REV PORT PNEUMOL VI (3): 205-216

PALESTRA/LECTURE

Utilidade clinica do Lavado Broncoalveolar nos tumores pulmonares disseminados

Clinical utility of Bronchoalveolar Lavage in Disseminated lung tumors

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Running title: Disseminated lung tumors and BAL

Key-words: Lung tumors, bronchioloalveolar cell carcinoma, lymphangitic carcinomatosis, lymphoproliferative lung disorders, BAL.

INTRODUCTION

Disseminated lung tumors can have an epithelial or a mesenchymal nature (infrequently divergent differentiation creates what are called mixed tumors) and they have two basic components: the proliferating neoplastic cells and supportive stroma made up of preexisting or *"de novo "* formed connective tissue and blood vessels. An inflammatory reaction in the supportive stroma can be present at different intenstity.

Dissemination in the lung parenchyma may occur through different patterns (Table I) that represent a specific anatomic distribution of neoplastic cells inside the secondary pulmonary lobule structures.

The knowledge of the growth patterns in the lung is useful in order to understand the roentgenological and clinical profiles with which these neoplasms reveal. Taking into account the nature of neoplastic cells and the dissemination spread into lung parenchyma different clinical-roentgenological and anatomical entities of disseminated lung tumors can be separated.

BRONCHIOLOALVEOLAR CELL CARCINOMA (BAC) (Fig 1)

It is a subset of pulmonary adenocarcinoma "in which cylindric tumor cells grow upon the walls of

TABLE 1
Growth patterns (anatomic distribution) of disseminated lung tumors

Growth pattern	Examples
*Lepidic	Bronchioloalveolar carcinoma
*Lymphatic	Lymphangitic carcinomatosis
	Lymphomas, Kaposi sarcoma
*Parenchymal consolidation	Breast carcinoma,
*Nodular (with or without escavation)	Metastases, Bronchioloalveolar cell
	Carcinoma, Lymphomas
*Angiocentric	Lymphomas
*Intravascular	Lymphomas
*Peribronchiolar	Lymphangitic carcinomatosis,
	Kaposi sarcoma
*Pleural/subpleural	Lymphangitic carcinomatosis,
	Lymphomas

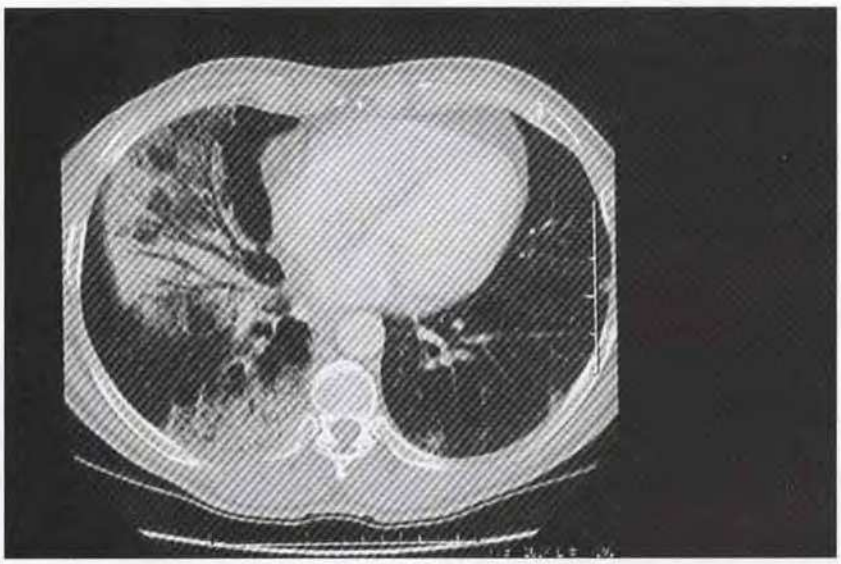

Fig. 1A – HRCT: areas of alveolar and ground glass opacification in the right lower lobe and in the left lobe (BAC, mucinous subtype)

