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Review Article

Pulmonary Mucosa-Associated Lymphoid Tissue Lymphoma- A Single Center Review of the Diagnostic Approach

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ABSTRACT

Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma is a rare disease, and diagnosis is difficult, often requiring multiple attempts at tissue sampling. The aim of this review was to evaluate the diagnostic pathway. A retrospective review was performed of patients diagnosed with pulmonary MALT lymphoma in a tertiary referral lung cancer center over 9 years. Ten patients were identified, and each diagnostic and treatment approach was analysed. 30% were diagnosed via transbronchial biopsy, two with the assistance of radial probe ultrasound guidance and one with transbronchial lung cryobiopsy of a predetermined CT-guided targeted segment. 70% were diagnosed following surgical biopsy. 40% had localized disease. The diagnosis was not successfully achieved until a large-sized tissue specimen was obtained. The implementation of novel bronchoscopy techniques can assist in reducing the number of invasive surgical procedures required to obtain a diagnosis. All cases should be discussed in a multidisciplinary setting prior to diagnostic attempts.

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Introduction

Primary pulmonary lymphoma is a clonal proliferation of lymphoid tissue [1]. It is a rare disease, accounting for less than 1% of all pulmonary neoplasms and 3-4% of all extra-nodal non-Hodgins lymphoma [2, 3]. Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma is the most common subset of primary pulmonary lymphoma [4, 5]. MALT is a low-grade B- cell extra-nodal lymphoma, which arises in multiple organs such as the lungs, gastrointestinal tract, orbit, and salivary glands [6, 7]. It typically presents in the fifth and sixth decade of life [8]. Smoking rates do not appear to higher amongst people with MALT Lymphoma than the general population [4].

The development of MALT lymphomas is associated with chronic antigen stimulation of autoantigen and/or microbial origin [7, 9]. Autoimmune disorders such as Sjogren's syndrome, systemic lupus erythematous, and multiple sclerosis, which involve chronic antigen stimulation, are known risk factors for the development of MALT lymphoma [7, 10, 11]. Chronic infections are also associated with the development of MALT lymphomas, by chronic stimulation of B-lymphocyte proliferation [7, 12, 13]. Cytogenic abnormalities have also been shown to lead to the development of MALT lymphomas, with t(11;18) (q21;q21) translocation being the most frequent abnormality associated with MALT lymphoma [13, 14].

The diagnosis of pulmonary MALT lymphoma can be challenging. Symptoms are non-specific and up to 50% of patients are asymptomatic, with investigations often only initiated following abnormal chest imaging [8, 15]. Tissue biopsy is the gold standard for diagnosis [15]. However, obtaining an adequate tissue sample suitable for histological and immunohistochemistry analysis to definitively classify lymphoma subtype can prove difficult. Several invasive diagnostic attempts are often required before a suitable specimen is obtained to make a diagnosis, ultimately subjecting patients to potentially multiple unnecessary procedures. The aim of this review was to evaluate the diagnostic pathway for primary pulmonary MALT lymphoma.

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Materials and Methods

We carried out a retrospective review of patients diagnosed with primary pulmonary lymphoma of the MALT subtype in a tertiary referral lung cancer center. A database of electronic clinical data from 2011 to 2019 was analysed using the terms 'lymphoma', 'MALT lymphoma' and 'primary pulmonary lymphoma' to identify possible cases.

To be included, patients had to have:

i. A pulmonary lesion(s) on computed tomography (CT) imaging without extra-pulmonary nodal involvement;
ii. A histologically proven diagnosis of extra-nodal marginal zone B cell MALT lymphoma from a pathological lung biopsy.

Patients were excluded if:

i. They had an alternative histological lymphoma subtype;
ii. This was a relapse of a prior nodal MALT lymphoma without evidence of an initial isolated pulmonary lesion.

Records were analysed, and the clinical history and supportive investigations were reviewed to confirm eligibility. We reviewed the patient characteristics, including clinical presentation, smoking status, and underlying autoimmune disorders and radiological characteristics. We then focused on the various diagnostic modalities and treatments received.

