



FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

**TRABALHO FINAL DO 6º ANO MÉDICO COM VISTA À ATRIBUIÇÃO DO
GRAU DE MESTRE NO ÂMBITO DO CICLO DE ESTUDOS DE MESTRADO
INTEGRADO EM MEDICINA**

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***PRIMARY LYMPHOPROLIFERATIVE LUNG
DISORDERS: A RETROSPECTIVE STUDY***

ARTIGO CIENTÍFICO

ÁREA CIENTÍFICA DE PNEUMOLOGIA

**TRABALHO REALIZADO SOB A ORIENTAÇÃO DE:
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MARÇO DE 2013

Primary Lymphoproliferative Lung Disorders: a retrospective study

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This work was made in accordance with the instructions for authors for research articles of Orphanet Journal of Rare Diseases (available on <http://www.ajrd.com/authors/instructions>)

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Abstract

Background: The lymphoproliferative lung disorders are an extended and heterogeneous group of diseases that can affect the lung either primarily or secondarily, and are characterized by an abnormal proliferation of the pulmonary lymphoid system. They are mostly rare and incompletely understood entities, having thus driven an important research effort in the last decades. We aim to improve the current knowledge of the various types of lymphoproliferative lung disorders, particularly the Portuguese reality.

Methods: A retrospective study, including all patients (23 patients, 8 males and 13 females) followed at our centre carrying a final diagnosis of lymphoproliferative lung disorders, between January 2006 and February 2012. All patients with a diagnosis of secondary pulmonary involvement were excluded. A database was created allowing the establishment of groups of patients according to the diagnosis and other variables.

Results: We found 9 patients with follicular bronchiolitis and 2 with lymphocytic interstitial pneumonia (both reactive disorders), 1 pulmonary Hodgkin's lymphoma, 5 with bronchus-associated lymphoid tissue lymphoma, 1 patient with large B-cell lymphoma, 1 with peripheral T-cell lymphoma unspecified and 1 with lymphoblastic T-cell lymphoma, representing the malignant disorders (there were also 3 B-cell lymphomas with no specified subtype). For all disorders we presented the demographic features, habits, associated disorders, presenting symptoms, imaging and histological findings, treatment used and follow-up.

Discussion: The characteristics of the lymphoproliferative lung disorders found in our hospital are similar to those described in the literature.

Conclusion: We provide an update on the classification of lymphoproliferative lung disorders. Our study gives an indication that most recommendations on diagnosis, treatment

and prognosis derived from international studies can be applied to the Portuguese population. Finally the description of this case series is a valuable addition to the available knowledge on the characteristics of patients with pulmonary lymphoproliferative disorders, particularly concerning the Portuguese reality.

Keywords: Lymphoproliferative Lung Disorders; Follicular Bronchiolitis; Lymphocytic Interstitial Pneumonia; Lymphoma; MALT

Resumo

Introdução: As doenças linfoproliferativas do pulmão são um grupo extenso e heterogéneo de doenças que podem afectar o pulmão quer de forma primária quer secundária e que se caracterizam pela proliferação anormal do sistema linfóide pulmonar. São entidades raras e não completamente conhecidas, que levaram a um importante esforço de investigação nas últimas décadas. O nosso objectivo é melhorar o conhecimento sobre os vários tipos de doenças linfoproliferativas do pulmão, em especial da realidade Portuguesa.

Métodos: Estudo retrospectivo, incluindo todos os doentes (23 doentes, 8 do sexo masculino e 13 do sexo feminino) seguidos no nosso centro com o diagnóstico final de doença linfoproliferativa pulmonar, entre Janeiro de 2006 e Fevereiro de 2012. Os doentes com envolvimento pulmonar secundário foram excluídos. Foi criada uma base de dados de forma a estabelecer grupos de doentes de acordo com o diagnóstico e outras variáveis.

Resultados: No nosso estudo, houve 9 doentes com bronquiolite folicular, 2 com pneumonia intersticial linfocítica (ambas doenças reactivas), 1 caso de linfoma de Hodgkin pulmonar, 5 linfomas de tecido linfóide associado aos brônquios, 1 doente com linfoma B de grandes células, 1 com linfoma T periférico não especificado e 1 linfoma T linfoblástico, representando as doenças malignas (houve ainda 3 linfomas B sem subtipo especificado). Para todas as doenças apresentámos as características demográficas, hábitos, doenças associadas, sintomas de apresentação, achados imagiológicos e histológicos, tratamento aplicado e o seguimento.

Discussão: A maioria das características das doenças linfoproliferativas do pulmão encontradas no nosso hospital, são semelhantes às já descritas na literatura.

Conclusão: Este artigo fornece uma classificação actualizada das doenças linfoproliferativas do pulmão. O nosso estudo dá uma indicação de que a maioria das recomendações sobre o

diagnóstico, tratamento e prognóstico, proveniente de estudos internacionais podem ser aplicados à população Portuguesa. Finalmente, a descrição desta série de casos é uma adição valiosa ao conhecimento disponível sobre as características dos doentes com doenças linfoproliferativas do pulmão, particularmente sobre a realidade Portuguesa.

Palavras-chave: Doenças Linfoproliferativas do Pulmão; Bronquite Folicular; Pneumonia Intersticial Linfocítica; Linfoma; MALT

Background

The lymphoproliferative lung disorders (LPLD) are an extended and heterogeneous group of diseases that can occur as primary pulmonary disease or as a secondary involvement by a systemic disorder.[1] LPLDs are characterized by an abnormal proliferation of the pulmonary lymphoid system, and development of parenchymal infiltrates consisting of cells of this lineage.[2] They can be asymptomatic or symptomatic presenting with cough, dyspnea, pain, fever and systemic symptoms.[3,4] Radiological features include pulmonary consolidations and opacities, pleural effusion and mediastinal adenopathies.[3,4] Histological analysis and assessment of clonality (with immunochemistry and molecular biology) are required for the diagnosis, which sometimes is difficult to achieve.[3] Treatment and prognosis depend on the histology.[3,4]

They are mostly rare and incompletely understood entities[4], having thus driven an important research effort in the last decades.[5] A clear classification of LPLDs would certainly be important for an improved understanding of the various diseases and easier patient approach, but this has been difficult to achieve. The currently most accepted classification system is based primarily on the diseases being either reactive or malignant. [3,5] A proposed classification of LPLDs can be seen at Fig.1. Lymphoma's staging was made using the Ann Arbor classification.[6] Due to the rarity of these disorders, there is also a general lack of data concerning their various forms, particularly regarding their epidemiology and clinical, imaging and phenotypic features. This paper is thus an attempt at improving our knowledge of the various types of LPLDs, by describing our local cohort of patients, including their clinical and laboratory characteristics. We also establish a comparison between our reality and the one described by other case series. Our goal is to ultimately contribute to a better knowledge of these disorders, particularly the Portuguese reality.

