Case Reports in Oncology

Case Rep Oncol 2023;16:1528–1535
DOI: 10.1159/000534802
Received: June 9, 2023
Accepted: October 9, 2023
Published online: December 1, 2023

Case Report

Pulmonary Mucosa-Associated Lymphoid Tissue Lymphoma Treated with Radiation Therapy: A Case Report and Review of the Literature

Paul Armstrong[a] Patrick Hayden[b] Michael Jeffers[c] Lisa Fitzpatrick[d] Aoife Mcknight[e] John Armstrong[f]

[a]Medical Student, University College Dublin, Dublin, Ireland; [b]Consultant Haematologist, St. James Hospital, Dublin, Ireland; [c]Consultant Histopathologist, Beacon Hospital, Dublin, Ireland; [d]Radiation therapist, Beacon Hospital, Dublin, Ireland; [e]Radiation Physicist, Beacon Hospital, Dublin, Ireland; [f]Consultant Radiation Oncologist, Beacon Hospital, Dublin, Ireland

Keywords
Case report · Pulmonary mucosa-associated lymphoid tissue lymphoma · Mucosa-associated lymphoid tissue lymphoma · Radiation therapy

Abstract
Introduction: Mucosa-associated lymphoid tissue lymphoma (MALT lymphoma or MALToma) is a prevalent type of primary pulmonary lymphoma. Typically, the primary therapeutic approaches involve surgery or chemotherapy, although there have been instances of radiation therapy being employed. ***Case Report:*** We present a case of pulmonary MALToma that exhibited progression despite rituximab therapy. Subsequently, the patient demonstrated a positive response to radiation therapy. ***Conclusion:*** This case highlights the potential efficacy of radiation therapy as a treatment option for pulmonary MALToma, especially in cases where other conventional treatments like rituximab have proven ineffective. Further research and studies are warranted to better understand the role of radiation therapy in managing pulmonary MALToma and to determine optimal treatment strategies for patients with this condition.

Introduction

Primary pulmonary lymphomas (PPLs) – excluding diffuse large B-cell lymphomas – are traditionally defined as lymphomas presenting as pulmonary lesions with no clinical, pathological, or radiographic evidence of lymphoma elsewhere in the past, at present, or for 3 months after presentation, are rare lymphoproliferative disorders involving one or both

Correspondence to:
Paul Armstrong, paul.armstrong1@ucdconnect.ie

Case Rep Oncol 2023;16:1528–1535
DOI: 10.1159/000534802

lungs [1]. They account for roughly 0.5–1% of all pulmonary malignancies [2] and 3.6% of extranodal lymphomas. The most frequent type of PPLs – accounting for 90% – are mucosa-associated lymphoid tissue lymphoma (MALT lymphoma or MALTomas) [3]. They most frequently develop in the 6th and 7th decades of life with equal prevalence in men and women, particularly in patients with a background of chronic infection or inflammation [4].

There is evidence to suggest that MALT lymphomas are associated with chronic antigenic stimulation, either due to an autoimmune response or due to a pathogen. This chronic stimulation results in an accumulation of lymphoid tissue in the organs involved [5, 6], for example, *Helicobacter pylori* is a well-established causative pathogen of gastric MALT lymphomas [7]. It has also been shown that up to 15% of patients suffering with PPLs have autoimmune diseases such as systemic lupus erythematous, rheumatoid arthritis, or Sjogren's syndrome [8].

Typically, pulmonary MALTomas have an indolent course and remain within the lung for a relatively long period of time before disseminating, and show few signs of aggression or lymph node involvement [9]. Signs and symptoms are non-specific, with one-third of patients clinically asymptomatic at diagnosis [10]; however, patients can often present with dyspnoea, cough, chest pain, or haemoptysis [9]. Most patients have a favourable prognosis with 5-year and 10-year survival rates being 90% and 70%, respectively [11].

