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Primary pulmonary MALT lymphoma – case report and literature overview

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Abstract. – OBJECTIVE: Primary pulmonary lymphomas (PPL) are rarely taken into consideration in the differential diagnosis of lung lesions. The aim of this report is to characterize the symptoms, diagnosis and treatment of primary MALT lymphoma of the lung.

CASE REPORT: We present the case of a 48-year-old man who was admitted to hospital with a history of coughing, fever, fatigue and non-specific lesions on his chest X-ray.

RESULTS: The patient was treated for pneumonia, but showed no improvement. A computer tomography revealed atypical lesions. After an initial examination and tests, no diagnosis could be established. A thoracotomy with an open lung biopsy was performed and MALT lymphoma was finally diagnosed. The patient underwent chemotherapy and showed a significant improvement.

CONCLUSIONS: Primary MALT lymphoma is a rare disease and its diagnosis is difficult. There is no non-invasive test that is specific enough, so a proper diagnosis can only be established by a histopathological examination. The disease has a slow and mild course and the response to treatment is satisfactory.

Key Words:
Primary pulmonary lymphomas, Mucosa-associated lymphoid tissue lymphoma (MALT), Open lung biopsy.

Introduction

Primary pulmonary lymphoma (PPL) is a rare clonal proliferation of lymphoid tissue involving one or both lungs. PPL does not involve any mediastinal or hilar lymph nodes. It constitutes 0.5% of primary lung neoplasms. It develops more often in the sixth and seventh decades of life, in men as often as women[1]. Isolated pulmonary lymphoma is very rare (1% of all extranodal localization). The most frequent type of PPL is mucosa-associated lymphoid tissue lymphoma (MALT), which accounts for 90% of PPL[2]. Less frequent types are: diffuse large B-cell lymphoma (DLBCL) and aplastic large cell lymphoma (ALCL)[3].

MALT is a low grade B-cell extranodal lymphoma. It develops in many different organs, most commonly in the gastrointestinal tract, salivary glands, orbit, thyroid gland and lungs (in 15% of all cases)[4]. It has been indicated that MALT occurs more often after chronic antigen stimulation of the lymphoid tissue, as with an infection, smoking or autoimmune disorders[5]. About 15% of patients with PPL suffer from autoimmune disease, i.e. systemic lupus erythematosus, rheumatoid arthritis or Sjögren's syndrome[4].

Symptoms are non-specific. The diagnostic process of a pulmonary MALT lymphoma is very difficult as there are no tests which are specific enough. Diagnosis includes laboratory tests, imaging and invasive procedures. Diagnosis should always be based on histopathological findings, immunohistochemistry, gene re-arrangement studies, cell marker studies and molecular techniques. A specimen for testing is obtained during a bronchoscopy, a needle biopsy or a thoracotomy.

MALT lymphomas remain localized for a prolonged period of time and show no signs of aggression. There is no unified treatment strategy for MALT. In summary, asymptomatic patients may be better candidates for a watch-and-wait

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policy than for immediate aggressive therapy[6]. When symptoms are present, chlorambucil-based chemotherapy with or without immunotherapy should be administered[4]. The overall survival rate of patients with MALT lymphoma is approximately 85-95% at five years and about 90% at ten years. Long-term follow-up is recommended[3,4].

