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## Air Leak Syndrome Due to Graft Versus Host Disease

### *Síndrome de fuga aérea por enfermedad del injerto contra huésped*

To the Editor:

Chronic graft versus host disease (GVHD) is a serious late complication of allogenic bone marrow transplantation, occurring in 60% to 80% of transplanted patients.<sup>1</sup> Bronchiolitis obliterans is a pulmonary manifestation of GVHD, and the appearance of air leak syndrome is very rare.<sup>1,2</sup> We report the case of a patient with air leak syndrome as the first sign of lung disease associated with GVHD.

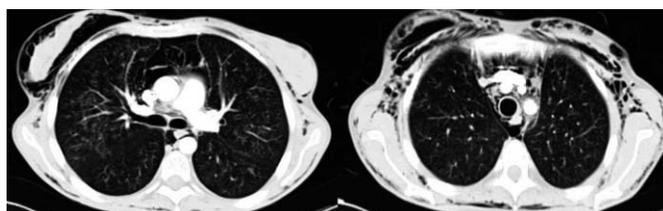
A 30-year-old female patient was admitted to our service with dyspnea, subcutaneous emphysema, and pneumomediastinum. Two years earlier the patient had been diagnosed with a type of myelodysplastic syndrome (refractory anemia with excess blasts-1) and paroxysmal nocturnal hemoglobinuria. Initial treatment with implantation of umbilical cord stem cells failed and was followed by allogenic bone marrow transplantation, resulting in complete recovery and no side effects. A year later, the patient experienced a relapse and developed acute myeloblastic leukemia, requiring another stem cell transplant using umbilical cord blood. Chronic immunosuppressive therapy was given with cyclosporin and prednisone.

The patient was admitted with subcutaneous cervical emphysema and spontaneous pneumomediastinum in the upper hemithorax, with no signs of pleuropulmonary involvement or mediastinal abnormalities on the chest radiograph. A high-resolution computed tomographic scan (HRCT) showed extensive subcutaneous emphysema and pneumomediastinum without pneumothorax or tracheobronchial lesions, in addition to significant bronchiectasis with marked thickening of the bronchial walls and an alveolar-interstitial pattern with centrilobular nodules of tree-in-bud appearance suggestive of pulmonary involvement due to GVHD (Figure). A flexible fiberoptic bronchoscopy and a transbronchial biopsy showed no abnormalities. *Pseudomonas aeruginosa* was isolated from the bronchial aspirate and the infection was treated. The patient showed clear clinical improvement with resolution of subcutaneous emphysema and pneumomediastinum.

One month after discharge, forced spirometry showed deterioration in lung function with a forced vital capacity (FVC) of 72% (previous result, 102%); forced expiratory volume in 1 second (FEV<sub>1</sub>) of 41% (previous, 107%); FEV<sub>1</sub>/FVC of 54% (previous, 89%); midexpiratory flow rate of 12% (previous, 121%); residual volume of 178% (previous, 75%); and carbon monoxide diffusing capacity of 48% (previous, 70%). This severe obstruction with rapid-onset air trapping in a patient with the history described here suggested a diagnosis of bronchiolitis obliterans due to GVHD according to international criteria.

Subcutaneous emphysema and spontaneous pneumomediastinum have been linked to asthma, addiction to inhaled drugs, occult pneumothorax, and forced Valsalva maneuvers.<sup>3</sup> Allogenic bone marrow transplantation represents a risk for recipients due to systemic immune cross-reactivity caused by the graft. GVHD follows a bimodal pattern with an early and late peak.<sup>1,4,5</sup> GVHD-bronchiolitis obliterans is rare<sup>1,2</sup> and diagnosis is based on the following clinical findings: a) inexplicable chronic airflow obstruction (FEV<sub>1</sub>, <80% in the absence of respiratory infection), b) flow-volume curves suggestive of small-airway disease, and c) residual volume greater than 115% of predicted.<sup>4</sup> Radiographic images and lung biopsy are nonspecific. Treatment consists of corticosteroids and clinical outcome is generally unfavorable. Overall mortality is 50% to 55%.

The true incidence of air leak syndrome is unknown. It has been described as the presence of extra-alveolar gas and includes pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema, and interstitial emphysema. The pathogenesis tends to be alveolar rupture that causes interstitial emphysema, which then dissects along bronchovascular sheaths to the hilum and into the mediastinum (Macklin effect).<sup>6</sup> Rupture occurs in the presence of increased intraalveolar pressure (bronchial obstruction with coughing or vomiting) or damage to the alveolar walls (infectious causes, such as invasive aspergillosis, or noninfectious causes, such as pulmonary emphysema and bronchiolitis obliterans). The appearance of air leak syndrome in our case is linked to poor prognosis due to the presence of bronchiolitis obliterans in association with invasive aspergillosis. A wait-and-see surgical approach is therefore advisable, and conservative treatment is usually enough.



