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Bleomycin-induced lung injury following intralesional sclerotherapy for vascular malformation

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ABSTRACT

The objective is to describe the presentation, evolution, and treatment of a child who presented with acute lung injury secondary to intralesional sclerotherapy with bleomycin for a venous malformation. The patient was a 4-year-old boy with a venous vascular malformation in his left lower limb, treated with percutaneous sclerosis with bleomycin (0.46 mg/kg). In the immediate postoperative period, he developed acute respiratory failure. During his evolution, pulmonary injury secondary to bleomycin was suspected. He received treatment with intravenous corticosteroids, oral corticosteroids, and supportive measures. At one year of follow-up, he was clinically stable and breathing adequately, although imaging studies showed persistent parenchymal involvement.

This case reports a rare but serious complication of percutaneous bleomycin treatment. It highlights the need to maintain a high index of suspicion for acute respiratory symptoms, even at low doses, to enable timely diagnosis and treatment.

Keywords: *acute lung injury; bleomycin; sclerotherapy; vascular malformations; pediatrics.*

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INTRODUCTION

Bleomycin is a cytotoxic agent that causes cell death through free radicals. Due to its sclerosing effect, it is used to treat vascular malformations.[1,2]

Pulmonary toxicity associated with its use as a chemotherapeutic agent is a known complication, especially with cumulative doses >400 mg or single doses >30 mg/m^2.[2,3-5]

As a sclerosing agent, bleomycin is recognized as a safe drug with a low incidence of adverse events and serious complications.[1,6] However, isolated cases of acute pulmonary toxicity have been reported in previously healthy children following its administration for this purpose.[7-10] The recommended dose for these procedures is 0.5 to 1 mg/kg.[1]

We present the case of a child who presented with acute pulmonary injury secondary to intralesional sclerotherapy with bleomycin for a venous malformation.

CLINICAL CASE

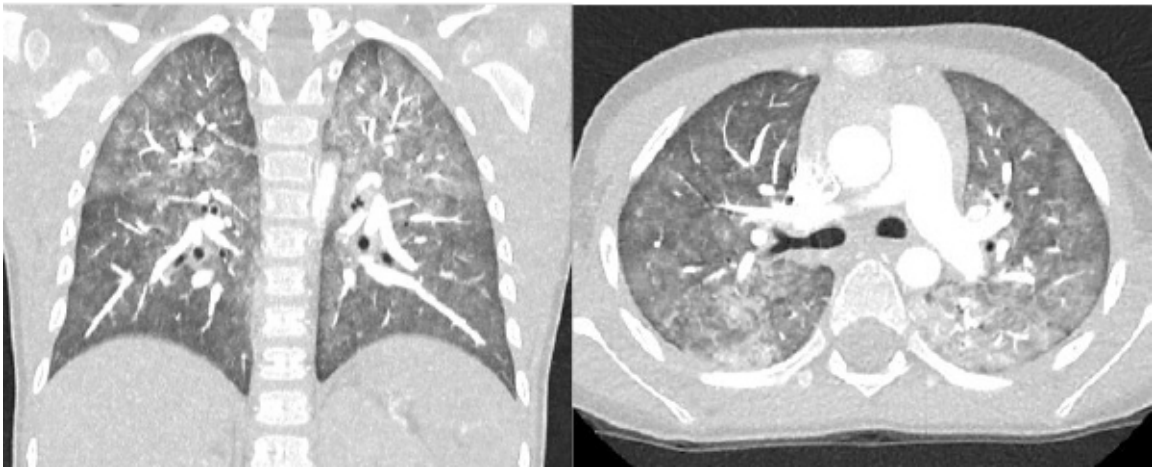
We present a 4-year-old boy with a type II venous malformation in the left lower limb, as classified by Puig, studied by Doppler ultrasound and contrast-enhanced magnetic resonance imaging, with no other history. Percutaneous sclerosis was performed under ultrasound guidance with bleomycin (7 mg; 0.46 mg/kg) and 3% sodium tetradecyl sulfate in emulsion with lipiodol (3 ampoules, 120 mg). Angiographic control before sclerosis showed systemic drainage to normal veins. Therefore, during the procedure, the appropriate tourniquet technique was applied to the affected limb to limit systemic circulation.