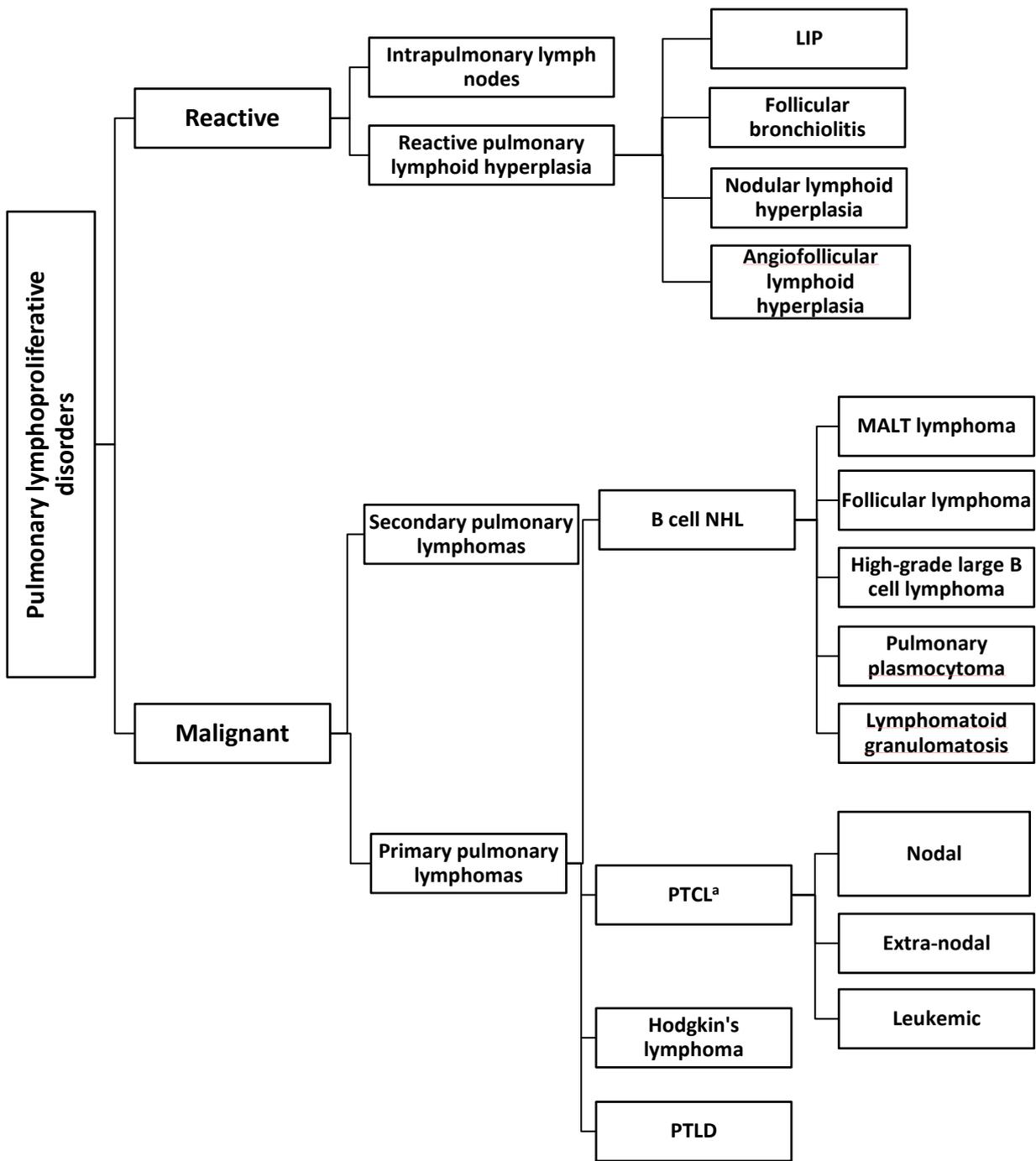


Figure 1 Proposed classification of Lymphoproliferative lung disorders (adapted from 5)

LIP: lymphocytic interstitial pneumonia; PTCL: peripheral T-cell lymphoma; PTL: post-transplant lymphoproliferative disorder

^a WHO divided PTCL in 3 categories (nodal, extra-nodal and leukemic) according to their localization. T-cell lymphomas are divided in 13 subtypes: anaplastic large-cell lymphoma, anaplastic large cell lymphoma (primary cutaneous), cutaneous T-cell lymphomas, angioimmunoblastic T-Cell lymphoma, peripheral T-Cell lymphoma unspecified, enteropathy-associated lymphoma, hepatosplenic lymphoma, nasal Natural Killer (NK)/T-cell lymphoma, subcutaneous panniculitis-like lymphoma, precursor T-Cell acute lymphoblastic lymphoma or leukemia, adult T-cell acute lymphoblastic lymphoma or leukemia, Mycosis fungoides/Sézary syndrome and blastic NK-Cell lymphoma[7,8]

Methods

We performed a retrospective study, including all patients (23 patients, 8 males and 13 females) followed at our centre carrying a final diagnosis of LPLD, between January 2006 and February 2012. Patients were identified through a search of the hospitals' diagnosis database. All patients with a diagnosis of secondary pulmonary involvement were excluded from the analysis. The relevant data were collected from the individual case files, and included the patients' clinical, imaging and laboratory characteristics. Special care was given to the immunophenotyping, as this frequently gives important information about the specific patient's diagnosis.

A database was created allowing the establishment of groups of patients according to the diagnosis and other variables. Values are presented as median \pm interquartile range (IQR). Means \pm standard deviation (σ) are also displayed in order to allow comparison with previous studies. Comparisons among groups were tested by Chi-square. In order to compare the survival between the group of patients with reactive disorders and the group of those who had malignant disorders and also to compare with the group with normal and the group with elevated lactate dehydrogenase (LDH) value (LDH value is considered elevated if > 248 U/L), we used the survival function with Kaplan-Meier. All statistical tests were two-tailed and a p value <0.05 was considered significant. The analysis was performed using SPSS20.0 for Windows (SPSS Inc, Chicago, IL, USA).

This study was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra.

Results

A total of 23 patients were included (8 males and 13 females). The patients' demographic characteristics and diagnosis distribution can be seen in Table 1. The most frequent diseases were FB (nine patients) and BALT lymphoma (five patients). A significant female predominance was found in almost all the groups. There was an even distribution between reactive and malignant disease. No significant age differences were found between these two groups, as well as between female and male groups. Due to the significant heterogeneity in these disorders, the results are presented and discussed in groups.

Table 1 Distribution of the sample by disorder and gender with respective median and mean age of onset of symptoms

		Nr (% males)	Median Age (\pm IQR)	Mean Age ($\pm \sigma$)
Total		23 (34.8%)	64,5 (\pm 13)	61.4 (\pm 15,6)
Benign	FB	9 (33.3%)		
	LIP	2 (50%)		
	Total	11 (36.4%)	66 (\pm 16)	60.8 (\pm 18,2)
Malignant	Hodgkin's lymphoma	1 (0%)		
	B-cell lymphoma	9 (3.3%)		
	T-cell lymphoma	2 (50%)		
	Total	12 (33.3%)	64 (\pm 7)	62.0 (\pm 13,3)

IQR: interquartile range; σ : standard deviation; FB: follicular bronchiolitis; LIP: lymphocytic interstitial pneumonia

Reactive diseases

The demographic, clinical and radiological characteristics, also as follow-up of patients with reactive diseases are described in Table 2.

