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Author(s)	Shimizu, Kaoruko; Konno, Satoshi; Nasuhara, Yasuyuki et al.
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A case of follicular bronchiolitis associated with asthma, eosinophilia, and increased immunoglobulin E

Kaoruko Shimizu[1], Satoshi Konno[1], Yasuyuki Nasuhara[1], Mishie Tanino[2], Yoshihiro Matsuno[3], and Masaharu Nishimura[1]

[1]First Department of Medicine, Hokkaido University School of Medicine, and [2]Laboratory of Cancer Research, Department of Pathology, Hokkaido University Graduate School of Medicine [3]Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Hokkaido, Japan

Correspondence to: Satoshi Konno

First Department of Medicine, Hokkaido University School of Medicine

Kita-15 Nishi-7 Kita-ku, Sapporo 060-8638, Japan

Tel. +81-11-716-1161 (Ext. 5911), Fax +81-11-706-7899

E-mail satkonno@med.hokudai.ac.jp

Abstract

A 49-year-old woman, who had been diagnosed with asthma, showed a bilateral diffuse pattern of small centrilobular nodules on CT. Laboratory data revealed peripheral eosinophilia and a marked increase in total serum IgE levels. The nodules detected on CT were initially considered to be associated with bronchiolar infiltration of eosinophils. Pathological findings from thoracoscopy revealed infiltration of eosinophils into the airway lumen and walls, goblet cell hyperplasia, and thickening of the basement membrane in large bronchi, consistent with asthma. However, hyperplastic lymphoid follicles with reactive germinal centers were observed along the bronchioles. The follicles had no evidence of monoclonality suggested by immunohistological analysis, and no remarkable infiltrates of eosinophils, suggesting follicular bronchiolitis. After treatment with prednisolone, the small diffuse nodules improved markedly, and peripheral eosinophilia and total serum IgE levels also decreased. To the best of our knowledge, this is the first documented case report of follicular bronchiolitis associated with asthma, eosinophilia, and elevated IgE with a definite pathophysiological diagnosis.

(160/350 words)

Key Words: asthma, eosinophilia, follicular bronchiolitis, IgE, MALT lymphoma

Running Title: Follicular bronchiolitis associated with asthma (47/50 character spaces)

Introduction

Follicular bronchiolitis (FB), a well-defined pathological entity consisting of abundant lymphoid follicles limited to the peribronchiolar area,[1] is associated with a number of conditions, including collagen diseases,[2,3,4] immunodeficiency,[4,5,6] and several hypersensitivity reactions.[7] Asthma was included as a hypersensitivity reaction that could cause FB in a review of 19 cases of FB by Yousem et al.[7] However, there have been no detailed case reports showing this association.

Here we report a patient in whom diffuse centrilobular nodules on CT were associated with asthma, eosinophilia, and elevated total serum IgE levels. We initially considered that the centrilobular nodules might be associated with eosinophil infiltration of the bronchioles. However, histopathological examination revealed hyperplastic lymphoid follicles with reactive germinal centers but no remarkable peribronchiolar infiltrates of eosinophils. To the best of our knowledge, this is the first documented case report of FB associated with asthma, eosinophilia, and an increase in total serum IgE levels in which a definite pathophysiological diagnosis was made.

Case report

A 49-year-old woman, who had undergone excision and radiotherapy for extranodal marginal zone B-cell lymphoma of MALT type in the right orbit at the age of 31, was diagnosed with recurrence of MALT lymphoma in the left orbit. She was referred to our respiratory department in August 2006 to rule out lung involvement of MALT lymphoma, after bilateral small diffuse nodules were found on chest radiography performed at the department of ophthalmology in our hospital. The patient had no history of smoking and occupational exposure, including to that of nylon and polyethylene flocks. She had no apparent history of respiratory infections including that caused by atypical pathogens, such as mycoplasma. She had been diagnosed with asthma in her twenties and had been treated with theophylline alone. She reported dyspnea on effort, which had been gradually worsening for the past 3 years. Physical examination revealed bilateral wheezes, but absence of superficial lymphadenopathy, skin eruption, or joint swelling suggested no association with collagen vascular diseases. Laboratory data revealed marked increases in peripheral eosinophil counts (19.0%, 1368 /μL) and total serum IgE levels (11,112.6 IU/mL). IgE multiple antigen simultaneous tests were positive for *Dermatophagoides farinae,*