During recovery from anesthesia, he developed acute respiratory failure (ARF) with refractory hypoxemia and required mechanical ventilation (MV). Chest X-ray showed bilateral peribronchovascular interstitial infiltrates. Acute post-extubation pulmonary edema or pulmonary thromboembolism (PTE) was initially suspected. Angiotomography showed diffuse bilateral ground-glass opacities, ruling out PTE (*Figure 1*). Laboratory tests interpreted as disseminated intravascular coagulation (DIC): decreased platelets and fibrinogen, D-dimer at the upper limit, normal prothrombin time, activated partial thromboplastin time, and factor V. There was also a decrease in hemoglobin (Hb) from 12 to 9.1 g/dL, with no hemoptysis or other signs of bleeding.

He received intravenous dexamethasone and MV for 6 hours, with rapid improvement and extubation to room air. He completed 48 hours of intravenous corticosteroids. Due to suspected DIC, he received enoxaparin, which was suspended due to normalization of laboratory values within the first 24 hours and an incompatible clinical course. The decrease in Hb was related to lung injury, but could not be confirmed. Hemosiderophages were sought in 3 gastric lavage samples with negative results. Given his rapid, favorable evolution, the ventilation complication was prioritized as a diagnosis.

On the fifth day, he presented clinical

Figure 1. Chest angiotomography after sclerotherapy with bleomycin



Multiple diffuse and bilateral ground-glass opacities. Pulmonary artery and its branches without signs of intraluminal filling defects.

deterioration with dyspnea at rest, tachypnea, and bilateral subcrepitant rales. A consultation was made with the Pulmonology Department. With suspected lung injury secondary to bleomycin, oral meprednisone (1 mg/kg/day) was started. He was discharged after one week; he had adequate respiratory function, mild tachypnea, bilateral basal crackles, and a normal 6-minute walk test (6MWT).

Three weeks after the initial event, he presented with ARF in the context of rhinovirus infection and discontinuation of corticosteroid therapy. High-resolution computed tomography (HRCT) showed marked worsening, with alveolar-interstitial involvement (*Figure 2*). Cardiovascular pathology was ruled out. With unfavorable evolution and suspicion of progression of his preexisting pulmonary condition, he began treatment with methylprednisolone pulses (10 mg/kg/day) and resumed oral methylprednisolone (1 mg/kg/day) between pulses. He required low-flow oxygen therapy for 21 days.

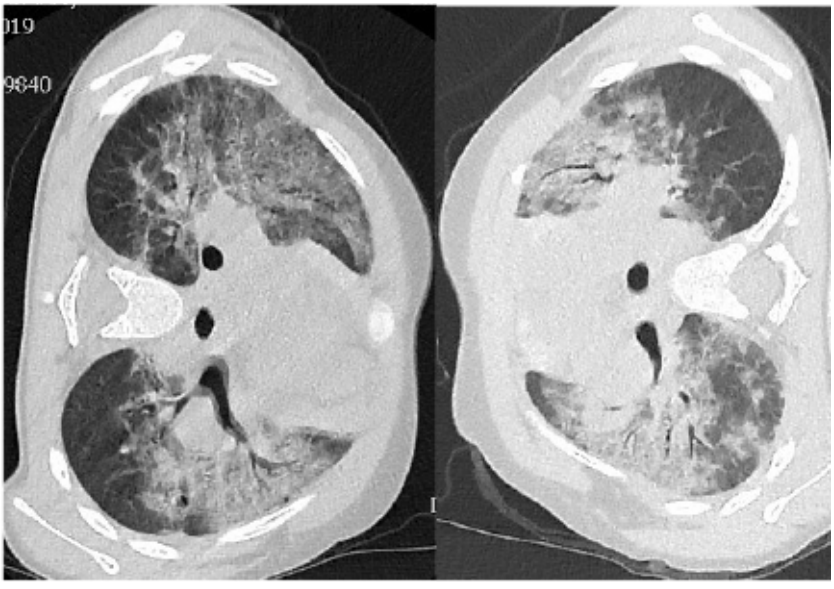
He received four pulses of methylprednisolone (on days 21, 35, 48, and 100 after sclerosis), mepredisone for 2 months, with a subsequent decrease until its suspension at month 6, and azithromycin three times a week. The use of corticosteroids was based on case reports, expert opinions, and the approach to bleomycin-induced pulmonary toxicity in cancer patients. Azithromycin was based on its potential immunomodulatory and anti-inflammatory effects described in other chronic lung diseases. He showed sustained clinical improvement from the third pulse onward. From the fourth pulse onward, he remained asymptomatic, with normal vital signs and auscultatory findings, no dyspnea, and good weight gain.