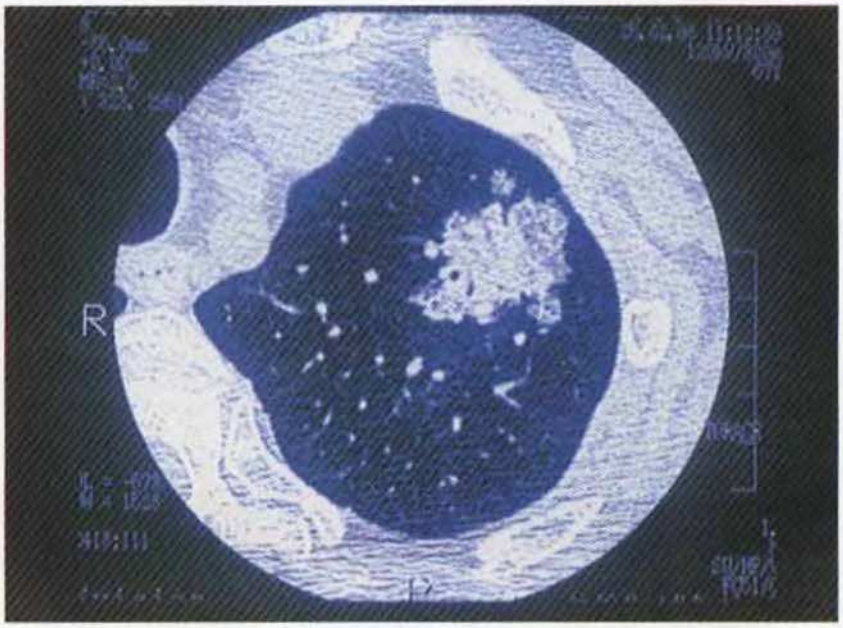

Fig. 1B – HRCT: a core of alveolar opacification surrounded by ground glass atenuation and a crazy paving in the upper right lobe (BAC, nonmucinous subtype)

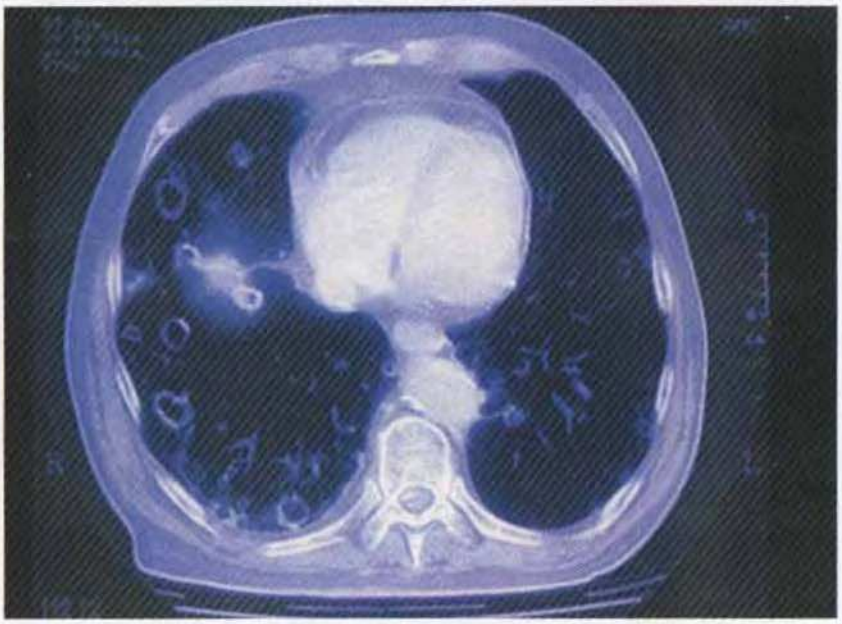

Fig. 1C – HRCT: cysts with a thick wall in the lung ("socalled cherrios in the lung") (BAC with papillary aspects)

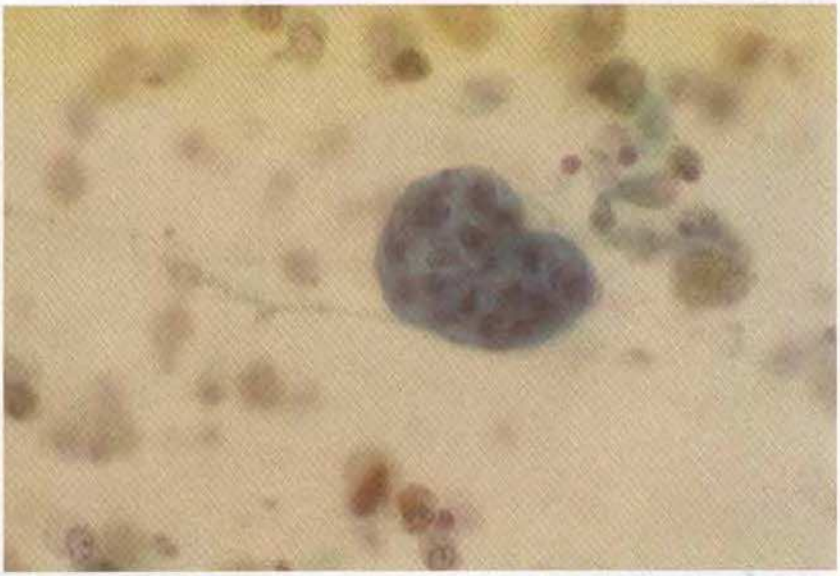

Fig. 1D – BAL, Papanicolaou stained smear. A true papilla consisting of neoplastic epithelial cells