Results

I Patient Characteristics

Table 1 shows the main patient characteristics of our cohort. A total of ten cases were identified over the nine-year period. There was a slight female predominance at 60%. The ages ranged from 49 to 77 in this cohort with a mean age of 61.4 years. There were no active smokers in this group; however 50% were ex-smokers.

Table 1: Patient characteristics.

Characteristics	Value
Age (years)	61.4 (49-77)
ECOG Score	0
Females	6 (60)
Former Smokers	5 (50)
Underlying Autoimmune Disorder	5 (50)
Respiratory Symptoms	5 (50)
B Symptoms	3 (30)

Values are presented as mean (range) or n (%); ECOG: Eastern Cooperative Oncology Group.

Five patients had underlying autoimmune disorders at diagnosis, including Sjogren's syndrome (n =3), polymyalgia rheumatica (n=1), and Coeliac disease (n=1). Half of this cohort were completely asymptomatic. The most commonly reported symptoms were dyspnea (40%) and dry cough (20%). One patient reported streaky hemoptysis. The majority of patients (70%) reported no B symptoms. Weight loss was observed in two cases and night sweats in one. All were fit patients at presentation with an Eastern Cooperative Oncology Group (ECOG) performance score of zero.

II Laboratory Investigations

A full blood count was carried out in all patients; there were no findings of anemia, thrombocytopenia, or leukopenia. Serum protein electrophoresis was available in the majority of cases (90%). This was normal in 8 cases with a faint band present in 1 case. Lactate dehydrogenase level was available in 90% of patients. 44% of patients showed a mildly elevated serum LDH level, a mean of 460.5 (range 0-450). Beta 2 micro-globulin measurement was available in 50%. This was within normal limits (1.19-2.42) in 4 cases and mildly elevated in one case at 3.98.

III Radiology

Table 2 shows the main radiological characteristics of pulmonary MALT lymphoma in our cohort. All patients underwent pulmonary computed tomography (CT), which showed that lesions were bilateral in 40% and multiple in 70% of cases. The most common patterns were ground-glass opacification (60%), nodules (60%) and consolidations (50%). Cavitating lesions and mass lesions were less commonly noted (20% in both cases). 30% had evidence of airways within the lesions. Only one case showed a pericardial effusion, and there was no CT evidence of pleural effusions. 20% of the cases showed hilar lymphadenopathy.

An F-2-fluro-2-deoxy-D-Glucose (FDG) Positron emission tomography- computed tomography (PET CT) was carried out in 7 cases (70%), and in all patients within the last 5 years (Table 2). The majority (5/7) of MALT lymphomas were non FDG avid, 1 was mildly FDG avid while the remaining 2 were strongly FDG avid. None demonstrated extra-pulmonary dissemination.

Table 2: Radiology evaluation.

Pulmonary CT Findings	Value
Bilateral Lesions	4 (40)
Multiple Lesions	7 (70)
Pericardial Effusion	1 (10)
Pleural Effusion	0
Hilar Lymphadenopathy	2 (20)
PET CT Findings	
Pulmonary non FDG avid Lesion (SUV <2.5)	4 (57)
Pulmonary mild FDG avid lesion (SUV 2.5 -5)	1 (14)
Pulmonary FDG avid lesions (SUV >10)	2 (29)
Extra-pulmonary FDG avid lesions	0

Values are presented as n (%).

IV Diagnostic Pathway

Figure 1 demonstrates the diagnostic pathway used in this cohort of patients. 20% were not amenable to bronchoscopy or CT guided biopsy and referred straight to surgery following lung cancer multidisciplinary meeting (MDM) recommendation. Bronchoscopy was carried out in 80% of cases, and all were macroscopically normal. Bronchoalveolar

lavage was performed in two patients; a mild lymphocytosis was demonstrated in one case. 30% were diagnosed via transbronchial biopsy, two with the assistance of radial probe ultrasound guidance, and one with transbronchial lung cyrobiopsy (TBLC) of a predetermined CT-guided targeted segment. CT guided percutaneous biopsy was attempted in 30% of cases; however, an adequate tissue sample for diagnosis was not obtained.

