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Intravascular large B cell lymphoma presenting in the lung: the diagnostic value of transbronchial cryobiopsy

Venerino Poletti[1], Carlo Gurioli[1], Sara Piciucchi[2], Andrea Rossi[3], Claudia Ravaglia[1], Alessandra Dubini[4], Silvia Asioli[4], Gian Luca Casoni[1]

[1] Pulmonology Unit, Morgagni-Pierantoni Hospital, Forlì, Italy; [2] Radiology Unit, Morgagni Hospital, Forlì, Italy; [3] Pulmonology Unit, University and General Hospital of Verona, Verona, Italy; [4] Pathology Unit, Morgagni-Pierantoni Hospital, Forlì, Italy

Abstract. *Background and objective*: Intravascular large B-cell lymphoma is a distinct subtype of mature B-cell neoplasms, with uncommon primary presentation in the lungs. Diagnosis could be very difficult due to the lack of detectable tumor masses and it is usually made by surgical lung biopsy or autopsy examination. *Methods*: Two patients occurred primarily with interstitial lung disease and underwent a pulmonary biopsy using cryoprobes. *Results*: The pathological analysis of the lung biopsies revealed in both cases a conclusive diagnosis of intravascular large B-cell lymphoma with primary lung involvement and patients have been safely diagnosed using transbronchial cryobiopsy for the first time in the literature. *Conclusions*: Transbronchial cryobiopsy could be used as valid surrogate for surgical lung biopsy in lymphoprolipherative lung disorders (including intravascular lymphomas), as allows larger samples of tissue, greater diagnostic yield, no crush artifacts and much less complications than surgical biopsy. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 354-358)*

Key words: intravascular large B-cell lymphoma, transbronchial cryobiopsy, interstitial lung diseases, lymphoproliferative disorders, lung

Introduction

The WHO 2008 classification differentiates intravascular large B-cell lymphoma (IVLBCL) from diffuse large B-cell lymphoma (DLBCL), and lists IVLBCL as a unique subtype among mature B-cell neoplasms (1). IVLBCL is characterized by the selective growth of lymphoma cells within the lumina of vessels, particularly capillaries (1). Two main patterns of clinical presentation have been recognized: a Western form characterized by symptoms related to the organs involved, predominantly neurological or cutaneous, and an Asian variant in which patients present with multiorgan failure, hepatosplenomegaly, pancytopenia and hemophagocytic syndrome (1). Conventional diagnostic/staging procedures are generally associated with a high proportion of false negatives because of the lack of detectable tumor masses. Although autopsy findings have revealed that pulmonary involvement is common in this disease, primary presentation in the lungs is distinctly uncommon (2-4). Here are two cases that occurred primarily with interstitial lung disease and, ultimately, have been proven by transbronchial cryobiopsy.

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Correspondence: Venerino Poletti, MD
Pulmonology Unit, Department of Thoracic Diseases
Morgagni - Pierantoni Hospital
via C. Forlanini 34,
47100 Forlì, Italy
Tel. +390543735042
E-mail: venerino.poletti@gmail.com

Methods

Case N. 1. A 68 year-old male, physician, former smoker, was admitted to the Thoracic Department of the Morgagni Hospital, Forlì (Italy), for the recent (two months) appearance of low grade fever, asthenia and dyspnea on effort. Two years before, he was submitted to radiofrequency ablation for atrial fibrillation. Laboratory findings and pulmonary function tests at admission are reported in Table 1. Electrocardiogram documented a sinusal rythm. Transthoracic echocardiogram documented an increased systolic pulmonary pressure (50 mmHg). Bone marrow biopsy was not diagnostic. Multiple areas of patchy bilateral ground glass opacities were documented on Computed Tomography (CT), particularly in both upper lobes and in the apical segments of the lower lobes; moreover, these areas were associated to small consolidations in the lower lobes. In the lower lobes, a smooth thickening of the interlobular septa and a dendriform calcification/ossification were present, as well (figure 1). A mild pleural effusion was identified in the left side.