Follicular bronchiolitis

Nine patients with FB were found, with an average age of 60.7 years. Most patients exhibited symptoms, and prior medical history included autoimmune thyroiditis in one patient and pulmonary tuberculosis in another. Normal lung function tests was the most common pattern found. Concerning blood tests, the erythrocyte sedimentation rate (ESR) was only measured in two patients, showing 16 and 32 mm/h and LDH wasn't measured in any patient. The diagnosis of FB was always made by lung biopsy. Pathological analysis described the normal pulmonary architecture being replaced by lymphoid follicles with associated reactive germinal centers. Immunohistochemically, the presence of lymphoid cells was confirmed by the positivity to CD45, and an epithelial nature was excluded (negativity for MNF116). The presence of B-cells was confirmed by CD20 marker, and the T-cells of the interstitial component, by the positivity for the CD3 marker.

No patient was subjected to any specific treatment for this disorder. In terms of prognosis, two of the 9 patients died during the follow-up. Patient 6 died with 72 years, more than a year after FB diagnosis, from renal cell carcinoma. Patient 7 died at 90 years, two years after FB diagnosis, from terminal chronic cardiac and renal failure.

Lymphocytic interstitial pneumonia

There were two patients with LIP, with an average age of 61.5 years old. They were both smokers (average 12.5 pack-years) and had no other relevant medical history. Pulmonary function study showed a restrictive pattern in one patient and a normal pattern in the other.

Both patients had bronchoscopy, where inflammatory changes were found. Bronchoalveolar lavage was performed in one patient and revealed a lymphocytic alveolitis. The serum proteins were studied in one patient and revealed hypergammaglobulinemia. Regarding laboratory findings (only available for patient 10), the ESR was 21mm/h and the LDH of 730 U/L.

The diagnoses were made by transbronchial or by transthoracic lung biopsy: pathology showed a dense polymorphous interstitial inflammatory infiltrate diffusely expanding to the inter-alveolar septa. At the biopsy, alveolar content was scarce and showed thickened alveolar spaces in association with type II pneumocyte hyperplasia (in both).

One patient received no specific treatment, whereas the other was treated with steroids (0.5mg/kg per day of prednisone equivalent for 5 months). The latter patient died in less than a year from prostate carcinoma.

Table 1 Patients with reactive disorders.

Patient	Diagnosis	Age	Gender	Clinical manifestations		Main imaging features	Follow-up (months)	Death
				Pulmonary symptoms	B symptoms			
1	FB	69	Female	Present	Absent	Centrilobular nodules	76.3	No
2	FB	54	Female	Present	Present	Reticular infiltrates, centrilobular nodules, lymphadenopathy and bronchiectasis	0.8	No
3	FB	26	Male	Present	Absent	Reticular infiltrates	42.7	No
4	FB	32	Male	Present	Present	Reticular infiltrates and bronchiectasis	31.9	No
5	FB	72	Female	Absent	Absent	Centrilobular nodules and reticular infiltrates	15.5	No
6	FB	70	Female	Absent	Absent	Centrilobular nodules	15.6	Yes
7	FB	90	Female	Present	Absent	Nodules	21.7	Yes
8	FB	65	Male	Present	Present	Ground glass opacification and reticulonodular images	43.8	No
9	FB	68	Female	Present	Absent	Bronchiectasis centrilobular and reticular infiltrates	31.6	No
10	LIP	66	Male	Present	Absent	Reticular infiltrates and ground glass opacification	6.0	Yes
11	LIP	57	Female	Absent	Absent	Bibasilar cystic lesions	11.4	No

FB: follicular bronchitis; LIP: lymphocytic interstitial pneumonia

Malignant diseases

The epidemiology, clinical and radiological characteristics, as well as staging, treatment and follow-up of patients with malignant diseases are described in Table 3.

Primary pulmonary Hodgkin's lymphoma

Only one case of this disease was found. No information concerning the patients' symptoms and imaging was available. The patient had an ESR of 50 mm/h and LDH of 221 U/L. The immunoglobulin test included IgG and IgA at normal range, low IgM, and normal levels of lambda and kappa light chains. The diagnosis was achieved histologically. The lung's common morphology was altered by the presence of a heterogeneous cell population, including T-lymphocytes, plasmocytes, eosinophils and atypical cells characterized by the cytological features of Reed-Sternberg cells (recognized by the strong expression of activation markers, CD30 and CD15). There were also lacunar cells with multilobar nucleus that characterizes nodular sclerosis. The stage of the tumor couldn't be defined due to lack of case file information. The patient was subjected to chemotherapy, but the agents were not specified. She died 15 months after diagnosis, from lymphoma.

B cell non-Hodgkin lymphoma

Bronchus-associated lymphoid tissue lymphoma

This disease was present in 5 patients, 2 of whom were active smokers (16.25 pack-years). The average age was of 60.6 years old. Most had associated immune

diseases, including HIV infection, connective tissue disorders (systemic lupus erythematosus and Sjögren's syndrome) and concomitant infectious diseases (*Helicobacter pylori*). At the time of diagnosis, only one patient was asymptomatic (Table 3). Pulmonary function tests showed an obstructive pattern in four of the 5 patients and normal result in the other. The most common radiological feature was an isolated, well-delineated mass (Fig.2A). A monoclonal band at the gamma fraction in the electrophoretic serum protein study was present in three patients. They also had an increased amount of IgG heavy chain and of the kappa light chain paraproteins. Only one patient had hypogammaglobulinemia with low levels of IgG and kappa chains. Concerning the laboratory findings, ESR was evaluated in three patients. The values were 5, 72 and 284 mm/h. The LDH was studied in all patients and was elevated in two.

On pathology, an abnormal pulmonary architecture with lymphoepithelial lesions was responsible for the formation of consolidative masses. The neoplastic cells were CD20-positive cells and also variably CD3-positive. The proliferation index, measured by Ki-67 antigen, varied between 4 and 50%.

Regarding treatment, four patients had surgery, (lobectomy with lymphadenectomy). CVP or CVP plus R (cyclophosphamide, vincristine and prednisolone with or without rituximab) were the most frequent chemotherapy combination, followed by CHOP (cyclophosphamide, doxorubicin (chemical name hydroxydaunomycin), vincristine (originally called oncovin) and prednisolone) and M-BACOD (methotrexate, bleomycin, Adriamycin-doxorubicin, cyclophosphamide, Oncovin–vincristine and dexamethasone). As for the outcome, no patient has died so far, but the patient with high-grade disease referred very poor quality of life.

Large pulmonary B-cell lymphoma

Only one patient with this kind of lymphoma was included. She had no associated diseases. The diagnostic was made by open lung biopsy. The patient had a pulmonary mass extending to mediastinal and vascular structures preventing surgical treatment. The chosen therapy was thus chemotherapy. After more than 5 years of follow-up, the patient is still alive, with no major complications.

Other B cell Lymphomas

Three patients had B-cell lymphoma with no specified subtype, with a mean age of 71.3 years old. One had a history of asthma and other positive serologies for Epstein-Barr and herpes *simplex* type 1 viruses. Smoking habits were recorded for two patients (both non-smokers). Presenting pulmonary symptoms included most commonly cough. Spirometry showed normal results in two patients. One patient had tracheobronchial, aortic and diaphragmatic involvement. ESR was measured in all patient and the results were 9, 18 and 96 mm/h. The LDH values were 173, 242 and 338 U/L. Serum protein electrophoresis presented changes in all patients: hypogammaglobulinemia, hypergammaglobulinemia or decreased alpha-2 band.

