

Primary gastric T cell lymphoma mimicking marginal zone B cell lymphoma of mucosa-associated lymphoid tissue

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Abstract Primary gastric T cell lymphoma is rare and mostly of large cell type. In this paper, we present a case of gastric T cell lymphoma morphologically similar to the gastric marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT). Morphologically, the cells are small with abundant clear cytoplasm. Lymphoepithelial lesions are readily identified with diffuse destruction of gastric glands. Immunohistochemically, the neoplastic cells are CD3+/CD4+/CD8-/Granzyme B-. Molecular studies revealed monoclonal T cell receptor γ gene rearrangement. Clinically, the patient responded initially to four cycles of R-CHOP, but then progressed. Because peripheral T cell lymphoma is usually associated with a poor prognosis, whereas marginal zone B cell lymphoma is an indolent lymphoproliferative disorder, this morphologic mimicry should be recognized and completely investigated when atypical small lymphoid infiltrates with lymphoepithelial lesions are encountered in the stomach.

Keywords Primary gastric T cell lymphoma · MALT ·
H. pylori · HTLV-1

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Introduction

Primary gastric lymphomas comprise 4.6% of non-Hodgkin lymphomas (NHL) and are one of the most common extranodal NHL (only less common than cutaneous NHL) [1]. While most of the primary gastric lymphomas are high-grade B cell lymphomas [2], one low-grade gastric B cell lymphoma has drawn particular attention in recent years due to its association with *Helicobacter pylori* infection [3]. Because this low-grade B cell lymphoma arises from the mucosa-associated lymphoid tissues (MALT), it was named by Peter Isaacson as “MALT lymphoma” [4, 5]. It is now defined by the WHO classification as a distinct pathological entity “extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)” [6]. MALT lymphoma is characterized by diffuse infiltration of monocytoid B cells with lymphoid aggregates invading the gastric glands, forming the so-called lymphoepithelial lesions, which is one of the hallmarks of “MALT lymphoma” [7]. Although being regarded as a low-grade malignancy, MALT lymphoma can regress spontaneously after eradication of *H. pylori* infection.

In contrast to the commonly occurring primary gastric B cell lymphomas, primary gastric T cell lymphomas (GTCL) are extremely rare. In a large study including a population of 2.8 million subjects over a period of 9 years in Western Denmark, only six cases of primary GTCL (including three cases of anaplastic large cell lymphomas) were documented [8]. Despite the fact that the gastric MALT contains both B cells and T cells, to our knowledge, a primary GTCL arising from MALT has never been reported. In this paper, we present a case of primary GTCL morphologically mimicking the B cell MALT lymphoma. Therefore, the differential diagnosis of atypical small lymphoid infiltrates with lymphoepithelial lesions in the stomach should also

include peripheral T cell lymphoma, in addition to chronic gastritis and MALT lymphoma.

Report of a case

A 51-year-old African-American male presented with nausea, vomiting and hematemesis, and profound anemia. There was no documented history of lymphadenopathy. Serologic test was negative for human T cell leukemia virus type 1 (HTLV-1). He had a gastric biopsy 5 months ago, which was diagnosed in another institution as a “possible T cell lymphoma versus B cell lymphoma with florid T cell response.” He was treated with rituxan, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). However, his condition declined after the fourth cycle of R-CHOP. He was transferred to our medical center for further evaluation.

On admission, a whole-body systemic survey by positron emission/computed tomography (PET/CT) showed multiple metabolically active nodular lesions involving the gastric wall and several perigastric lymph nodes. An esophagogastroduodenoscopy (EGD) showed many non-obstructing and nonbleeding cratered gastric ulcers. The largest lesion measured 3×2 cm and seemed to involve the muscularis propria. No perforation or bleeding was seen. A biopsy of this lesion was performed.

