



## Case report

## Spontaneous regression of primary endobronchial extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue

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## ABSTRACT

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) of pulmonary origin is a relatively rare disease. In particular, reports of MALT lymphoma occurring and localized in the trachea or bronchus have been limited. Pulmonary MALT lymphoma has been reported to demonstrate spontaneous regression, whereas there is only one reported case of spontaneous regression of primary endobronchial MALT lymphoma. We herein report the case of a 70-year-old man with primary endobronchial MALT lymphoma who showed spontaneous regression with an interest of endobronchial findings.

## 1. Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is a distinct subgroup of non-Hodgkin's lymphoma (NHL) that comprises more than two-thirds of all primary NHL of the lung [1]; however, it is extremely rare for MALT lymphoma to arise in the trachea or bronchus. Although spontaneous regression has been reported in patients with pulmonary MALT lymphoma [2], there is only one reported case with spontaneous regression of primary endobronchial MALT lymphoma [3].

We herein report a case of primary endobronchial MALT lymphoma presenting spontaneous regression.

## 2. Case report

A 70-year-old man presented to a local physician for cough in July 2018. As his symptom was not improved after more than one month, he visited another hospital. Chest computed tomography (CT) showed thickening of the bronchovascular bundle and stenosis at the introitus of the middle lobar branch (Fig. 1A and B). Bronchoscopy showed several endobronchial nodular protrusions and bronchial thickening along the right middle bronchus (Fig. 2A and B). The extent of the tumor margin was clearly identified as a magenta image by an autofluorescence imaging bronchovideoscope system (Fig. 2C).

He was suspected of having small cell lung cancer and therefore referred to our hospital for a further evaluation in August 2018. There were no changes or discontinuation of oral drugs or inhaled medicine. The patient was a current smoker (1 pack/day for 50 years) and had no known history of dust exposure, including asbestos. Laboratory test results were as follows: white blood cell count (WBC), 6100/mm<sup>3</sup>; hemoglobin, 14.3 g/dL; platelets, 26.0 × 10<sup>4</sup>/mm<sup>3</sup>; serum total protein, 7.0 g/dL; albumin, 3.8 g/dL; creatinine, 1.0 mg/dL; lactate dehydrogenase, 148 IU/L; C-reactive protein, 0.19 mg/dL; soluble IL2-receptor, 384 U/mL; carcinoembryonic antigen, 1.8 ng/mL; pro gastrin-releasing peptide, 63.55 pg/mL; and neuron-specific enolase, 7.3 ng/mL. Autoimmune antibodies were negative, and free triiodo thyronine, free thyroxine, and thyroid-stimulating hormone levels were within normal ranges. He underwent <sup>18</sup>F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT, which showed a mild FDG uptake (standardized uptake value [SUV] max 4.60) within the introitus of the right middle lobe bronchus but no other findings (Fig. 1C).