Radiological appearance of pulmonary MALT lymphomas can be variable, ranging from consolidations to large masses or nodules, with hilar lymphadenopathy being present in up to 30% of cases [12]. Diagnosis should include laboratory tests, tumour biopsy and should be based on histopathological findings supported by immunohistochemistry, clonality studies, and t(11:18) FISH studies as appropriate.

The optimal management of this rare disease is still under debate; patients with asymptomatic disease may be better candidates for a watch and wait approach rather than immediate therapy [13]. One study reviewed 51 cases of pulmonary MALTomas from the years of 2003 to 2015 and found the most common treatment modality to be surgical resection in low-stage patients and chemotherapy with no patients being treated with radiotherapy [14]. Another review of pulmonary MALToma cases found that out of 63 cases only one was treated with radiotherapy [8]. One single-institution study treated 10 patients with pulmonary MALT lymphomas with a total of 4 Gy with a 5-year progression-free survival rate of 87.5% [15]. Long-term follow-up with any treatment is recommended.

Case Report

Here, we present a 76-year-old woman, who presented to the hospital with flank pain due to a complicated UTI in December of 2018. The patient had a past medical history of psoriatic arthritis, two prior TIAs, hysterectomy, diverticulitis, and a neck injury in a road traffic accident. As part of the investigations for the UTI, a CT thorax abdomen pelvis was performed which revealed a 2.4 cm rounded pulmonary ground glass opacity (GGO) in the right middle lobe (Fig. 1a). In January of 2019, the patient underwent a CT-guided core biopsy of the lung which demonstrated a dense chronic inflammatory infiltrate, including lymphocytes and plasma cells (Fig. 2a, b). Lymphoepithelial lesions were not identified. The lymphoid population was B cell predominant (CD20+). The B cells were negative for CD5, CD10, CD23, and cyclin D1. Ki67 was low (<20%). Definitive light chain restriction was not demonstrated by immunohistochemistry but multiplex PCR confirmed a clonal B cell population (clonal immunoglobulin heavy chain gene rearrangements VFR1-J, VFR2-J, and VFR3-J) (Fig. 2c, d).

The morphology, immunophenotype, and molecular genetic information were consistent with a diagnosis of stage 1 low – grade B cell non-Hodgkin's lymphoma of mucosa-associated

