SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2024; 41 (2): e2024012 DOI: 10.36141/svdld.v41i2.15479

Bleomycin-induced pulmonary hypertension: an underrated phenomenon with important implications in the setting of high-risk clinical scenarios

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To the editor,

Bleomycin has been regarded as a widely used chemotherapeutic agent potentially associated with pulmonary toxicity that mostly presents with parenchymal interstitial changes (1,2). It exerts its antineoplastic effects through formation of reactive oxygen radicals primarily leading to oxidative DNA damage (2). Pulmonary tissue is particularly susceptible to bleomycin-induced damage due to its low content of hydrolase enzyme that accounts for bleomycin inactivation (2). Importantly, this form of pulmonary toxicity may be strongly augmented in the setting of hyperoxia, and may even emerge in the form of more serious conditions including acute respiratory distress syndrome (ARDS) in certain patients (1). The recent report by Jayakrishnan B, et al. (1) has described successful perioperative management of a young male patient with documented pulmonary changes associated with bleomycin use (1). Accordingly, we would like to underscore further aspects of pulmonary toxicity associated with bleomycin use:

In clinical practice, bleomycin, besides its association with pulmonary interstitial changes, is also renowned for its potential to trigger pulmonary hypertension (PHT) largely through endothelial dysfunction, formation of reactive oxygen species and associated hyperinflammation (3,5). However, most clinicians only focus on bleomycin-induced interstitial changes on pulmonary imaging, and generally ignore the potential association of bleomycin with PHT evolution. Based on the latest consensus, PHT is defined as a mean pulmonary arterial pressure value of > 20 mm Hg in cardiac catheterization (at rest) generally arising in a precapillary or postcapillary (or both) pattern due to various clinical conditions (3,4). PHT due to bleomycin therapy may be regarded as a form of precapillary PHT usually in association with pulmonary parenchymal changes (3). Notably, PHT in the general context of pulmonary interstitial disease might, to some extent, be regarded as an active phenomenon associated with direct involvement of the pulmonary vascular bed, and hence; should not be labeled as an entirely passive phenomenon solely attributable to hypoxic vasoconstriction and vascular obliteration in the affected pulmonary regions (5). In other terms, involvement of vascular structures in the intact pulmonary parenchyma is also quite likely in various forms of pulmonary interstitial disease (5). Based on these notions, the presence and degree of PHT may not be correlated with the extent of pulmonary parenchymal changes in patients treated with bleomycin (5). Importantly, an existing PHT (and its severity) in the presence of bleomycin-induced interstitial disease may serve an independent prognostic factor (5), and hence should be carefully handled particularly in the setting of

Received: 5 November 2023
Accepted: 5 December 2023
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high-risk conditions including major surgery for the improvement of perioperative outcomes including pulmonary edema, cardiac arrest, etc.

Notably, PHT associated with chemotherapeutic agents (including tyrozine kinase inhibitors, interferons) may be considered as a form of drug-induced PHT (a subcategory of group-1 PHT), and may be fully reversible particularly when diagnosed in its early stages (3). On the other hand, long-standing PHT might be partly reversible or irreversible upon cessation of the culprit chemotherapeutic agent (3). This may indicate further tests including pulmonary vasoreactivity test in an effort to determine the type of vasodilator strategies for the management of PHT (calcium channel blockers versus relatively novel modalities including endothelin receptor blockers (ERBs), etc.) (3). However, bleomycin-induced PHT is mostly regarded as a form of group-3 PHT (PHT associated with pulmonary disease) rather than drug-induced PHT (3). Of note, pulmonary vasoreactivity test has a limited value, and is not routinely indicated in the setting of group-3 PHT (4,6). Moreover, novel modalities including ERBs, guanyl cyclase activators, etc.) may do more harm than good (including ventilation-perfusion mismatch) potentially precluding their use in patients with group-3 PHT (5,6). Interestingly, use of inhaled treprostinil (a prostacyclin analogue) was recently reported to confer promising results in this context (6). Taken together, we wonder whether the patient also suffered bleomycin-induced PHT and associated cardiac changes as demonstrated on echocardiogram (or cardiac catheterization). Was the PHT (if any) of the patient reversible, partly reversible or irreversible following the cessation of bleomycin ? Did the authors initiate any vasodilator therapy ? We also wonder about the schedule of surveillance for their patient after discharge (frequency of visits, further tests, etc).

Importantly, since co-existing PHT in patients with bleomycin-induced interstitial disease might denote a state of severe vascular involvement (5) potentially accompanied by enhanced microvascular permeability, it might serve as an additional risk factor for the perioperative evolution of ARDS (that might be particularly intensified by excessive fluid use and oxygen toxicity, etc.(1)) in these patients. On the other hand, over-restriction of oxygen therapy leading to subnormal oxygen saturations (largely due to the clinician's fear of ARDS evolution in high risk patients) may further augment bleomycin-induced PHT (as a consequence of reactive arterial vasoconstriction and enhanced vascular resistance in response to hypoxia (5,7)), and hence warrants close monitoring of pulmonary arterial pressure on echocardiogram in the perioperative setting. However, the best strategy is to avoid both excessive use (1) and over-restriction of oxygen therapy in this context.

In summary, the present case report by Jayakrishnan B, et al. (1) may be considered as a clinical epitome describing successful perioperative management of a challenging case with bleomycin-induced pulmonary toxicity. However, clinicians should also focus on bleomycin-induced PHT (and its mitigation) (3,5) that might further aggravate clinical outcomes particularly in the setting of high-risk conditions including major surgery. This warrants early diagnosis (preferably in the preoperative setting in patients undergoing major surgery) and proper management of bleomycin-induced PHT for the improvement of clinical outcomes in this context.

Acknowledgements: None.

Conflict of Interest: None.

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