and no regional wall motion abnormalities with an ejection fraction of 30%. He was observed in the coronary care unit and his symptoms settled; however, the next day he suffered a sustained run of torsade de pointes deteriorating into three episodes of ventricular fibrillation from which he was successfully resuscitated and stabilized with intravenous amiodarone. Serum electrolytes at that time were normal. Definitive medical management consisted of amiodarone, ramipril and metoprolol, his rhythm remained stable and he was discharged home 6 days later. Follow-up echocardiogram 2 months later revealed normal cardiac dimensions and LV systolic function. His chemotherapy regimen was safely switched to the specific thymidylate synthase inhibitor raltitrexed, as has previously been described in this situation [9], with no further complications and the left bundle branch block pattern on the ECG resolved completely after 4 months.

Literature review

Coronary spasm became the most widely reported mechanism of 5FU cardiotoxicity after early descriptions of anginal symptoms and ischaemic ECG changes [2]. This prompted in-vitro [10] and, more recently, in-vivo [11] studies that confirmed vasospastic properties of 5FU. Two cases reporting direct visualization of coronary artery spasm at coronary angiography after 5FU-induced chest pain established vasospasm as the mechanism underlying 5FU cardiotoxicity [12,13]. Increasing reports depicting symptoms and characteristics in keeping with an acute nonischaemic dilated cardiomyopathy, however, called into question the role of vasospasm as the sole mechanism of toxicity [3–6]. These are cases of cardiogenic shock in patients with no cardiac history and normal LV function undergoing 5FU therapy. In no case was there a history of chest pain or objective evidence of myocardial ischaemia. One patient died [4]

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but complete recovery and restoration of LV function was seen in the others following periods of inotropic support. Two further reports describe similar presentations coupled with a histological diagnosis: one from a postmortem [7] and one from an endomyocardial biopsy [8]. Both revealed marked inflammation with vacuolization of myocytes similar to that seen in doxorubicin-induced myocarditis. A study in rabbits has recently confirmed that 5FU can induce a diffuse myocarditis, that is, with subendocardial sparing and therefore not in a pattern consistent with infarction as well as vasospasm-related myocardial infarction. These were seen to often coexist at postmortem histology [14].

Discussion

This case is notable for a number of reasons. First, the degree of the severity of toxicity is striking, especially with regard to the degree of LV dilatation and systolic dysfunction given the relatively short exposure time and the age and premorbid fitness of the patient. Second, the presenting symptoms and investigation findings cannot be explained either by coronary spasm or by myocarditis alone. The episodic ischaemic type of chest pain accompanied by autonomic symptoms and dynamic ischaemic territorial ECG changes are compatible with episodes of coronary spasm. The global nature of the profound LV systolic dysfunction that is not confined to the coronary territory implicated by the ECG, along with the gross acute LV dilatation, which subsequently normalizes is, however, in keeping with an independent, nonischaemic dilated cardiomyopathy.

Conclusion

5FU can cause coronary vasospasm and is also, less commonly, capable of inducing severe myocarditis leading to an acute nonischaemic dilated cardiomyopathy. With this case we are seeing for the first time these pathologies coexisting in the same presentation. Heightened awareness of the potential severity and the diversity of possible presentations of 5FU cardiotoxicity is required. If suspected, 5FU therapy should be immediately withdrawn with prompt assessment of LV function, characterization of the nature and degree of any myocardial ischaemia and careful monitoring. Ascertaining which patient subgroups are prone to cardiotoxicity, and why, would help to ensure that 5FU is used more safely with greater benefit to patients.

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