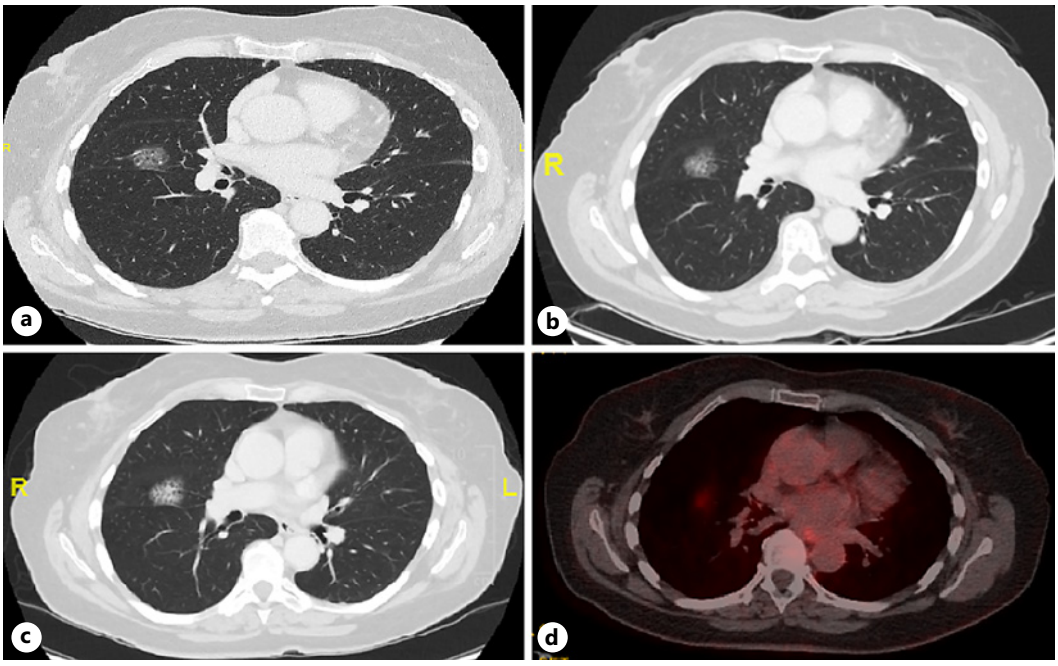

Fig. 1. a A CT-TAP taken on December 18, 2018 showing a 2.4 cm rounded ground-glass pulmonary opacity in the middle lobe of the right lung. **b** A CT thorax taken in July 2019 showing the GGO is stable and measures approximately 2.5 cm. **c**, **d** PET-CT whole body taken in September 2019 showing the lesion in the right lung to have increased in size from 16 × 17 × 22 mm to 19 × 28 × 17 mm, displaying low level FDG uptake (maximum SUV 2.6).

lymphoid tissue MALT type. The patient also underwent a bone marrow biopsy in March of 2019 and the bone marrow was found to be mildly hypercellular with increased megakaryocytes but no evidence of marrow involvement by lymphoma.

The patient was treated with 4 cycles of rituximab starting on the April 30, 2019 with the last cycle being administered on the 21st of May. A repeat CT thorax was done in July that same year and the GGO was found to be stable in size (Fig. 1b). During a follow-up positron emission tomography (PET)-CT scan in September 2019, the GGO was found to have increased slightly in size from 16 × 17 × 22 mm to 19 × 28 × 17 mm with low level FDG uptake and a maximum SUV of 2.6 (Fig. 1d), however no new pulmonary or pleural lesions were identified (Fig. 1c). The patient was then treated with radiotherapy during January and February of 2021 with a total of 30 Gy delivered in 15 fractions. The patient tolerated the treatment well and no significant toxicities or side effects were reported. After therapy, the patient has had a series of CT scans which have shown no new abnormalities. The radiological abnormality in the treatment site has remained stable, as seen in a follow-up CT-TAP performed in May 2021, with maximal axial dimensions having reduced from 24 mm to 15 mm at the corresponding level (Fig. 3). And follow-up CT scans in May of 2022 and May of 2023 showed stability in size. As this represents 2 years and 3 months of follow-up, we can assume that the disease is controlled.

Treatment

The patient was immobilised at CT simulation using the QFix® Breastboard with Wingboard attachment. A customised vacuum bag was also produced to immobilise the patient's arms above their head, removing them from the region of treatment. The addition of