Alternaria, Cladosporium, milk, and cheddar cheese, and negative for *Aspergillus*. Soluble interleukin-2 receptor level was slightly elevated at 626 U/ml. The following laboratory tests for collagen vascular diseases or immunodeficiency were either negative or normal: rheumatoid factor, antinuclear antibodies, anti-SS-A and anti-SS-B antibodies, antineutrophil cytoplasmic antibodies (ANCA), IgG, IgA, IgM, HIV antibodies, and HTLV-1 antibodies. Pulmonary function tests demonstrated reduced FEV_1 (1.35 L), %predicted FEV_1 (60.0%), and FEV_1/FVC (61.1%) but normal carbon monoxide diffusion capacity (DL_{CO} %predicted) (93.2%). Inhalation of a short-acting β_2-agonist (salbutamol 200 μg) improved FEV_1 from 1.35 to 1.58 L (17% improvement). A methacholine bronchoprovocation test using Astograph® [11] showed bronchial hyperreactivity [dose minimum (D-min = 0.116 U)]. High-resolution CT demonstrated bilateral centrilobular nodules throughout the lungs and a ground-glass opacity in the right middle lobe (Figure 1, a). Bronchoalveolar lavage fluid obtained from the right S^4 segment showed marked eosinophilia (total cells 21.2×10^4/mL; 41.6% eosinophils). **BAL cultures were negative for bacteria, mycobacteria, fungi.**

Lung biopsy of the right S^4 segment and histological examination was performed.

Infiltration of eosinophils into the airway lumen and wall, goblet cell hyperplasia (Figure 2, a), and thickening of the basement membrane were observed in large bronchi, consistent with bronchial asthma. Hyperplastic lymphoid follicles with reactive germinal centers were found to be along with narrowed bronchioles and peribronchiolar interstitium. Immunohistochemistry revealed a B-cell zone consisting of CD20-positive B-cells including germinal centers and an apparently separate T-cell zone in same areas. These findings are suggested of well-organized reactive lymphoid tissue, which is compatible with follicular bronchiolitis. Moreover, immunoglobulin light chain staining to exclude pulmonary involvement of low grade B-cell lymphoma of MALT type did not show light chain restriction. These findings exclude the possibility of this lesion being a manifestation of low grade B-cell lymphoma (Figure 3). Eosinophilic infiltrates were remarkable in alveolar walls and alveolar spaces (Figure 2, b).

Treatment with an inhaled corticosteroid (budesonide 800 μg) was started, but efficacy was modest. Wheezing and dyspnea on effort gradually worsened despite addition of a long-acting β_2-agonist (salmeterol 50 μg twice daily) and a leukotriene receptor antagonist (montelukast 10 mg). In January 2007, rituximab

was started for the recurrence of MALT lymphoma in the left orbit (600 mg for 4 cycles, given at weekly intervals). The lymphoma showed complete remission after 3 months, but there was no improvement in the pulmonary nodules or the respiratory symptoms. The peripheral eosinophil count and total serum IgE levels remained unchanged after starting rituximab. In November 2007, prednisolone (40 mg/day) was started, following which the respiratory symptoms and %predicted FEV_1 markedly improved. The pulmonary nodules also shrank (Figure 1, b), and peripheral eosinophil count and total serum IgE levels fell considerably. Prednisolone dosage was tapered gradually to 7.5 mg/day. Although total serum IgE levels remained relatively high (1207 IU/l), the patient's symptoms were stable and peripheral eosinophils (1.9%, 217 /μl) were well controlled at the time of documentation.

