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Bronchiolitis obliterans due to toxic epidermal necrolysis - a serious condition with a good therapeutic response

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TO THE EDITOR,

Bronchiolitis obliterans (BO) is a rare disease that can result from a large number of clinical conditions. The injury and inflammation of the small airways can be caused by different stimuli, such as viral diseases, gastroesophageal reflux, prolonged exposure to pollutants, autoimmune diseases, post-organ or bone marrow transplantation, and less frequently, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).[1,2] Clinically, BO is characterized by progressive dyspnea and dry cough, which progress from weeks to months.[1] Spirometry may be normal or exhibit an obstructive, restrictive, or mixed pattern.[1] High-resolution computed tomography (HRCT) of the chest can show early alterations, even with normal spirometry, with hypodense areas presenting reduced vascular caliber, suggestive of air trapping.[1,3]

SJS and TEN are different spectra of the same disease, differing by the extent of skin detachment.[4] This disease is characterized by severe skin reactions, with acute eruptions of the skin and mucous membranes that can affect the respiratory system, leading to laryngeal edema, epiglottitis, bronchiolitis, pneumonitis, and, in rare cases, pneumothorax.[4] Persistent pulmonary sequelae associated with SJS or TEN are considered uncommon, but when the involvement of the respiratory mucosa is extensive, the disease appears, in most reports, as severe, progressive, and with a poor prognosis.[2,3,5,6]

Here we describe a case of BO secondary to TEN, which presented with a favorable clinical outcome. This is the first case reported in adults in Brazil, according to searches on the PubMed database. The patient was a 32-year-old woman, who at the time was single, unemployed, from the state of Ceará, nonsmoker, and without previous lung diseases. She had a medical history of epilepsy, having used phenobarbital for 8 years. The patient evolved with TEN secondary to the use of such medication. She exhibited extensive involvement of oral, vaginal, corneal, and respiratory mucosa, having remained on mechanical ventilation in the ICU for 45 days due to acute respiratory failure. In the hospital ward, the patient persisted with dyspnea upon minimal exertion, wheezing, coughing with mucoid sputum, and oxygen dependence. She was discharged after 15 days and was referred to the Pulmonology Service of the Walter Cantídio University Hospital. At consultation, she complained of dyspnea (m-MRC 3) and reported the need for oxygen at night and oral corticosteroid use (prednisone 20 mg per day). Upon physical examination, the patient exhibited impaired overall condition; she was oriented, tachydyspneic, and presented bilateral amaurosis and normal cardiac auscultation. Pulmonary auscultation revealed diffusely diminished breath sounds, without adventitious sounds, and oxygen saturation was 93% in room air. Initial spirometry showed marked obstructive ventilatory disorder, with reduced FVC (pre-BD FEV1: 0.61 (23.9%), post-BD FEV1: 0.61 (23.9%), pre-BD FVC: 1.10 (37.4%), post-BD FVC: 1.05 (35.6%), pre-BD FEV1 / FVC: 55.32%, post-BD FEV1 / FVC: 57.78%). Chest radiography showed diffuse hyperinflation and a small focal condensation on the right base. The HRCT scan of the chest showed a diffuse mosaic attenuation pattern, with extensive areas of regional hyperinflation and discrete reticular infiltrates associated with a ground-glass area bilaterally dispersed in the anterior segments, notably in the left lung (Figure 1). Treatment with inhaled Budesonide / Formoterol was started, and progressive weaning from systemic corticosteroids was carried out. The patient evolved with significant improvement in dyspnea and weaning from oxygen therapy. She has been followed-up in the service for 6 years, with control of symptoms (m-MRC 1) and progressive improvement in lung function, and, in the last evaluation, she exhibited 930 mL pre-BD FEV1 (FEV1 pre-BD: 0.93 (38.4%), FEV1 post-BD: 0.97 (40.4%), FVC pre-BD: 1.63 (57.8%), FVC post-BD: 1.64 (58.3%), FEV1 / FVC pre-BD: 57%, FEV1 / FVC post-BD: 59.4%) and a 156-meter increase in the 6-minute walk test.

