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CASE REPORT

Case Report: Bronchial associated lymphoid tissue lymphoma and *Mycobacterium chelonae* [version 1; peer review: 2 approved with reservations]

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Abstract

Bronchial-associated lymphoid tissue (BALT) lymphoma is a rare condition that accounts for only 0.5-1% of all malignant lung tumours. We present the case of a 66-year-old man admitted with pneumonia for further study and therapy. Initially the sputum was positive for *Mycobacterium tuberculosis* complex using polymerase chain reaction technology and antituberculous therapy was initiated. Due to the lack of imagiological improvement, the patient underwent a pulmonary transthoracic biopsy that revealed BALT lymphoma. Months later, *Mycobacterium chelonae* was identified and specific therapy was started with clarithromycin and tobramycin, before initiating BALT treatment with cyclophosphamide. There are only a few documented cases of BALT lymphoma associated with *Mycobacterium*. In this case *M. chelonae* might have been present before BALT lymphoma, contributing as an immunologic stimulus, or appeared afterwards, in the neoplastic context. BALT has an indolent evolution with a good prognosis and that is the reason why some experts favour a “watchful waiting” option.

Keywords

BALT lymphoma , *Mycobacterium chelonae* , diagnosis , treatment

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Approval Status ? ?

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Extranodal marginal zone B cell lymphoma (MZL) is a low grade B cell lymphoma of mucosa associated lymphoid tissue (MALT). Primary pulmonary MALT, also called bronchial-associated lymphoid tissue (BALT), accounts for 0.5–1% of all malignant lung tumours and about 90% of all lung lymphomas^{1,2}. BALT represents 15% of all MALT lymphomas^{1,3}.

BALT lymphoma has been associated with chronic antigenic stimulation by autoimmune disease, smoking, infection or chronic inflammation, but a well-established connection has not yet been described^{3–5}. The paradigmatic example of that antigenic stimuli is the development of gastric MALT in *Helicobacter pylori* infection with chronic gastritis¹. There are some reports in literature correlating *Mycobacterium avium* complex and *Mycobacterium tuberculosis* infection with BALT lymphoma^{5–8}.

Nontuberculous mycobacterium (NTM) are ubiquitous in the environment, frequently colonize the skin, digestive and respiratory tract, sometimes developing disease, mainly in immunosuppressed chronic diseases patient's^{9,10}. *Mycobacterium chelonae* is a rapidly growing mycobacteria that has been implicated as an infrequent lung pathogen. Patients with severe underlying structural lung disease such as cystic fibrosis and bronchiectasis are the most predisposed¹¹.

Case report

We present a 66-year-old man's case, with subfebrile temperature, two months' history of persistent cough, purulent sputum, occasional small haemoptysis, anorexia and non-quantified weight loss. He reported no clinical response to previous antibiotherapy with amoxicillin (500 mg orally 3 times a day for 7 days) and after moxifloxacin (400 mg orally once a day for 7 days). The patient reported a gastric lymphoma at the age of 40, treated with chemotherapy for which we have no detailed information. He had a 32-pack-year tobacco smoking history. He had no changes on physical examination. Initial chest radiography showed a bilateral heterogeneous opacity, covering the lower two thirds of the left hemithorax and the lower third of the right hemithorax and the

lower third of the right hemithorax (Figure 1). Inflammatory parameters, such as erythrocyte sedimentation rate and C-reactive protein were normal as well as blood gas. Pneumonia was considered and antibiotherapy with amoxicillin/clavulanic acid (1000 mg/200 mg intravenously every 8 hours) and clarithromycin (500 mg orally twice a day) was initiated, which held during seven days. Later chest CT showed multiple foci of parenchymal consolidation with air bronchogram on the left upper lobe, lingula, apical segment of the left lower lobe, posterior segment of the right upper lobe and apical right lower lobe (Figure 2). Mantoux test was negative. He had elevated IgM (1451 mg/dl) as well as negative serology for HIV, B and C hepatitis. No endoscopic abnormalities were found on flexible bronchoscopy. Gastric endoscopy showed an antral gastritis with negative *Helicobacter pylori* biopsy test. Bacteriologic analysis of three sputum specimens were negative for either aerobic and anaerobic bacteria or acid fast bacilli, but positive for *Mycobacterium tuberculosis* complex (MTC) using polymerase chain reaction (PCR) technology, in two out of three samples, bronchial aspirate was bacteriologically negative. The patient was initiated on antituberculous treatment (ATT) with isoniazid (300 mg/day), rifampicin (600 mg/day), pyrazinamide (1500 mg/day) and ethambutol (1200 mg/day), orally, and was forwarded to an outpatient centre for respiratory diseases. Six weeks later, Lowenstein-Jensen cultures showed the presence of NTM. ATT was maintained due to clinical improvement while waiting for NTM identification. The lack of imagiologic improvement in the meantime, led to trans-thoracic lung biopsy realization. Immunohistochemistry showed positive lymphocyte identification to CD20 and BCL2, and CD23, CD10, CD5 and a negative CD3, consistent with the diagnostic of BALT lymphoma. There was no evidence of other extranodal or nodal involvement in complementary imagiologic study. Haematologists decided to reevaluate the patient's condition after the end of ATT, taking into account his clinical stability. In the meantime, NTM was identified as *M. chelonae* and the laboratory informed us that the initial positive PCR for MTC was a laboratorial contamination. The drug resistance patterns were not performed. At this time new sputum samples were bacteriologically negative and ATT was stopped, with six months of treatment.