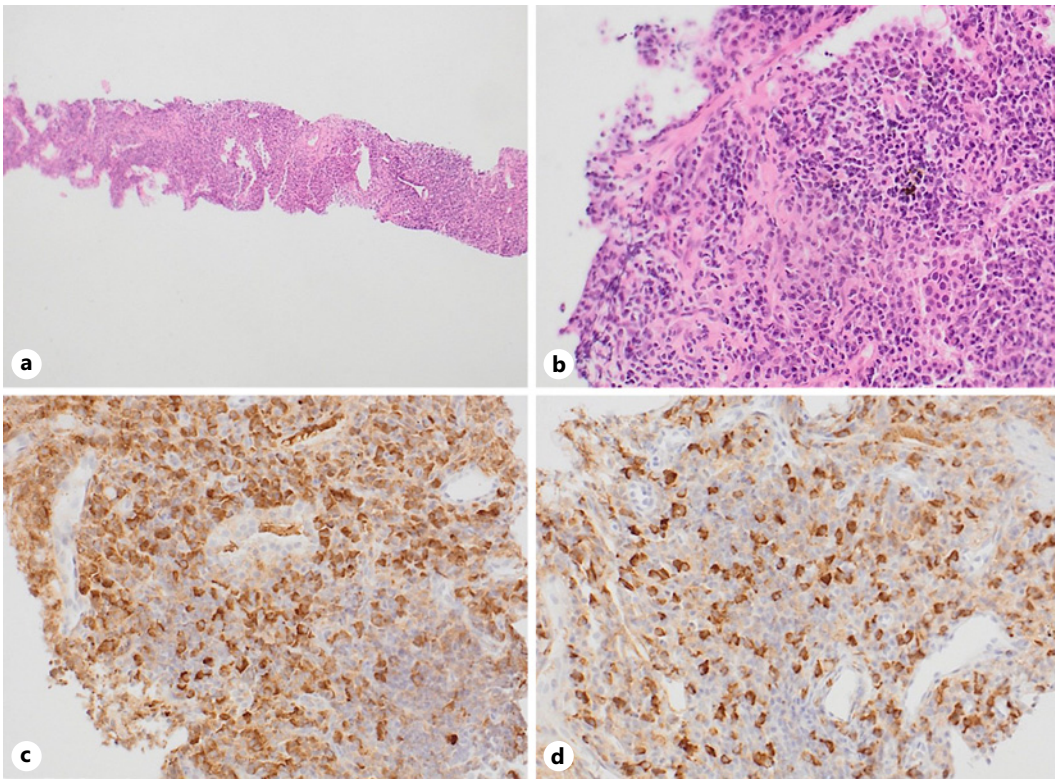

Fig. 2. **a** Lung core biopsy showing a dense chronic inflammatory infiltrate (H&E, ×25). **b** Infiltrate composed of lymphocytes and plasma cells (H&E, ×100). **c** Kappa immunoglobulin light chain immunohistochemistry. **d** Lambda immunoglobulin light chain immunohistochemistry.

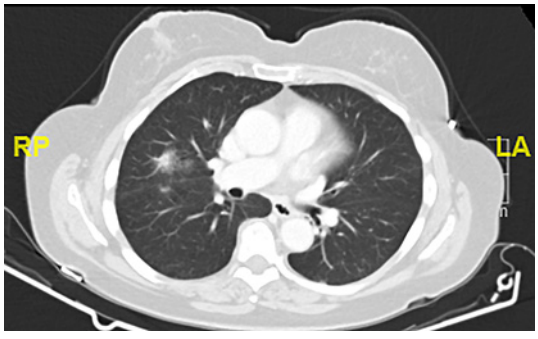

Fig. 3. Repeat CT thorax abdomen pelvis performed on May 12, 2021. Showing the previously noted mass in the right upper lobe had reduced in size and density compared with prior studies. With the maximal axial dimension having reduced from 24 mm to 15 mm at the corresponding level.

a vacuum bag increased patient comfort, supporting the arms and allowing them to maintain the treatment position for the duration of radiotherapy. A radiation design scan was obtained with the patient holding their breath in deep inspiration. An optical visual feedback system was used to monitor their breathing pattern to determine when breath is held versus when it is not, providing visual feedback for the patient. This allowed for delivery of therapy when the tumour was in the one reliable position within the thorax.

After the planning CT was obtained, the radiation oncologist then drew the gross tumour volume and the organs at risk on each transverse CT image. The gross tumour volume was isotropically expanded by 5 mm to a clinical target volume to account for microscopic extension beyond radiologically visible disease. A further 5 mm expansion was added to create a planning target volume to account for day-to-day setup and internal

motion of the tumour (Fig. 4a, b). The patient's treatment was planned using intensity modulated radiotherapy with a dose of 30 Gy in 15 fractions. The plan used five 6-MV beams entering through the ipsilateral lung only. Beams were angled off the heart and spinal cord to minimize entrance dose to these organs. The dose was prescribed to 99.5% isodose line to ensure at least 98% of the PTV received the full 30 Gy. Mean dose to PTV was 30.6 Gy and max dose was 31.1 Gy or 103.6% of prescribed dose. Dose to organs at risk met constraints outlined in the published literature (Fig. 4c). As the patient was treated with intensity modulated radiotherapy, individual patient QA dosimetry was performed using electronic portal imaging dosimetry.