TEN is caused by hypersensitivity to immune complexes, triggered mainly by drugs, with anticonvulsants being one of the most involved classes.[2,4,5] This reaction leads to injury to the epidermis and mucous membranes and is characterized as TEN when more than 30% of the epidermis presents necrosis.[4,5] In TEN, mucosal lesions are more commonly seen in the upper airways, but in the case of BO, a rare and severe complication associated with this syndrome, mucosal lesions reach the terminal bronchioles.[4,5]

In the healing process of these lesions, fibrin production and tissue invasion occur by inflammatory cells, such as lymphocytes and macrophages, as well as the proliferation of myofibroblasts and blood capillaries, leading to the

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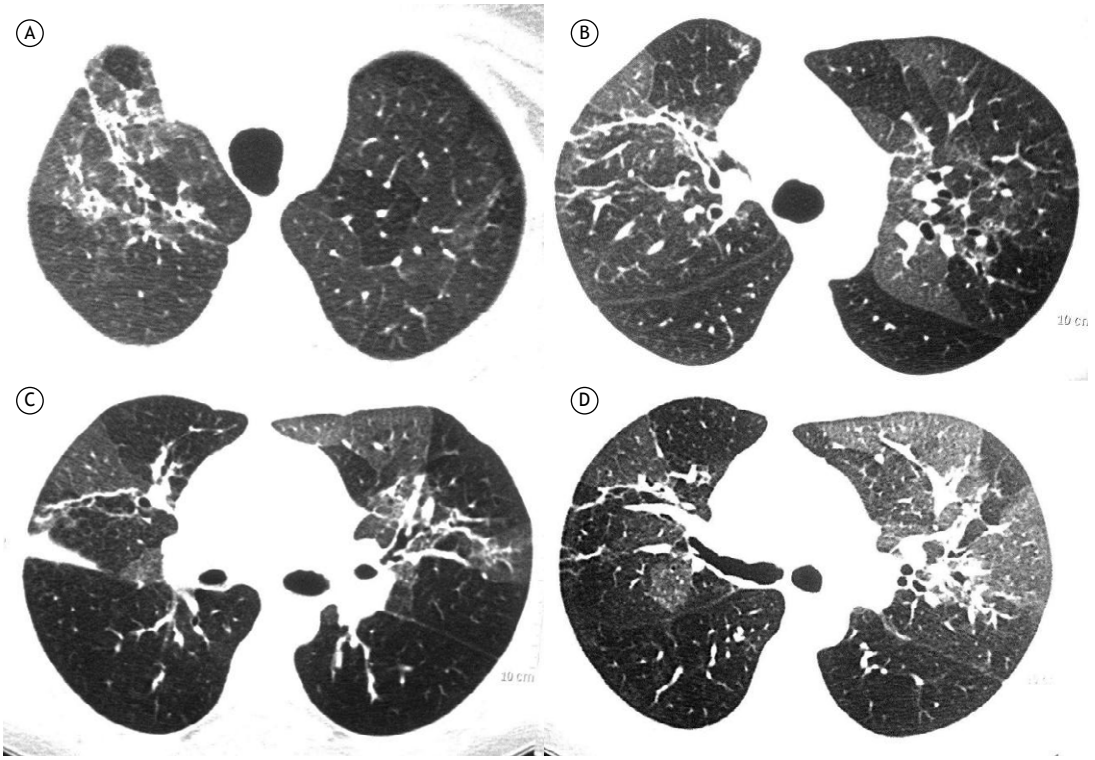

Figure 1. HRCT performed two months after hospital admission, showing pulmonary parenchyma with a pattern of attenuation in diffuse mosaic, with extensive areas of regional hyperinflation and discrete reticular infiltrates associated with ground-glass areas dispersed bilaterally in the anterior segments, notably in the left lung.

hyperproliferation of granulation tissue, with collagen deposition in the submucosa and consequent progressive concentric narrowing and bronchial lumen distortion, characterizing chronic inflammation.[2]