Case Report

We present the case of a 48-year-old man with no previous medical history, who was referred to our hospital by a family doctor with suspected drug-resistant pneumonia. He had complained of a cough, chest pain, night sweats and fever up to 38°C for the last two months. Additionally he suffered from muscle pain, mostly in the distal parts of both legs, occurring during normal activity. The physical examination upon admission revealed wheezes and rhonchi on auscultation, muscle tenderness and weakness. Laboratory tests disclosed elevated levels of inflammatory markers (C-reactive protein, erythrocyte sedimentation rate-ESR), anemia, slightly elevated liver enzymes, alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT). Diffuse shadowing, ground glass and reticular opacities were observed on his chest X-ray. An initial diagnosis of pneumonia was established. Antibiotic therapy with ceftriaxone 1.0 g twice a day and clarythromycin 0.5 g twice a day was administered. Because of muscle pain, an electromyography (EMG) was performed. It indicated myogenic-type muscle injury. Creatine kinase and a screening test for myositis-associated antibodies remained within normal ranges. An initial improvement (regression of the auscultation phenomenon and muscle pain) after 7-days of treatment with antibiotics was observed. However, inflammatory markers remained high. This is why a systemic disease was suspected. A broad-spectrum panel of diagnostic procedures was planned (chest computer tomography (CT), abdominal ultrasound, gastroscopy and colonoscopy, thyroid ultrasound). The gastroscopy revealed chronic gastritis, a hiatal hernia and esophageal varices. The Helicobacter pylori test was negative. On the abdominal ultrasound, mild splenomegaly (craniocaudal dimension 13.8 cm) was observed. A computer tomography of the chest was performed (Figure 1). The radiologist identified periseptal edema in the upper parts of the lungs and a thickening of the bronchial walls with dense mucus filling their dilated lumen. Also single nodules in both lungs and patchy consolidations were observed. A single enlarged mediastinal lymph node (16x14 mm) was noticed. The differential diagnosis should include inflammation and neoplastic processes. A bronchofiberoscopy was performed. A large amount of mucosal secretion with no macroscopic mucosal changes were observed. Bronchoalveolar (BAL) fluid was sent for cytological and microbiological (including tuberculosis) tests, but all the results were negative. Additional laboratory tests showed an increased level of antinuclear antibodies (1:320, speckled pattern of fluorescence), ENA panel, C1 and C3 complement elements were negative. Also, a mild elevation of B2-macroglobulin was noticed. Protein electroforesis revealed no monoclonal protein. All the serological tests which were performed (EBV, *Cytomegalovirus*, Flu, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, HBV, HCV, *Borrelia*) and oncological markers were negative. The patient was discharged with the recommendation to continue antibiotic therapy: levofloxacin 0.5 g twice a day. A follow up visit was arranged for after the full course of treatment.

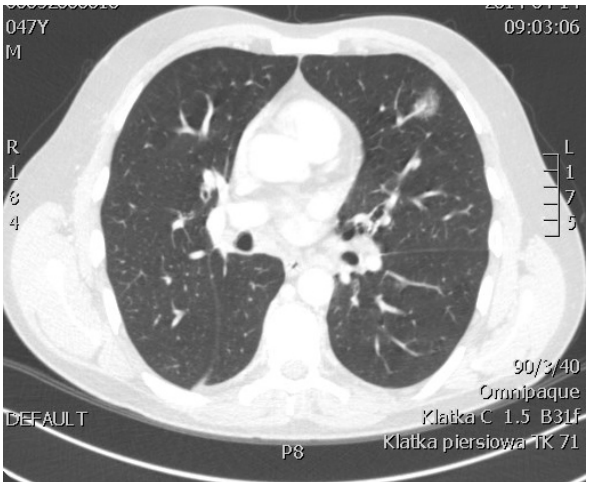

Figure 1. The chest CT scan shows periseptal edema in the upper parts of the lungs and a thickening of the bronchial walls, with dense mucus filling their dilated lumen. Also single nodules in both lungs and patchy consolidations can be observed. A single enlarged mediastinal lymph node (16x14 mm) is revealed.

When the patient was readmitted 4 weeks later, all the previously described signs and symptoms have relapsed. High inflammatory markers were still present in the blood test, i.e. elevated CRP, ESR >100 mm/h. A blood smear revealed anemia, thrombocytosis and mild leukocytosis (11.4 x10^3/μl) with a dominance of neutrophils. Liver enzymes and lactate dehydrogenase were back to