Materials and methods

Histology, immunohistochemistry, and in situ hybridization

Two endoscopic gastric biopsy specimens from the antrum, body, and fundus were initially obtained fresh. One sample from the gastric body and fundus was available for a second, follow-up evaluation. The specimens were prepared for light microscopy by fixing in 10% buffered formalin and embedding in paraffin. Three-micron tissue sections were stained with hematoxylin and eosin (H&E). The immunoperoxidase stains were performed on a BenchMark® XT autostainer (Ventana, Tucson, AZ, USA) using antibodies against CD3, CD4, CD5, CD8, CD10, CD20, CD43, CD56, CD79a, cyclin D1, Granzyme B, Ki-67, p53, pancytokeratin, and *H. pylori* as primary antibodies (Ventana). In situ hybridization for Epstein–Barr virus (EBV) early RNA (EBER) was performed similarly on the autostainer using a Ventana ISH iVIEW Blue Detection Kit. Additional paraffin immunoperoxidase stain was manually performed on paraffin sections using a mouse antihuman CD103 monoclonal antibody for frozen tissues (BioLegend, San Diego, CA, USA) with no success.

Flow cytometry

Portions of fresh tissue from the initial biopsy were analyzed on a BD FacExcalibur (Becton Dickinson, Franklin Lakes, NJ, USA) using a limited panel of antibodies against CD3, CD4, CD5, CD8, CD10, CD19, CD20, kappa, and lambda, conjugated with fluorochromes FITC, PE, Per-CP, and APC (Becton Dickinson).

Molecular studies

DNA was prepared from 10- μ paraffin sections using a QIAprep 96 Turbo BioRobot Kit (Qiagen, Valencia, CA, USA). The *TCR* genes were PCR-amplified using consensus V region primers and two J region primers [9] on a GeneAmp® 9700 PCR amplifier (Perkin Elmer Life And Analytical Sciences, Waltham, MA, USA). The PCR products were resolved on a polyacrylamide gel.

Results

Microscopically, the first biopsy showed multiple fragments of gastric mucosa with dense lymphoid infiltrates composed of predominately small lymphoid cells with small amount of clear cytoplasm, round to slightly irregular nuclei, and clumped chromatin. Lymphoepithelial lesions were readily identified (Fig. 1a). Some of the gastric glands were almost entirely destroyed by the lymphoid infiltrates. Because this morphology is characteristic for MALT lymphoma (Fig. 1b), our working diagnosis was “extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).”

A limited amount of fresh tissue was submitted for flow cytometry. With a limited panel of antibodies, the analysis demonstrated a predominant population of CD3+ T cells (92% of the total events). Paraffin immunoperoxidase stains showed that the atypical lymphoid infiltrates were CD3+, CD4+, CD5+, and CD43+. These cells were negative for CD8, CD10, CD20, CD56, CD79a, Granzyme B, or cyclin D1. Stains for CD20 and CD79a highlighted focal residual reactive small B cells and plasma cells. Stain for CD8 showed only scattered reactive small T cells. Pancytokeratin stain revealed the lymphoepithelial lesions commonly seen in MALT lymphoma (Fig. 2). Immunostain for *H. pylori* and in situ hybridization for EBV were negative. Because frozen tissue was not available, immunostain for CD103 was manually attempted on the paraffin sections using a commercially available antibody for frozen tissues (BioLegend). Our effort failed to stain the CD103+ intra-epithelial lymphocytes (IEL) in the control intestinal tissues with various antigen retrieval approaches. Molecular studies performed on paraffin-embedded tissue identified a

