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Letters

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5-Fluorouracil Cardiotoxicity: A Unique Mechanism for Ischaemic Cardiopathy and Cardiac Failure?

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5-FLUOROURACIL (5FU) cardiotoxicity has been widely reported since the initial report on the subject [1], involving myocardial ischaemia, arrythmias and congestive heart failure. Ischaemic cardiopathy is the most common manifestation of this toxicity, with an incidence of around 3% [2]. More recently, cases of cardiac failure have been reported [3–6] but the connection between these two forms of cardiotoxicity are unclear [7]. We report the first observation of 5FU toxicity whose initial manifestation was cardiac failure, with subsequent ischaemic symptoms when 5FU was resumed. This original observation prompts a reappraisal of the suspected mechanism of cardiotoxicity.

A 16-year old girl was admitted to our ICU for acute pulmonary oedema following 5FU infusion. Six days before admission, she started a chemotherapy regimen containing from days 1 to 4: 5FU 700 mg/m^2/day, bleomycin 12 mg/m^2/day and corticosteroids 1 mg/kg/day, and then epirubicin 70 mg on day 5 and cisplatin 100 mg/m^2 on day 6, for undifferentiated carcinoma of nasopharynx, stade IIIc. Two days before admission, she complained of coughing, haemoptisis and chest pain but no changes were observed on ECG. At the time of admission, chest X-ray revealed cardiothoracic ratio enlargement (0.55) with bilateral pleural effusion and diffuse alveolar syndrome. Creatine phosphokinase and lactate deshydrogenase enzymes were normal. The ECG remained unchanged. Haemodynamic measurements via a swan ganz catheter showed a high wedge pressure (23 mm Hg) and a low cardiac index (21/mn/m^2). Echocardiography confirmed left cardiac failure with a dilated hypokinetic left ventricle and a shortening fraction (SF) of 25%. Response to dobutamine, nitrate and furosemide was excellent, and all symptoms resolved within 4 days with a SF rising to 34%. Given the good antitumour response, the same chemotherapy regimen was resumed 2 weeks later under careful monitoring. Thirty-six hours after its initiation, angina pectoris occurred with T-wave inversion on ECG. Cardiac enzymes remained normal. Cardiac function was normal at that time, both clinically and at echocardiography. Serological analyses for cytomegalovirus, coxsackie, B and C hepatitis, HIV, chlamydiae and mycoplasma were negative. With supportive therapy, chest pain aborted, and 5FU was therefore eliminated in the following cycles. No cardiac symptom occurred during the subsequent courses, and echocardiography remained normal. Six months later, after completion of chemotherapy and local radiotherapy, this patient is in complete remission of her disease, without any cardiac symptom.

5FU is one of the most common drugs used in oncology, especially in squamous cell carcinomas, primarily adenocarcinomas (breast, colon etc...) and gynaecological tumours. Systemic toxicities have been described since its introduction in 1957 [8]. The main toxicities are myelosuppression, gastrointestinal, cutaneous and cerebelar manifestations.

Since 1975, 5FU cardiotoxicity has been reported as ischaemic manifestations [1], with an incidence ranging between 0.82% [9] and 8% [10], and a lethality rate between 12.5% [11] and 28.5% [7]. Moreover, electrocardiographic changes have been reported to be as high as 68% when Holter monitoring is performed [12]. Risk factors for cardiac events have been identified but continue to be discussed. Age, a previous history of coronary disease, the chemotherapy regimen (high dose intravenous infusion [13]), past or concomitant radiation exposure involving the heart [14], or ionic imbalances of potassium or magnesium induced by cisplatin [9] could potentiate 5FU-related cardiotoxicity. The pathophysiological mechanism of this toxicity is still unclear. The ischaemic manifestations seem to be related to coronary spasms [15] since printzmetal angina is the most common clinical feature and coronary angiogram is usually normal. This hypothesis is strengthened by our observation because of the age and the lack of past record in our patient. However, provocative tests using methylergometrine are not convincing. Other mechanisms have been proposed, such as 5FU thrombogenicity, increased oxygen consumption, decreased fractional oxygen extraction, changes in mitochondria, immunoallergic pathways and impurity in 5FU vials [16–18].