Figure 1. Chest radiography: bilateral heterogeneous opacity, covering lower two thirds of the left hemithorax and the lower third of the right hemithorax (A: posteroanterior view; B: lateral right view).

Figure 2. Thoracic computed tomography, axial view: pulmonary consolidation with air bronchogram, in the left upper lob, lingual, apical segment of the left lower lobe, posterior segment of the right upper lobe and apical right lower lobe (**A**: pulmonary window; **B**: with contrast).

One month later the patient resumed his previous respiratory symptoms. Specific therapy for *M. Chelonae* with tobramycin (150 mg intramuscularly once a day) and clarithromycin (500 mg orally twice a day) was initiated, but discontinued due to nephro and hepatic toxicity, after seven weeks of treatment. Haematologists at this time decided to begin treatment with cyclophosphamide (50 mg orally once a day). After 6 months of cyclophosphamide treatment the patient showed significant clinical improvement, without any signs of pulmonary infection and partial imagiologic resolution. For this reason the patient remains in treatment, waiting for a reevaluation with new clinical and imagiologic data.

Discussion

The diagnosis of BALT lymphoma is challenging and frequently misdiagnosed as pneumonia, pulmonary tuberculosis or interstitial lung disease, because clinical and radiologic findings are nonspecific. According to retrospective analysis, average time to achieve diagnosis is around 20 months⁴. Chronic cough, sputum, progressive dyspnoea, fatigability, fever, night sweats and weight loss are the most common manifestations. Imagiologic findings are generally nonspecific, such as single or multiple nodules, consolidation areas, bronchiectasis, bronchiolitis phenomena or diffuse interstitial lung disease^{2,4,12}.

Pulmonary tuberculosis was assumed initially with the identification of *Mycobacterium tuberculosis* complex by PCR, leading us to treat the patient with ATT. When the presence of an NTM was identified in two out of three sputum specimens together with clinical and imagiologic changes, an infection was assumed according to the criteria of American Thoracic Society (ATS) for NTM lung disease¹². Nevertheless the doubt about *M. chelonae* infection or colonization emerged, when BALT lymphoma was diagnosed, because imagiologic changes could either be attributed to BALT or *M. chelonae*, which compromises ATS criteria for infection. Also the absence of clinical signs of pulmonary infection after stopping a short period of specific therapy, but with the beginning of chemotherapy, led us to consider that *M. chelonae* was possibly just a colonizer.

We were unable to establish if *M. chelonae* had a role as a chronic antigenic stimulus to BALT lymphoma or if it was BALT lymphoma that led to secondary infection or colonization by *M. chelonae*.

Optimal therapy is unknown. Chemotherapy with CHOP or R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone, with or without rituximab) is the most common treatment described by authors; however monotherapy with cyclophosphamide also presents a high rate of disease control and can be used as a single agent^{13,14}. Some experts favour a “watchful waiting” option in early stages and on asymptomatic patients due to the indolent evolution and the good prognosis of BALT, generally expected to have more than 80–90% of a five year survival rate^{14,15}.