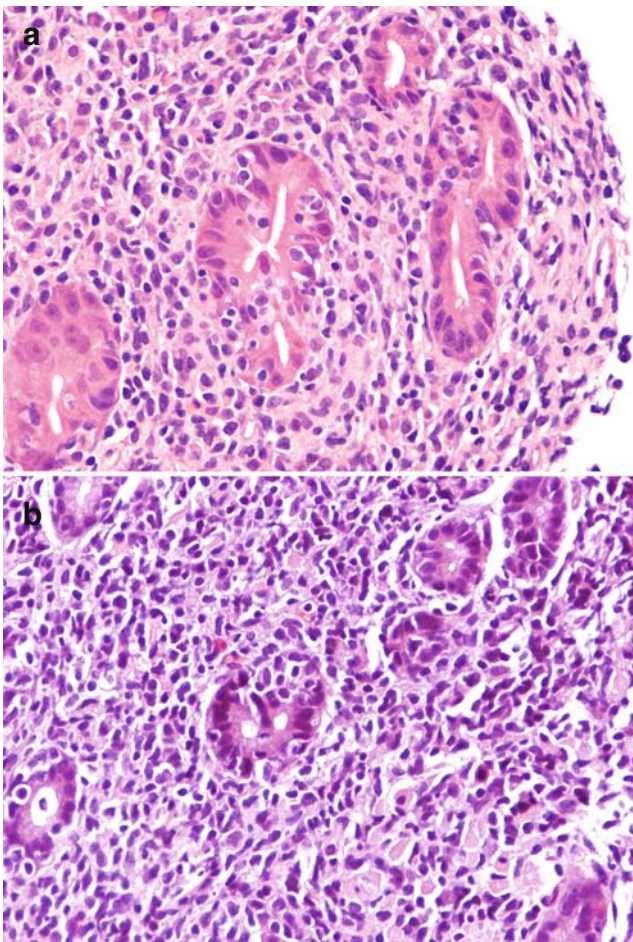


Fig. 1 Morphologic comparison between the current primary GTCL and a B cell MALT lymphoma (H&E, ×400 amplification). Similar lymphoepithelial lesions are present in both GTCL (a) and MALT lymphoma (b)

monoclonal T cell receptor (TCR) γ gene rearrangement (Fig. 3, lane 2). These findings were consistent with a T cell lymphoma with morphologic features of MALT lymphoma and helper/inducer T cell phenotype.

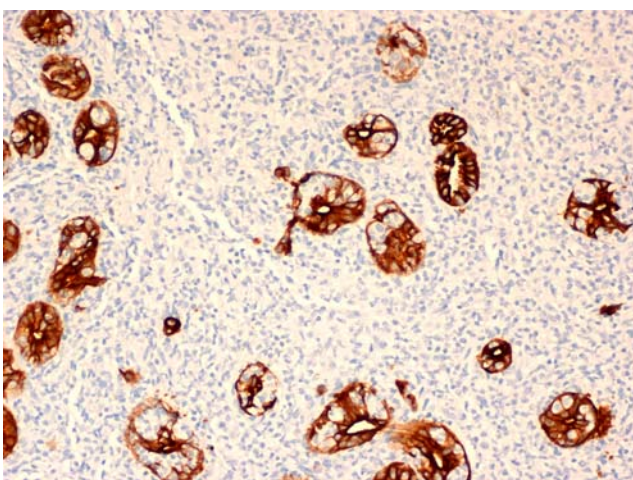


Fig. 2 Lymphoepithelial lesions of the primary GTCL (antipancytokeratin immunoperoxidase stain, ×400 amplification)

Intrigued by this morphologic similarity, we compared the distribution of CD4 (helper/inducer) and CD8 (cytotoxic/suppressor) T cells in duodenitis, gastritis, and our case. In duodenitis, while small numbers of CD4+ T cells were found to be located predominantly in the interglandular area, the CD8+ cells, i.e., IEL, were present within the epithelium of the duodenal glands (data not shown). In contrast, CD4+ T cells were identified both interglandularly and within the epithelium, whereas CD8+ cells were present predominantly within the glandular epithelium in chronic gastritis. In the current lymphoma case, CD4+ neoplastic cells were predominantly in the interglandular area of the lamina propria where the T cell lymphoma might have originated. Conversely, CD8+ T cells displayed a similar distribution as in the chronic gastritis. These findings suggest that the T cell lymphoma might have arisen from the interglandular CD4+ small T cells seen in chronic gastritis.