Case N. 2. A 56 year-old male, teacher, never smoker, was admitted to the Thoracic Department of the Morgagni Hospital, Forlì (Italy), for the recent appearance (one month) of asthenia, dyspnea on effort and low grade fever. His past clinical history was not relevant. Laboratory findings and pulmonary function tests at admission are reported in Table 1. Electrocardiogram documented a sinusal rythm. Transthoracic echocardiogram documented a systolic pulmonary pressure of 40 mmHg. Bone marrow biopsy was not diagnostic. The computed tomography showed diffuse areas of patchy ground glass attenuation in both hemithoraxes. A few tiny nodules were also present bilaterally. No air trapping was documented in the expiratory images (Figure 2). No septal thickening or lobular architecture distorsion was visible. Several small mediastinal adenopathies were present. In the upper abdomen slices a mild spleen enlargment was visible. A pulmonary biopsy using cryoprobes was performed in both patients according to the procedure already described. Briefly, they were deeply sedated using propofol and remyphentanyl and intubated with a rigid tracheoscope. A 2,4 mm cryoprobe was introduced through the operating channel of a fiberoptic bronchoscope. Then under fluoroscopic control transbronchial cryobiopsies were carried out (four samples in the apical segment of the right lower lobe in case N 1 and two samples in the lateral segment of the right lower lobe in case N 2). Bleeding was hampered by inflated Fogarty balloon. No pneumothorax was observed in the days after biopsy.

Table 1. Laboratory findings and lung function tests

	Case N. 1	Case N. 2
WBC (white blood cells), 10^9/L	6,18	5,84
RBC (red blood cells), 10^12/L	3,84	3,76
Hb (haemoglobin), g/dl	11,4	10,4
PLT (platelets), 10^9/L	140	87
Lymphocytes, 10^9/L	0,760	1,118
AST (aspartate aminotransferase), U/L	65	59
CRP (C-reactive protein), mg/L	190,4	5,9
LDH (lactate dehydrogenase), U/L	977	1438
aPTT, ratio	1,41	1,40
PaO2, mmHg	69	66
PaCO2, mm Hg	32	26
Autoimmunity (ANA, ENA, ANCA)	Negative	ANA + (1/160) nucleolar pattern
Monoclonal gammopathy	IgG/Lambda	IgM/Kappa
FVC (forced vital capacity), L/% pred	2,37/86%	4,88/114%
DLCO (diffusing capacity for carbon monoxide), L/% pred	13,2/53%	11,9 / 42%

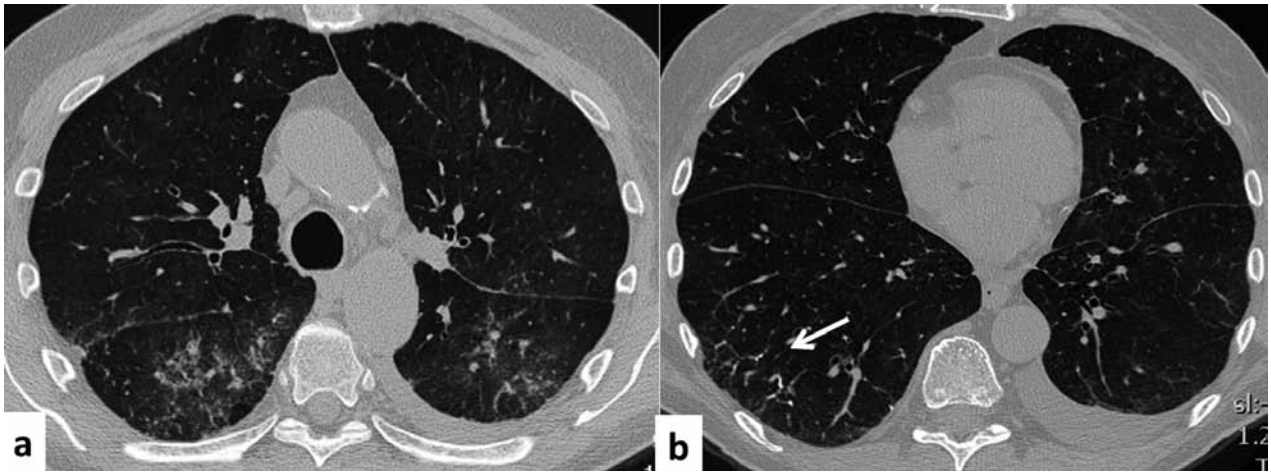

Fig. 1. Multiple areas of bilateral patchy ground glass opacities mainly in the apical segments of both lower lobes (a). In the right lower lobe multiple dendriform calcifications are present (b)