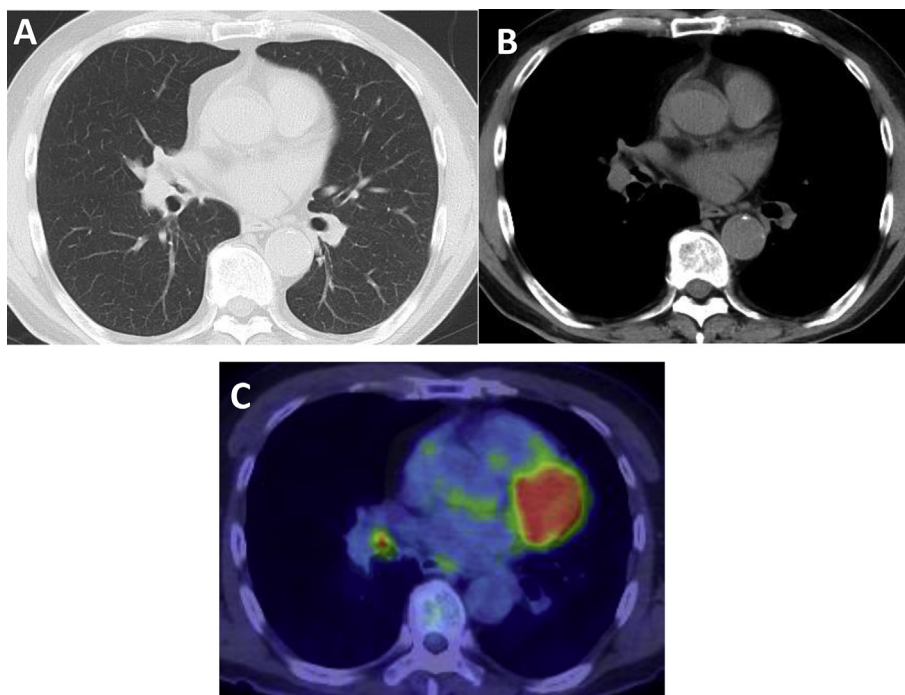
Bronchoscopy was performed again to obtain sufficient material to confirm the pathological diagnosis, and the endobronchial lesions were found to have regressed while the mucosal surface appeared relatively regular without atrophy or stenosis. (Fig. 2D–F). Histology of an endobronchial biopsy specimen showed diffuse infiltrates of small-sized atypical lymphoid cells within the mucosa. Immunohistochemistry demonstrated predominance of CD20- and CD79a-positive and CD5-

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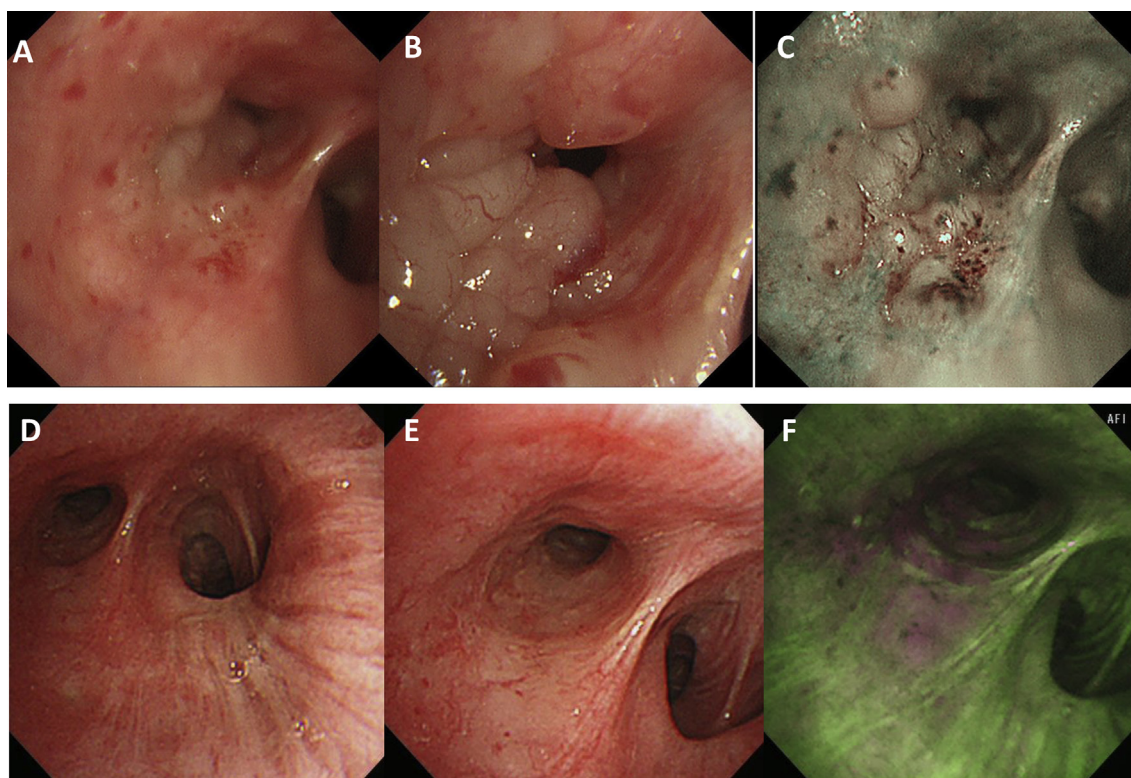
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**Fig. 1. Radiological findings.** (A, B): Chest computed tomography (CT) at the initial consultation revealed tracheobronchial stenosis at the introitus of the middle lobar branch. (C):  $^{18}\text{F}$ -fluorodeoxyglucose-positron emission tomography ( $^{18}\text{F}$ FDG-PET) showed a hot spot in the right middle lobe bronchus.