Follow-up

Because the patient did not tolerate R-CHOP chemotherapy, he underwent a local radiation therapy (total 30 Gy in 10 fractions) to the gastric lesions and perigastric lymph nodes. Two and a half weeks after radiation, a PET/CT scan showed interval progression even in the radiation field with an increase in the size of gastrohepatic and retroperitoneal lymph nodes and celiac nodes. Furthermore, a repeat biopsy showed residual

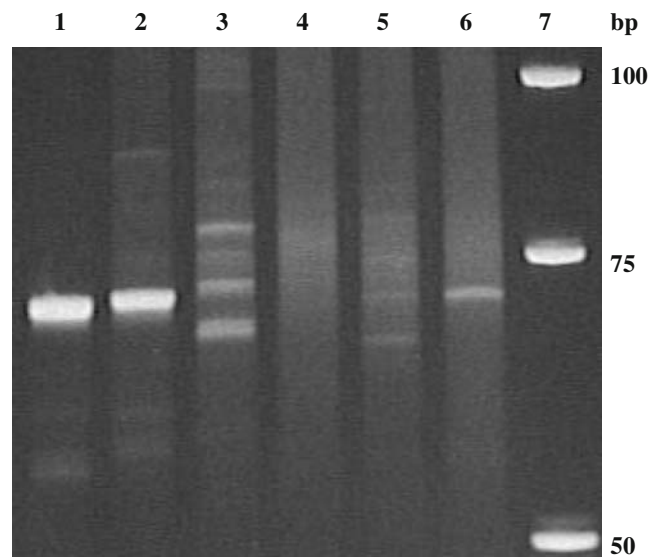


Fig. 3 Molecular studies of the primary GTCL before and after the radiation therapy. DNAs from gastric biopsies before and after radiotherapy were isolated for PCR amplification using primers for T cell receptor γ gene. Lane 1 monoclonal control, lane 2 initial diagnostic biopsy, lane 3 3-month follow-up biopsy, lane 4 polyclonal control, lane 5 oligoclonal control, lane 6 5% sensitivity monoclonal control, lane 7 25-bp DNA marker (Invitrogen, Carlsbad, CA, USA)

lymphoma with large cell atypia and acute inflammation (Fig. 4a). No molecular study was performed on this specimen.

The patient was sent home with monthly follow-ups. At 2 months after the radiation therapy, the patient reported feeling better and gained 20 lbs. About 3 months after the completion of radiation therapy, a follow-up PET/CT scan showed resolution of the metabolic activity in the stomach. However, new pathologic lymphadenopathy was noted in the chest and abdomen outside of the original radiation ports. The follow-up gastric biopsy taken at the 3-month mark showed rare large atypical lymphoid cells in a background of reactive lymphoplasmacytosis (Fig. 4b). The T cell receptor γ gene rearrangement study showed oligoclonality (Fig. 3, lane 3). Among the oligoclonal bands, there was no band matching the monoclonal band amplified from the original diagnostic specimen (Fig. 3, lane 2).