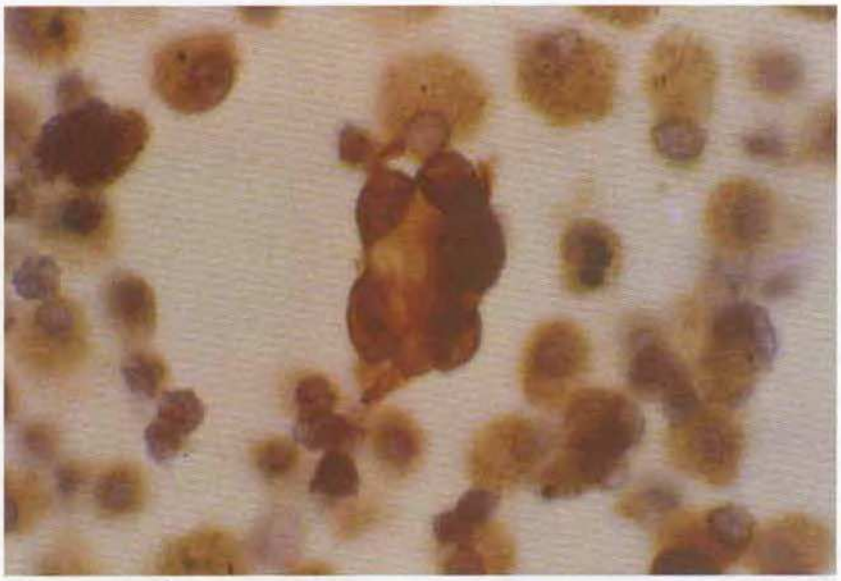

Fig. 1E – BAL. Neoplastic cells are depicted by a anti PE-10 monoclonal antibody (PAP method)

preexisting alveoli". The growth pattern is called "lepidic" because the tumor cells resemble butterflies sitting or alighting on a fence. Neoplastic cells have ultrastructural and immunohistochemical features indicating an origin from Clara cells, bronchiolar goblet cells or type II pneumocytes.

The key feature of BAC is preservation of the underlying architecture of the lung. Histologically BACs are separatd into major subtypes: nonmucinous consisting of cuboidal or hobnail-shaped cells and mucinous variant composed of tall, uniform, columnar mucinous cells. Most nonmucinous BACs have mild interstitial thickening and fibrosis and a mild interstitial infiltrate of T lymphocytes and plasmacells.Electron microscopy and immunohistochemistry have also identifed Langherans cells in the interstitial infiltrate. When discernible "scar" can be recognized both grossly and microscopically the term "sclerosing BAC " is used.

Mucinous BACs may be associated with a B-cell lymphocytic response in the form of lymphoid hyperplasia of BALT (bronchus associated lymphoid tissue). A BOOP-like reaction around neoplastic infiltration can also be observed.

A characteristic histologic feature of BACs which probably correlates with aerogenous spread, is the presence of single cells, acinar clusters, and papillary groups lying free in alveolar spaces. Multifocality has also been documented and atypical adenomatous hyperplasia is considered a preneoplastic trasnformation. Diffuse fibrotic process such as idiopathic usual interstitial pneumonitis (UIP), UIP associated to collagen-vascular diseases, busulfan induced fibrosis, radiation fibrosis, lipoid pneumonia, histiocytosis X, Hodgkin's disease can develop diffuse BAC. Small nodules with histology and immunohistochemistry findings identical to that found in BAC but with an umpredictable biological behavior have been described in young people treated wtih bleomycin for germ cell tumors or osteosarcoma. Numerous extrapulmonary tumors can metastatize to the lung parenchyma in a manner indistinguishable from a primary BAC: tumors from colon, breast, pancreas, stomach, ovary, biliary tract, prostate, uterus, kidney, urinary bladder, esophagus, adrenal, larynx, smal bowel, skin, melanoma and mesothelioma.Clinically patients with diffuse form of BAC present with progressive dyspnea, cough, bronchorrea, fatique and weight loss. Increased ESR and, rarely, eosinophilia or a leukemoid reaction can be observed. Prerenal azotemia, hyponatremia, and hypocloremia may result from bronchorrea.Carcinoembryonic antigen and serum CA 19-9 may be elevated.

