haematologica
Journal of the Ferrata Storti Foundation

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Received: August 7, 2025.
Accepted: November 19, 2025.

Citation: Teresa Antonia Kiener, Gregor Schweighofer-Zwink, Gundula Rendl, Jan Marco Kern, Lenka Baskova, Daniel Neureiter, Thomas Melchardt, Markus Raderer, Richard Greil and Christian Pirich. Complete remission of bronchus-associated lymphoid tissue lymphoma after antibiotic treatment for Tropheryma whipplei. Haematologica. 2025 Nov 27. doi: 10.3324/haematol.2025.288045 [Epub ahead of print]

Complete remission of bronchus-associated lymphoid tissue lymphoma after antibiotic treatment for *Tropheryma whipplei*

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AUTHOR DISCLOSURES:

MR received honoraria from AbbVie, BeiGene, Eli Lilly, Ipsen, Novartis, Johnson + Johnson and Gilead in the past 36 months as potential competing interests. The other authors have no competing interests.

DATA AVAILABILITY STATEMENT:

All data generated are included in this article. Further enquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS:

Kiener TA wrote and revised the manuscript.

Schweighofer-Zwink G and Rendl G interpreted the PET-CTs, aided in PET-CT-guided transbronchial biopsy of the mass and revised the manuscript.

Kern JM and Baskova L performed real-time PCR, corresponded with the Consultant Laboratory for *T. whipplei* at the Charité University Hospital in Berlin, Germany and revised the manuscript.

Neureiter D performed and interpreted the histopathology, immunohistochemistry and clonality analysis and revised the manuscript.

Melchardt T and Greil R were in charge of clinical decision-making, treated and followed the patient and revised the manuscript.

Raderer M was consulted and involved in clinical decision-making and revised the manuscript.

Pirich C was involved in clinical decision-making and revised the manuscript (major revisions).

KEY WORDS**:** BALT lymphoma, *Tropheryma whipplei*, PET, PCR, Antibiotics

Extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma) is an indolent lymphoma that accounts for approximately 7-8% of newly diagnosed lymphomas. MALT lymphoma most commonly originates from the stomach while extra-gastric MALT lymphoma is located most frequently in the ocular adnexa, the parotid gland and the lung. (1) MALT lymphoma arising in the lung is also called bronchus-associated lymphoid tissue (BALT) lymphoma. It is the most common primary lymphoma of the lung but accounts for less than 0.5 % of pulmonary malignancies. (2, 3)

BALT lymphoma develops primarily in patients older than 60 years of age. Patients are often asymptomatic and present with a mass on routine chest X-ray. Some patients display non-specific symptoms like cough, dyspnea or constitutional symptoms. (4) On imaging, BALT lymphoma might present as a unifocal mass, multifocal peribronchovascular consolidations or ground-glass opacities. (2, 3) The natural course of the disease is slow, compared with other low-grade lymphoproliferative disorders, and there is no consensus on optimal treatment. Patients might undergo complete resection without systemic treatment. For advanced disease, therapeutic options include surgery, chemotherapy, immunotherapy and radiation, alone or in combination. (2, 4) For patients with early-stage BALT lymphoma, watchful waiting might also be a suitable approach. (4)

There is evidence to suggest that BALT lymphoma, like other MALT lymphomas, develops in the setting of chronic antigenic stimulation following inflammation due to autoimmune or infectious diseases. First, this leads to the development of BALT in the lung, which physiologically does not harbor

lymphoid tissue. Genetic mutations then lead to the transformation of reactive BALT into BALT lymphoma. (2) Several autoimmune diseases have been associated with the development of MALT lymphoma, like Hashimoto thyroiditis in thyroid MALT lymphoma or Sjögren syndrome in salivary gland lymphoma. (1) Furthermore, bacterial infections might lead to MALT lymphoma. *Helicobacter pylori* was identified as the leading cause of gastric MALT lymphoma, a finding that has revolutionized the treatment of this condition. *Campylobacter jejuni* is associated with intestinal MALT lymphoma, *Borrelia burgdorferi* with cutaneous MALT lymphoma and *Chlamydia psittaci* with ocular adnexal lymphomas. (1, 5)