Discussion

Follicular bronchiolitis (FB) is a well-defined pathological entity consisting of abundant lymphoid follicles limited to the peribronchiolar area. It may occur secondarily to antigenic stimulation and may be a part of the general lymphoid response of the lung.[2] The etiology of FB has been described in a review of 19

cases by Yousem et al. in 1984.[7] They classified the etiology into 3 groups: (i) collagen vascular diseases such as rheumatoid arthritis and Sjögren's syndrome, (ii) immunodeficiency syndromes, and (iii) hypersensitivity reactions. They classified 7 cases of FB as hypersensitivity reactions, 6 of which showed peripheral eosinophilia. Although they described asthma as one of the conditions in this group, they did not make a definite pathophysiological diagnosis of asthma, and did not report total serum IgE levels. Since then there have been no reports of FB associated with asthma.

Because the present patient showed a marked eosinophilia in serum and in bronchoalveolar lavage fluid, we initially considered that the centrilobular nodules detected by CT might be associated with the infiltration of eosinophils in the bronchiolar walls. The term "eosinophilic bronchiolitis" has been used in several reports, irrespective of eosinophilic pneumonia or asthma.[8,9,10] Accordingly, the present case, together with the review by Yousem et al., suggests that both eosinophilic bronchiolitis and FB should be considered in the differential diagnosis when centrilobular nodules are seen in patients with asthma and eosinophilia.

In addition, because the present patient showed recurrence of MALT lymphoma in the left orbit, lung involvement of MALT lymphoma was also considered as a differential diagnosis. Although rare, a diffuse pattern of small nodules has been reported as a radiographic pattern of pulmonary MALT lymphoma.[12, 13, 14] However, pathological findings of the pulmonary lesions were not indicative of malignant neoplasm in the present case, and this was confirmed by immunostaining. The difference in the response to rituximab between orbital masses and lung nodules also suggests that the small pulmonary nodules did not have a MALT lymphoma component.

In the present case, it seems unlikely that several disease conditions such as follicular bronchiolitis, MALT lymphoma and asthma together with marked eosinophilia and increased IgE levels co-existed incidentally. Among the etiology of FB classified by Yousem et al.[7], collagen vascular diseases, Sjögren syndrome in particular, are known to present with a wide spectrum of lymphoproliferative disorders, including follicular bronchiolitis (FB), lymphoid interstitial pneumonia (LIP), and MALT lymphoma. Although the underlying

mechanisms are unclear, hypersensitivity states corresponding to Sjögren syndrome may exist, and this may have caused all the disease conditions involved in the present case.

In summary, we describe a case of FB associated with asthma, eosinophilia, and increased total serum IgE levels. This is the first case report showing an association with FB with a definite pathophysiological diagnosis of asthma.

Acknowledgement

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Romero S, Barroso E, Gil J, Aranda I, Alonso S, et al. Follicular bronchiolitis: clinical and pathologic findings in six patients. *Lung* 2003; 181: 309-19.
2. Hayakawa H, Sato A, Imokawa S. Bronchiolar disease in rheumatoid arthritis. *Am. J. Respir. Crit. Care Med.* 1996; 154: 1531-6.
3. Kinoshita M, Higashi T, Tanaka C, Tokunaga Nl, Ichikawa Y, et al. Follicular bronchiolitis associated with rheumatoid. *Internal Medicine* 1992; 31: 674-7.
4. Fortoul TI, Cano-Valle F, Oliva E, Barrios R. Follicular bronchiolitis in association with connective tissue diseases. *Lung* 1985;163:305-14.
5. Aerni MR, Vassallo R, Myers JL, Lindell RMl, Ryu JH. Follicular bronchiolitis in surgical lung biopsies: clinical implications in 12 patients. *Respiratory Medicine* 2008;102: 307-12.
6. Exley CM, Suvarna SK, Matthews S. Follicular bronchiolitis as a presentation of HIV. *Clinical Radiology* 2006; 61: 710-3.
7. Yousem SA, Colby TV, Carrington CB. Follicular Bronchitis/Bronchiolitis. *Hum. Pathol.* 1985; 16: 700-6.
8. Takayanagi N, Kanazawa M, Kawabata Y, Colby TV. Chronic bronchiolitis with associated eosinophilic lung disease (eosinophilic bronchiolitis)

Respiration 2001; 68: 319-22.