HRCT findings in BAC are singly or in combination: diffuse,patchy or multifocal areas of alveolar consolidation that contain air-bronchograms or ground glass attenuation; ill-defined centrilobular nodules; diffuse small nodules mimicking the appearance of hematogenous metastases. Rarely a *crazy paving* pattern or escaveted nodules ("cherrios in the lung") have been reported.

The clinical-roentgenological list of disorders that need to be differentiated from disseminated BAC is reported in Table 2.

An alveolar opacification appearing in a fibrotic lung need to be considerd as BAC until the contrary is proven.

Diagnosis is established by either sputum cytology BAL and/or transbronchial lung biopsy.

Bronchoalveolar lavage has a high diagnostic yield (more than 90%) expecially in cases with an alveolar or ground *glass* attenuation on HRCT Scan. Clusters of cells with three-dimensional configuration are the cytological counterpart of tumor papillae.The clear cytoplasm and a mosaic-appearance clustering of neoplastic cells is typical of the mucinous variant. The simility of single cancer cells to alveolar macrophages is sometimes very stiking, except for the configuration of the nuclei.

A summary of cytologic features of BAC is listed in Table 3.

From the practical point of view smears are to be preferred to cytospin preps because more cells are screened and Papanicolaou stain is the favorite method to use for a definitive diagnosis.

The differential diagnosis of BAC in BAL preps is

TABLE 2

List of disorders mimicking BAC

* chronic infections
* BOOP
* chronic eosihophilic pneumonia (CEP)
* pulmonary lymphomas (expecially low grade lymphocytic lymphomas)
* alveolar proteinosis
* lung metastases with nodular or alveolar pattern or other multifocal nodular tumors primary in the lung (epithelioid hemangioendothelioma...)
* pulmonary infarction
* chronic thromboembolism with pulmonary hypertension
* drug induced lung disease
* Desquamative interstitial pneumonitis (DIP)
* Hypersensitivity Pneumonitis (HP)

TABLE 3

Cytologic features of BAC in BAL preps

* bland neoplastic cells in clusters
* papillary fronds
* cells with clear cytoplasm and a mosaic pattern of clustering
* psammoma bodies (infrequent) single cells resembling alveolar macrophages
* depth of focus (three-dimensional clusters)
* nuclear pseudoinclusions
* nuclei have slight degree of lobulation

with organizing pneumonia, pulmonary infarction, diffuse alveolar damage (in this cases extracellular amorphous cyanophilic, metacromatic, material is usually evident), drug induced cell damage. A good criterium to use is time: infact atypical cells are no more detectable in BAL fluid performed one month later the starting of inflammatory-reactive process.

BAL fluid profile in BAC can be characterized by an increase of lymphocytes, neutrophils or also eosinophils. A relationship between the number of neutrophils and the level of IL-8 in BAL fluid was reported; the tumor cells were the predominant cells that appeared to express IL-B.The neutrophil percentage in BAL fluid appeared to be an independent predictor of poorer outcome in patients with BAC.

LYMPHANGITIC CARCINOMATOSIS

As the name implies, pulmonary lymphangitic carcinomatosis (LC) is characterized by metastatic tumor growth in the pulmonary lymphatics.Grossly

the lungs usually show diffuse linear and nodular thickening of the bronchovascular bundles, interlobular septa, and pleural and subpleural regions, that is the location of pulmonary lymphatics. Submucosal involvement is endoscopically visible in a minority of cases. Hilar or mediastinal lymph nodes can be infiltrated by neoplastic cells.

Microscopically tumor cells are found as plugs within open lymphatics, with variable associated amounts of free interstitial tumor, intraalveolar tumor (so-called "tumor pneumonia"), neoplastic trombi, edema, inflammation and desmoplastic response. The cell type is usually adenocarcinoma, and the most common primary sites are lung, breast and gastrointestinal site. However the list of epithelial or mesenchymal tumors that can metastasize to the lung through lymphatics is quite long (kidney, prostate, lung, thyroid, uterus, ovary, liver, bladder, nasopharynx, malignant carcinoids tumors arising in the abdomen, melanoma, leyomiosarcoma, mesothelioma). Clinically the syndrome is characterized by the insidious onset of dyspnea and an irritating cough due to submucosal endobronchial lymphatic involvement. Rarely asmathic symtoms are present. LC produces restrictive ventilatory impairment, stiff noncompliant lungs, a reduction in the diffusing capacity for carbon monoxide, severe hypoxiemia. Pulmonary hypertension is observed during the clinical course.