Concerning BALT lymphoma, the evidence for a causative pathogen remains scarce. *Achromobacter xylosoxidans*, a gram-negative bacterium with low virulence, was suggested by Adam et al, who found higher rates of *A. xylosoxidans* DNA in biopsy samples of BALT lymphoma (57/124; 46%) than within control biopsies (15/82; 18%). (6) Another pathogen discussed as a trigger is *Chlamydia psittaci*, a gram-negative bacterium that causes respiratory psittacosis in humans. Aigelsreiter et al found *C. psittaci* DNA in significantly more BALT lymphoma samples (5/5; 100%) than in control samples (0/10; 0%). (7) Both associations were not confirmed in a follow-up study, that found *A. xylosoxidans* DNA in more control samples (4/10; 40%) than in BALT lymphoma samples (4/13, 31%) and did not identify any sequences of *C. psittaci* in a series of 13 patients with BALT lymphoma. (8)

Below, we report a case of BALT lymphoma associated with *Tropheryma whipplei (T. whipplei).* The patient achieved complete remission after antibiotic

therapy only. The institutional ethics committee approved the preparation and publication of this report and the patient gave informed consent.

A 61-year-old male presented to our clinic in 2021 with a history of unintentional weight loss and sporadic episodes of nausea and vomiting. There was no complaint of dysphagia, fever or night sweats. Apart from longstanding asthma, the patient had no comorbidities. Physical examination was unremarkable. Erythrocyte sedimentation rate was increased (20 mm/h; normal range: < 15 mm/h) and C-reactive protein was mildly elevated (0.8 mg/dl; normal range < 0.6 mg/dl). Complete blood count, protein electrophoresis, liver and renal function tests were within normal limits. Diagnostic gastroscopy with stepwise biopsies of the stomach and duodenum revealed chronic atrophic gastritis and regular mucosa in the duodenum. There was no evidence of Helicobacter pylori. Abdominal sonography was unremarkable. Computed tomography showed a 6 cm left hilar mass suspicious for lung cancer.

The patient underwent Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography (F18-FDG PET/CT)-guided transbronchial biopsy of the suspicious lesion. The FDG-avid hilar mass is depicted in **Figure 1a**. Histopathologic examination and immunohistochemistry revealed a diffuse infiltration of subepithelial tissue with lymphoid differentiated cells, as shown in **Figure 2a**. Molecular pathology found a VDJ gene rearrangement (two monoclonal bands in FR2, one monoclonal band in FR3; IdentiClone® IGH Gene Clonality Assay and IdentiClone® TCRG

Gene Clonality Assay, see **Figure 2b**). These findings supported the diagnosis of BALT lymphoma. Apart from F18-FDG PET/CT, staging consisted of bone-marrow biopsy, gastroscopy with multiple biopsies, colonoscopy, ophthalmologic and otorhinolaryngologic examinations. There was no evidence of extrapulmonary involvement, defining stage I E according to Ann Arbor modified by Ferraro et al.(9)

To exclude an underlying infectious disease, we performed multiplex PCR on the bronchial biopsy samples. Furthermore, a real-time PCR for *T. whipplei* DNA was done due to an increased vigilance of our clinical microbiology department regarding this pathogen. PCR detected *T. whipplei* DNA in biopsy samples of the hilar mass, targeting the rpoB-gene of the pathogen (Primer and probe as follows: TW1_Fw: gTT CTT ACg Agg TCg gAT ATT ATC; TW1_Rev: ACC gCA ACC TCg gAg AAA C; TW1_Probe: AAC AAT TCg TTA TCT CgC ggC CTT gC). Tissue from a neighboring paraoesophageal lymph node tested negative. Furthermore, PCR for *T. whipplei* DNA was negative in urine samples, as well as in duodenum, colon and bone marrow biopsies. There was no evidence for Whipple's disease in duodenal biopsies. All biopsy samples were sent for repeat PCR to the Consultant Laboratory for *T. whipplei* at the Institute of Microbiology, Infectious Diseases and Immunology of Charité University Hospital in Berlin, Germany, where *T. whipplei* DNA was again detected solely in the hilar mass.

Different treatment options were discussed, namely watchful waiting, surgery, radiotherapy and immunotherapy with Rituximab. However, based on our

assumption that *T. whipplei* contributed to the development of lymphoma, we initiated antibiotic therapy alone - after shared decision making with the patient.

