Silent hereditary hematochromatosis as a susceptibility factor of doxorubicin-induced acute cardiac failure

A healthy (no specific medical past) 40-year-old Caucasian male with metastatic leiomyosarcoma was treated by doxorubicin (60 mg/m² for 3 weeks) plus dacarbazine. His left ventricular function (LVEF: 68%) and hemoglobin level were normal (12.4 g/dl) at baseline. After the second cycle (total dose of doxorubicin: 120 mg/m²), he presented with a febrile neutropenia without documented infection. He experienced a dyspnea and lower limbs edema that were thought to be related to a severe anemia (6.4 g/dl). Transferrin saturation was 84% (normal value < 66%) and the serum ferritin was 1200 μg/l (normal value < 300 μg/l). Symptomatic treatment consisted of large-spectrum antibiotics and red blood cells transfusion. Under treatment, the fever rapidly disappeared but the dyspnea and the lower limbs edema persisted beyond the anemia correction. Two months after the baseline assessment, echocardiography revealed a dramatic drop out of the LVEF (38%). Further symptomatic treatment (diuretic and conversion enzyme inhibitor) alleviates the cardiac symptoms; however, LVEF remained definitely altered. Regarding the iron overload and the unexpected acute cardiotoxicity, we suspected underlying hereditary hemochromatosis (HH) and proposed a genetic testing. The patient was HFE C282Y homozygote, the most common form of HH seen in Europe. The patient died 10 months later of tumor progression, after two further lines of chemotherapy (gemcitabine and trabectedin).

HH affects about 1 of 200 Caucasians and is less frequent in other ethnic groups. HFE gene mutations (especially, the C282Y and H36D mutations) are the most common forms. The revealing symptoms are arthritis (chondrocalcinosis), asthenia (liver dysfunction, diabetes and hypothyroidism) and cardiomyopathy [1]. Ultimately, lethal complications such as cirrhosis and hepatocarcinoma may be seen. Early diagnosis, familial screening and venesection limit the occurrence of severe complications.

Doxorubicin is a large-spectrum anticancer drug, characterized by its potential acute and chronic cumulative cardiotoxicity. The production of reactive oxygen species during its intracellular metabolism drives its cytotoxic effect. Doxorubicin and ferric iron complexes are transformed in superoxide anion and hydroxyl radicals that cause lipid peroxidation and DNA damage, especially in cells accumulating numerous mitochondria, such as cardiac cells. The iron overload exacerbates this cytotoxic effect, and HFE-deficient mice exhibit significant greater sensitivity to doxorubicin-induced cardiotoxicity compared with wild mice [2].

Regarding the frequency of HH, we advocate a screening of iron overload before doxorubicin administration. In case of elevated ferritinemias, preventive strategies regarding anthracycline administration are possible, such as replacement by less cardiotoxic drugs or the use of iron chelators as cardioprotectant.

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references

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