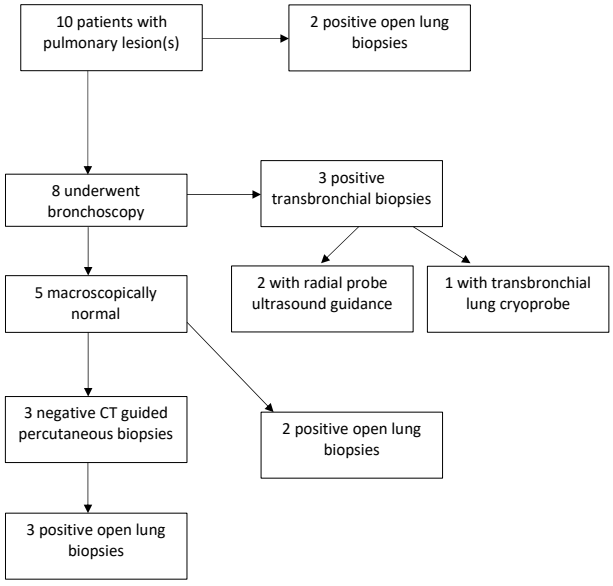


Figure 1: Diagnostic Pathway for diagnosing Pulmonary MALT.

7 patients (70%) underwent surgical resection in order to obtain an adequate tissue sample. 6 of these patients underwent a wedge resection and 1 had a lobectomy. All cases were confirmed extra-nodal marginal zone B cell MALT lymphoma following histopathology and immunohistochemistry analysis. All cases were formally diagnosed following discussion at a lung cancer and lymphoma MDM. A bone marrow aspirate was carried out in 50% of cases. No evidence of lymphoma dissemination was found.

V Treatment

Figure 2 demonstrates the treatment our cohort received. 60% of our patients had localized disease. Of these patients, four were diagnosed following surgical resection, which simultaneously treated their disease, given its localized nature. Two patients were diagnosed with transbronchial biopsy under radiological guidance. One patient was treated with single-agent anti CD20 monoclonal antibodies therapy (rituximab) alone. The second patient did not receive any treatment, and a 'watch and wait' approach was taken.

40% of our patients had extensive disease. One patient was not deemed a surgical candidate and underwent treatment with multiple agent chemotherapy with rituximab, cyclophosphamide, vincristine sulfate, and prednisolone (R-CVP) regimen. The remaining three patients underwent a simultaneous diagnostic and therapeutic surgical resection and post-surgical R-CVP chemotherapy regimen. All three were then commenced on maintenance rituximab. 100% of patients underwent interval CT surveillance. Two patients (20%) of our cohort showed progression. Both initially were diagnosed with localized disease and treated with surgical resection alone; all had negative resection margins. One patient showed moderate progression at 2 years and was commenced on multiple agent chemotherapy (combination rituximab and bendamustine) followed by maintenance rituximab. One patient showed very mild progression at 4 years, and a continued 'watch and wait' approach was taken. Death did not occur in any of the cases during this study period.

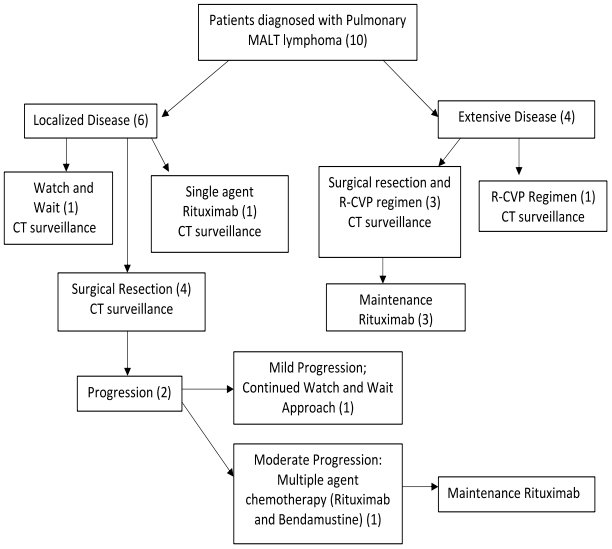


Figure 2: Treatment Pathway for Pulmonary MALT; R-CVP Regimen: rituximab, cyclophosphamide, vincristine sulfate and prednisolone regimen.