The patient was started on i.v. ceftriaxone 2g once daily for two weeks, followed by p.o. trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg twice daily for one year. Over the next months, the index lesion at the left hilum decreased in both size and metabolic activity on 18F-FDG PET/CT, as shown in **Figure 1b**. A new lesion appeared at the left lower hilum, as depicted in **Figure 1c**, which was primarily suspicious for lymph node progression due to its location and FDG-avidity. However, the patient refused biopsy of the new lesion, and based on the clinical remission of any symptoms, antibiotic therapy with TMP/SMX was continued. Serial 18F-FDG PET/CT imaging demonstrated a slow and steady decrease of both lesions, which finally disappeared after one year of antibiotic therapy. Complete remission was still maintained at the last follow-up 27 months after initiation of treatment, as shown in **Figure 1d**.

This is the first report of a complete remission of BALT lymphoma after long-term antibiotic therapy for *T. whipplei.*

T. whipplei is a gram-positive bacterium, identified as the cause of Whipple's disease not until the 1990s. Whipple's disease is a rare multisystem infectious condition, characterized by polyarthritis, steatorrhea, malabsorption and unintentional weight loss, associated with a pronounced infiltration of the duodenal lamina propria by macrophages. Meanwhile it is known, that *T. whipplei* is a ubiquitous bacterium and infections are quite common. Primary

infections might be symptomatic and manifest as gastroenteritis, pneumonia, arthritis or infectious endocarditis. Most acute infections result in bacterial clearance and seroconversion or less frequently in asymptomatic carriage of *T. whipplei* in the gastrointestinal tract. Only in very few patients *T. whipplei* replicates freely, leading to classical Whipple's disease. (10)

Infections caused by *T. whipplei* can lead to polysymptomatic disease patterns that often cannot be immediately attributed to this pathogen. Our patient presented with constitutional symptoms and sporadic episodes of nausea and vomiting, that were possibly unrelated to *T. whipplei* infection. Workup showed a pulmonary mass harboring BALT lymphoma, the biopsy of which was guided by F-18 FDG PET/CT imaging. *T. whipplei* DNA was consistently found in lymphoma tissue, while urine samples and biopsies from duodenum, colon and bone marrow tested negative.

Even though it is not a guideline-conform treatment approach, we opted for antibiotic therapy in our patient, since we assumed a causative role of *T. whipplei* in the development of the disease. A standard regimen for classical Whipple's disease was applied consisting of i.v. ceftriaxone 2g once daily for two weeks, followed by a continuation therapy with p.o. TMP/SMX 160/800 mg twice daily for a year. (10) Clinical improvement of the patient continued throughout the treatment period, though a new suspicious lesion appeared temporarily at the left lower hilum. Since the patient refused biopsy, we were not able to confirm our suspicion of lymph node progression. However, both lesions resolved over the following months.

Even though we cannot rule out a certain fluctuation of tumor mass due to the natural waxing and waning growth pattern commonly seen in indolent lymphomas, the complete resolution of disease in our patient raises the question whether *T. whipplei* was not only a trigger, but the main driver for BALT lymphoma development in this case. Recent findings of Haslbauer et al. on two cases of BALT lymphoma associated with *T. whipplei* support this suspicion. (11) Their molecular analysis revealed few mutations and the absence of mutations in genes encoding for the NF-κB pathway. They suggested that *T. whipplei* infection might substitute for mutations that typically play an important role in the pathogenesis of MALT lymphomas. Unfortunately, antibiotic therapy was attempted in only one of the two reported cases. It successfully eliminated *T. whipplei*, but had no effect on BALT lymphoma. However, the treatment duration was only four months in this case, after which total lobectomy was performed.

In our patient, F18-FDG PET/CT was utilized to guide biopsy and for restaging purposes. Moving forward, we would incorporate CXCR4-PET/CT imaging, as it has demonstrated superior diagnostic accuracy compared to FDG-PET/CT in the evaluation of MALT lymphomas. (12)

Our case exemplifies the unspecific disease pattern of BALT lymphoma that cannot be immediately attributed to a pathogen. Stepwise diagnostic approaches including PET/CT-guided biopsy and real-time PCR for *T. whipplei*

DNA might be required. Antimicrobial treatment alone might lead to complete remission of BALT lymphoma associated with *T. whipplei*.

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FIGURE LEGENDS

Figure 1: F18-FDG PET/CT staging at the time of diagnosis (a), restaging after four months of antibiotic treatment (b+c) and at the last follow up 27 months after initiation of treatment (d):

a. Pathologic FDG uptake in a left hilar mass (white arrow) with a max. diameter of 6.0 cm and a SUVmax of 13.0. b. Decrease in size and FDG uptake (SUVmax of 4.8) of the index lesion (white arrow). c. Pathologic FDG uptake in a new 3.0 cm lesion at the left lower hilum with a SUVmax of 5.1 (arrowhead). d. Complete metabolic and morphologic resolution of the index lesion at the left hilum (white arrow).