Biopsy showed agglomerated lymphocyte population, with no preserved lung parenchyma or lymph nodes. The cells were small and round with scant cytoplasm and nuclear regularity. Mitoses were not identified. B-lymphocytes were arranged as diffuse infiltrates or in small clusters bounded by collagen deposition. T-lymphocytes were focally dispersed and some macrophages were also identified. The neoplastic cells showed generalized immunostaining for CD20, and also positive staining for CD10, CD5, BCL2 and BCL6. Cyclin D1 staining was negative. The proliferative index

approached 60%, as assessed by Ki-67. Regarding treatment, all patients were submitted to chemotherapy, one had CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisone), another R-CVP and the third patient was submitted to multiple chemotherapy combinations (CNOP, COP (cyclophosphamide, vincristine and prednisolone), M-BACOD, COP + rituximab and R-CVP). Two patients are still alive. The death of the other patient was related to his lymphoma, and occurred 9 months after the diagnosis.

T cell primary pulmonary lymphomas

Two patients with T-cell primary pulmonary lymphomas were found: one case of lymphoblastic T-cell lymphoma and one of unspecified peripheral T-cell lymphoma.

The lymphoblastic T-cell lymphoma occurred in a 64 year old female. Clinical and radiological data were missing from the case file. The diagnosis was performed by transthoracic lung biopsy. Histologically, the *lamina propria* was replaced by neoplastic cells, with irregular cytoplasm and polymorphic nuclei, showing general immunostaining for CD3. There were also dispersed CD20-positive cells. No information on treatment and outcome were available.

Unspecified peripheral T-cell lymphoma (Fig.2B) occurred in a smoking man (40 pack-years), with a history of necrotizing cutaneous sarcoidosis. The symptoms lasted for one year before the diagnosis. The spirometry showed an obstructive pattern, his ESR was 49mm/h and LDH was 200 U/L. The serum protein electrophoresis showed a possible monoclonal peak in the beta-gamma transition. There was also a hypergammaglobulinemia.

Histologically, a mixed inflammatory infiltrate distributed in a tumefactive fashion with a zone of coagulative necrosis. In many areas the infiltrate included striking numbers of macrophages resulting in a vaguely granulomatous appearance. At immunochemistry evaluation, the atypical cells showed aberrant T-cell phenotype with loss of CD5 and CD7. In addition, the large atypical cells expressed T-cell associated antigen CD3, CD2 and CD4 with co-expression of CD30 and CD15.

In terms of treatment, he was submitted to chemotherapy with the CHOP protocol. After a year of follow-up the patient is alive but reports poor quality of life.

Table 2 Patients with malignant lymphoproliferative disorders. Staging was made using the Ann Arbor classification.

Patient	Diagnosis	Age	Gender	Clinical manifestation		Imaging features	Stage	Treatment	Follow-up (months)	Death
				Pulmonary symptoms	B symptoms					
12	Pulmonary Hodgkin's lymphoma	64	Female					CTP	15.6	Yes
13	BALT lymphoma	58	Female	Present	Present	Generalized alveolar opacities, bronchiectasis and ground glass opacification	I-B	Surgery	46.6	No
14	BALT lymphoma	49	Male	Present	Present	Solitary mass and mediastinal involvement	IV-B	CTP	36.0	No
15	BALT lymphoma	73	Female	Present	Present	Pulmonary masses and adenopathies	II-A-E	CTP and surgery	20.1	No
16	BALT lymphoma	58	Male	Present	Present	Multiple masses, pleural effusion and centrolobular emphysema	II-B	Surgery	1.6	
17	BALT lymphoma	65	Female	Absent	Absent	Reticular infiltrates	I-A	CTP and surgery	66.4	No
18	Large B-cell lymphoma	37	Female	Present	Present	Pulmonary mass and adenopathies	II-B	CTP	64.5	No
19	B-cell lymphoma	65	Female	Absent	Absent	Adenopathies	II-A	CTP	45.9	No
20	B-cell lymphoma	90	Male	Present	Present	Adenopathies	IV-B	CTP	0.8	Yes
21	B-cell lymphoma	59	Female	Present	Absent	Multiple adenopathies and nodules, aortic, diaphragm and tracheobronchial involvement	IV-A	CTP	18.9	No
22	Peripheral T-cell lymphoma	64	Male	Present		Random pulmonary nodules	IV-B-E	CTP	16.9	No
23	Lymphoblastic T-cell lymphoma		Female							

BALT: bronchus-associated lymphoid tissue; CTP: Chemotherapeutic protocol

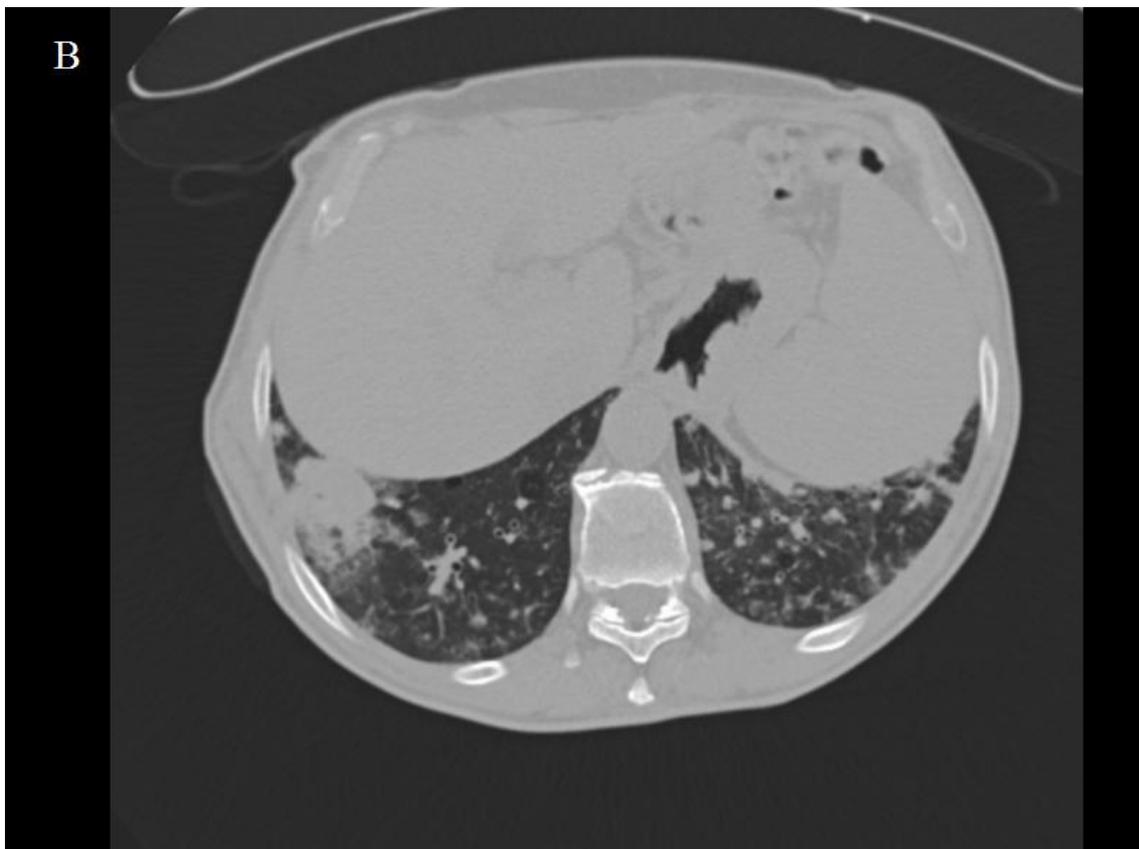


Figure 2 CT scans of **A.**BALT Lymphoma, showing a bulky tumoral mass with mediastinal involvement at the lower left lobe **B.** Unspecified peripheral T-cell lymphoma, with multiple nodular and irregular lesions and extensive micronodular opacities, at lower lobes

Survival analysis

For survival analysis, data was available for 22 patients (14 females and 8 males).