In our case a less aggressive approach was decided due to the indolent evolution of BALT, the clinical stability of the patient, and to avoid a severe immunocompromised state, which could lead to a mycobacterial infection.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Author contributions

JN and LA conceived the study and carried out the research. All authors contribute in the diagnosis and follow up of the patient. JN prepared the first draft of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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The authors report on the case of a 66-year-old man presenting with subacute respiratory and constitutional symptoms. Interestingly the patient has a history of gastric lymphoma but little additional information is available for this very pertinent piece of his medical history. Following failure of empiric therapy for typical pulmonary pathogens and a misleading polymerase chain reaction (PCR) result showing *Mycobacterium tuberculosis* complex (MTC) in the sputum (later found to be laboratorial contamination) the diagnosis of *Mycobacterium chelonae* infection is made. This was based on sputum cultures that eventually resulted positive for nontuberculous mycobacterium (NTM) six weeks after incubation. It is important to note that the authors mention that antituberculous therapy (ATT) was continued despite the results since the patient was improving clinically.

Due to lack of radiological improvement a transbronchial biopsy was performed revealing a lymphocytic infiltrate positive for CD20, BCL2, CD23, CD10, CD5 and negative for CD3. This serves as the basis for the diagnosis of bronchial-associated lymphoid tissue (BALT) lymphoma in this patient. **In my opinion this is the weakest link in the logical chain for this case report.** No evidence of clonality was demonstrated by analysis of surface immunoglobulin light chain or IgH gene rearrangement. Testing for chromosomal translocations typically associated with mucosa-associated lymphoid tissue (MALT) lymphomas such as t(11;18)q21;q21 or t(11;14)(p22;q32) was not performed. Although the absence of such translocations does not necessarily exclude MALT lymphomas, a positive result would substantiate the claimed diagnosis. As demonstrated by Ye and colleagues¹, BALT lymphomas harbor the t(11;18) translocation in 38.3% of cases. Another useful test would be BCL10 staining, knowing that 26% of t(11;18)-negative cases will have moderate BCL10 expression based on results from the same cohort. In the absence of these additional tests the authors leave their claim for the diagnosis of BALT lymphoma exceedingly vulnerable to challenge. A reactive lymphoid infiltrate therefore cannot be excluded as a reasonable alternative diagnosis.

The report progresses to describe that the patient was treated with oral cyclophosphamide (CTX) resulting in clinical and radiological improvement. The association between treatment with CTX

and improvement however can only offer circumstantial evidence to support that BALT lymphoma was indeed the correct diagnosis. One could argue that response to specific therapy against *M. chelonae* was delayed and coincided with the initiation of therapy with CTX. Alternatively, one could also argue that the correct diagnosis in this patient is interstitial lymphocytic pneumonia (ILP) for which immunosuppressive agents such as CTX has demonstrated efficacy.

The discussion is naturally built on the assumption that BALT lymphoma is the correct diagnosis in this case. Since this publication is largely targeted to the general audience I would suggest including a list of differential diagnosis for patients with suspected BALT lymphomas (preferably in tabular format). Another point to add in the discussion is the role of single-agent rituximab or radiotherapy in the treatment of patients with early-stage disease.

In summary, given that the central hypothesis of this manuscript (diagnosis of BALT lymphoma) is supported by weak evidence I would suggest the following revisions before the manuscript can be considered for publication:

1. Provide additional evidence for the diagnosis of BALT lymphoma by demonstrating clonality (minimum) and/or specific genetic lesions associated with MALT lymphomas.
2. Consider another attempt obtaining more information about this patient's previous history of gastric lymphoma. Should you be able to demonstrate that this patient had MALT lymphoma of the stomach this would open another set of questions such as: is the BALT lymphoma truly a primary event or is it a recurrence from the previously treated MALT lymphoma? Does this patient carry a genetic predisposition for this disease?
3. Consider a list of differential diagnosis to be considered in someone suspected to have BALT lymphoma, possibly in tabular format for ease of read.
4. Add to the discussion the role of single-agent rituximab or radiotherapy in early-stage disease.

I would be happy to review the revised manuscript after changes are made.

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Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 18 February 2016

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Joana Neves et al. presented a case of BALT lymphoma. This patient was admitted with pneumonia and then his sputum was positive for Mycobacterium tuberculosis complex using polymerase chain reaction technology. However, there was no imagiological improvement after antituberculous therapy. Therefore, the patient underwent a pulmonary transthoracic biopsy that revealed BALT lymphoma. After 6 months of cyclophosphamide treatment the patient showed significant clinical improvement.

1. Please provide pertinent laboratory data at the time of the patient's initial evaluation, such as white blood cell count, erythrocyte sedimentation rate, antinuclear antibody titer, β 2-microglobulin.
2. Please provide relevant computed tomography findings following antituberculous treatment and cyclophosphamide treatment.
3. Please provide microscopic examination results about pulmonary transthoracic biopsy.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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