Abbreviations: F18-FDG PET/CT = Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography, FDG = fluoro- D-glucose, SUVmax = max. standardized uptake value

Figure 2: Histochemical and immunohistochemical presentation of the bronchial tissue biopsy (a) and clonality analysis of the DNA extracted from the bronchial tissue biopsy (b).

H&E staining revealed a diffuse infiltration of subepithelial tissue with small to medium-sized lymphoid differentiated cells (A1/A2 and B). Immunohistochemical staining highlighted the lymphoid infiltrate by positivity for CD20, CD79a and Bcl2 and negativity for CD5 and CD10 (E-I) as well as Bcl6 (not shown). Immunohistochemistry for CD3 and CD5, in combination with a

polyclonal TCR rearrangement (data not shown), revealed a prominent bystander population of T lymphocytes. In conclusion, the pancytokeratin (AE1/3) and low Ki-67 proliferation index (C and J), together with the clonality analysis (Figure 2b), supported the diagnosis of indolent B-cell non-Hodgkin lymphoma and, in particular, BALT lymphoma. Magnification: A1 9.1x (magnification bar of 300 µm), A2 20.8x (100µm), B 40x (50 µm), C to J each 23.1x (each 90 µm).

Clonality analysis (Figure 2b) reported a clonal VDJ rearrangement for framework 2 with two clonal bands and for framework 3 (each line D) with one clonal band in comparison to water control, polyclonal control and clonal control (each lines A, B and C respectively).

Abbreviations: H&E = Hematoxylin and eosin, TCR = T-cell receptor, Framework = FR