We started by comparing the survival between the group of patients with reactive disorders and malignant disorders, and no statistically significant differences were found (sig=0.63) (Fig.3). After that, we compared the LDH value with the survival, in order to test if an elevated value of LDH was associated with an increased mortality, and though mortality was higher in the group of patients with increased LDH value, no statistically significant differences were found (sig=0.39) (Fig.4).

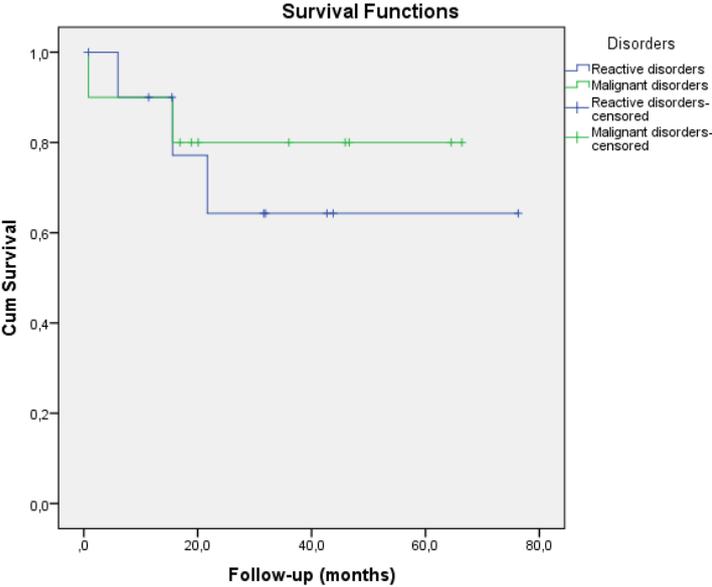


Figure 3. Survival curve (Kaplan-Meier), based on the diagnosis of reactive or malignant disorder

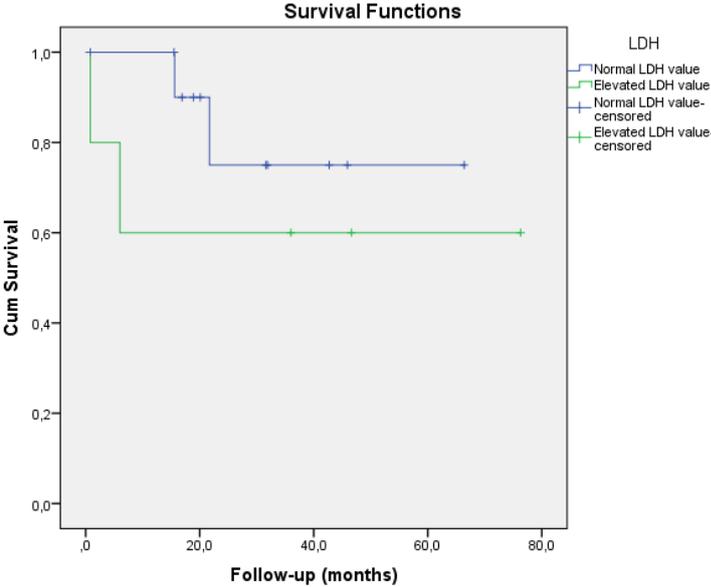


Figure 4. Survival curve (Kaplan-Meier), based on the value of LDH (normal or elevated)

Discussion

This study provides a detailed analysis of a significant cohort of patients with pulmonary lymphoproliferative lung disorders. We included patients with both reactive and malignant diseases, having diverse clinical and pathological manifestations.

Reactive diseases

Follicular bronchiolitis

Follicular bronchiolitis (FB), also known as bronchus-associated lymphoid tissue (BALT) hyperplasia is a term used to describe the presence of hyperplastic follicles with abundant reactive germinal centers that predominate near the airways but can also be present at interlobular septa and visceral pleura.[1,3,5,9-11] It is thought that both FB and LIP result from antigenic stimulation of BALT by a variety of unknown factors, leading in both cases to polyclonal lymphoid hyperplasia.[5,9,10]

The disorder tends to be associated with a variety of systemic conditions, including immunodeficiency, collagen vascular diseases, familial lung disorders or chronic infections.[1,3,5,9,11,12] There are also some cases in which the etiology is uncertain (idiopathic group) possibly related to hypersensitivity states.[5,11] In our study only 9% of patients had a defined etiology.

FB is more prevalent in females and can occur in any age, but more frequently in middle-aged adults.[2,5,10,11,13] These demographic parameters were similar to those found in our study.

At initial assessment, the most frequent complaints were dyspnea and cough, but fever, recurrent upper respiratory tract infections, weight loss or fatigue can be also

present.[1-3,5,9-11,13,14] Our cohort is in agreement with those previously described. Two of the 9 patients did not have symptoms.

In the literature, various patterns on pulmonary function tests are reported.[3,9-11,13] Our patients showed mostly normal results. Chest radiographs characteristically show interstitial reticular or reticulonodular shadowing, sometimes associated with nodular opacities.[3,5,9] All of our patients showed these typical findings. The main CT findings included bilateral centrilobular and peribronchial nodules (often less than 3mm in diameter but sometimes larger).[2,3,9-11,13] Reticular opacities, ground glass opacities, thoracic enlarged lymph nodes and bronchiolar dilatation, are other possible findings.[3,9,10,13] Our results were mostly the same as previously reported, but other changes such as fibrotic traces and air bronchogram were also seen.

Surgical lung biopsy is often required to obtain a definite histological diagnosis.[3,10] This disorder is characterized by the abundant presence of peribronchiolar lymphoid follicles with associated reactive germinal centers and a minor interstitial inflammatory component, formed by lymphocytes that often infiltrate the bronchioles' epithelium.[2,5,9,11] There is sometimes macrophage proliferation in the alveolar spaces leading to changes such as small foci of organizing pneumonia.[9] Other possible findings (that are also present in our patients) included bronchiectasis and bronchiolar fibrosis.

The reactive lymphoid follicles are usually described as staining for the CD20 B-cell marker, whereas the interstitial component, when present, for the CD3 T-cell marker.[9,11] Our results are similar to these.

Steroids are usually considered first line treatment for FB.[9-11,13-15] In those patients without an associated disease, some authors argue that treatment is sometimes unnecessary.[10] Other options would include azathioprine and macrolides. Sometimes

relapse is observed.[9,11,14] We found no registry of specific treatment for any of our patients.

The prognosis of patients with FB is generally favorable, but some tend to have a progressive disease and poor prognosis.[9-11,13] This progressive disease is most often found in patients with disease at young age [1,9] and in those with underlying disorders (the prognosis being depending on the associated disease).[9-11,13] In our study, the two patients that died had advanced age and died from unrelated illness.