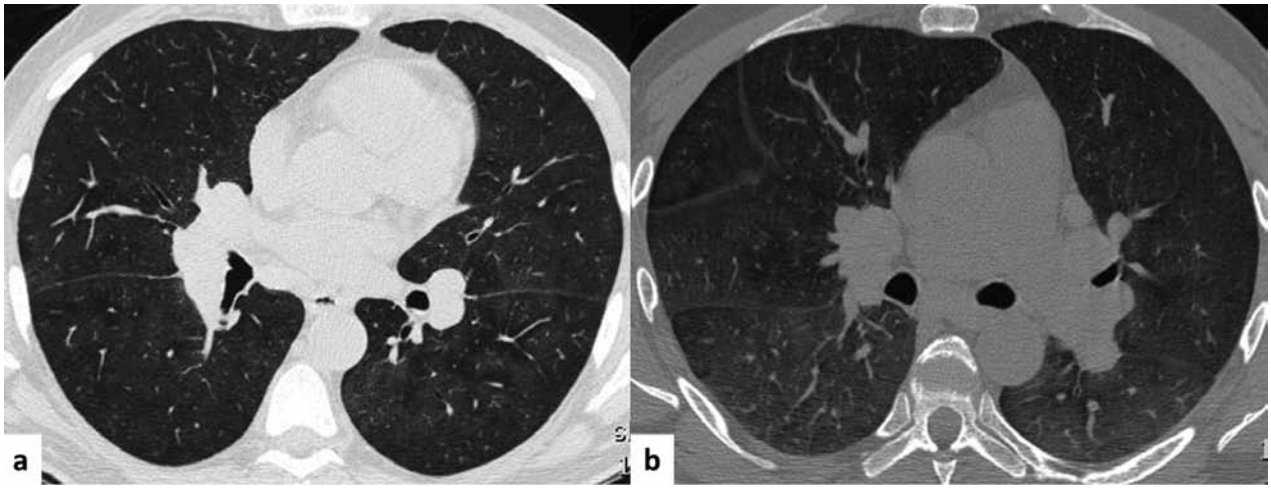

Fig. 2. Mild centrilobular ground glass attenuation (a). No air trapping in the expiratory images is visible (b)

Results

Aggregate biopsy specimens size of 126 squared millimeters in case N. 1 and 85 squared millimeters in case N. 2.

The pathological analysis of the lung biopsies revealed in both cases small pulmonary vessels (arteries and veins) and inter-alveolar capillaries containing large atypical lymphoid cells of B phenotype (CD20+, MUM1/IRF4+, CD5-, CD3-); these neoplastic cells presented a high proliferation index (80% in case N 1 and 90% in case N 2 respectively expressed the Ki-67 nuclear marker) and were EBERs (Epstein-Barr virus-encoded small RNAs) negative. A conclusive diagnosis of intravascular large B-cell lymphoma was made (Figure 3).

Discussion

The characteristic clinical-radiologic and laboratory findings in both patients may be summarized as follow: subacute onset with asthenia, low grade fever and shortness of breath, normal pulmonary volumes but a significant decrease of diffusion capacity index,