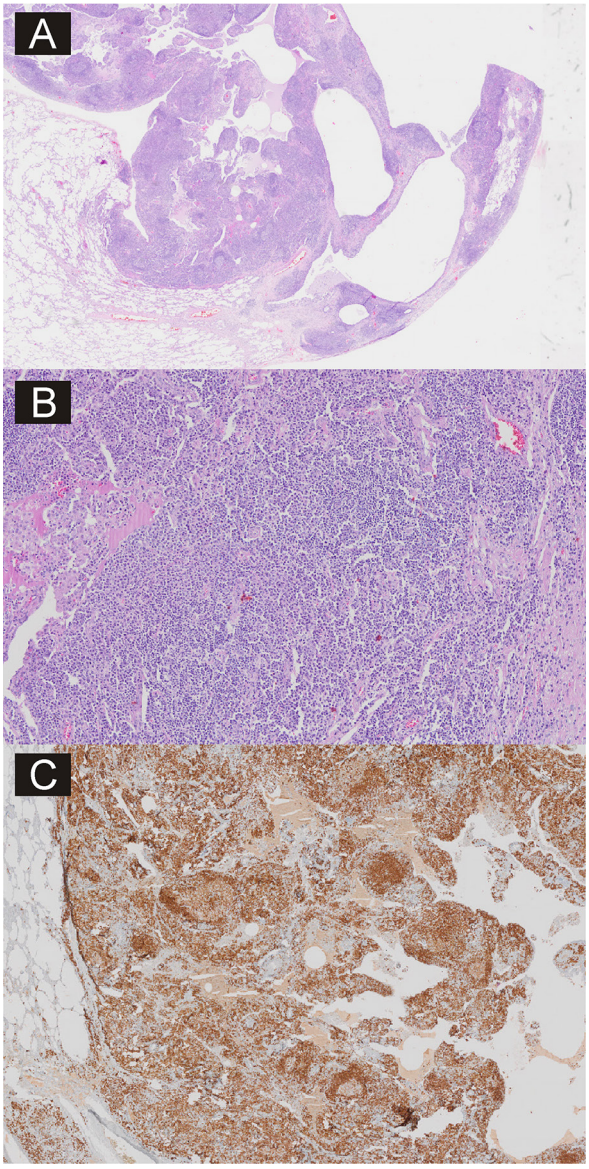

Figure 2. The histopathological examination (hematoxylin and eosin stain) shows the sample of the lung tissue with confluent infiltration of the lymphoid cells, which blurs the proper structure of the parenchyma. There is cystoid parenchyma at the periphery as well (***A***, magnification x 200, and ***B***, magnification x 400). On immunohistochemical examination (magnification x 200), CD20 reaction ***C,*** is positive and numerous lymphocytes B can be seen.

normal levels. Beta-2-microglobulin was still elevated, while antibodies typical for vasculitis were negative (cANCA, pANCA, aGBM). Taking into consideration all the lab tests, the patient had a consultation with a hematologist. A bone marrow biopsy was performed and no signs of hematological disease was discovered. The patient underwent a control chest-CT scan which showed no significant changes in comparison with the previous one. We decided to perform a PET scan. The picture corresponded with an inflammatory process. The patient was referred to the thoracic surgery ward, where an open thoracotomy and lung biopsy was performed. The histopathological examination indicated B-cell MALT lymphoma with focal lymphocytic vasculitis (Figure 2). However, an autoimmune disease could not be excluded. The immunochemistry type was: CD20+, CD79a+, CD3+, bcl-2+, Ki-67 (50%), CK PAN in epithelium, kappa and lambda chains +. Additional stains were made: amyloid (-), Masson's trichome (-). No cytogenetic abnormalities were observed, i.e. no chromosomal aberrations, normal karyotype, no gene rearrangement in IGH and CCDN1.

The patient was then referred to the hematology department, where a second bone marrow biopsy was performed, but no attributes of lymphoma were declared. Because the patient was symptomatic, chemotherapy with immunotherapy was initiated (R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) and was well tolerated.

Discussion

Primary pulmonary lymphomas are rare. Usually lungs are involved in a disseminated pattern caused by aggressive lymphomas by means of hematogenous dissemination or invasion from adjacent lymph nodes. The most common type of PPL is MALT.

There are no specific signs and symptoms of pulmonary MALT lymphoma. Patients are asymptomatic at the moment of diagnosis in 36% of cases. The most frequent symptoms include a cough and chest pain as well as exertional dyspnea, fatigue, weight loss, fever and night sweats[7]. Hemoptysis sometimes occurs.

Laboratory tests often reveal anemia, thrombocytopenia and an elevated LDH level. An elevated C-reactive protein level, elevated erythrocyte sedimentation rate and an increase of monoclonal immunoglobulin (Ig) are also observed. Monoclonal Ig is more often present in patients with extrapulmonary lesions, i.e. gastric tract involvement[1].

Computer tomography is a sensitive method for diagnosing lung lesions, but its specificity is very low[8]. MALT lymphoma manifests itself in many different ways. The most common CT findings are nodules, masses and patchy consolidations with air

bronchogram. Interlobular septal thickening, centrilobular micronodules and bronchial wall thickenings are also observed. Mediastinal lymphadenopathy and pleural effusions are not typical for primary pulmonary MALT lymphoma. CT changes require a differential diagnosis with bronchopneumonia, bronchoalveolar cancer, cryptogenic organizing pneumonia, rheumatoid nodules, abscesses and vasculitis. One cannot exclude fibrosis accompanying autoimmune disease[8].