Lymphocytic interstitial pneumonia

Lymphocytic interstitial pneumonia (LIP) is a rare interstitial lung disorder with unknown incidence and prevalence rates.[3,10] It's characterized by a polymorphous inflammatory infiltrate and diffusely expands alveolar septa.[1,9,11,16] LIP was first described in 1969 as a form of interstitial pneumonia,[1,2,11,16,17] although there are some doubts about this inclusion. In the 2002 International Consensus Classification of Interstitial Pneumonias, LIP is still incorporated. It is currently considered part of the spectrum of pulmonary lymphoid hyperplasia along with follicular bronchiolitis.[2,5,11]

The specific cause for LIP is unknown and the etiology is most likely multifactorial. LIP is associated with a variety of conditions including dysproteinemias, autoimmune disorders, collagen vascular diseases, bone marrow transplant, and the acquired immunodeficiency syndrome. True idiopathic LIP is very rare[1,3,5,9-11,17,18] There is some evidence that Epstein-Barr virus, HIV and human herpes virus 8 infection may have a role in pathogenesis in some patients.[2,5] However, the specific pathways through which these viruses induce lymphoid hyperplasia are not known.[2] In our study, we found no

associated diseases in LIP patients. This can be because the associated disorders were not diagnosed and or maybe because there is a different incidence of idiopathic LIP in the Portuguese population, which is less probable, given that this is a retrospective analysis and all the other patient's characteristics are similar to previous series.

In previous series, a slightly female preponderance is described and the average age of presentation is 50 years, with some patients being as old as 70 and as young as 30.[1-3,5,9-11,17] We found equal gender prevalence and a similar average age to previous reports.

Patients are usually symptomatic. The most common symptoms are gradual onset of cough and dyspnea.[1-3,5,9-11,17] Other possible complaints include hemoptysis, weight loss, fever, chest pain, arthralgia and asthenia.[1-3,9-11]

Pulmonary function test usually reveal a restrictive pattern.[1-3,5,9-11,17] This defect was seen in only one of our 9 patients. On laboratory testing, the majority of patients have serum dysproteinemia, generally a polyclonal hypergammaglobulinemia. Nevertheless, some patients may have hypogammaglobulinemia.[1,9-11] One of our patients showed hypergammaglobulinemia.

Findings at chest radiograph are mostly unspecific and bibasilar reticular or reticulonodular infiltrates can be seen.[2,3,9,11] In our study, patient 10 had an atypical localization: right upper lobe. On CT scans, LIP causes bilateral areas of ground glass opacities that can be accompanied by centrilobular and subpleural nodules, along with bronchovascular bundles and interlobular septal thickening, cystic lesions and lymph node enlargement.[1,2,9-11] Our patients showed ground glass opacification and cystic lesions.

We performed bronchoalveolar lavage in one patient, that revealed lymphocytosis, a nonspecific findings that can be encountered in other infiltrative lung diseases.[10]

Bronchoalveolar lavage may also be of value because an increase in the total cell count of CD3-positive T-cells and of polyclonal CD20-positive B-cells suggests the diagnosis.[2,19]

Although transbronchial lung biopsy is usually insufficient for diagnosis[10], leading to surgical lung biopsy, in one of our 2 cases the fragment was considered representative, allowing the diagnosis. The main pathological features are a dense interstitial lymphoid infiltrate with variable but usually slight peribronchial/perivascular involvement. Granulomatous tissue is sometimes present. Fibrosis is either absent or minimal.[5,10,17] For an unequivocal diagnosis of LIP, polyclonality in the lymphoid population should be established.[2,17,18] Immunohistochemistry shows that CD20- -positive B-cells are mainly limited to the germinal centers, often highlighting more follicles than are seen on routine sections. The interstitial lymphocytes are predominantly CD3-positive T-cells mixed with scattered CD20-positive B-cells.[5] Our patient presented most of those characteristics.

Often the initial therapy is based on steroids [1-3,5,9-11,17], and this was the choice in our patients who underwent treatment. Cytotoxic therapy is an additional option.[2,5] Other immunomodulating agents have been used in patients not responding to steroids, but no consensus exists about the preferred drug.[1] One of our patients died within a year of diagnosis, but the cause of death was unrelated to LIP. The usual reported median survival is 11.5 years.[3] The outcome varies from resolution to death, due to progression to fibrosis, *cor pulmonale* and respiratory failure, superimposed infection, or development of lymphoma.[1-3,11,20]

Malignant diseases

Primary pulmonary Hodgkin's lymphoma

Primary pulmonary Hodgkin's lymphoma is an extremely rare entity constituting less than 1% of all patients with Hodgkin disease.[1,3,4] It is defined by 3 main criteria: 1) histologic features of Hodgkin's disease within the pulmonary parenchyma, 2) no or minimal hilar or mediastinal lymph node involvement and 3) no or with minimal disease outside the lung.[1,4,21] Although, there are only a few cases described, the average presentation age is 50 years, and there is a female preponderance.^[1,3] In our study, the only patient was a woman with 64 years. No data concerning associated diseases or clinical and imaging results from this patient was found, so a comparison with previous reports cannot be done. Patients are rarely asymptomatic. The most common symptoms are cough, fever and weight loss. Other possible complaints are dyspnea, chest pain, hemoptysis, fatigue or night sweats.[1,3] The chest x-ray findings include solitary or multiple pulmonary nodules (when multiple, they tend to be bilateral), and less commonly cavitating nodules, reticulonodular infiltrates, consolidation with air bronchogram and pleural effusion.[1,3] Thoracic CT scan findings are nonspecific, but it is important for staging (ruling out mediastinal or abdominal adenopathy), in conjunction with abdominal CT, biopsy of suspicious nodes and bone marrow examination.[1] Pathologically, Reed-Sternberg cells must be present in an appropriate cellular background. The most frequent histologic type is nodular sclerosis, followed by mixed cellularity.[1,3,4] Our patient had the nodular sclerosis subtype.

About treatment, it is now known that combination chemotherapy provides better results than other possible options (chemotherapy with single agent or surgical procedures).[1] Our patient was submitted to chemotherapy, but we don't have information about the protocol used.

The outcome of patients with primary pulmonary Hodgkin's lymphoma is usually poor, particularly in patients older than 60 years with B symptoms, multiple and bilateral lesions and HIV infection. Most patients relapse in 12 to 14 months and this is associated with high mortality.[1,3] This poor prognosis could be confirmed by our patient's outcome.

B cell non-Hodgkin lymphoma

Bronchus-associated lymphoid tissue lymphoma

Pulmonary Marginal Zone B-cell Lymphoma of MALT Type, or BALT lymphoma is a low-grade B cell non-Hodgkin's lymphoma arising from BALT.[3] It is the most common primary lung lymphoma, representing 50-90% of all cases.[3,4,22,23]

Patients are generally between 50 and 70 years at initial assessment, with a slight male preponderance.[2,5] In our study, the mean age was 60.6 years, but there were a female preponderance.

Pulmonary MALT lymphoma seems to arise from preexisting inflammatory lymphoid tissue. These inflammatory processes are likely related to chronic antigen stimulation as in other extranodal lymphomas. BALT is inconspicuous in adults, but becomes hyperplastic in chronic immune mediated diseases such as chronic infections, connective tissue diseases, rheumatoid arthritis and Sjögren's syndrome.[3,4] This relationship was evident in our study, as our patients' history included acquired immunodeficiency, systemic lupus erythematosus and Sjögren's syndrome. There was also a case with prior *Helicobacter pylori* infection. Although it is well known that gastric lymphomas arise from MALT hyperplasia as a result of *Helicobacter pylori* infection, these stimuli are less well defined in the lung.[2,4,5] BALT

expression is increased in smokers[24], and in our study 40% of the patient with BALT lymphomas had a history of smoking.