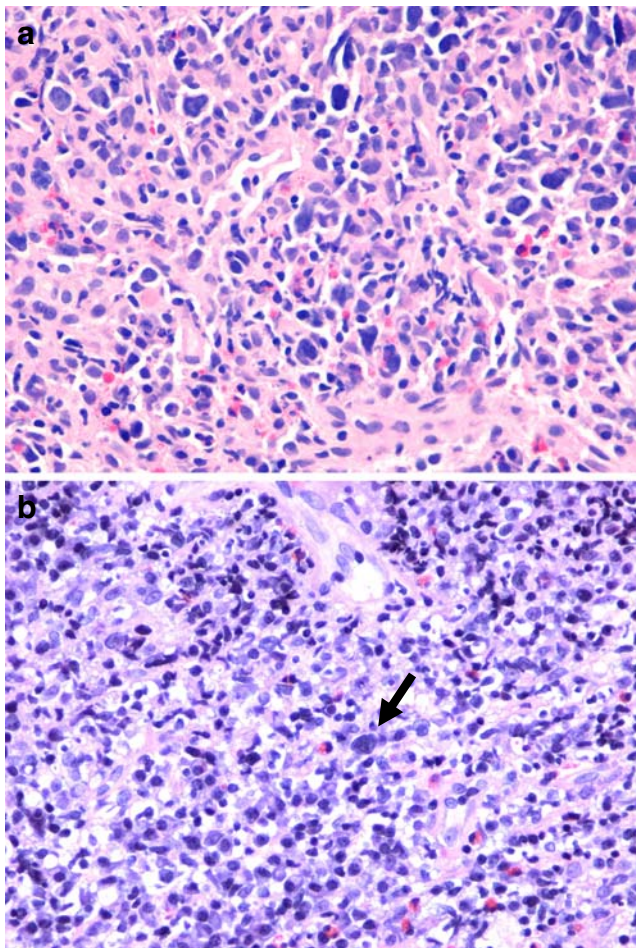


Fig. 4 Morphologic changes of the primary GTCL after the radiation therapy (H&E, $\times 400$ amplification). **a** The large neoplastic cells show hyperchromatic giant nuclei in a background of acute inflammation (at 2 1/2 weeks after radiation); **b** rare large atypical T cells are present (arrow) in a background of reactive lymphoplasmacytosis (at 3 months after radiation)

Discussion

We presented a rare case of primary GTCL morphologically mimicking MALT lymphoma. This case expanded our knowledge on the differential diagnosis of atypical small lymphoid infiltrates with lymphoepithelial lesions to include peripheral T cell lymphoma.

Many cases of primary GTCL had been reported with the majority of the GTCL being large cell type (Table 1) [10–19]. Only less than 10 reported GTCL had a small- to medium-sized cell morphology [12, 19–23]. Some of these cases occur frequently in HTLV-1 endemic areas and may represent examples of adult T cell leukemia/lymphoma (ATLL) [21]. Because gastric lymphomas in patients with HTLV-1 infection (mostly in Japan) might be better regarded as involvement by ATLL, those cases were not included in Table 1. Based on the immunophenotypes of the reported cases, GTCL can be classified into two major subtypes: (1) helper/inducer T cell subtype (CD4+/CD8-/CD103-) and (2) cytotoxic/suppressor T cell subtype (CD4-/CD8+ or CD4-/CD8- with expression of CD103 and/or CD56 (Table 2).

Most of the previously reported primary GTCL was of the helper/inducer T cell subtype (CD4+/CD8-/CD103-; Table 1). Due to the lack of fresh tissue and commercially available anti-CD103 antibody for paraffin immunohistochemistry, we could neither confirm nor exclude the presence of CD103 in the tumor cells of our patient. However, according to the previous reports, almost all the primary CD103+ GTCL were CD4-/CD8+, whereas none of the CD4+ cases were CD103+ (Table 1). One exceptional case of GTCL with a CD4+/CD8+/CD103+ immunophenotype was reported [17]. Because a CD4+/CD8+ phenotype is more consistent with immature T cells, the possibility of a bona fide lymphoblastic lymphoma could not be excluded in that case. Based on the CD3+/CD4+/CD8-/Granzyme B- immunophenotype, we assume that our case is more likely CD103-, and thus may fall into this subtype of primary GTCL. When this subtype occurred primarily in the stomach, it resembled nodal T cell lymphomas as they displayed a CD4 phenotype and lacked cytotoxic granules [5]. However, because the stomach does not normally have organized lymphoid tissue [24], the lymphoma cells might have either migrated from the lymph nodes or arisen from the CD4+ T cells of MALT, as a result of chronic inflammation [18]. With immunohistochemistry, we identified many CD4+/CD8- T cells in the MALT of *H. pylori* chronic gastritis and the current lymphoma. We thus speculate that it is possible that peripheral T cell lymphoma could originate from the T cells of MALT. Because the current patient did not show evidence of *H. pylori* infection, these T cells may have migrated to the stomach in response to other unidentified stimulation.