**Figure.** Computed tomographic scan showing extensive subcutaneous emphysema and pneumomediastinum without pneumothorax, in addition to significant bronchiectasias with marked thickening of the bronchial walls and an alveolar-interstitial pattern with a patchy ground-glass appearance.

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## Kikuchi-Fujimoto Disease in an Atypical Site

### *Enfermedad de Kikuchi-Fujimoto: una localización atípica*

To the Editor:

Kikuchi-Fujimoto disease or histiocytic necrotizing lymphadenitis is a rare entity that is generally associated with cervical lymphadenopathy and fever. We report a case of this disease in an atypical location, the anterior mediastinum, associated with multiple pulmonary nodules.

A 27-year-old woman was evaluated in the internal medicine department for a 3-month history of fever, mainly in the evening, night sweats, and nonpruriginous maculopapular lesions. Physical examination was normal, with no evidence of cervical or supraclavicular adenopathy. Laboratory tests showed no abnormalities. Agglutination tests for *Typhi* and *Brucella* were negative, as were antibody titers against Epstein-Barr virus, rheumatic and immunological tests, and the Mantoux test. A computed tomography scan of the chest and abdomen revealed small peripherally distributed subpleural nodules (the largest measuring 9 mm in diameter) in the right lung, discrete paratracheal and bilateral hilar lymph nodes, and an enlarged subcarinal lymph node (Figure). Fiberoptic bronchoscopy was normal. Microbiology and cytology of transbronchial and bronchial biopsy samples and bronchoalveolar lavage fluid did not provide conclusive findings.

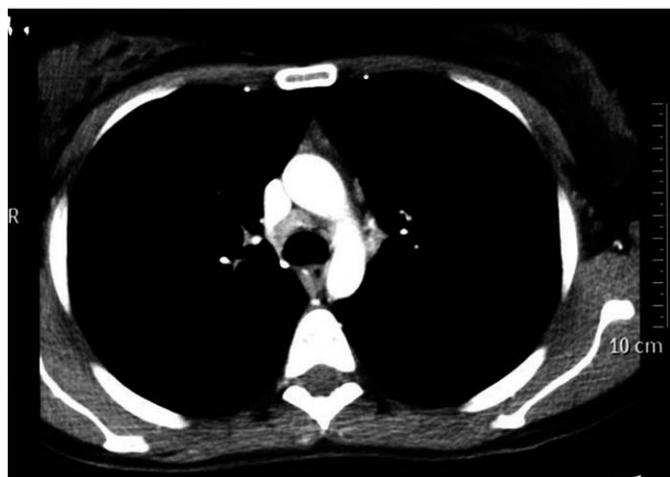


Figure. Computed tomography.

Mediastinoscopy revealed a level 4R lymph node conglomerate, which was biopsied for microbiological and pathological examination. The microbiological analysis was negative, and the pathology report showed reactive lymphadenitis with nonneutrophilic necrosis suggestive of Kikuchi's disease. One month after surgery, the patient had no fever and was asymptomatic.

Kikuchi-Fujimoto disease, nonneutrophilic necrotizing lymphadenitis or histiocytic necrotizing lymphadenitis is a self-limiting disorder that runs a benign course. It mainly affects young Asian women generally less than 30 years of age. Of unknown origin, the disease has been associated with viruses such as parvovirus B19, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus type 6, and with microorganisms such as *Toxoplasma*, *Yersinia*, and *Brucella* species. Some authors have described an exaggerated immune response to different agents as the cause of disease.<sup>1</sup>

In 70% to 90% of cases, Kikuchi-Fujimoto disease manifests as cervical lymphadenopathy, which is generally unilateral. The parotid gland is a less common location. Fever is another frequently observed symptom, occurring in 30% to 50% of cases. Other symptoms that may accompany this disease include fatigue, night sweats (as in our patient), weight loss, gastrointestinal disorders, and various skin alterations such as rash.<sup>2,3</sup>

The diagnosis of this disease is complex as there are no conclusive laboratory or imaging test findings, though they may serve to exclude other disorders. Diagnosis can only be made by lymph node biopsy, since fine needle aspiration does not provide sufficient information.<sup>4</sup>

From a pathologic point of view, the disease has 3 phases: proliferation (with an increase in mononuclear cells), necrosis (with necrosis and a predominance of histiocytes), and xanthoma. This means that diseases such as systemic lupus erythematosus, lymphomas, Hodgkin's disease, and tuberculosis should be considered in the differential diagnosis of Kikuchi-Fujimoto disease.

Kikuchi-Fujimoto disease usually runs a benign, self-limiting course, though recurrence has been reported in some cases. Patients should be closely monitored, however, as there appears to be a clear association between lupus and Kikuchi-Fujimoto disease.<sup>1,6</sup>

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