At the time of the diagnosis, about half of patients are asymptomatic.[3] In our study, only one patient lacked symptoms. Symptomatic patients most commonly present with cough, dyspnea and more rarely chest pain, and hemoptysis. Systemic symptoms such as fever and weight loss are not uncommon.[2,3,5] These previous descriptions match our findings. Spirometry shows either obstructive or restrictive ventilator defects, but in majority of cases is normal.[2] Only one of our patients had normal pulmonary function tests and obstruction was the most common finding.

Imaging features include unilateral or bilateral disease, with isolated or multiple opacities on the chest x-ray. Air bronchogram can be present in low-grade lesions, but is nonspecific. Diffuse infiltration, reticulonodular shadowing and pleural effusions have all been described. Hilar and mediastinal lymphadenopathy and nodal involvement are not prominent radiologic findings, but can also be present.[2,3,5] Our patients displayed most of these features. Other characteristic CT findings of this disease include the angiogram sign (demonstration of an enhancing vascular network within areas of consolidated lung), peribronchovascular nodules and tree in bud pattern.[2-4]

Laboratory findings are nonspecific. A few patients have increased levels of LDH in the serum and also less frequently a monoclonal band in serum eletrophoresis is found^[3] LDH results meet those in our study, but no monoclonal band was found.

Pulmonary MALT lymphomas, like MALT lymphomas of other origins, are formed by the accumulation of monoclonal lymphoid cells characterized by the morphological and biological features of marginal-zone B-cells. These cells are similar to normal marginal-zone cells, characterized by small and irregular nuclei, inconspicuous nucleoli, and abundant clear

cytoplasm. Neoplastic lymphocytes typically accumulate around non-neoplastic lymphoid follicles, forming poorly defined sheets of cells at the periphery of the mantle zones and extending into the lung parenchyma. The pulmonary structures are affected by abnormal lymphocyte infiltration, predominantly localized along the bronchovascular bundles, interlobular septa and visceral pleura. Other typical features include the presence of vascular infiltration, pleural involvement, granuloma formation, giant lamellar bodies and sclerosis.[3-5] In high-grade pulmonary MALT lymphoma, the lesions are more diffuse and destructive, often necrotic, and the vascular infiltration can cause alveolar hemorrhage.[25] On immunohistochemistry, the cells are CD20-positive, and there is a variable CD3-positive T-cell population in the background,[4,5] findings similar to those in our study.

Regarding staging, there is preferential spread to other mucosal sites rather than to lymph nodes. The most common stages are Ie (unilateral or bilateral pulmonary involvement) and Iie (Ie with hilar/mediastinal involvement).[5] In our study, only a patient was in a different stage (IVe).

There is no standard treatment for pulmonary MALT lymphomas.[4,23] Surgical procedures can be used in localized resectable disease.[2-5] When resection is high risk (bilateral or unresectable unilateral disease), systemic chemotherapy is generally used in order to prevent relapse. Single agent chemotherapy has been shown to be effective, but patients with high-grade lymphoma require combination chemotherapy.[2-5] Our patients' treatments consisted of combination chemotherapy, surgery or both. The used chemotherapy protocols were the most frequently described ones.

BALT lymphomas are mostly indolent and remain confined to the lung for long periods. This slow progression has resulted in cases of pulmonary MALT lymphoma being defined as "pseudolymphoma". The 5-year survival rate is quoted at 84-94% for low-grade

lymphomas and 0-60% for high-grade tumors.[2-5] No patient died in our study, but our follow-up time was not very long.

Large pulmonary B cell lymphoma

Large pulmonary B-cell lymphomas are rare low-grade lymphomas representing a small and not very well characterized fraction of pulmonary lymphomas.[3,4] They are clinically indistinguishable from other low-grade pulmonary lymphomas,[4] and mostly seen in patients with underlying immune disorders[3], although this was not the case of our patient. At the initial assessment, common symptoms include cough, dyspnea, hemoptysis, fever and weight loss.[3] Our patient presented with some of these complaints and also with a sudden onset of chest pain.

Our patient's radiological features included a single pulmonary mass, a typical finding in previous case reports. This mass frequently displays cavitation, and atelectasis and pleural effusion can also be found.[3] Morphologically, these lymphomas are heterogeneous, and the lymphoma cells are large cells with round nuclei, prominent nucleoli, dispersed chromatin and high mitotic count.[4]

Treatment requires chemotherapy or combined-modality therapy.[3] Our patient had chemotherapy, although specific information was not available.

Systemic progression is frequent, and median survival time is 8-10 years.[3] The prognosis is poorer in patients with underlying immunologic disorders,[3] but this was not our patient's case.

Other B-cell Lymphomas

There were 3 patients, in which the subtype of B-cell lymphoma could not be defined, so the comparison with literature was not possible. Nevertheless, they had specific treatment, most commonly with CNOP and R-CVP chemotherapeutic combinations. Only a death was reported, and this occurred in the patient that had a worse response to chemotherapy.

T cell primary pulmonary lymphomas

Primary pulmonary T-cell lymphomas are an extremely aggressive rare group of cancers that are not yet [3,4,8,26,27] very well characterized.[4,8] Our series included a patient with lymphoblastic T-cell lymphoma and another with unspecified peripheral T-cell lymphoma.

T-cell lymphomas occur at a greater rate in HIV-positive adults,[3,4] but none of our patients had history of this. The most common clinical findings are cough and dyspnea associated with systemic symptoms.[8,27] Our patients complained of cough and weigh loss. In terms of blood tests, there is usually elevated LDH,[27] which was not observed in our study. Chest CT scans show small nodules, mass-like consolidations, interstitial infiltrates, peribronchial and perivascular thickening, hilar or mediastinal lymph node enlargement and pleural effusions.[27] The two firsts CT findings were those present in our patients. In patients with disseminated conditions, the imaging features are not distinguishable from those of the other subtypes of lymphoma.[8]

The treatment of pulmonary T-cell lymphomas usually consists of CHOP based chemotherapy [26,27], that was the choice in the only patient that we had data. Surgical resection can be the option in focal tumors and can lead to cure (with adjuvant chemotherapy

given after surgery).[26] T-cell lymphomas have a poor prognosis [3,4,27] with 50% of mortality at 2-years, even with combined modality treatment.[3,4] Our patient with available data had less than 2-years of follow-up and reports poor quality of life.

The previous diagnosis of necrotizing sarcoid granulomatosis was probably a misdiagnosis of the peripheral lymphoma displaying granuloma morphology.

Survival analysis

We compared the survival between the group of patients with reactive disorders and malignant disorders, and between the groups of patients with normal or increased value for LDH. No significant differences were found in both tests.

In the first comparison (survival between the group of patients with reactive disorders and malignant disorders), we found that overall mortality was higher in patients with reactive disorders, but they died from unrelated causes. Mortality related to LPLD was higher in the group of patients with malignant disorders. Primary lung lymphomas are a heterogeneous group that include disorders with prolonged survival and others with an aggressive course.[4,28] In the literature, the overall survival is more often described as 86% at 3-years and 57% at 5-years,[28] which is in agreement with our findings (survival of 80% at 3-years).