9. Nakagome K, Yamaguchi M, Shimada H, Komiya A, To Y, et al. A case of eosinophilic lung disease presenting asthma-like symptoms and centrilobular shadows in both lung fields. *Nihon Kokyuki Gakkai Zasshi* 2003; 41: 722-7.
10. Nagata N, Harada S, Wakamatsu K, Shigyo M, Kajiki A, et al. A case of chronic eosinophilic bronchiolitis associated with bronchial asthma. *Nihon Kokyuki Gakkai Zasshi* 2004; 42: 767-71.
11. Takishima T, Hida W, Sasaki H, Suzuki S, Sasaki T. Direct-writing recorder of the dose-response curves of the airway to methacholine. Clinical application. *Chest* 1981; 80: 600-6.
12. Lewis ER, Caskey CI, Fishman EK. Lymphoma of the lung: CT findings in 31 patients *AJR* 1991; 156: 711-4.
13. Knisely BL, Mastey LA, Mergo PJ, Voytovich MC, Zander D, et al. Pulmonary mucosa-associated lymphoid tissue lymphoma: CT and pathologic findings. *AJR* 1999; 172: 1321-6.
14. McCulloch GL, Sinnatamby R, Stewart S, Goddard M, Flower CDR. High-resolution computed tomographic appearance of MALToma of the lung. *Eur. Radiol*.1998; 8: 1669-73.

Figure legends

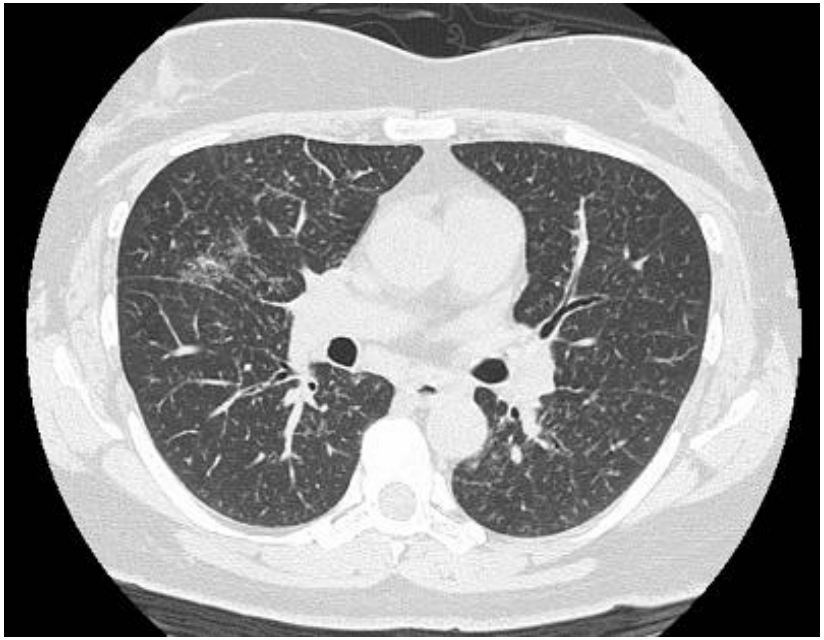
Figure 1 Chest CT findings a) before treatment with corticosteroid and b) after treatment with corticosteroid

Figure 2 a) Goblet cell hyperplasia was observed in large bronchi, along with eosinophilic infiltration (Hematoxylin-eosin (HE) stain). b) Eosinophilic infiltrates were remarkable in the vessels, alveolar walls, and alveolar spaces (HE stain).