PET-CT has limited effectiveness in diagnosing primary pulmonary lymphomas. Its sensitivity depends on the location and stage of the disease. The maximum uptake of FDG is usually <5. Limited uptake is observed in about 80% of patients and no uptake in about 20%[4].

A bronchoscopy can show no macroscopic changes. Sometimes bronchial edema, inflammation or external compression is observed. Bronchoalveolar lavage can be useful, if the fluid reveals a lymphocyte rate >20% of total cells and >10% of them are B-cells (especially with clonal gene rearrangement)[9].

Because MALT is localized in parenchymal tissue, often the cytology of bronchial lavage fluid, a transcutaneous biopsy or pleural effusion is negative. It usually leads to a surgical open biopsy during video-assisted thoracoscopic surgery (VATS) or a thoracotomy.

The histopathology of MALT shows monomorphical infiltration of B-lymphocytes around lymphoid follicles in a marginal zone distribution and spread outwards to form diffuse interfollicular sheets. The immunophenotype of MALT cells is: CD20+, CD19+, and CD79a+, and is in most cases CD5−, CD10−, CD23−, CD43–/−, cyclin D1−, and BCL6−[6].

In some cases the morphological and immunohistological findings may be insufficient for a diagnosis, in which case molecular biology techniques prove helpful. The three major translocations seen in MALT lymphomas are: t(11;18)(q21;q21)/API2-MALT1, t(14;18)(q32;q21)/IGH-MALT1 and t(1;14)(p22;q32)/IGH-BCL10. The presence of a MALT t(11;18)(q21;q21) resulting in the *API2/MALT1* fusion transcript is more frequent in pulmonary MALT lymphoma[10].

There are several treatment options for MALT. At present, treatment options are surgery or radiotherapy for localized lymphoma and chemotherapy with or without the anti-CD20 monoclonal antibody for disseminated lymphoma. Some authors suggest a "watch and wait" strategy, because spontaneous regression (not remission) of MALT lymphoma has been documented. Specifically primary MALT lymphoma of the lung shows no progression or signs of dissemination for a long time. Periods of increase together with consecutive regression ("wax and wane") in the pulmonary lesions are observed regardless of MALT lymphoma-specific aberrations. This has been observed only in pulmonary lesions, not in extrapulmonary locations[10].

As symptoms and signs of progression occur or a disseminated process is observed, chemotherapy would be a proper way to proceed. Also, patients with MALT with coexisting large cell lymphoma are treated as diffuse large B-cell lymphoma. A chlorambucil-based treatment should be the first choice option, because it gives better results, disease control and a longer remission period than cyclophosphamide or anthracycline. Immunotherapy is also available for MALT: anti CD-20 antibody-rituximab administered alone or with conventional chemotherapy[4]. It is proven that the admission of rituximab results in a higher rate of remission, especially for an extranodal MALT lymphoma which has not responded to previous chemotherapy[11].

Troch et al[10] described the remission of symptoms after administering clarithromycin to patients previously suspected of having pneumonia. Patients were subsequently diagnosed with MALT lymphoma. The good results from antibiotic therapy might be similar to Helicobacter pylori eradication in gastric MALT by means of decreasing the concomitant inflammatory process.

The prognosis in MALT lymphoma is good, with a high 5-year survival rate[12]. No difference in survival rates has been observed between gastrointestinal and non-gastrointestinal lymphoma or between the disease when it is localized or disseminated[3]. Relapses are more frequent in patients with non-gastric localizations. Advanced age and low economic status are the only two negative prognostic factors for survival. The median time to relapse is 47 months and is significantly longer for patients with t(11;18)(q21;q21)+. There is no correlation between the relapse rate and the initial stage of the disease or the treatment strategy. Because of the high relapse rate, patients with MALT lymphoma should be kept under long-term observation. No post-treatment procedures have been established so far. Follow-up visits every 3-6 months are widely recommended[3,4].

Conclusions

Primary MALT lymphoma of the lung is a rare disease and is rarely taken into consideration in

the differential diagnosis of non-specific symptoms and pulmonary lesions. A proper diagnosis can be established only by an experienced pathologist. There are no guidelines for treatment. A watch-and-wait policy might be a proper choice for asymptomatic patients and chlorambucil-based chemotherapy with or without immunotherapy should be administered when disease progression, dissemination or general symptoms are observed. The prognosis is good in all stages of the disease.

Conflicts of interest

The authors declare no conflicts of interest.

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