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Case Report

Helicobacter pylori-Negative Gastric Mucosa-Associated Lymphoid Tissue Lymphoma in a Girl

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Keywords

Gastric mucosa-associated lymphoid tissue · Non-Hodgkin lymphoma · *Helicobacter pylori* eradication · Low-dose radiation · Children

Abstract

Introduction: Extranodal marginal zone lymphoma (MZL) arises in a number of epithelial tissues, including the stomach, salivary gland, lung, small bowel, thyroid, ocular adnexa, skin, and elsewhere. It has also been called low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT). MALT lymphoma predominantly occurs in adults and is rare in children. ***Case Presentation:*** We report a case of MALT lymphoma involving the stomach, which is the most common subtype, in a 12-year-old girl. Initially, the patient relapsed after antibiotic therapy but achieved successful treatment subsequently through irradiation. ***Conclusion:*** *Helicobacter pylori* eradication therapy should be given to all patients with gastric MZL, irrespective of stage. In patients who do not respond to antibiotic therapy, treatment options such as irradiation and systemic cancer therapies should be considered, depending on the disease stage.

Introduction

Extranodal marginal zone lymphoma (EMZL) is a relatively uncommon subtype of non-Hodgkin lymphoma. It is mainly seen in adults with a median age at diagnosis of 66 years [1]. In the USA as a whole, EMZL accounts for 5–10% of non-Hodgkin lymphomas overall but

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makes up approximately half of the lymphomas in particular sites, such as the stomach, ocular adnexa, and lung [2]. There are some geographic areas, such as north-eastern Italy, where the frequency of primary gastric lymphoma is particularly high, with an incidence as high as 13.2 cases per 100,000 per year, which is significantly higher than that of other European countries [3]. EMZL occurs equally among men and women. Gender disparities are seen by site with men more commonly having involvement of the stomach, small intestine, skin, and kidney and women more commonly having involvement of the salivary gland, soft tissue, and thyroid. Some of these gender disparities are explained by differences in the incidence of Sjögren's syndrome and Hashimoto's thyroiditis, both of which are more common in women than in men and which predispose to EMZL of the salivary gland and thyroid, respectively [2]. However, MALT lymphomas are exceedingly rare in children. Among 2,703 children and adolescents registered in the prospective multicenter NHL-BFM treatment studies since 1986, only 4 patients (0.1%) displayed features of MALT lymphoma [4]. These tumors were localized in the stomach, breast, lower lid, and conjunctiva, respectively. All children are alive, but long-term follow-up will be mandatory to assess the behavior of MALT lymphoma in this age-group [4].

Global reports of MALT lymphoma in pediatric populations are rare. This case report represents the first diagnosis reported of MALT lymphoma in an adolescent patient in Vietnam. Diagnostic confirmation was achieved through histopathological examination and immunohistochemistry (IHC) methods. The clinical presentation mirrored the symptoms typically observed in adult cases [5]. The treatment adhered to the guidelines set by the European Society of Medical Oncology [6], resulting in the patient achieving long-term complete remission, suggesting a potential cure.

Case Report

History

A 12-year-old girl presented with a 4-month history of recurring epigastric pain. The pain worsened when she was hungry and improved after eating. She appeared to have clinical signs of anemia with paleness but an overall stable condition.

Diagnosis

The initial complete blood count (CBC) test revealed microcytic hypochromic anemia (Hgb 8.8 g/dL, MCV 70 fL, MCH 23.4 pg). Iron studies indicated significantly low serum iron (2.13 μg/dL) and ferritin levels (4.51 ng/mL), suggesting iron deficiency anemia. Based on these suggesting gastric disease findings, the child underwent an upper gastrointestinal endoscopic exam with the following results: esophagus, duodenal bulb: normal mucosa, gastric body: infiltrating, indurated lesions originating beneath the mucosal layer at the cardia region, occupying nearly 2/3 of the cardia. The surface shows shallow ulcers and there was blood clot at the ulcer base. The stomach contains a small amount of blackish blood (Fig. 1).

Four biopsy samples were taken for histology and IHC. The result of the *Campylobacter*-like organism (CLO) test was negative. Additionally, there is no detection of *H. pylori* in 4 gastric biopsy samples.

