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ANAEMIA OF INFLAMMATION PRECEDING DYSPNOEA, DRY COUGH AND WEIGHT LOSS IN PRIMARY PULMONARY LYMPHOMA

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ABSTRACT

Introduction: There is little information in the literature on the early, sub-clinical stage and laboratory test results in patients with primary mucosa-associated lymphoid tissue (MALT) lymphoma of the lung, a rare disease.

Case description: In a 75-year-old man, an open lung biopsy-confirmed diagnosis of primary pulmonary lymphoma was preceded by almost six months of anaemia of inflammatory disease and monocytosis without any pulmonary symptoms. When he developed a dry cough, increasing dyspnoea and marked weight loss, these changes deepened and became associated with reactive thrombocytosis; markedly increased ferritin and C-reactive protein (positive acute-phase reactants), as well as reduced albumin and transferrin (negative acute-phase reactants). Globulins increased, due to an increase in the alpha1, alpha2 and gamma fractions, and mild hyponatraemia developed due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to the intrathoracic disease. All these changes were completely reversible following successful treatment and complete remission.

Conclusion: The previously unreported detailed laboratory features of early, sub-clinical and advanced primary pulmonary lymphoma are presented. When a potentially susceptible patient develops an unexplained anaemia of inflammatory disease, primary pulmonary lymphoma should be added to the differential diagnosis.

KEYWORDS

Primary pulmonary lymphoma diagnosis, anaemia of inflammation, monocytosis, primary pulmonary lymphoma, hyperferritinaemia

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LEARNING POINTS

- B-cell pulmonary lymphoma without extra-pulmonary disease (primary pulmonary lymphoma) remains a rare entity, often arising from mucosa-associated lymphoid tissue, presenting with non-specific symptoms (cough, dyspnoea) and imaging (nodules <5 cm or areas of consolidation on CT), and diagnosed by an adequate biopsy.
- Our patient's course demonstrates early, pre-clinical changes: anaemia of inflammation and monocytosis, which became more severe as symptoms developed and imaging abnormalities progressed, and was associated with marked acute-phase response (for example, substantially increased ferritin levels), increased globulins and hyponatraemia due to the syndrome of inappropriate antidiuretic hormone secretion.
- In patients with unexplained anaemia of inflammatory disease, occult pulmonary lymphoma should be considered in the differential diagnosis.

INTRODUCTION

Primary pulmonary lymphoma (PPL) without extra-pulmonary disease remains a rare entity and a diagnostic challenge. Surprisingly little can be found in the literature on the laboratory features characteristic of PPL, and studies in the early phase of disease evolvement are practically non-existent. We report such a study in a single case, yielding data that may suggest the diagnosis and allow possible insight into disease pathogenesis.

CASE DESCRIPTION

A 75-year-old man presented with dyspnoea on exertion and a dry cough, worse at night, associated with fatigue, anorexia and marked weight loss (87 to 77 kg) over six months. He had no symptoms of heart failure, no pain, fever or sweating. Abnormal routine blood tests preceded the symptomatology. Past history included diabetes (HbA1c 6.6% on metformin) and mild hypertension (on ramipril) without target organ damage. He never smoked and, as a software engineer, he had no occupational exposures, had no pets, and an unremarkable travel and family history. One year before presentation, normocytic anaemia (Hb 10.6 g/dl) was discovered on routine laboratory tests and gradually worsened, with neither nutrient deficiencies nor apparent cause. Rather, marked positive and negative acute-phase activation developed, of which ferritin levels of 1,514 mg/dl were especially notable *(Table 1)*. Important negatives included absent autoantibodies, normal free light chains and no monoclonal peak (serum/urine). Physical examination was unremarkable. He was comfortable, 96% oxygen saturation on ambient air, had no clubbing, and lung percussion/auscultation were normal. Chest X-ray showed scattered parenchymal densities at the lung bases, with normal heart and mediastinum *(Fig. 1A)*. Chest and abdominal CT demonstrated multiple patchy opacities mostly in the lower lobes *(Fig. 1B)* without mediastinal lymph nodes or effusions. There were no abnormal imaging findings outside the lungs, but pulmonary changes became more pronounced. After two transbronchial CT-guided biopsies were inconclusive, a video-assisted thoracoscopic lung biopsy was performed, establishing the unequivocal diagnosis of PPL *(Fig. 2)*. Bone marrow biopsy was reactive, and PET CT showed no extra-thoracic activity (not shown). Treatment with cycles of rituximab, cyclophosphamide, vincristine and prednisone (R-CHOP) was started in April 2023. This was well tolerated, and the patient gradually became asymptomatic and gained