Table 1 Summary of reported cases of primary GTCL

| Case ^a | Age/sex | Diagnosis | Immunophenotype | Reference |
|-------------------|---------|---------------------------------------|---|-----------|
| 1 | 66/F | HG primary GTCL | CD2+/CD4+/CD8-/CD30- | [10] |
| 2 | 18/M | HG primary GTCL | CD2+/CD4+/CD8- | [10] |
| 3 | 46/M | Primary GTCL, large cell | CD3+/CD4+/CD8-/CD30+/ALK-1-/TIA-1+/CD103-/EBER(-) | [11] |
| 4 | 62/M | Primary GTCL, large cell | CD3+/CD4+/CD8-/CD30-/CD56-/TIA-1-/EBER(-) | [11] |
| 5 | 49/F | Primary GTCL, large cell | CD3+/CD4-/CD8+/CD30+/ALK-1-/TIA-1+/EBER(+) | [11] |
| 6 | 47/F | Primary GTCL, large cell | CD3+/CD4-/CD8-/CD30-/CD56-/TIA-1+/EBER(-) | [11] |
| 7 | 75/M | Primary GTCL, mixed small and large | CD3+/CD4+/CD8- | [12] |
| 8 | 24/M | Primary GTCL, NK-like | CD3+/CD8±/CD56+/TCR+/H. pylori(+) | [13] |
| 9 | 73/F | Primary GTCL, cytotoxic | CD3+/CD4±/CD8+/CD30-/CD56±/TIA-1+/Granzyme B+/Perforin+/HTLV-1(-)/H. pylori(-)/EBV(-) | [14] |
| 10 | 47/F | Primary GTCL, cytotoxic | CD3+/CD4-/CD8-/CD30-/TIA-1+/Granzyme B+/EBER(-) | [15] |
| 11 | 56/M | Primary GTCL, pleomorphic | CD3+/CD4-/CD8-/TIA-1+/CD30+/Granzyme B+/Perforin+/CD103+/H. pylori(-)/EBER(-) | [16] |
| 12 | 41/M | Primary GTCL, pleomorphic | CD3+/CD4+/CD8-/TIA-1-/CD30+/Granzyme B-/H. pylori(-) | [16] |
| 13 | 33/M | Primary GTCL, pleomorphic mixed cell | CD3+/CD4-/CD8+/CD30-/CD56+/TIA-1+/Perforin-/Granzyme B+/EBV(+)/HTLV(-) | [17] |
| 14 | 58/M | Primary GTCL, diffuse pleomorphic | CD3+/CD4+/CD8-/CD16+/CD30±/CD103-/EBER(-)/HTLV-1(-)/H. pylori(+) | [18] |
| 15 | 62/M | Primary GTCL, diffuse pleomorphic | CD3+/CD4+/CD8-/CD16,56+/CD30+/CD103-/EBER(-)/HTLV-1(-)/H. pylori(-) | [18] |
| 16 | 45/M | Primary GTCL, mixed cell | CD3+/CD4+/CD8-/CD30+/CD56-/ALK-1-/TIA-1-/EBER(-) | [11] |
| 17 | 66/M | Primary GTCL, mixed cell | CD3+/CD4+/CD8-/CD30+/CD56-/TIA-1+/EBER(-) | [11] |
| 18 | 64/M | Primary GTCL, mixed cell | CD3+/CD4+/CD8-/CD30+/ALK-1-/TIA-1+/CD103-/EBER(+) | [11] |
| 19 | 70/M | Primary GTCL, mixed cell | CD3+/CD4-/CD8+/CD30-/CD56-/ALK-/TIA-1-/EBER(-) | [11] |
| 20 | 62/F | Primary GTCL, mixed cell | CD3+/CD4-/CD8-/CD30+/ALK-1-/TIA-1-/CD103-/EBER(-) | [11] |
| 21 | 51/M | Primary GTCL, medium-sized | CD3+/CD4+/CD8-/CD30+/CD56-/ALK-1-/TIA-1+/EBER(-) | [11] |
| 22 | 44/M | Primary GTCL, medium-sized | CD3+/CD4-/CD30-/CD56-/TIA-1-/EBER(-) | [11] |
| 23 | 76/F | Primary GTCL, medium-sized | CD3+/CD4+/CD8+/CD30-/CD56-/CD103+/TIA-1+/Perforin-/Granzyme B-/EBV(-)/HTLV(-) | [17] |
| 24 | 52/M | Primary GTCL, small- and medium-sized | CD3+/CD4+/CD8- | [12] |
| 25 | 73/M | Primary GTCL, small cell | CD3+/CD45RO+/HTLV-1(-) | [19] |
| 26 | 51/M | Primary GTCL, small cell | CD3+/CD4+/CD8-/CD30-/CD56-/HTLV-1(-)/H. pylori(-)/EBER(-) | This case |