**Fig. 2. Bronchoscopic findings in July 2018 (A–C) and after one month (D–F).** (A, B). Bronchoscopic view showing several endobronchial nodular protrusions along the right middle bronchus. (C) The extent of the tumor margin was clearly identified as a magenta image by an autofluorescence imaging bronchovideoscope system (AFI). (D–F) Bronchoscopic findings after one month revealing the lesion had regressed, and the mucosal surface appeared regular with normal vessel translucency.

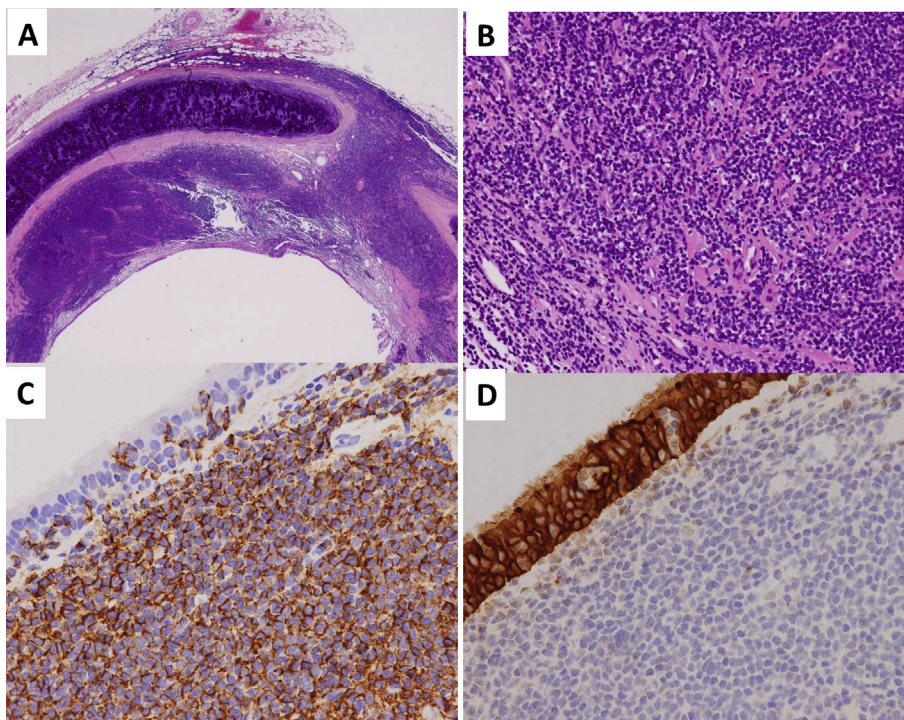
negative lymphocytes, indicating a diagnosis of MALT lymphoma. We then performed sleeve lobectomy of the right middle lobe. The **bronchus intermedius** was divided at the level just proximal to the right upper lobe, and the right inferior lower lobe bronchus was divided

distal to the bronchus intermedius. The **bronchus intermedius** was anastomosed to the right inferior lower bronchus after removal of the middle lobe. Regarding macroscopic findings, a protruded lesion (10 × 5 mm) was seen at the introitus of the middle lobar branch





**Fig. 3.** The resected segment of the right middle lobar branch and right middle lobe contained a smooth-surfaced, nodular mass, 10 × 5 mm in diameter, without any other findings in the right middle lobe. The lesions were localized to the right middle lobar branch.