In the second comparison (between the group of patients with a normal and increased LDH), despite being non-significant, survival was worst in the group of patients with elevation of the LDH value. In primary lung lymphomas, the prognostic factor influencing survival are the histologic type, T-cell lymphoma, the presence of pleural effusion, bilateral disease and the need for adjuvant therapy.[28] Although not statistically significant, further studies have to be made in order to understand if LDH value has clinical utility as a prognosis factor for primary lung lymphomas, or even to all LPLD.

Limitations

This study has some important limitations. This study had a retrospective design, and there was a lack of important information on some patient's clinical files. The follow-up time was narrow in some of our patients. Being a single-centre study, the results may not be representative of the Portuguese reality. A multi-centric study, involving a larger number of patients would allow an improved knowledge of the Portuguese reality. A national registry could be very useful both for gathering more data and, perhaps more importantly, to facilitate the development and inclusion of patients in clinical trials. Our study provides an updated proposal for the classification of lymphoproliferative lung disorders, but its usefulness will probably depend on clinical validation in a large series.

Conclusion

This study allowed us to propose an update to the classification of lymphoproliferative lung disorders. The majority of our findings meet those previously described. The differences found were especially related to demographic features. This may be explained by the small sample both in our study and in the studies already published as well as by specific characteristics of the Portuguese population. Nevertheless, our study gives an indication that most recommendations on diagnosis, treatment and prognosis derived from international studies can be applied to the Portuguese population. Finally the description of this case series is a valuable addition to the available knowledge on the characteristics of patients with pulmonary lymphoproliferative disorders, particularly concerning the Portuguese reality.

Acknowledgements

I would like to express my gratitude to my supervisor, Professor Doutor Carlos Robalo Cordeiro, for its expertise and incentive, to my co-supervisor, Dr. Tiago Alfaro, for all the time invested in this work, to Professor Doutor Vitor Rodrigues, for the help in the statistical analysis, and to Dra. Helena Donato, for the support on the bibliographic search. I also would like to thank the Pneumology unit, CHUC-HUC for allowing this research.

References

1. Thompson GP, Utz JP, Rosenow EC, Myers JL, Swensen SJ: **Pulmonary lymphoproliferative disorders**. *Mayo Clin Proc* 1993, **68**(8):804-817.
2. Nicholson AG: **Lymphocytic interstitial pneumonia and other lymphoproliferative disorders in the lung**. *Semin Respir Crit Care Med* 2001, **22**(4):409-422.
3. Poletti V ZP, Tomassetti S, Chilosi M: **Lymphoproliferative lung disorders**. *Prog Respir Res* 2007, **36**.
4. Chilosi M, Zinzani PL, Poletti V: **Lymphoproliferative lung disorders**. *Semin Respir Crit Care Med* 2005, **26**(5):490-501.
5. Nicholson AG: **Pulmonary lymphoproliferative disorders**. *Curr Diagn Pathol* 2000, **6**(2):130-139.
6. Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL, eds: **Harrison's principles of Internal Medicine**, vol. 2, 18th edn. New York: McGraww Hill; 2012.
7. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K: **Peripheral T-cell lymphoma**. *Blood* 2011, **117**(25):6756-6767.
8. Shin CH, Paik SH, Park JS, Kim HK, Park SI, Cha JG, Koh ES: **Primary Pulmonary T-Cell Lymphoma: a Case Report**. *Korean J Radiol* 2010, **11**(2):234 - 238.
9. Travis WD, Galvin JR: **Non-neoplastic pulmonary lymphoid lesions**. *Thorax* 2001, **56**(12):964-971.
10. Xinlun T ES, Jay HR: **Lymphocytic Interstitial Pneumonia and Other Benign Lymphoid Disorders**. *Semin Respir Crit Care Med* 2012, **33**:450-461.
11. Guinee DG, Jr.: **Update on nonneoplastic pulmonary lymphoproliferative disorders and related entities**. *Arch Pathol Lab Med* 2010, **134**(5):691-701.

12. Ryu JH: **Classification and approach to bronchiolar diseases.** *Curr Opin Pulm Med* 2006, **12**(2):145-151.
13. Aerni MR VR, Myers JL, Lindell RM, Ryu JH: **Follicular bronchiolitis in surgical lung biopsies: clinical implications in 12 patients.** *Respir Med* 2008, **102**(2):307-312.
14. Romero S, Barroso E, Gil J, Aranda I, Alonso S, Garcia-Pachon E: **Follicular bronchiolitis: clinical and pathologic findings in six patients.** *Lung* 2003, **181**(6):309-319.
15. Lynch DA: **Imaging of small airways disease and chronic obstructive pulmonary disease.** *Clin Chest Med* 2008, **29**(1):165-179, vii.
16. Liebow AA, Carrington CB: **The interstitial pneumonias.**In *Frontiers in pulmonary radiology.* Edited by Simon M, Potchen EJ, Lemay E.New York: Grune Stratton; 1969:102-141.
17. Bragg DG, Chor PJ, Murray KA, Kjeldsberg CR: **Lymphoproliferative disorders of the lung: histopathology, clinical manifestations, and imaging features.** *AJR Am J Roentgenol* 1994, **163**(2):273-281.
18. Cruz JF GA, Casas PF, Benítez SG, Guirao MA, Borderas F: **Pulmonary lymphoproliferative disorders with affinity to lymphoma: a clinicopathologic study of 16 cases.** *Eur Radiol* 1993, **3**:106-114.
19. Poletti V, Kitaichi M: **Facts and controversies in the classification of idiopathic interstitial pneumonias.** *Sarcoidosis Vasc Diffuse Lung Dis* 2000, **17**(3):229-238.
20. Johkoh T, Ichikado K, Akira M, Honda O, Tomiyama N, Mihara N, Kozuka T, Koyama M, Hamada S, Nakamura H: **Lymphocytic interstitial pneumonia: follow-up CT findings in 14 patients.** *J Thorac Imaging* 2000, **15**(3):162-167.

21. Guinee Jr DG: **Update on pulmonary and pleural lymphoproliferative disorders.** *Diagn Histopathol* 2008, **14**(10):474-498.
22. Cavalli F, Isaacson PG, Gascoyne RD, Zucca E: **MALT Lymphomas.** *Hematology Am Soc Hematol Educ Program.* 2001:241-258.
23. Thieblemont C, Berger F, Dumontet C, Moullet I, Bouafia F, Felman P, Salles G, Coiffier B: **Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed.** *Blood* 2000, **95**(3):802-806.
24. MacDonald SL, Rubens MB, Hansell DM, Copley SJ, Desai SR, du Bois RM, Nicholson AG, Colby TV, Wells AU: **Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT.** *Radiology* 2001, **221**(3):600-605.
25. Cohen SM, Petryk M, Varma M, Kozuch PS, Ames ED, Grossbard ML: **Non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue.** *Oncologist* 2006, **11**(10):1100-1117.
26. Laohaburanakit P, Hardin KA: **NK/T cell lymphoma of the lung: a case report and review of literature.** *Thorax* 2006, **61**(3):267-270.
27. Vahid B: **Pulmonary manifestations of peripheral T-cell lymphoma: case report and review of the literature.** *Clin Respir J* 2007:114-117.
28. Parissis H: **Forty years literature review of primary lung lymphoma.** *J Cardiothorac Surg* 2011, **6**:23.