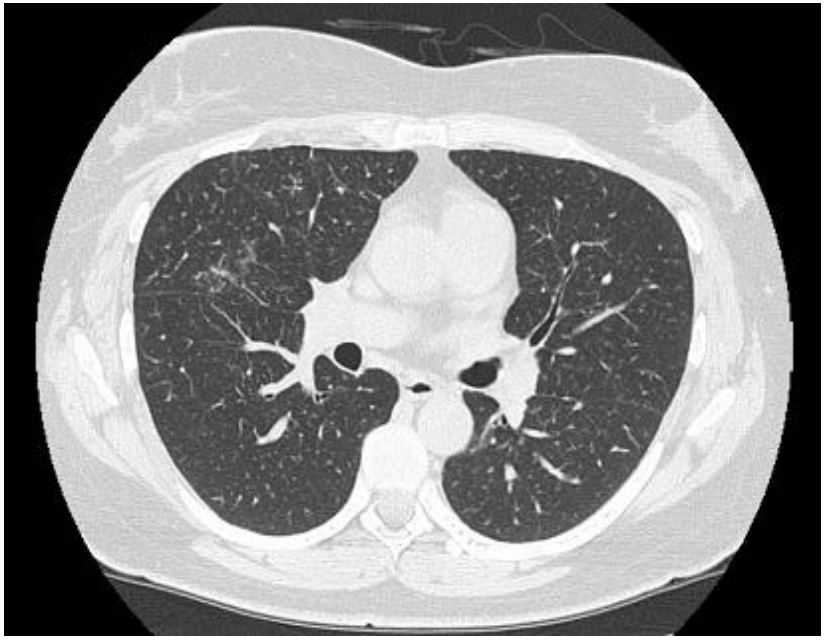
Figure 3 a), b) HE stain, c) CD3 immunostaining, d) CD20 immunostaining.

Lymphoid follicles with reactive germinal centers were found along the bronchioles. These follicles had no evidence of monoclonality suggested by CD3 or CD20 immunostaining and no remarkable eosinophilic infiltrates.