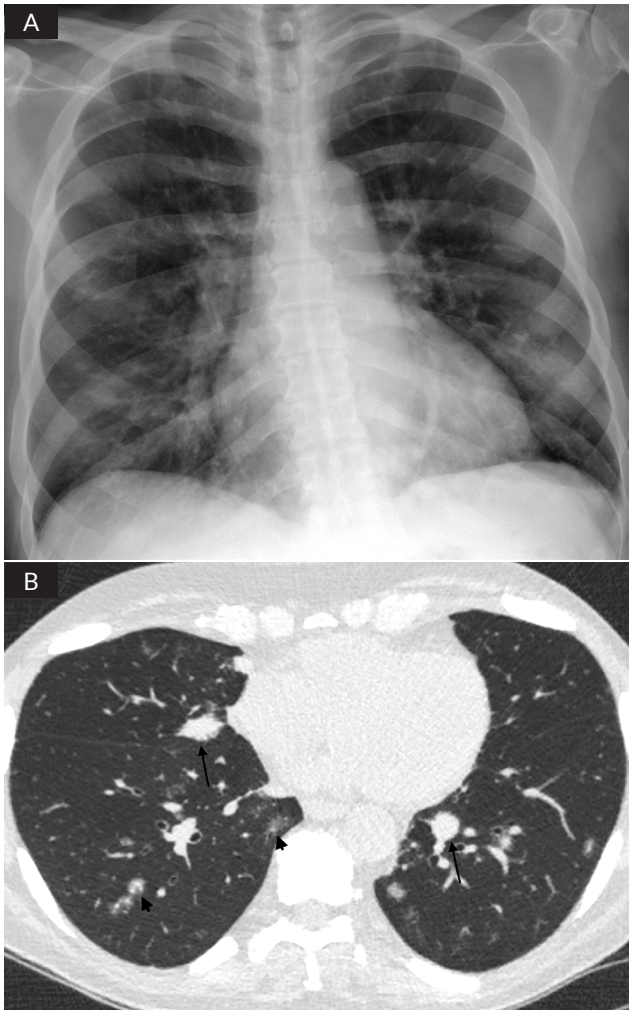


Figure 1. Patient's chest X-ray and CT at presentation. A) AP chest radiograph shows multiple bilateral vague nodular opacities, most visible in the left lower lobe, without associated lymph node enlargement or pleural effusion; B) Axial CT image at the level of the lung bases (thin sections in lung windows) revealing numerous nodules. Multiple small ground glass opacities with a peripheral rim of higher attenuation can be seen (arrowhead), and two solid nodules in the right middle lobe and left lower lobe (arrows).

Variable (normal values)	**Jan 2021** Background results	**Mar 22** 'Isolated' anaemia found	**Aug 22** Symptoms developing	**Mar 23** PPL diagnosis	**Sep 23** Treated	**Mar 24** Treated
Hb (13.3-16.2 g/dl)	12.8	**10.6**	**8.7**	**7.4**	**10.9**	13.2
MCV (80-98 fl)	86	81.4	**76.5**	**76.1**	87.5	88.6
RDW (11-14.5%)	13.5	14.9	**17.4**	**20.5**	14.4	13.5
Iron (65-175 µg/dl)	52	-	**16**	**9**	-	78
TIBC (200-380 mg/dl)	221	-	**148**	**111**	-	200
TIBC Saturation (15-50%)	16	-	**8**	**6**	-	28
Ferritin (20-275 ng/ml)	102	-	**683**	**1514**	-	**454**
Neutrophils (1.8-6.6 ×10³/µl)	6.5	8.6	**10.2**	**12.4**	4.7	6.2
Lymphocytes (1.5-3.5 ×10³/µl)	2.5	2.3	**1.5**	**0.7**	1.6	1.8
Monocytes (0.1-0.9 ×10³/µl)	1	**1.35**	**1.4**	**1.1**	0.89	0.87
Eosinophils (<0.5 ×10³/µl)	0.19	0.15	**0.04**	**0.04**	0.15	0.22
Platelets (140-400 ×10³/µl)	268	332	**397**	**546**	201	229
CRP (<5.0 mg/l)	6	-	**187**	**254**	8.4	-
ESR (<20 mm/hr)	37	-	-	**120**	-	28
Albumin (3.5-5 g/l)	4	-	**3.2**	**2.4**	4	4
Globulins (2-3.5 g/l)	2.9	-	**3.7**	**4.1***	2.1	2.1
LDH (100-220 U/l)	-	172	157	152	170	172
β2M (970-2640 µg/l)	-	-	-	**4468**	**3007**	**3482**
Sodium (135-145 mEq/l)	143	140	139	**132****	144	142

* Hyperglobulinemia due to increased α1 + α2 + γ fractions (IgG, IgA, IgM increased), without monoclonal component.
** Consistent with syndrome of inappropriate antidiuretic hormone (SIADH) secretion according to associated natriuresis and lack of an alternative cause.
Abbreviations: PPL, primary pulmonary lymphoma; Hb, haemoglobin; MCV, mean corpuscular volume; RDW, red cell distribution width; TIBC, total iron binding capacity (transferrin); CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; β2M, beta 2 microglobulin.