Discussion

Diagnosis of pulmonary MALT lymphoma can be challenging given its non-specific presentation, and often, investigations are only initiated following abnormal chest imaging. Almost half of the MALT lymphoma cases are asymptomatic and respiratory symptoms, when they occur, are most frequently dyspnea and dry cough. Our study population presented similarly with 50% completely asymptomatic. General symptoms such as weight loss and night sweats were observed in 30% of our cohort, similar to findings previously published [8].

Initial workup should include a CT Thorax. Pulmonary MALT lymphomas frequently present with multiple lesions on CT imaging, and our study corresponded with these findings as 70% had multiple lesions [16]. Nodules and consolidations are the most frequent patterns, although our study also showed ground-glass opacities in 60%, which is higher than has previously been reported [17, 18].

The use of PET CT for the staging for pulmonary MALT lymphoma is controversial [19]. PET CT was carried out in 70% of our study population. The majority were not FDG avid, with only two cases showing strong FDG avidity. For pulmonary disease, PET CT has a sensitivity of 50-89%; however, its sensitivity for other organ sites is not as high [20]. It cannot adequately assess bone marrow involvement, necessitating further investigations, such as bone marrow aspirate for disease staging [4]. As previously discussed, the pathogenesis of this disorder is associated with infectious and inflammatory conditions, which can be FDG avid, potentially increasing the false-negative rate

[21]. As such, the role of PET CT in the workup for primary pulmonary lymphoma remains debatable, and its use is not supported by our study. Bone marrow biopsy may show dissemination in up to 30% of cases but is not considered to be an essential component in the staging of primary pulmonary lymphoma [7]. Of those who underwent a bone marrow aspirate in our cohort (50%), there was no evidence of lymphoma dissemination.

Tissue biopsy is the gold standard for diagnosis [7]. Bronchoscopy is generally the first-line diagnostic modality for PPL. However, It is usually macroscopically normal, and thus necessitates further diagnostics [8, 18, 22, 23]. The presence of endobronchial lesions generally implies an alternative diagnosis [7]. Bronchoscopy was carried out in 80% of our cases and all were macroscopically normal. All required further investigations before successful diagnosis were achieved. This questions the justification for standard bronchoscopy in the diagnostic algorithm of PPL.

Bronchoalveolar lavage (BAL) may be helpful in distinguishing chronic alveolar opacities on radiology. Lymphocytic alveolitis (>20%) can be supportive of a MALT lymphoma neoplasm [24, 25]. However, a negative result does not out-rule its presence [26]. In particular, a B-lymphocyte level above 10%, and the clonality of lymphocytes demonstrated may occasionally be a helpful diagnostic tool [15, 18, 27]. Only two cases in our study population had a BAL sample analysed, with one demonstrating a mild lymphocytosis. Given this was only carried out in a small proportion of our cases, it could represent an underutilized diagnostic modality in our cohort.

If bronchoscopy fails to yield a diagnosis, CT guided percutaneous biopsy may be indicated, especially in peripheral lesions. CT guided percutaneous biopsy has been reported to have a sensitivity of approximately 80% [4]. In our cohort, however, only 30% were suitable for CT guided percutaneous biopsy, and none yielded an adequate sample for definitive diagnosis.

In the latter years of our study, the introduction of advanced bronchoscopy diagnostic techniques, such as transbronchial lung cryobiopsy (TBLC), achieved a successful diagnosis without the need for surgical referral. Conventional bronchial and transbronchial biopsies have a higher success rate when guided by targeted ultrasound or CT scanning [4, 18]. In our study population, diagnosis of pulmonary MALT lymphoma was successfully achieved in two patients who underwent transbronchial biopsy with the assistance of radial probe ultrasound guidance and in one patient with TBLC of a predetermined CT-guided targeted segment. Prior to this, the previous investigations had been inconclusive, and a definitive diagnosis had not been achieved. Although not without its risks, most commonly related to bleeding, TBLC has a lower mortality rate compared with surgical lung biopsy (0.3% and 1.7% respectively), has shorter recovery time and is more cost-effective [28, 29]. There have been a small number of case reports on the successful use of cryoprobe assisted transbronchial lung biopsy as a diagnostic tool for the diagnosis of primary pulmonary diffuse large B cell lymphoma [30, 31]. To the authors' knowledge, this is the first successful diagnosis of pulmonary MALT lymphoma with TBLC. This diagnostic method should be considered as a potential surrogate to surgical biopsy in selected cases when there is a suspicion of a PPL, especially if surgical lung biopsy is contraindicated [32]. Optimization of patient selection and increased operator experience should improve adverse outcomes [29].