The patient was treated on a Varian Edge® linear accelerator with a 6 degrees of freedom couch capability allowing for both translational and rotational corrections to be applied. As per our department protocol, daily online image-guided radiotherapy was used for pre-treatment verification of patient position and target coverage. The image-guided radiotherapy protocol was as follows: Fluoroscopy images were acquired on day 1 to verify the patient's DIBH prior to starting treatment. The cone beam CT (CBCT) was acquired while the patient was achieving the required breath hold. For the CBCT treatment delivery, the patient's DIBH was monitored using Varian respiratory gating system. Patient positioning was achieved using surface guidance eliminating the need for permanent skin marks. CBCT images were reviewed by radiation therapists to assess tumour position with soft tissue matching employed to achieve optimal coverage with corrections applied in 6 degrees of freedom.

Discussion

As mentioned previously, PPLs account for roughly 0.5–1% of all pulmonary malignancies [2], with the most common type being pulmonary MALToma accounting for nearly 90% of PPLs [3]. They are often present in elderly patients with a background of chronic infection or inflammation [4].

The presentation of pulmonary MALTomas can vary. In 36% of cases, patients are asymptomatic at diagnosis, with another third of cases presenting with non-specific symptoms such as dyspnoea, cough, chest pain, weight loss, fever, fatigue, night sweats, and haemoptysis [16].

Pulmonary MALTomas are diagnosed mainly through imaging and biopsy, although some laboratory findings such as anaemia [17] and an elevated LDH can be found [18]. CT scans and PET scans are essential in diagnosing this form of lung cancer, the most common CT findings include nodules, masses, and patchy consolidations. In most cases, PET-CT shows increased FDG uptake correlating with tumour size, therefore it can be used in diagnosis and follow-up [19]. Because MALT lymphomas are typically localised in the lung parenchyma, the cytology from bronchial alveolar lavage is often negative, so a surgical biopsy is often needed for diagnosis.

Treatment can vary depending on multiple factors including tumour site or patient factors. Current 2023 NCCN guidelines recommend using radiotherapy as a first-line treatment for stage IIE and for stage IV for extranodal lymphomas of non-gastric sites, with surgery being considered first line in sites like the lung, thyroid breast, or small bowel and monoclonal antibodies such as rituximab being considered in selected cases with a response rate of 70% but also a recurrence rate of up to 36% [20]. Here, we demonstrate that radiotherapy could be considered as a first line for pulmonary MALToma given the lack of morbidity in this case.