The radiographic manifestations of pulmonary LC include reticular opacities, septal lines (Kerley B lines), hilar and mediastinal lymphoadenopathy, and pleural effusion. HRCT Scan findings are more specific: thickening of the peribronchovascular interstitium surrounding vessels and bronchi in the parahilar lung; interlobular septal thickening and subpleural interstitial thickening that is smooth, or nodular and "beaded"; thickening of the peribronchovascular axial interstitium in the centrilobular zones and a preservation of normal lung architecture at the lobular level. Areas of ground glass attenuation can coexit for the presence of "tumoral pneumonia" or secondary changes (alveolar hemorrhage, BOOP). The distribution can be diffuse, patchy or unilateral.

As many as 50 per cent cases of histologically proven pulmonary lymphatic carcinomatosis present with normal radiographs; perfusion scan may highlight abnormalities in blood vessels. However HRCT Scan increases the diagnostic sensitivity significantly.

The differential diagnosis of LC is listed in Table 4.

Bronchoscopy is the favorite diagnostic approach. Mucosal biopsies can be diagnostic also in cases in which submucosal is not evident. Transbronchial lung biopsy has a high diagnostic yield because forceps sample the centrilobular zone where lymphatics are numerous. Bronchoalveolar lavage has a diagnostic yield of about 80 per cent. Anaplastic tumors can be hardly identified in BAL smears because neoplastic cells are usually not arranged in clusters and can easily be missed. Immucytochemistry can be used to detect proteins expressed by neoplastic cells (PSA, tyreoglobulin, antimelanoma antibodies).

TABLE 4
List of disorders mimicking lymphangitic carcinomatosis

* sarcoidosis
* coal worker pneumoconiosis
* silicosis
* pulmonary edema
* veno-occlusive disease

HEMATOGENOUS (NODULAR) METASTASES (Fig. 2)

The lung is a particularly receptive organ because it recieves the entire cardiac output and a meshwork of capillaries may easily entrap tumor cells. Hematogenous metastases typically result in multiple well-defined nodules. The nodules has smooth, weel-defined borders and some of them may be seen to be related to small branches of pulmonary vessels. Cavitation can occur. It is most often seen in squamous cell carcinoma but can be observed in adenocarcinoma or sarcomas.

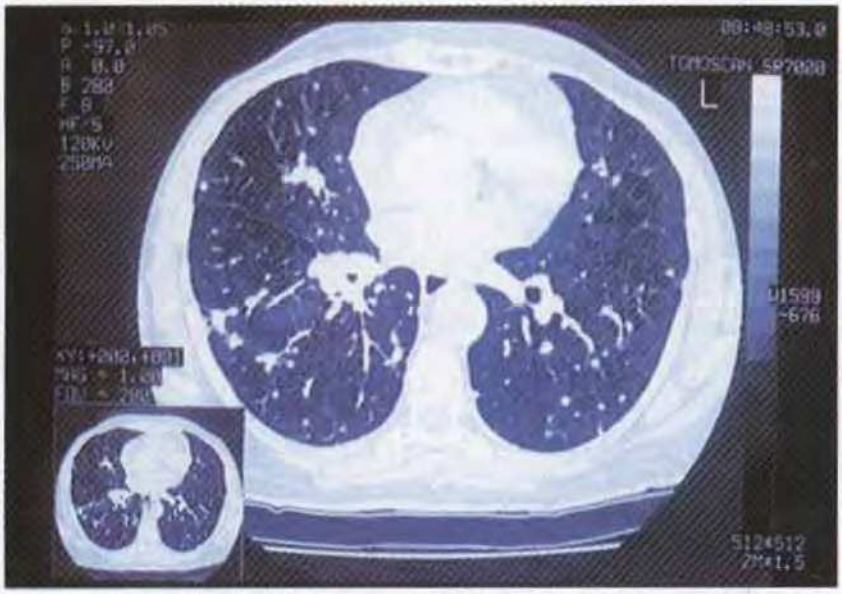

Fig. 2 – HRCT. nodules with a random distribution. Metastases from colon adenocarcinoma

The relationship of metastatic nodules to lobular structures has been studied using HRCT, specimen radiographs, and stereomicroscopy by Murata et al.

Nodules appear widely distributed throughout pulmonary lobules as seen on HRCT, and no predominance in specific lobular regions was noted. Eleven per cent of small nodules appeared centrilobular, 68 per cent were intralobular, and 21 per cent were seen in relation to interlobular septa (random distribution).