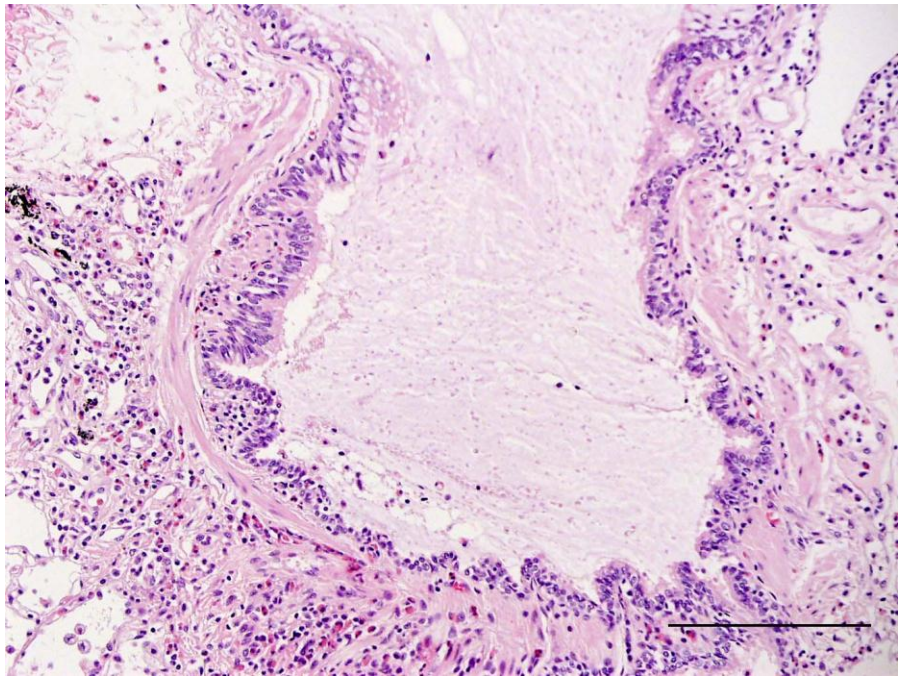
a



b

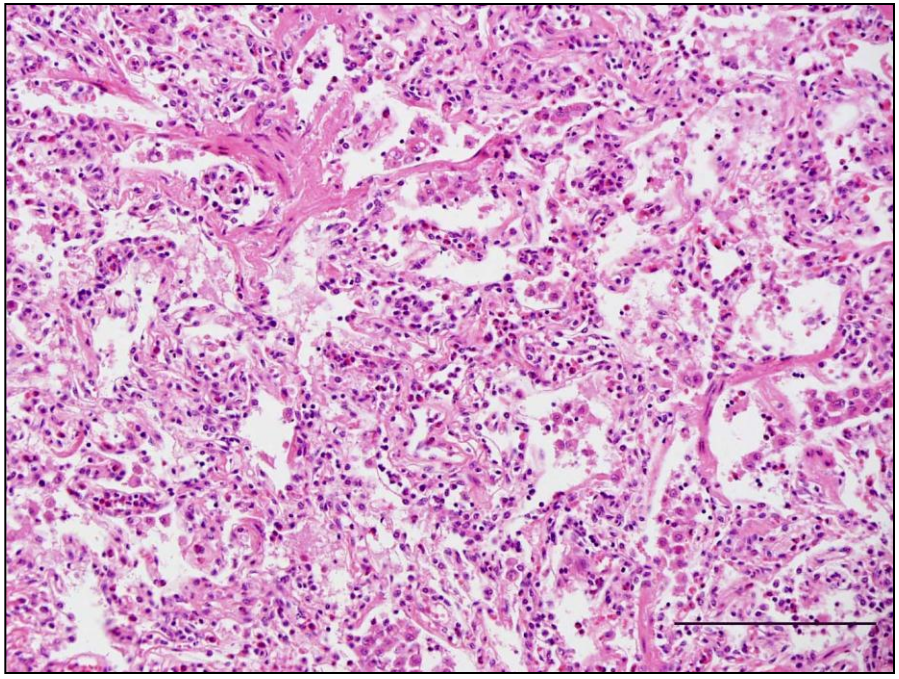


a



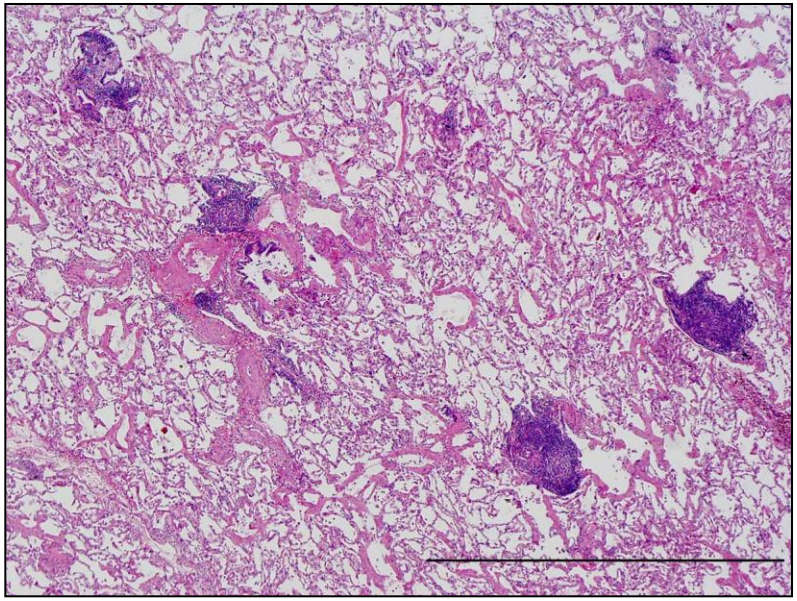
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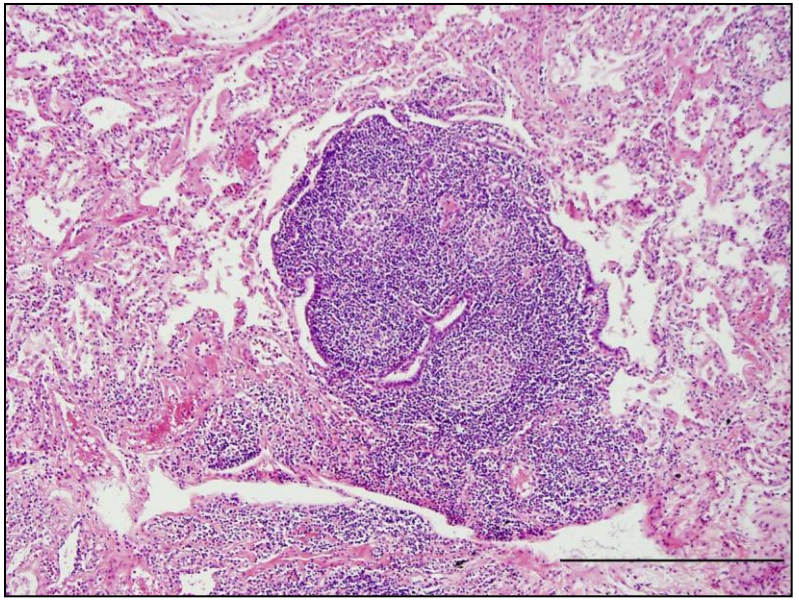
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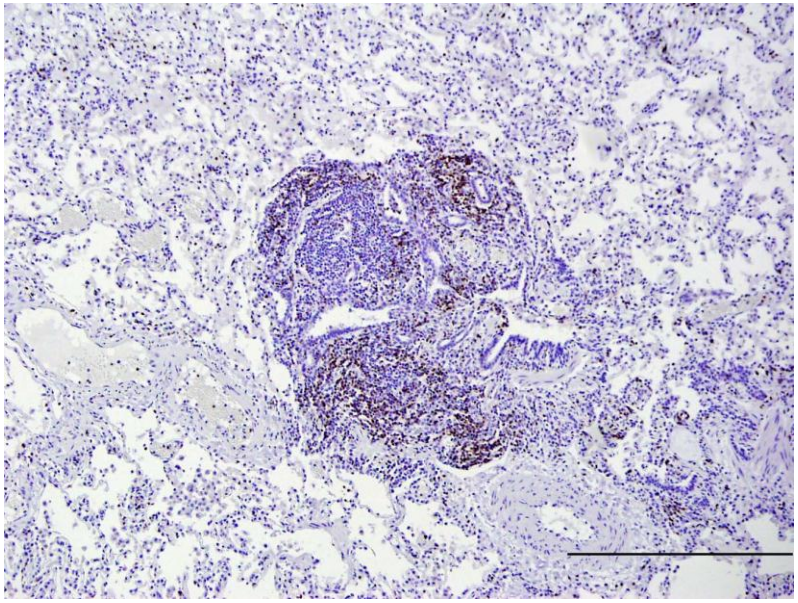
Scale 2mm