As the structure of the bronchial wall, including the smooth muscle layer and elastic fibers, is not destroyed and is surrounded by fibrosis tissue, the histological pattern is characterized by constrictive bronchiolitis, which can lead to partial or complete bronchiole obstruction, aspects that determine the severity of the condition.[2,6] The presence of bronchial cartilage involvement has also been described as a factor associated with a worse prognosis.[2,6]

Currently, biopsy has been dispensed with for the diagnosis of BO, which is based on clinical and radiological criteria, when there is a clinical history and compatible pathological history, associated with pulmonary function test with a fixed obstructive pattern and tomography with a mosaic attenuation pattern, with vascular attenuation and central bronchiectasis.[3,5,7]

Ideally, the effective treatment of TEN prevents these serious respiratory sequelae from being generated.[8] For that, early recognition of the syndrome and the causative agent is necessary, and the exposure to the agent must be stopped immediately, given that the disease has rapid evolution.[4]

According to the literature, when BO is already installed, the prognosis is generally unfavorable, with a fatal outcome in most cases in adults.[2,3,5,6,8] There is no specific treatment established for this disease, with poor outcomes based on corticosteroid treatment, in most cases.[3,8] Differently, in the case reported, the patient evolved with good control of respiratory symptoms and improved lung function, thus making inhalation therapy an option to be considered.

AUTHOR CONTRIBUTIONS

ALBPF: conception and planning of the study, writing and reviewing the preliminary and final versions of the manuscript, approval of the final manuscript. RCR: conception and planning of the study, reviewing the preliminary and final versions of the manuscript, approval of the final manuscript. RCPP: conception and planning of the study, approval of the final manuscript. JFF: writing and reviewing the preliminary and final versions of the manuscript, approval of the final manuscript. MAH: reviewing the preliminary and final versions of the manuscript, approval of the final manuscript.

REFERENCES

1. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. N Engl J Med. May 2014; 370 (19): 1820-28. https://doi.org/10.1056/nejmra1204664.
2. Sugino K, Hebisawa A, Uekusa T, Hatanaka K, Abe H, Homma S. Bronchiolitis obliterans associated with Stevens-Johnson Syndrome:

histopathological bronchial reconstruction of the whole lung and immunohistochemical study. Diagn Pathol. Aug 2013; 8: 134. https://doi.org/10.1186/1746-1596-8-134.

3. Park H, Ko YB, Kwon HS, Lim CM. Bronchiolitis obliterans associated with Stevens-Johnson syndrome: a case report. Yonsei Med J. Mar 2015; 56(2): 578-81. https://doi.org/10.3349/ymj.2015.56.2.578.
4. Wong A, Malvestiti AA, Hafner MFS. Stevens-Johnson syndrome and toxic epidermal necrolysis: a review. Rev Assoc Med Bras (1992). Sep-Oct 2016; 62(5):468-73. https://doi.org/10.1590/1806-9282.62.05.468.
5. Fielli M, Ceccato A, González A, Villaverde M. Bronquiolitis obliterans associated with Stevens-Johnson syndrome. Medicina (B Aires). 2015; 75 (6): 413-15. Disponível em: http://www.medicinabuenosaires.com/PMID/26707668.pdf.
6. Tsunoda N, Iwanaga T, Saito T, Kitamura S, Saito K. Rapidly progressive bronchiolitis obliterans associated with Stevens-Johnson syndrome. Chest. Jul 1990; 98(1): 243-45. https://doi.org/10.1378/chest.98.1.243.
7. Wang WP, Ni YF, Wei YN, Li XF, Cheng QS, Lu Q. Bronchiolitis obliterans complicating a pneumothorax after Stevens-Johnson syndrome induced by lamotrigine. J Formos Med Assoc. Mar 2015; 114(3): 285-89. https://doi.org/10.1016/j.jfma.2012.02.026.
8. Yatsunami J, Nakanishi Y, Matsuki H, Wakamatsu K, Takayama K, Kawasaki M et al. Chronic bronchobronchiolitis obliterans associated with Stevens-Johnson syndrome. Internal Med. Aug 1995; 34(8): 772-75. https://doi.org/10.2169/internalmedicine.34.772.