**Fig. 4. Pathological findings.** A, B: Light microscopic image showing infiltration of small-to medium-sized lymphoid cells into the epithelium (Hematoxylin and Eosin staining; 10×, 100× magnification). C: CD20 staining of the cells was positive, indicating a B-cell origin (CD20 staining; 200× magnification). D: Lymphoepithelial lesions were identified (cytokeratin [AE1/AE3] staining; 200× magnification).

(Fig. 3). Frozen sections were analyzed, and the margins were negative. A pathological examination showed the diffuse infiltrate of small-to medium-sized lymphoid cells in the mucosa (Fig. 4A and B). Small lymphocytes had invaded the epithelial structures of the glands forming lymphoepithelial lesions. The lymphoid cells were positive for CD20 and negative for cytokeratin (AE1/AE3) (Fig. 4C and D). A fluorescence *in situ* hybridization analysis to detect API2-MALT1 translocation was positive. These findings were compatible with the endobronchial biopsy findings. The final diagnosis was low-grade B cell MALT lymphoma. The patient has been followed without any additional treatment and has remained free of recurrence.

### 3. Discussion

We herein report a case of primary endobronchial MALT lymphoma that showed spontaneous regression. MALT lymphomas are most

frequently diagnosed in the stomach and gastrointestinal tract but may occur at various extragastric sites. Other affected sites include the ocular adnexa, salivary gland, thyroid, lung, thymus, and breast. Regarding the non-gastrointestinal tract sites, pulmonary lymphomas are the most frequent, accounting for up to 19% of MALT lymphoma cases [4]. In our patient, the lesions were localized to the right middle bronchus. Therefore, we diagnosed him with primary endobronchial MALT lymphoma. Endobronchial MALT lymphoma is rarely found in clinical situations. A previous study reported that endobronchial MALT lymphoma was seen in only 1 (1.3%) of 75 cases of nongastrointestinal MALT lymphoma [5]. Including the present case, 28 cases [6–22] in a PubMed search and 7 cases in Japanese journals of primary endobronchial MALT lymphoma have been reported.

The course of our patient is considered to have important clinical implications, indicating that primary endobronchial MALT lymphoma can spontaneously regress without treatment. A previous report

examining 11 cases of pulmonary MALT lymphoma that did not receive any treatment revealed that 6 of the 11 patients showed spontaneous regressions following the initial diagnosis [2]. To our knowledge, however, only one case of spontaneous regression of primary endobronchial MALT lymphoma has been reported [3]. Tamai et al. reported a patient with asbestosis who showed spontaneous regression of endobronchial MALT lymphoma at six months after the first biopsy. MALT lymphoma has been known to occur after long-term preexisting disorders, such as *Helicobacter pylori* infection, salivary gland inflammation in Sjögren's syndrome, and Hashimoto's thyroiditis. Several studies have now demonstrated that eradication of *H. pylori* in patients with low-grade gastric MALT lymphoma can result in regression of the tumor [23–27]. There have also been several reports of patients with NHL showing regression after a biopsy, indicating that trauma, including a biopsy, is related to regression [28,29]. The leading hypothesis regarding spontaneous regression in relation to NHL involves modulation of the host immune system to viral or bacterial infection and the anti-inflammatory effect of macrolide-induced apoptosis of lymphocytes via the downregulation of overexpressed Bcl-xL [30,31]. However, no clear causal relationship between an inflammatory or infectious agent and pulmonary and endobronchial MALT lymphoma has been established, and the present case did not have underlying infections or autoimmune disorders; therefore, the precise mechanism underlying the spontaneous regression in our patient is unclear.