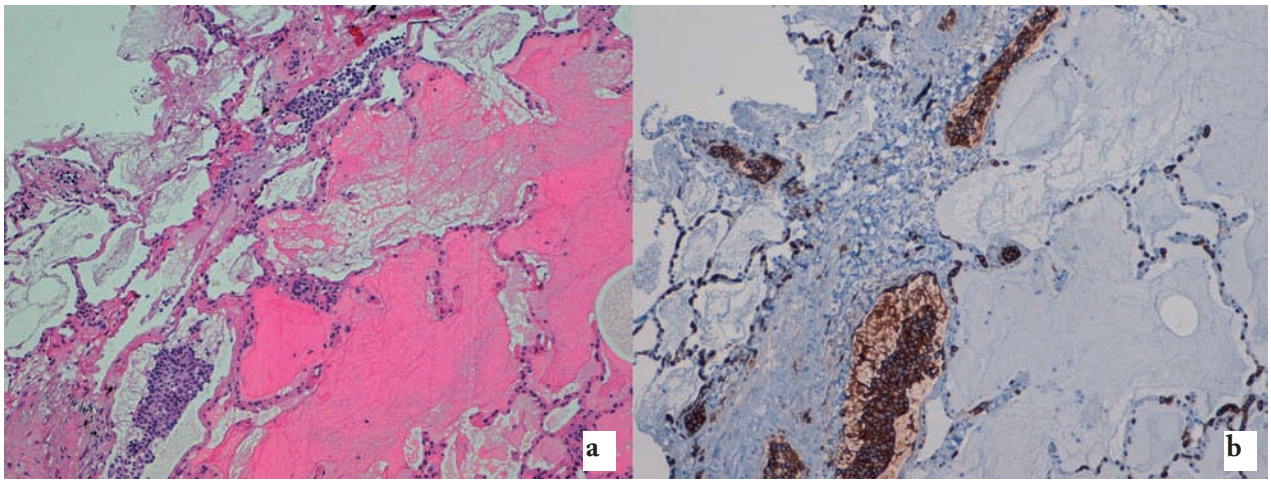

Fig. 3. a) Lower lobe transbronchial cryobiopsy. Small pulmonary vessels (arteries and veins) and inter-alveolar capillaries contain large atypical lymphoid cells (E&H, low power); b) These cells express B lymphocyte markers (CD20+, low power)

mild to moderate hypoxemia associated with a significant hypocapnia, a significant increase of LDH and the presence of serum monoclonal gammopathy. All these findings (systemic symptoms and pulmonary symptoms, pulmonary function tests, arterial blood gases values favoring a diagnosis of pulmonary thromboembolism and lab tests suggesting a lymphoproliferative disorder) are a strong clue for a diagnosis of intravascular lymphoma mainly localized to the lungs (5). CT scan findings are also in favor of this hypothesis: the presence of ground glass attenuation, smooth thickening of the interlobular septa and, in one case, the presence of bilateral pleural effusion have been already described in lymphoprolipherative lung disorders (5). However, disorders that need to be considered in the differential diagnosis are numerous including tumors which spread along the lymphatic routes, thrombotic neoplastic microangiopathy (6) (mainly observed in metastatic mucinous adenocarcinomas), amyloidosis (7), veno-occlusive vasculopathy associated to a "forme fruste" of collagen vascular disease (8), veno-occlusive disease related to radiofrequency ablation (9), and rarer disorders such as Erdheim Chester disease (10) and human T-cell leukemia virus type I related inflammatory lung involvement (11).

Conventional transbronchial lung biopsy has already been reported as a valid mini-invasive diagnostic tool of intravascular B cell lymphoma mainly by far-East Authors, presumably in the Asiant variant of the disease (12-15); however diagnosis of this rare lymphoproliferative disorder is usually made by surgical lung biopsy or it is delayed until autopsy examination (1). Transbronchial cryobiopsy is a new method that allows to obtain larger samples of lung tissue without crush artifacts and increases the diagnostic yield of traditional transbronchial biopsies in diffuse parenchymal lung diseases (16-18). In these two cases, this method was carried out despite the presence of a slight increase of pulmonary pressure, as assessed by echocardiography, and despite (in one case) a mild thrombocytopenia, but complications such as bleeding or pneumothorax were not observed. The samples obtained were even twenty times bigger than that usually recruited by conventional transbronchial lung biopsy. Immunohistochemical investigations were performed in these samples obtained without technical problems. This brief report confirms that transbronchial lung biopsy through cryoprobes is a very interesting diagnostic tool in diffuse parenchymal lung disorders and it should be considered a valid surrogate for surgical lung biopsy also in patients with lymphoproliferative disorders with lung involvement (5, 19), with much less complications, feasible also in patients with mild thrombocytopenia and increased pulmonary artery pressure. This case series underlines that this new technique should be known not only by Pulmonologists, but also by Haematologists and Oncologists who daily deal with oncohaematological diseases with pulmonary involvement (5).

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