Table 1. The patient's 'background' blood test results (left column, January 2021) and their changes over time, when still asymptomatic (March 2022); with the appearance of symptoms (August 2022) - until the diagnosis was established (March 2023), and treatment was given (2 right hand columns). Abnormal results are marked in bold type and the 'worst' result is underlined.

weight. Within one year, all blood tests normalised (*Table 1*, March 2024) and a repeat PET CT demonstrated a complete disappearance of hypermetabolic foci in both lungs.

I. Malignant
1. Low-grade marginal zone B-cell lymphoma of MALT: Up to 90% of lymphomas originating in the lungs.
2. Other primary pulmonary lymphomas (rare, typically involve other organs): Diffuse large B-cell lymphoma; intravascular large B-cell lymphoma (IV-LBCL); follicular lymphoma; Hodgkin disease presenting in the lung.
3. Lymphomatoid granulomatosis (LYG): A rare B lymphoma associated with Epstein-Barr virus (EBV) infection and presenting with bilateral, poorly defined lower lobe nodules or mass in 30 to 50-year-old patients who are usually symptomatic (respiratory ± systemic, and often skin/neurological manifestations) and exhibit increased EBV viral load and often hyper-gammaglobulinemia. In situ hybridisation for EBV-encoded small ribonucleic acid determines grade 1–3.
II. Benign ('Reactive')
1. Lymphocytic interstitial pneumonia: Usually not a pulmonary mass but histology (and presentation) may strongly resemble MALT lymphoma with diffuse infiltration of mature, polyclonal, predominantly T cells and often background of an autoimmune disease or chronic infection with associated dysgammaglobulinemia.
2. Nodular lymphoid hyperplasia (formerly 'pseudolymphoma'): Often asymptomatic non-clonal lymphoproliferation (predominantly T cells) in patients ~60 years old that usually forms a single ~3 cm nodule (multiple in one third, lymphadenopathy: infrequent) without fluorodeoxyglucose uptake on PET scans.
3. Follicular bronchiolitis: Polyclonal bronchial MALT hyperplasia in and around the bronchioles, usually associated with rheumatoid arthritis/Sjogren syndrome in young adults who show bilateral 1–3 mm peribronchial nodules. Disease is limited to the small airways.

* Both clinical and imaging features may overlap, and diagnosis is dependent on meticulous immunohistochemical analysis of an adequate biopsy specimen.
** Secondary malignant lymphoproliferative disorders (Hodgkin or non-Hodgkin lymphoma) that are by far more common than primary disease and those arising in immunocompromised patients (AIDS-related lymphoma, post-transplantation lymphoproliferative disorder) were excluded. The rare HHV-8-associated primary effusion B-cell lymphoma involving unilateral pleural effusion without pulmonary lesions in HIV patients and multicentric Castleman disease, characterised primarily by lymphadenopathy and hepatosplenomegaly, were also excluded.

Table 2. Primary pulmonary MALT lymphoma in the context of other primary pulmonary lymphoproliferative disorders[4-6].

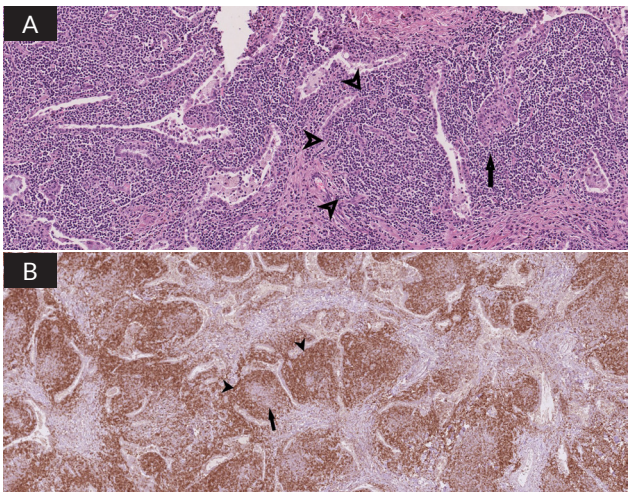


Figure 2. A) Haematoxylin and eosin stain of lung biopsy (×400) showing enlarged marginal zone with increased cellularity consisting predominantly of small lymphocytes with plasmacytic differentiation (arrows); B) Bcl-2 stain (×160) of lung biopsy specimen. Pointed arrows demonstrate positive staining in the marginal zone and long arrow shows negative staining in the germinal centres.