In the present case, bronchoscopic findings showed several endobronchial nodular protrusions along the right middle lobe bronchus. A previous report reviewing the bronchoscopic findings of 20 cases of MALT lymphoma summarized the patterns of endobronchial lesions as follows: 61% had several nodular protrusions, 22% had solitary intraluminal nodules, and 17% had diffuse bronchial wall thickening. The locations of the lesions ranged from the trachea to the segmental bronchi. Among the 20 cases, 14 (70%) were located on the trachea or main bronchus [2]. The major bronchoscopic findings were similar to those of the present patient. Our patient showed spontaneous regression of bronchoscopic findings after a month. The mucosal surface appeared regular without atrophy or stenosis, findings that were similar to those of a previous report [4].

In conclusion, we herein report a case of primary endobronchial MALT lymphoma that showed spontaneous regression. A pattern of endobronchial nodular protrusions may be one of the manifestations of endobronchial MALT lymphoma, and these mucosal lesions can regress spontaneously. Clinicians should recognize such bronchoscopic findings and the clinical course as a manifestation of primary endobronchial MALT lymphoma.

## Conflicts of interest

The authors declare no conflicts of interest in association with the present study.

## References

- [1] K. Arnaoutakis, T.H. Oo, Bronchus-associated lymphoid tissue lymphomas, *South. Med. J.* 102 (2009) 1229–1233, <https://doi.org/10.1097/SMJ.0b013e3181bfdd2d>.
- [2] M. Troch, B. Streubel, V. Petkov, K. Turetschel, A. Chott, M. Raderer, Does MALT lymphoma of the lung require immediate treatment? An analysis of 11 untreated cases with long-term follow-up, *Anticancer Res.* 27 (5B) (2007) 3633–3637.
- [3] K. Tamai, K. Monden, N. Okada, Y. Suzuki, Spontaneous regression of primary endobronchial MALT lymphoma in a patient with asbestosis, *J. Jpn. Soc. Bronchol.* 39 (2017) 392–397 (Japanese).
- [4] S.H. Malek, A.J. Hatfield, I.W. Flinn, MALT lymphomas, *Curr. Treat. Options Oncol.* 4 (2003) 269–279.
- [5] P.L. Zinzani, M. Magagnoli, P. Galièni, M. Martelli, V. Poletti, F. Zaja, S. Molica, A. Zaccaria, A.M. Cantonetti, P. Gentilini, L. Guardigni, F. Gherlinzoni, M. Ribersani, M. Bendandi, P. Albertini, S. Tura, Nongastrointestinal low-grade mucosa-associated lymphoid tissue lymphoma: analysis of 75 patients, *J. Clin. Oncol.* 17 (1999) 1254.
- [6] T. Kawaguchi, D. Himeji, N. Kawano, Y. Shimao, K. Marutsuka, Endobronchial mucosa-associated lymphoid tissue lymphoma: a report of two cases and a review of the literature, *Intern. Med.* 57 (2018) 2233–2236.