Figure 1a-d

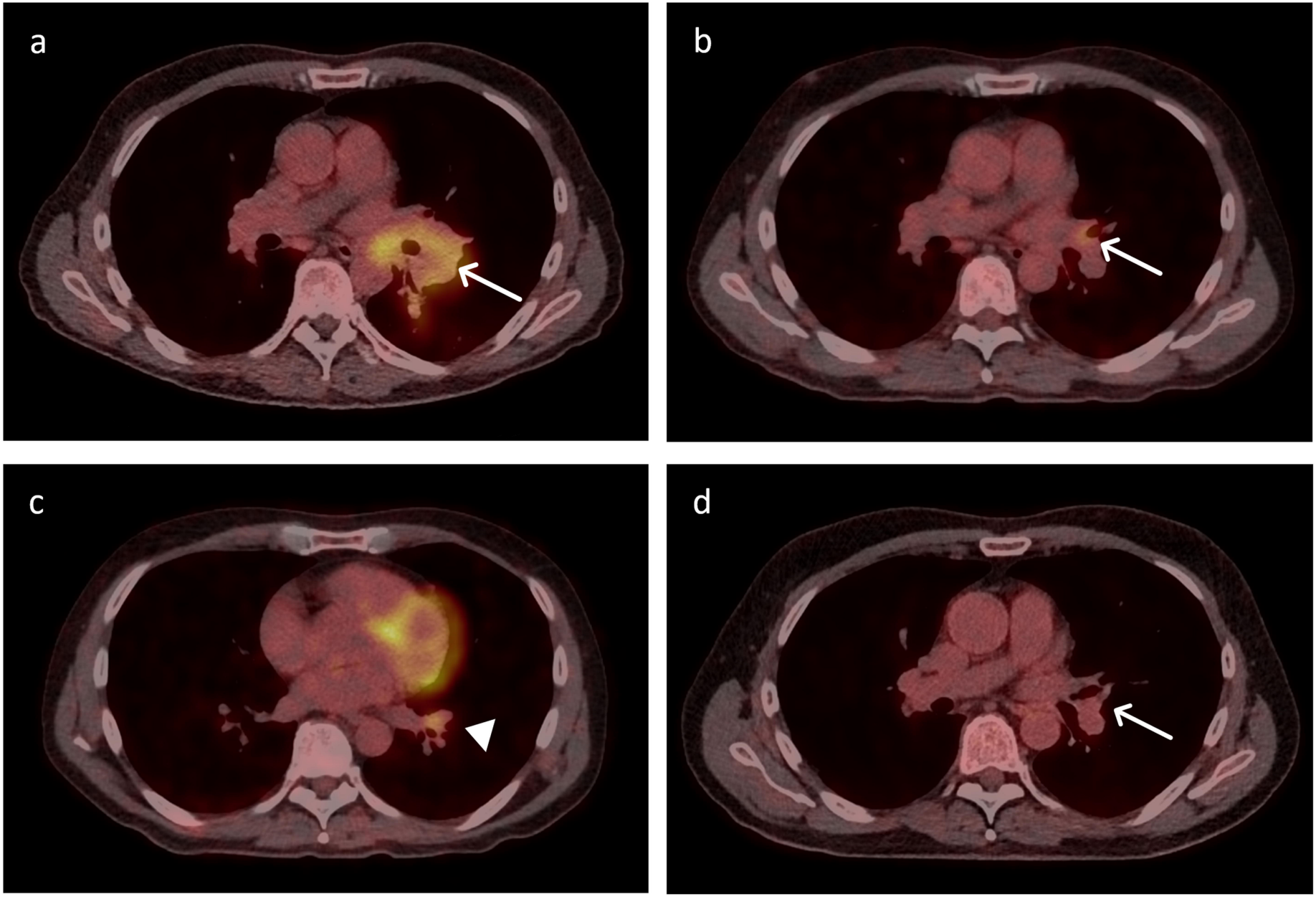

Figure 2a

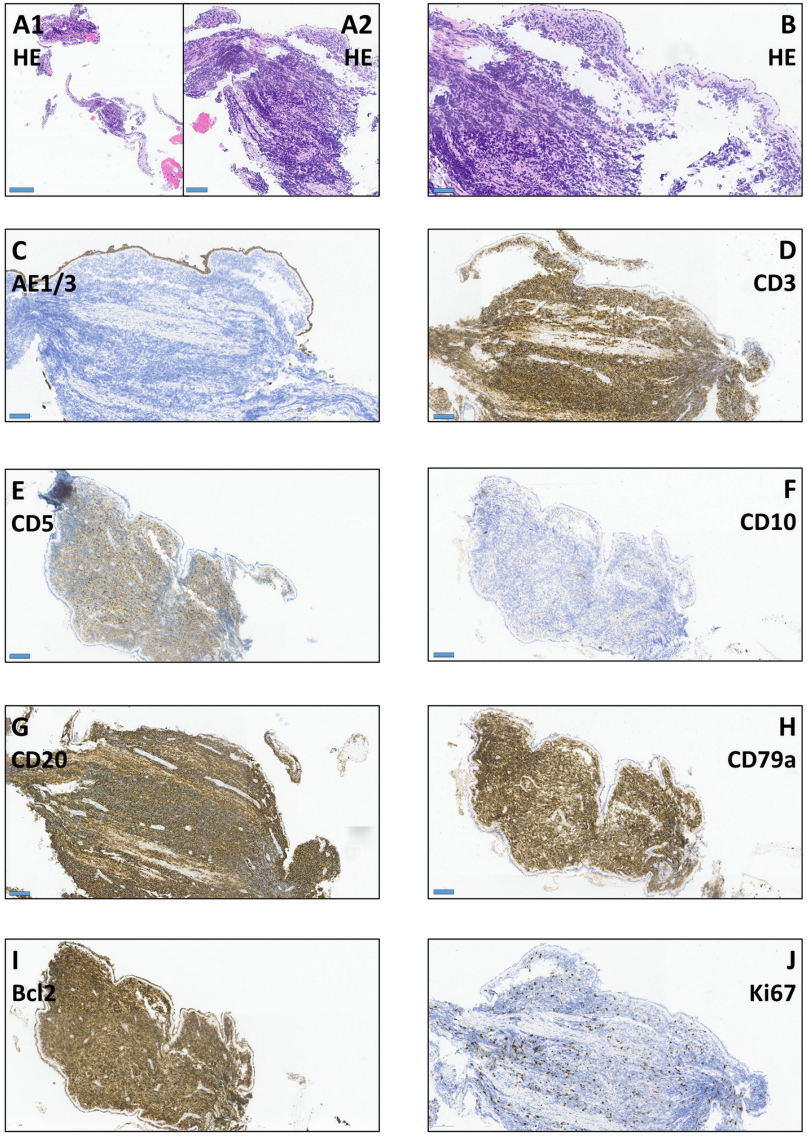

Figure 2b