At one year of follow-up, he was clinically stable, with 98% saturation and normal 6MWT. The follow-up chest HRCT showed persistent alterations in lung architecture (*Figure 3*), consistent with alveolar interstitial damage. Spirometry could not be performed due to the child's difficulty in understanding how to execute it.

DISCUSSION

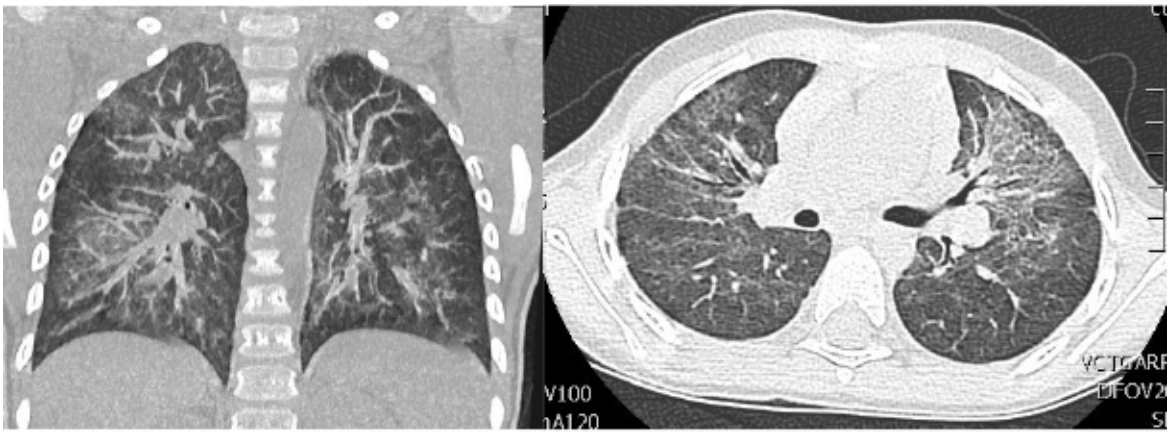
Vascular malformations in childhood are localized congenital defects of vascular development, classified as high-flow or low-flow.[11] Percutaneous sclerosis is a frequently used therapeutic strategy due to its effectiveness, safety, and minimally invasive nature. Bleomycin, alone or in combination with other agents such as sodium tetradecyl sulfate, is used as the treatment of choice.[1,12] As a sclerosing agent, it has proven

Figure 2. High-resolution computed tomography of the chest in the lateral decubitus position at 3 weeks



A: Left lateral decubitus position. B: Right lateral decubitus position.
Patchy areas of ground-glass opacity predominantly in the perihilar and anterior regions, bilateral, associated with septal thickening, with minimal distortion of the pulmonary architecture.