In certain cases, a more invasive approach with a surgical lung biopsy, including VATS and open procedures, is required to obtain a definite diagnosis. This method provides larger specimen size and subsequent improved histological analysis; however, is associated with increased patient risk and post-procedure recovery time is higher. Therefore, consideration should only be made on an individual basis following a multidisciplinary discussion. 70% of our study population required a surgical resection to obtain an adequate pathological specimen, and thus, it is clear that there is a need for novel diagnostic modalities to reduce the number of invasive surgical procedures.

Our study showed that a definitive diagnosis was not successfully achieved until a large-sized tissue specimen was obtained; 70% of patients required a surgical biopsy, and 30% were diagnosed with a transbronchial biopsy, guided by targeted ultrasound or CT scanning. Although not supported by our study, the use of CT guided percutaneous biopsy has been shown to be useful [4].

The aim of diagnostics is to limit the number of invasive procedures required to achieve adequate sampling and improve the yield of minimally invasive techniques. Therefore, the authors conclude that if PPL is suspected, a standard bronchoscopy is not justified as part of the diagnostic algorithm, and patients should be evaluated for suitability for CT guided percutaneous biopsy or advanced bronchoscopy techniques, such as TBLC, prior to surgical referral.

At present, there is no current management protocol for pulmonary MALT lymphoma, and therapeutic options can include interventions such as surgery, chemotherapy, radiotherapy, immunotherapy, or in certain cases, a 'watch and wait' approach is taken [7, 15]. The survival rate is approximately 90% at 5 years; however, the recurrence rate is high and continued surveillance is advised [6, 33].

In localized disease, surgical resection or radiotherapy alone may be sufficient [17, 34]. Of the six patients with localized disease in our cohort, surgical resection was carried out in four of those. Two of these patients ultimately showed disease progression on surveillance CT scan imaging, and thus, close follow-up of all patients is supported by our study.

Chemotherapy is preferred in patients with bilateral or extrapulmonary disease and in cases of disease progression or recurrence [7]. Multiple agent chemotherapy treatment does not appear to be superior to single-agent treatment [18]. Anti CD20 monoclonal antibodies, such as rituximab, are also effective [35]. In our cohort, 40% had extensive disease, and these patients underwent a combination of surgical resection and chemotherapy or chemotherapy alone. Three patients were commenced on maintenance rituximab. None of these patients showed disease progression on interval CT imaging.

The absence of clinical trials means comparative groups do not exist, and thus, formally assessing the relative effectiveness of different treatment options at this time is not possible. If their disease is localized, surgical resection alone may offer a simultaneous diagnostic and therapeutic

option. The authors, therefore, recommend a lung cancer MDM discussion as part of the diagnostic algorithm, taking into consideration the individual patient's clinical presentation and functional status as well as disease burden and progression prior to invasive diagnostic attempts.

The weakness in our study includes its small numbers and the relatively short time period over which it was conducted. Only one lung cancer center was included in this study and thus may have been subject to regional bias. This was also a retrospective review, with the inherent bias associated. In some areas, such as laboratory analysis, there was a lack of complete data in recordings available.

Conclusion

The rarity of pulmonary MALT lymphoma along with the non-specific radiological and clinical presentation makes the diagnosis of this disorder difficult. Multiple attempts at tissue sampling are often required to obtain an adequate pathological specimen to facilitate a definitive diagnosis, and a multidisciplinary discussion should be included as part of the diagnostic pathway, prior to invasive diagnostic procedures. The implementation of novel bronchoscopy techniques such as transbronchial lung cryobiopsy can assist in reducing the number of invasive surgical procedures required to obtain a diagnosis. This is a promising area but requires further research. To date, there are only a small number of isolated case reports in this area, and thus larger-scale studies are needed to establish the safety profile and efficacy of this potentially valuable diagnostic modality in this patient group.

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Conflicts of Interest

None.

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