b



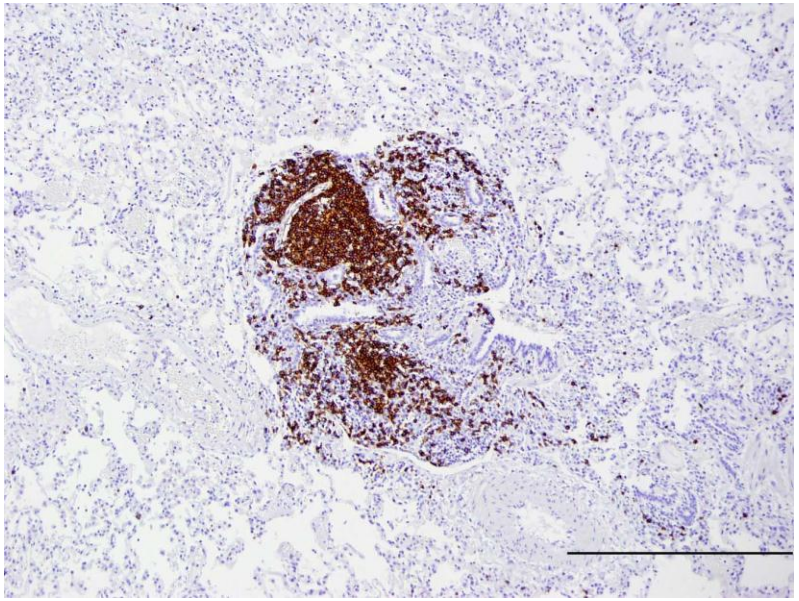
Scale 500 um

c



Scale 500 um

d



Scale 500 um