Figure 3. High-resolution chest CT scan at 12 months



Decreased pulmonary involvement, with areas of disorganization of the pulmonary architecture persisting in the upper and middle lobes and lingula, with septal thickening and ground-glass attenuation. Air trapping in slices taken during expiration.

to be an effective and safe drug, with a low incidence of serious adverse events.[1]

Bleomycin is an antibiotic with cytotoxic action used in oncology, and pulmonary involvement is one of its most serious complications.[13] Interstitial pneumonia is the most frequently described pattern and presents a risk of fibrosis. The pathophysiological mechanism involves endothelial damage, interstitial inflammatory infiltrate, and fibroblastic activation with collagen deposition.[5,13]

The risk of pulmonary toxicity ranges from 3% to 5%, with a mortality rate of 1% to 2%. The risk factors described are advanced age (>70 years), cumulative dose >400 mg or single doses >30 mg/m^2 , and preexisting lung or kidney disease.[3,4,13] In pediatrics, pulmonary functional impairment has been reported with cumulative doses ≥60 mg/m^2.[3,14] However, four cases of pulmonary toxicity were reported in children treated with bleomycin as a sclerosing agent at doses lower than those mentioned as risk factors.[7-10]

One of them describes an 8-month-old infant with venolymphatic malformation in the left upper limb. She received bleomycin sclerotherapy (1.2 mg/kg). She developed ARF within 24 hours, complicated by pneumothorax and pneumomediastinum. She progressed favorably with systemic corticosteroids and pentoxifylline.[7]

Two cases reported a fatal outcome. A 15-month-old girl with a facial lymphatic malformation (dose: 0.7 mg/kg) developed ARF, pneumothorax, and diffuse alveolar damage; she died within a month, despite treatment with high-dose corticosteroids,[8] and a 4-year-old girl who underwent three sessions (cumulative dose: 0.75 mg/kg) on her lower limb for a venous malformation. On the fourth day after the last session, she developed ARF. She received methylprednisolone and MV. She remained on home oxygen for a year and died of pneumonia.[9]

Finally, a 5-year-old boy developed ARF after the second sclerotherapy session for a cervical venous malformation (dose 0.28 mg/kg per procedure). He received methylprednisolone, montelukast, and prednisone and progressed well.[10]

In this case report, the bleomycin dose was 0.46 mg/kg. To date, this is the lowest documented dose associated with pulmonary toxicity. Regardless of the presence or absence of a residual systemic connection through which the drug could have entered the systemic circulation, the concentration used was low and within range, suggesting an idiosyncratic reaction to the medication.

The initial clinical improvement may have been due to early corticosteroid administration. In cancer patients receiving bleomycin, high-dose systemic corticosteroids are recommended for the treatment of acute respiratory symptoms.[5] The indication for methylprednisolone pulses was based on the experience of previously described cases.[7-10] Treatment was supplemented with azithromycin due to its immunomodulatory and anti-inflammatory effects described in other chronic lung diseases.[15]

As a measure to prevent lung damage, it is recommended to avoid hyperoxia during sclerotherapy, discouraging the use of supplemental oxygen with SpO_2 ≥94% to reduce the formation of free radicals.[12]

The prognosis is uncertain due to the low frequency of this complication. Pulmonary fibrosis could be the outcome. Early corticosteroid therapy could improve clinical outcomes. Cancer patients with bleomycin-induced pulmonary toxicity who survive interstitial pneumonia usually recover complete pulmonary function.[5]

At 12 months, the patient remained clinically and functionally stable. We considered the risk of progression to pulmonary fibrosis to persist, warranting periodic monitoring. There are no standardized follow-up guidelines. It is suggested that follow-up be carried out by pulmonologists in tertiary care centers with access to respiratory function tests, including spirometry, plethysmography, carbon monoxide diffusion, 6MWT, and HRCT.

The presentation of this case aims to raise awareness about a rare but serious complication of percutaneous bleomycin treatment. We emphasize the importance of maintaining a high index of suspicion in patients with acute respiratory symptoms, even at low doses. Early administration of corticosteroids is associated with better clinical outcomes, although there are no standardized treatment regimens. ■

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