- [7] R.G. Yoon, M.Y. Kim, J.W. Song, E.J. Chae, C.M. Choi, S. Jang, Primary endobronchial marginal zone B-cell lymphoma of bronchus-associated lymphoid tissue: CT findings in 7 patients, *Korean J. Radiol.* 14 (2013) 366–374, <https://doi.org/10.2169/INTERNALMEDICINE.0150-17>.
- [8] J. Ding, Z. Chen, M. Shi, Tracheal stenting for primary tracheal mucosa-associated lymphoid tissue lymphoma, *Eur. J. Med. Res.* 2 (18) (2013) 8, <https://doi.org/10.1186/2047-783X-18-8>.
- [9] D. Minami, C. Ando, K. Sato, K. Moriwaki, F. Sugahara, T. Nakasuka, Y. Iwamoto, K. Fujiwara, T. Shibayama, T. Yonei, T. Sato, Multiple Mucosa-associated lymphoid tissue lymphoma of the trachea, *Intern. Med.* 56 (2017) 2907–2911, <https://doi.org/10.2169/INTERNALMEDICINE.8269-16>.
- [10] J. Tsurutani, A. Kinoshita, H. Kaida, H. Fujii, F. Narasaki, M. Fukuda, M. Oka, S. Kohno, Bronchoscopic therapy for mucosa-associated lymphoid tissue lymphoma of the trachea, *Intern. Med.* 38 (1999) 276–278.
- [11] I. Mira-Avendano, G. Cumbo-Nacheli, J. Parambil, Mucosa-associated lymphoid tissue lymphoma of the trachea, *J. Bronchol. Interv. Pulmonol.* 19 (2012) 44–46, <https://doi.org/10.1097/LBR.0b013e31823fad2>.
- [12] K. Okubo, N. Miyamoto, C. Komaki, Primary mucosa-associated lymphoid tissue (MALT) lymphoma of the trachea: a case of surgical resection and long term survival, *Thorax* 60 (1) (2005) 82–83, <https://doi.org/10.1136/thx.2003.018721>.
- [13] J.Y. Kang, H.J. Park, K.Y. Lee, S.Y. Lee, S.J. Kim, S.H. Park, Y.K. Kim, Extranodal marginal zone lymphoma occurring along the trachea and central airway, *Yonsei Med. J.* 49 (5) (2008) 860–863, <https://doi.org/10.3349/ymj.2008.49.5.860>.
- [14] M.A. Kaplan, C.L. Pettit, L.R. Zukerberg, N.L. Harris, Primary lymphoma of the trachea with morphologic and immunophenotypic characteristics of low-grade B-cell lymphoma of mucosa-associated lymphoid tissue, *Am. J. Surg. Pathol.* 16 (1) (1992) 71–75.
- [15] S.M. Hashemi, M.A. Heitbrink, M. Jiwa, W.G. Boersma, A patient with endobronchial MALT lymphoma successfully treated with radiotherapy, *Respir. Med.* 101 (10) (2007) 2227–2229.
- [16] Y. Hiraiishi, M. Iikura, Y. Kogure, J. Hirashima, S. Izumi, H. Sugiyama, Two tracheal MALT lymphoma patients successfully treated with chemotherapy including rituximab, *Respir. Investig.* 52 (2) (2014) 144–146, <https://doi.org/10.1016/j.resinv.2013.07.006>.
- [17] N. Bhatt, J.M. Sloan, C.J. O'Hara, R. Oommen, K. Steiling, V.R. Litle, Extranodal marginal zone endobronchial lymphoma associated with hepatitis C, *Ann. Thorac. Surg.* 102 (5) (2016 Nov) e407–e408, <https://doi.org/10.1016/j.athoracsur.2016.04.060>.
- [18] A. Solomonov, T. Zuckerman, L. Goralnik, Y. Ben-Arieh, J.M. Rowe, M. Yigla, Non-Hodgkin's lymphoma presenting as an endobronchial tumor: report of eight cases and literature review, *Am. J. Hematol.* 83 (5) (2008) 416–419, <https://doi.org/10.1002/ajh.21112>.
- [19] T. Nakajima, K. Yasufuku, Y. Sekine, S. Yoshida, I. Yoshino, Mucosa-associated lymphoid tissue lymphoma of the left mainstem bronchus, *Ann. Thorac. Surg.* 91 (4) (2011) 1281–1283, <https://doi.org/10.1016/j.athoracsur.2010.10.009>.