More recently, several cases of cardiac failure have been reported [3–6], with various degrees of severity from hypotension to severe congestive heart failure. After interruption of 5FU and intensive cardiac treatment, cardiac failure resolved completely in a few days in all patients. Such a clinical presentation has been compared with the Stunned Myocardial Syndrome [6, 19]. The pathophysiological pathway of this new clinical presentation remains unclear as does that of the ischaemic attacks. It has been linked to 5FU myocardial accumulation in rats [20] and to direct myocardiotoxicity in guinea pigs, probably due to the 5FU degradation compound, 5-fluoroacetate [21].

To our knowledge, this is the first observation of 5FU reintroduction after 5FU-induced cardiac failure. Such a re-

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introduction of 5FU after a cardiac failure episode has never been reported to lead to coronary spasms. This observation supports the hypothesis that a single pathophysiological mechanism could explain 5FU cardiotoxicity in terms of both ischaemic symptoms and cardiac failure. Our hypothesis is that 5FU might be responsible for coronary spasms, either proximal and localised with chest pain and ischaemic manifestations, or distal and global with cardiac failure, with or without chest pain. In this hypothesis, coronary spasms could be the common mechanism for all cardiac symptoms. More data are required to determine if prevention of coronary spasms could reduce the incidence of such manifestations.

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Severe 5-Fluorouracil Toxicity Possibly Secondary to Dihydropyrimidine Dehydrogenase Deficiency in a Breast Cancer Patient with Osteogenesis Imperfecta

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DIHYDROPYRIMIDINE DEHYDROGENASE (DPD) is the initial and rate-limiting enzyme in the uracil and thymine catabolism. DPD is also the principal enzyme involved in the degradation of the chemotherapeutic drug 5-fluorouracil, which acts by inhibiting thymidylate synthase. The clinical importance of DPD has recently been demonstrated with the identification of rare cases of a severe toxicity in patients with suspected or proven DPD deficiency [1, 2]. We report here a case of severe 5-FU toxicity related to DPD deficiency in a patient with concurrent congenital osteogenesis imperfecta (OI). A 45-year-old woman with phenotypic OI type I (multiple fractures since childhood, blue sclerae, hearing loss, normal stature) was treated with neoadjuvant chemotherapy for a stage II breast cancer. Familial history failed to find any previous case of tumour or OI. She received a first cycle of mitoxantrone 19 mg on day (d)1, cyclophosphamide 900 mg d1 and d8, 5-FU 900 mg d1, 3, 5, 8. By day 16, she was hospitalised with the following symptoms: fever, stupor, and WHO grade 4 diarrhoea and stomatitis. Biological tests demonstrated serious leucopenia (0.300 leucocytes/μl) and thrombopenia (31 000 platelets/μl). The patient defervesced on antibiotic therapy. She slowly improved and was discharged on day 30. She received a second course with reduced doses of mitoxantrone (14 mg d1) and cyclophosphamide (600 mg d1 and d8) and omission of 5-FU. The induced toxicity was mild with grade 2 neutropenia. Lymphocyte DPD activity, determined by a radioenzymatic assay using ^{14}C-5FU as substrate, was extremely low: 85 pmol/min per mg of protein, similar to other case reports of major toxicity with 5-FU. In fact, a close analysis of these few cases [1] revealed that, in these patients who developed severe 5-FU-related toxicity, lymphocyte DPD activity was always below 100 pmol/min/mg/protein. A population study of DPD performed on 185 unselected cancer patients [3] shows a median lymphocytic DPD activity value at 211 pmol/min/mg protein (range 65–559); 3% of this population exhibited a DPD activity below 100 pmol/min/mg protein. The incidence of OI

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