BAL has a minor role in the diagnosis of hematogenous metastases the sensitivity beeing less than 50 per cent. If the nodules are cavitated or a rim of ground glass attenuation around the central portion of the nodules is evident (and it is expression of a peripheral "lepidic " o "lymphangitic" growth in lung parenchyma) the diagnostic yield of BAL can increase.

LYMPHORETICULAR TUMORS (Fig. 3)

Lymphoreticular tumors commonly involve the lung particularly in patients with systemic disease or lymph node based lymphomas. Rarely the lung may be the site of presentation and the only site initially involved. The clinical and roentgenological features of these disorders are nonspecific and the differential diagnosis is usually with pulmonary infections, drug or radiation related disorders. From the practical point of view four rules are being presented:

1. the cytological spectrum of lymphomyeloproliferative lung disorders is large varying from small lymphocytic and monocytic disorders to large cell anaplastic lymphomas and other entities with cytological elements frankly indicating a malignant nature.
2. with lymphoreticular infiltrates, the lymphatic channels are usually incospicuous, although the cellular infiltrates show the same distribution as the lymphatic channels (lymphatic distribution or "lymphatic tracking").
3. the monoclonal nature of the disorder can easily be documented in B cell lymphomas that have a rich neoplastic component; clonal population of B cells with Ig heavy and usually light chain gene rearrangements or a monoclonal rearrangement of TCR is hard to document expecially in BAL fluid samples in

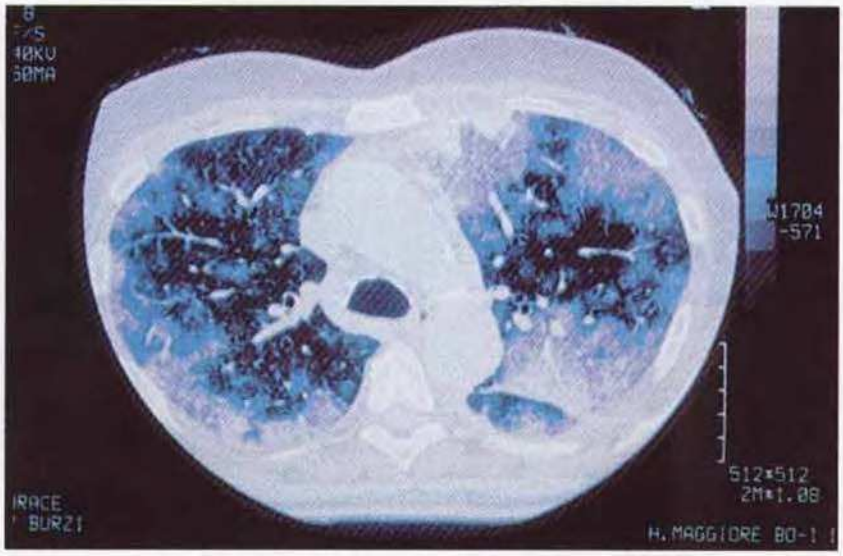

Fig. 3 A – HRCT: patchy, subpleural areas of ground glass attenuation (Low grade B cell lymphoma of MALT type)

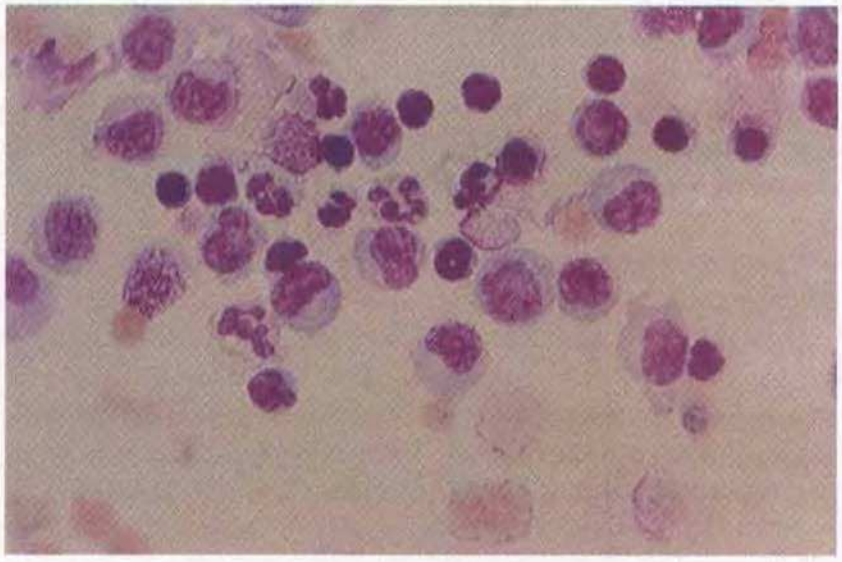

Fig. 3 B – BAL. MGG smear with atypical lymphoid cells (lymphoplasmocytoid and centrocytic like cells) in the case of Fig. 3A)