- [20] A.E. Erbaycu, I. Karasu, F.G. Ozdemir, N. Yücel, A. Ozsöz, O. Bilgir, Endobronchial low-grade MALT lymphoma causing unilateral hypertranslucency, *Monaldi Arch. Chest Dis.* 61 (4) (2004) 237–240.
- [21] H. Yamashita, Y. Ueda, K. Tomita, T. Kitaura, T. Koshobu, Y. Suzuki, E. Shimizu, Mucosa-associated lymphoid tissue lymphoma of the trachea in a patient with breast cancer, *Intern. Med.* 54 (16) (2015) 2041–2044, <https://doi.org/10.2169/INTERNALMEDICINE.54.3925>.
- [22] H.E. Dincer, Endobronchial mucosa-associated lymphoid tissue (MALT) lymphoma: a diagnostic consideration, *J. Bronchol.* 15 (2008) 284–286, <https://doi.org/10.1097/LBR.0b013e31818550a9>.
- [23] A. Savio, G. Frazin, A.C. Wotherspoon, G. Zamboni, R. Negrini, M. Graffo, T.C. Diss, L. Pan, P.G. Isaacson, Diagnosis and post-treatment follow up of *Helicobacter pylori* positive gastric lymphoma of mucosa associated lymphoid tissue: histology, PCR or both? *Blood* 87 (1996) 1255–1260.
- [24] D.M. Weber, M.A. Dimopoulos, D.P. Anandu, W.C. Pugh, G. Steinbach, Regression of gastric lymphoma of mucosa-associated lymphoid tissue with antibiotic therapy for *Helicobacter pylori*, *Gastroenterology* 107 (1994) 1835–1838.
- [25] A.C. Wotherspoon, C. Dogliani, T.C. Diss, L. Pan, A. Moschini, M. de Boni, P.G. Isaacson, Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*, *Lancet* 342 (8871) (1993) 575–577.
- [26] G. Cammarota, A. Tursi, M. Montalto, A. Papa, G. Branca, F.M. Vecchio, C. Renzi, A. Verzi, A. Armuzzi, S. Pretolani, G. Fedeli, G. Gasbarrini, Prevention and treatment of low grade B-cell primary gastric lymphoma by anti-H. Pylori therapy, *J. Clin. Gastroenterol.* 21 (1995) 118–122.
- [27] E. Roggero, E. Zucca, G. Pinotti, A. Pascarella, C. Capella, A. Savio, E. Pedrinis, A. Paterlini, A. Venco, F. Cavalli, Eradication of *Helicobacter pylori* infection in primary low-grade gastric lymphoma of mucosa-associated lymphoid tissue, *Ann. Intern. Med.* 122 (1995) 767–769.
- [28] K.I. Fukushima, S. Hirosako, Y. Tenjin, Y. Mukasa, K. Kojima, S. Saeki, S. Okamoto, H. Ichiyasu, K. Fujii, Y. Kikukawa, K. Kawanaka, H. Kohrogi, Pulmonary mucosa-associated lymphoid tissue lymphoma with spontaneous regression after computed tomography-guided needle biopsy: a case report and summary of 8 reported cases, *Intern. Med.* 55 (24) (2016) 3655–3660, <https://doi.org/10.2169/INTERNALMEDICINE.55.6874>.
- [29] R. Abe, K. Ogawa, Y. Maruyama, N. Nakamura, M. Abe, Spontaneous regression of diffuse large B-cell lymphoma harbouring Epstein-Barr virus: a case report and review of the literature, *J. Clin. Exp. Hematop.* 47 (1) (2007 Apr) 23–26.
- [30] M. Kumamoto, H. Nakamine, T. Hara, Y. Yokoya, J. Kawai, H. Ito, S. Nishioka, T. Takenaka, R.S. Wickert, D.W. Mitchell, Spontaneous complete regression of high grade non-Hodgkin's lymphoma, *Cancer* 74 (1994) 3023–3028.
- [31] Y. Ishimatsu, J. Kadota, T. Iwashita, T. Nagata, H. Ishii, C. Shikuwa, H. Kaida, H. Mukae, S. Kohno, Macrolide antibiotics induce apoptosis of human peripheral lymphocytes in vitro, *Int. J. Antimicrob. Agents* 24 (3) (2004 Sep) 247–253.