DISCUSSION

While secondary involvement of the lung may occur in up to one-quarter of all patients with non-Hodgkin's lymphoma, B-cell pulmonary lymphoma without extra-pulmonary disease (PPL) remains a rare entity comprising less than 1% of all non-Hodgkin's lymphoma, just 3-4% of all extranodal forms, and less than 1% of primary lung neoplasms[1]. The most frequent type of PPLs (70-90%) is the indolent marginal zone lymphoma arising from the mucosa-associated lymphoid tissue (MALT) as in our patient. The median age of appearance is in the late 60s, supporting the theory of chronic inflammatory stimulation in carcinogenesis by prolonged exposure to local antigens or, less often, an underlying autoimmune disease[2]. In contrast with the more common *Helicobacter pylori*-associated gastric MALT lymphoma, no causative agent had been robustly identified in PPL, and smoking is not present in many patients. Clinical presentation is variable, from asymptomatic (in a third or more) to cough, dyspnoea or malaise. In contrast, systemic symptoms, chest pain or haemoptysis are less often encountered, and when present, are non-specific and frequently misdiagnosed as 'unresolving pneumonia'. CT is the imaging modality of choice, but just like the non-specific clinical presentation, the appearance of nodule(s) <5 cm or area(s) of consolidation, not uncommonly in both lungs (~25%), mimics several reactive diagnoses (e.g. lymphoid interstitial pneumonia) and neoplastic diagnoses (e.g. adenocarcinoma), making pathology indispensable[2,3]. Thus, MALT PPL must be considered in the context of several other malignant and benign primary lymphoid pathologies of the lungs *(Table 2)*[4-6]. Histology and immunostaining are diagnostic and characterised by the presence of lymphoid infiltrate expanding the marginal zone of reactive follicles and showing a low proliferative index (Ki-67 <10%) and monoclonality (positive B-cell immunoglobulin gene

rearrangement) as in our patient. The infiltrate is composed of small, atypical cells expressing B-cell antigens CD20 and CD79a and Bcl-2 positivity *(Fig. 2)*, whereas CD10, Bcl-6 and cyclin D1 are negative.

Surprisingly little can be found in the literature on the laboratory features characteristic of PPL. The only mention is that lactate dehydrogenase activity is mostly normal, beta 2 microglobulin may be elevated and in some patients, 'mild to moderate anaemia, slight leukocytosis' and monoclonal gammopathy may be associated. Early-phase changes characteristic of sub-clinical PPL have never been reported to the best of our knowledge. Our patient's detailed laboratory data, however, afforded a month-by-month insight not only into the presentations that clinicians are likely to encounter, but indirectly into disease evolvement and pathogenesis *(Table 1)*. Anaemia of inflammatory disease and monocytosis were the first to appear, preceding any symptom by five months. Its relevance was demonstrated by the changes noted with clinical progression and ultimately, remission. When symptoms developed, these changes deepened and became associated with reactive thrombocytosis; increased ferritin, C-reactive protein and erythrocyte sedimentation rate (positive acute-phase reactants), and reduced albumin and transferrin (negative acute-phase reactants). Globulins increased, due to an increase in the α1, α2 and γ fractions, and mild hyponatraemia due to SIADH secondary to the intrathoracic disease appeared. All changes were related to the PPL, as their complete resolution with treatment demonstrates. These changes have in common a postulated (but unmeasured here) surge of inflammatory cytokines, and their inferred presence months before any symptom is intriguing - and useful to clinicians - and has not been previously reported, to our knowledge. Anaemia of inflammation was the initial manifestation, preceding all symptoms and other accruing laboratory markers. Its mechanism involves the release of multiple inflammatory cytokines by cells of the immune system in response to tumour antigens: IL-6, IL-1 and TNF-α appear to be the most important, stimulating hepcidin production by hepatocytes, which inhibits duodenal iron absorption and blocks release of senescent erythrocytes iron from macrophages[7]. Inflammatory cytokines (mostly produced by $CD4^+$ T cells but also by activated lymphoma cells and macrophages), also directly reduce iron absorption, reduce production/activity of erythropoietin, and mediate hypoferremia, hyperferritinaemia and additional changes such as megakaryocyte growth with reactive thrombocytosis, and neutrophilia (both also related to the expression of colony-stimulating factor cytokines). Recent *in vivo* studies have established a pathogenic role of increased ferritin levels, for example in mediating macrophage commitment towards an inflammatory phenotype[8]. Thus, cytokine network changes in B-cell neoplasms, and in MALT lymphomas in particular, are complex. The tumour microenvironment in primary pulmonary MALT lymphoma including tumour cells, epithelial cells, infiltrating immune cells and cytokines[9] has a key role in the progression and prognosis of the lymphoma. Our report indirectly highlights the early and primary role of inflammatory cytokines in the pathogenesis of PPL. Early recognition of their effects on basic laboratory tests can lead to a more timely suspicion, histology verification of PPL and treatment.

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