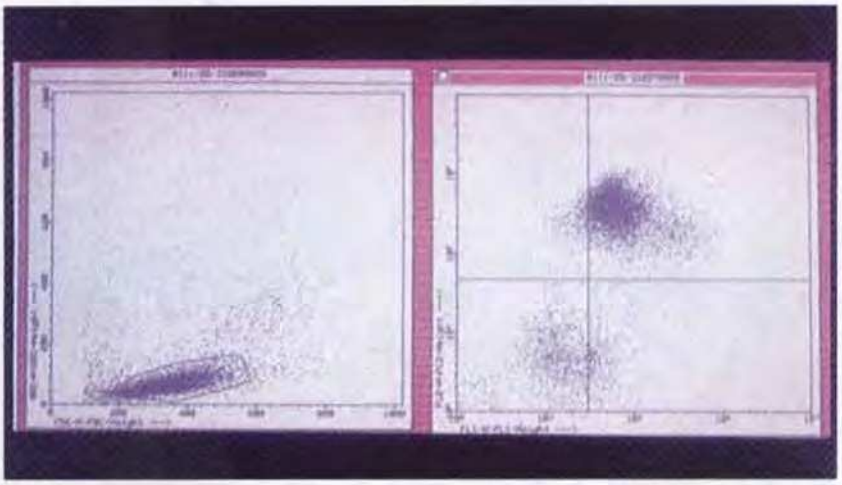

Fig. 3 C – BAL. Flow cytometry analysis. A monotypic light chain restriction is evident (Kappa + cells=76 per cent)

T cell-rich B cell lymphomas or in T cell lymphomas. The diagnosis of Hodgkin' s disease relies on the evidence of typical Reed Sternberg cells or Hodgkin's cells (if a previous diagnosis of extrapulmonary Hodgkin's lymphoma has been documented).

4. BAL sensitivity and specificity is much higher in lymphomas with a rich component of neoplastic cells and with an alveolar or ground glass pattern in HRCT Scan films.

Two entities have gained special interest in this group of lesions expecially because they can present as primary in the lung and mimick other nonneoplastic lung lesions: low grade B cell lymphomas presumably derived from the MALT (Mucosa associated lymphoid tissue) and the so-called "Lymphomatoid Granulomnatosis".

MALT lymphomas were first described by Isaacson and Wright in 1983 in a small series of patients with low-grade B-cell gastrointestinal lymphomas.

Although MALT lymphomas occur most frequently in the stomach they have also been reported in various nongastrointestinal sites and the lung ranks as one of the most involved organs outside GI tract.

MALT-lymphomas are characterized by neoplastic marginal cells (that have a centrocytic-like appearance), wich display a variable combination of colonization of reactive germinal centers, plasmacytic differentiation, and destructive epithelial infiltration forming lymphoepithelial lesions. Paradoxically, MALT lymphomas only occasionally arise from sites where MALT is normally present, such as tonsil and Peyer's patches.The reason for this seems to be that MALT lymphomas generally arise in lymphoid tissue that has been acquired as a result of some pre-existing disorder, eg, *Helicobacter pylori* colonization in the stomach, follicular bronchoectasis in the lung, autoimmune diseases (Sjogren's disease), myasthenia gravis and reactive or inflammatory lesions. The literature contains reports of a correlation between hepatitis C virus infection and extranodal MALT lymphomas. The neoplastic cells of MALT lymphomas express surface and (to a lesser extent) cytoplasmic immunoglobulin, *bcl-2* protein and show light chain restriction. They are CD5-,CD10- and Cdl9+CD2O+. The *bcl-2* oncogene is not rearranged in low grade MALT lymphomas, in contrast to follicular lymphomas. The outcome and prognosis for low

grade MALT lymphomas are more favorable than other extranodal lymphomas.

In the lung MALT lymphomas can present with alveolar shadowing on HRCT Scan films or less frequently with areas of ground glass attenuation or with a nodular pattern. The **diagnosis can be easily made with BAL** in the cases with alveolar and/or gound glass attenuation. BAL fluid is usually characterized by the presence of centrocytic-like cells or plasmacytic cells. Sometimes morphology is not characteristic and the differential diagnosis is with BOOP, hypersensitivity pneumonitis, drug induced lung disease or other disorders with an increase of lymphocytes in BAL fluid.

