Letter by Belge et al Regarding Article, “Mitomycin-Induced Pulmonary Veno-Oclusive Disease: Evidence From Human Disease and Animal Models”

To the Editor:

We read with great interest the article by Perros et al., which reported mitomycin C (MMC)–induced pulmonary veno-occlusive disease (PVOD) in patients displaying anal squamous cancer and in a rat preclinical model.

We would like to share our experience with 2 more patients with pulmonary hypertension related to MMC exposure who did not show radiological evidence of PVOD. It concerns a 59-year-old man with an anal carcinoma and a 53-year-old woman with an anorectal spinocellular carcinoma. Both were treated by radiochemotherapy (MMC plus 5-fluorouracil) and developed dyspnea on exertion within 4 years and 1 year. Echocardiogram showed increased systolic pulmonary arterial pressure, right ventricular dilatation and dysfunction, and D-shaped septum, with preserved left ventricle function. In both patients, right heart catheterization showed elevated mean pulmonary arterial pressure (38 and 53 mm Hg), normal pulmonary arterial wedge pressure (6 and 5 mm Hg), and low cardiac index (2.02 and 1.19 L/min/m²). Percutaneous saturation was 87% at room air, and 92% with 15 L/min O₂, respectively. Pulmonary embolism was excluded by ventilation/perfusion scintigraphy. High-resolution computed tomography did not reveal any emphysema, interstitial lung disease, pleural effusion, centrilobular ground-glass opacities, or septal lines. Pulmonary function tests showed normal spirometry and lung volumes, but low diffusion capacity for carbon monoxide (25% predicted) in the 59-year-old man; pulmonary function tests could not be performed in the 53-year-old woman because of severe hypoxemia and the need of high-flow oxygen. Both displayed clubbing. They did not present any BMPR2 mutation. The 59-year-old man received an endothelin receptor antagonist and improved clinically. The 53-year-old woman was started on intravenous epoprostenol with initial favorable evolution, and oxygen was decreased to 2.5 L/min; unfortunately she died 6 months later because of septic cardiogenic shock.

At first instance, the quasi-normal high-resolution computed tomography could suggest drug-induced pulmonary arterial hypertension (PAH), similar to anorexigen-, interferon-, or dasatinib-induced PAH, because (1) recovery of MMC-induced PAH under endothelin receptor antagonist therapy had been recently reported and (2) patients with PVOD had typical radiological abnormalities on high-resolution computed tomography (pleural effusion, centrilobular ground-glass opacities, or septal lines). However, severe hypoxemia, low diffusion capacity for carbon monoxide, the presence of clubbing previously observed in PVOD patients, the identification of 16 cases of PVOD induced by cyclophosphamide, another chemotherapeutic alkylating agent, and the 7 cases of MMC-induced PVOD from the French registry described by Perros et al. led us to conclude on the diagnosis of MMC-induced PVOD rather than drug-induced PAH in the 2 presently reported cases.

Consequently, we confirmed the recent finding published in Circulation, ringing the alarm on the possible development of PVOD secondary to the use of chemotherapeutic alkylating agents, including MMC, emphasizing the possible presentation as PAH in the absence of radiological signs of PVOD. Considering that PVOD has a poor prognosis and does not respond well to PAH drugs, we encourage increased awareness of physicians for this rare complication of MMC therapy.

Disclosures

None.

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References


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