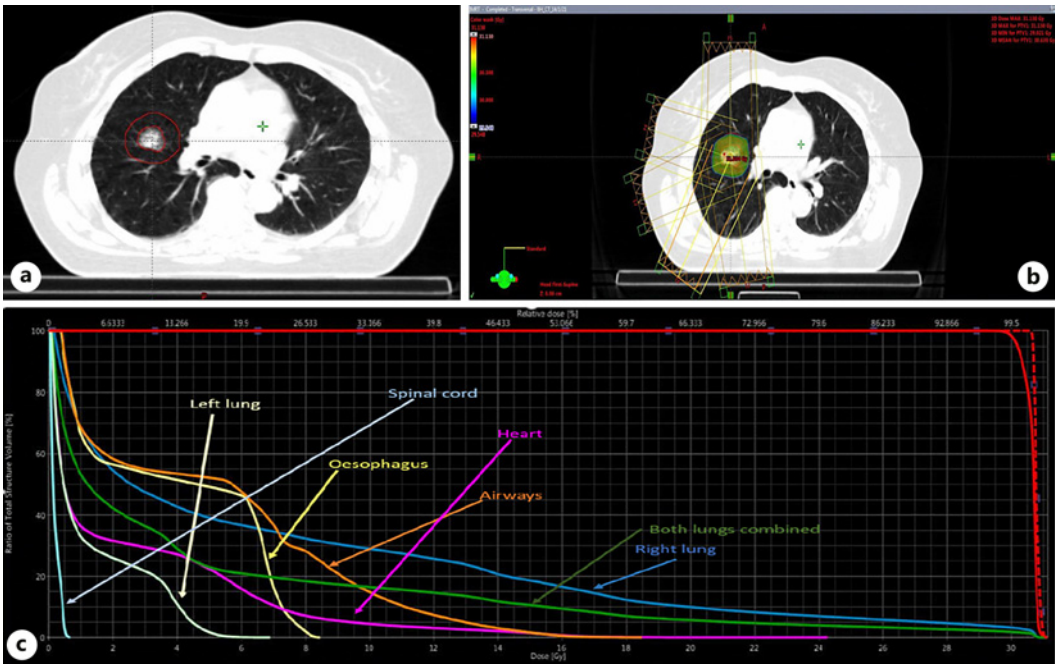

Fig. 4. a Planning CT showing tumour GTV and PTV. **b** Field setup showing dose coverage. **c** A dose-volume histogram of the treatment. This graph quantifies the amount of radiation received by each organ and the target (tumour). The y-axis depicts the percent of the organ and the x-axis details the dose received. For example, the dose to the target is depicted by the red line. The area under the curve is large and almost 100% of the target receives the full 30 Gy. The normal organs have a limited "area under the curve" demonstrating how the technology restricts dose to critical normal structures. The mean heart dose is 2.4 Gy which is very far below acceptable limits. GTV, gross tumour volume.

Here, we present a case of a 76-year-old woman, diagnosed with a right pulmonary MALToma in January of 2019. The patient was treated with 4 cycles of rituximab starting on the April 30, 2019, with the last cycle being administered on the 21st of May. This initially showed a good response on CT in July 2019 but in November 2020 the lesion was shown to have increased in size. Following treatment with radiotherapy in January and February of 2021, she is currently well and showing no signs of progression. This intriguing and atypical treatment pathway prompted us to document and share this case report. By doing so, we hope to shed light on this unique situation and potentially offer insights that could benefit future patients with similar challenges. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534802).

Conclusion

Here, we present a novel approach to treatment of pulmonary MALT lymphomas. The standard treatment for MALT lymphomas is rituximab chemotherapy or surgical removal. This case is unique in the sense that the tumour did not respond to 4 cycles of rituximab therapy resulting in tumour growth, however radiation therapy was able to achieve local control and the patient remains stable after 2 years of follow-up. This could be a potential therapeutic option for pulmonary MALT lymphomas in the future.

Acknowledgment

Author Lisa Fitzpatrick was not available to confirm co-authorship, but the corresponding author Paul Armstrong affirms that author Lisa Fitzpatrick contributed to the paper, had the opportunity to review the final version to be published and guarantees author Lisa Fitzpatrick's co-authorship status and the accuracy of the author contribution and conflict of interest statements.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study protocol was reviewed and the need for approval was waived by Beacon Hospital Research Ethics Committee.

Conflict of Interest Statement

There are no conflicts of interest to disclose.

Funding Sources

No funding was received during this case study.