Flow cytometry analysis is mandatory because it confirms the B nature of the cells (CDl9+,CD2O+) and frequently the light chain restriction (Kappa or Lambda). Some case reports have shown that in BAL fluid a monoclonal rearrangement of the genes coding for immunoglobulins can be detected by molecular biology techniques.

In cases with nodular pattern the definitive diagnosis requires a surgical lung biopsy. Liebow and coworkers first described lymphomatoid granulomatosis in a classic article in 1972. This entity still exists but ,pratically speaking, it is clinically and histogenetically closest to lymphomas. Lesions described as lymphomatoid granulomatosis (LYG), polymorphic reticulosis, lymphocytic benign and malignant angiitis and granulomatosis, and angiocentric immunoproliferative lesions (AIL) are all included in the group called by Katzenstein and Colby AIL/LYG. Early studies suggested AIL/LYG was a T-cell proliferative process, although recent data suggest that some cases (probably the majority of them) are T-cell-rich, B-cell proliferations in which the B cells are infected by Epstein-Barr virus. Similar lesions have been reported in immunocompromised hosts or as post-transplant lymphoproliferative lesions.

Patients with AIL/LYG usualy present with symptoms related to lung involvement such as cough, chest pain, or hemoptysis or with various systemic complaints including fever, weight loss, and malaise. Extrapulmonary manifestations, expecially skin lesions and neurologic signs, are common and occasionally preced the onset of lung lesions.

Macroscopically there is nodular consolidation of the lung with nodules up to 10 cm in diameter,often with central necrosis and a rim of viable tissue... Microscopically the nodules and infiltrates tend to be centered on, or adjacent to, the structures along lymphatic routes. The infiltrating cells consist of a polymorphous mixture of mononuclear cells, including small lymphocytes, plasma cells, histiocytes, and depending on the spectrum from low grade to high grade, large transformed lymphoid cells.

Radiographically, bilateral nodules are present in three fourths of the patients. The nodules may wax and wane spontaneously, and cavitation is relatively common. Less common patterns include diffuse interstitial or alveolar infiltrates, localized infiltrates and solitary nodules. The diagnosis is made on the basis of a lung surgical biopsy. BAL can be useful because scattered lymphoid atypical large cells can be seen.

BAL can be useful and may allow to make a definitive diagnosis in lymph node based lymphoproliferative lesions involving the lung: chronic lymphocytic leukemia, follicular B cell lymphomas, anaplastic large cell lymphomas and other large cell lymphomas, Hodgkin disease, HTLV-1 related lymphomas/leukemias, with a diagnostic yield variyng from 60-70 per cent to a low 33 per cent (Hodgkin disease) as reported by Poletti and coworkers.

BAL is useful also in the diagnosis of lung involvement due to myeloid leukemias.

OTHER USUALLY RARER DISSEMINATED LUNG TUMORS

Primary nonepithelial lung tumors that can be disseminated at the onset are: Kaposi's sarcoma; epithelioid hemangioendothelioma (the so called intravascular bronchioloalveolar tumor or IVBAT); sarcomas of the pulmonary arteries; minute pulmo-

nary meningoendothelial-like nodules, multinodular hyperplasia of type II pneumocytes. BAL is not useful for diagnostic purposes but it can be part of the diagnostic steps to exclude infections or othe more usual entities.

CONCLUSIONS

Disseminated lung tumors are a relevant clinical problem in the era of chemotherapy salvage protocols and the differential diagnosis is with drug and radiation induced lung toxicity, pulmonary infections in immunocompromised host or idiopathic infiltrative lung diseases. BAL is a useful diagnostic tool in this field. Its diagnostic sensitivity is higher in bronchioloalveolar carcinoma, lymphangitic carcinomatosis; some lymphoproliferative lung neoplasms can be neatly diagnosed if morphology is coupled with flow cytometry analysis (Table 5).

Clinicians can predict the diagnostic yield and utility of BAL if HRCT Scan findings are taken into account, alveolar and ground glass opacification and linear and nodular opacities along the lymphatics beeing the more favorable patterns.

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TABLE 5

Diagnostic yield of BAL in disseminated tumors (Poletti V, personal experience)

Bronchioloalveolar cell carcinoma	93%
Lymphangitic carcinomatosis	86%
Nodular hematogenous metastases	45%
Non Hodgkin lymphomas	67% (§)
Hodgkin disease	33%

(§) In cases with alveolar and or ground glass opacifications in HRCT Scan films BAL has a higher diagnostic sensitivity

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