ALK-1: anaplastic lymphoma kinase 1, *EBV*: Epstein–Barr virus, *EBER*: EBV early RNA, *GTCL*: gastric T cell lymphoma, *HG*: high grade, *HTLV-1*: human T cell leukemia virus type 1, *TCR*: T cell receptor, *TIA-1*: T cell intracellular antigen 1

^aOnly the HTLV-1(-) cases with detailed immunohistochemical studies were included in this table.

The second subtype of GTCL is cytotoxic/suppressor T cell subtype (CD4-/CD8+/CD103+) with expression of TIA-1 and Granzyme B [13–17]. Rare CD4-/CD8-/CD56+ cases were also included in this subtype [18]. Because the immunophenotype of these lymphoma cells resembled CD103+ IEL of the small and large intestines [24], it was suggested that these lymphoma cells originated from the IEL [17]. The IEL also give rise to the enteropathy-associated T cell lymphoma (EATL), an aggressive intestinal malignancy frequently associated with celiac disease [25]. Because of this, CD103 is considered specific for EATL. However, gastric lymphomas in HTLV-1 patients were also frequently CD103+, questioning the specificity of CD103 for EATL [18]. A possible link between EATL and

Table 2 Classification of primary GTCL

| Subtypes | Helper/inducer T cell | Cytotoxic/suppressor T cell |
|------------|-----------------------|-----------------------------|
| CD3 | + | + |
| CD4 | + | - |
| CD8 | - | +/- |
| CD56 | - | -/+ |
| CD103 | - | +/- |
| Granzyme B | - | +/- |
| TIA-1 | -/+ | + |

TIA-1: T cell intracellular antigen 1

EBV infection is still controversial [26, 27]. Some studies indicated that *H. pylori* could be the cause of some EATL [18]. Even though EATL can be of small cell type and can occur primarily in the stomach, our current case neither showed an immunophenotype of the IEL nor had a history of celiac disease. In addition, our studies showed no evidence of EBV, HTLV-1, or *H. pylori* infection in the patient. Although the EATL arising from the small intestine IEL were usually associated with a poor prognosis, there was at least one report that a primary GTCL regressed after the eradication of *H. pylori* and the patient remained in remission for over 2 years [13].

With very few cases, the etiology of primary GTCL is unknown. An association was found between primary GTCL and various infections, such as HTLV-1 [21, 28], *H. pylori* [13, 18], or EBV [17, 26, 29] infections. In a study of 233 gastric lymphomas, Nakamura et al. reported that 73% (11/15) of the GTCL had coexisting *H. pylori* infection [30], supporting a possible role of *H. pylori* in the development of GTCL. We have sought for evidence of infections in our patient. However, the patient was seronegative for HTLV-1. Immunohistochemical stain for *H. pylori* and in situ hybridization for EBV were both negative. The pathogen that led to the development of the current T cell lymphoma, if it exists, remains to be determined.

The majority of the reported GTCL have large cell morphology. This may suggest that the small cell type GTCL is rare or that they rapidly undergo large cell transformation before detection. As reported in B cell MALT lymphomas [7], it is also possible that peripheral T cell lymphoma arising from gastric MALT may also have small cell and large cell variants. When the small cell variants transform into large cell variants, they may be associated with CD30 expression [11]. Future cytogenetic and molecular studies may help to further define these rare lymphomas.

In summary, we have described a rare case of GTCL and reviewed all the previously reported GTCL in the English literature. Small cell GTCL are extremely rare. However, because small cell GTCL can morphologically mimic extranodal marginal zone B cell lymphoma, we should recognize this entity in the differential diagnosis when encountering atypical lymphoid infiltrates with lymphoepithelial lesions in the stomach. Our report also raises a question: whether a T cell lymphoma could ever arise from the gastric MALT as well?

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Conflict of interest The authors declare that they have no conflict of interest.

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