Author Contributions

Paul Armstrong: main author. Patrick Hayden: provided case details, treatment summary, and imaging. Michael Jeffers: paragraph on histology in case report section. Lisa Fitzpatrick, Aoife McKnight, and John Armstrong: treatment section.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

References

1 Borie R, Wislez M, Antoine M, Cadranel J. Lymphoproliferative disorders of the lung. Respiration. 2017;94(2):157–75.
2 Zhu Z, Liu W, Mamlouk O, O'Donnell JE, Sen D, Avezbakiyev B. Primary pulmonary diffuse large B cell non-hodgkin's lymphoma: a case report and literature review. Am J Case Rep. 2017;18:286–90.
3 Kubisa B, Bocheńska A, Piotrowska M, Dec P, Lesińska A, Kubisa A, et al. Primary pulmonary mucosa-associated lymphoid tissue lymphoma: a case report. Adv Respir Med. 2015;83(1):45–9.
4 Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. Cancer. 1983;52(8):1410–6.
5 Royer B, Cazals-Hatem D, Sibilia J, Agbalika F, Cayuela JM, Soussi T, et al. Lymphomas in patients with Sjogren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. Blood. 1997;90(2):766–75.

6 Suarez F, Lortholary O, Hermine O, Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation. Blood. 2006;107(8):3034–44.
7 Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet. 1993;342(8871):575–7.
8 Borie R, Wislez M, Thabut G, Antoine M, Rabbat A, Couderc LJ, et al. Clinical characteristics and prognostic factors of pulmonary MALT lymphoma. Eur Respir J. 2009;34(6):1408–16.
9 Cadranel J, Wislez M, Antoine M. Primary pulmonary lymphoma. Eur Respir J. 2002;20(3):750–62.
10 Le Tourneau A, Audouin J, Garbe L, Capron F, Servais B, Monges G, et al. Primary pulmonary malignant lymphoma, clinical and pathological findings, immunocytochemical and ultrastructural studies in 15 cases. Hematol Oncol. 1983;1(1):49–60.
11 Koss MN, Hochholzer L, Nichols PW, Wehunt WD, Lazarus AA. Primary non-Hodgkin's lymphoma and pseudolymphoma of lung: a study of 161 patients. Hum Pathol. 1983;14(12):1024–38.
12 Hare SS, Souza CA, Bain G, Seely JM, Gomes MM, Quigley M. The radiological spectrum of pulmonary lymphoproliferative disease. Br J Radiol. 2012;85(1015):848–64.
13 Bacon CM, Du MQ, Dogan A. Mucosa-associated lymphoid tissue (MALT) lymphoma: a practical guide for pathologists. J Clin Pathol. 2007;60(4):361–72.
14 Lee H, Yang B, Nam B, Jeong BH, Shin S, Zo JI, et al. Treatment outcomes in patients with extranodal marginal zone B-cell lymphoma of the lung. J Thorac Cardiovasc Surg. 2017;154(1):342–9.
15 Girinsky T, Paumier A, Ferme C, Hanna C, Ribrag V, Leroy-Ladurie F, et al. Low-dose radiation treatment in pulmonary mucosa-associated lymphoid tissue lymphoma: a plausible approach? A single-institution experience in 10 patients. Int J Radiat Oncol Biol Phys. 2012;83(3):e385–9.
16 Borie R, Antoine M, Cadranel J, Wislez M. Pulmonary MALT lymphoma. Bull Cancer. 2014;101(2):195–202.
17 Huang H, Lu ZW, Jiang CG, Li J, Xu K, Xu ZJ. Clinical and prognostic characteristics of pulmonary mucosa-associated lymphoid tissue lymphoma: a retrospectiveanalysis of 23 cases in a Chinese population. Chin Med J. 2011;124(7):1026–30.
18 Kocatürk Cİ, Seyhan EC, Günlüoğlu MZ, Ürer N, Kaynak K, Dinçer Sİ, et al. Primary pulmonary non-Hodgkin's lymphoma: ten cases with a review of the literature. Tuberk Toraks. 2012:246–53.
19 Perry C, Herishanu Y, Metzer U, Bairey O, Ruchlemer R, Trejo L, et al. Diagnostic accuracy of PET/CT in patients with extranodal marginal zone MALT lymphoma. Eur J Haematol. 2007;79(3):205–9.
20 Conconi A, Martinelli G, Thiéblemont C, Ferreri AJM, Devizzi L, Peccatori F, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. Blood. 2003;102(8):2741–5.