The gastric endoscopic biopsy sample consists of 4 small fragments: 2 fragments showed inflammatory mucosal lining changes, with excessive proliferation of lymphocytes. The other 2 exhibit images of a tumor in the connective tissue, consisting of medium-sized cells with basophilic nuclei and scant cytoplasm. The tumor cells appear uniform with distinct nuclei and scattered areas of necrosis. The tumor cells have invaded into the muscularis mucosae, submucosal tissue, and glands. There is increased vascularity, and in some areas, there are signs of cellular enlargement and death of cells (Fig. 2). IHC results were as follows: CD20:

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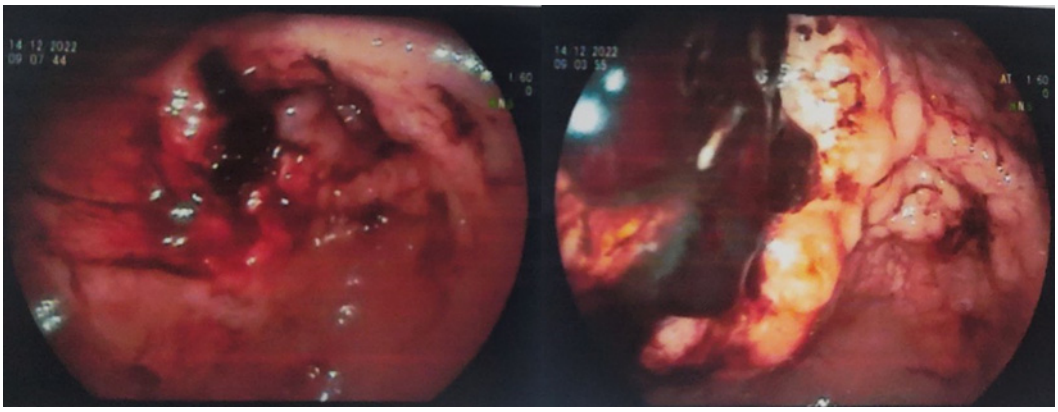

Fig. 1. Endoscopy before treatment.

positive LCA: positive Ki67: positive (10%) CD21, CD35, CD23, CD10, CD5, CD3, CKAE1/AE3, MUM1, Bcl6, CD5 and cyclin D1: negative. The result concluded gastric MALT lymphoma (Fig. 3).

The bilateral bone marrow biopsies were normal. Whole-body CT scan: stomach: thickened lesions were detected in the antrum region. The thickened wall is approximately 21 mm in height and extends over a segment of about 71 mm. This area has a slight contrast uptake and is not uniform. No other abnormalities relevant to other organs were found (Fig. 4). CEA: 0.306 ng/mL, CA19-9: 4.37 U/mL, liver and renal function, lactate dehydrogenase (LDH), electrolytes were normal. We do not have resources to check the presence of trisomy 3, a BCL10 gene mutation, and/or t(11;18), which may identify people less likely to benefit from therapy directed at *H. pylori*. According to Lugano staging system for gastrointestinal lymphomas [7], along with the negative result of *Helicobacter* test, the patient was diagnosed with stage I *Helicobacter pylori*-negative gastric MALT lymphoma.

Treatment

We commenced treatment according to treatment algorithm for localized gastric MZL (European Society for Medical Oncology – ESMO) [8]. We administered *Helicobacter pylori* eradication therapy regardless of the *Helicobacter pylori* status, including a combination of metronidazole, amoxicillin, bismuth, and PPI for 4 weeks. Additionally, oral iron therapy was initiated at a dosage of 5 mg/kg of elemental iron per day.

Two weeks after the therapy, the abdominal pain was completely relieved, with improved lips and mucosa coloration, and could perform regular activities. The hemoglobin level raised to 10.6 g/dL, although the Fe/ferritin levels were still low (3.81 μg/dL and 9.03 ng/mL). The gastroscopy revealed mildly rigid lesions in the antrum. These signs indicated a clinical and endoscopic response. We continue iron therapy afterward targeting the ideal level of Hb, serum iron, ferritin level and monitor the patient closely. After the next 3 weeks, the patient underwent endoscopy with result of high-grade glandular dysplasia.

After the next 1 month, the abdominal pain recurred but with reduced intensity compared to the initial time. The patient received treatment with Phosphalugel at home before being readmitted to the hospital for a follow-up examination. Endoscopy revealed a sizable ulcer #4 cm on the body, extending close to the pylorus, exhibiting a whitish pseudomembrane, swollen edges, and a tendency to bleed. Histopathology and IHC illustrated MALT lymphoma. We evaluated the child's failure with initial treatment and decided on radiation therapy.

Involved site radiotherapy with the low dose of 30 Gy in 15 fractions was used for definitive treatment. There was no side effect found. Treatment response to radiotherapy was assessed at 1 and every 3 months by follow-up EGDs.

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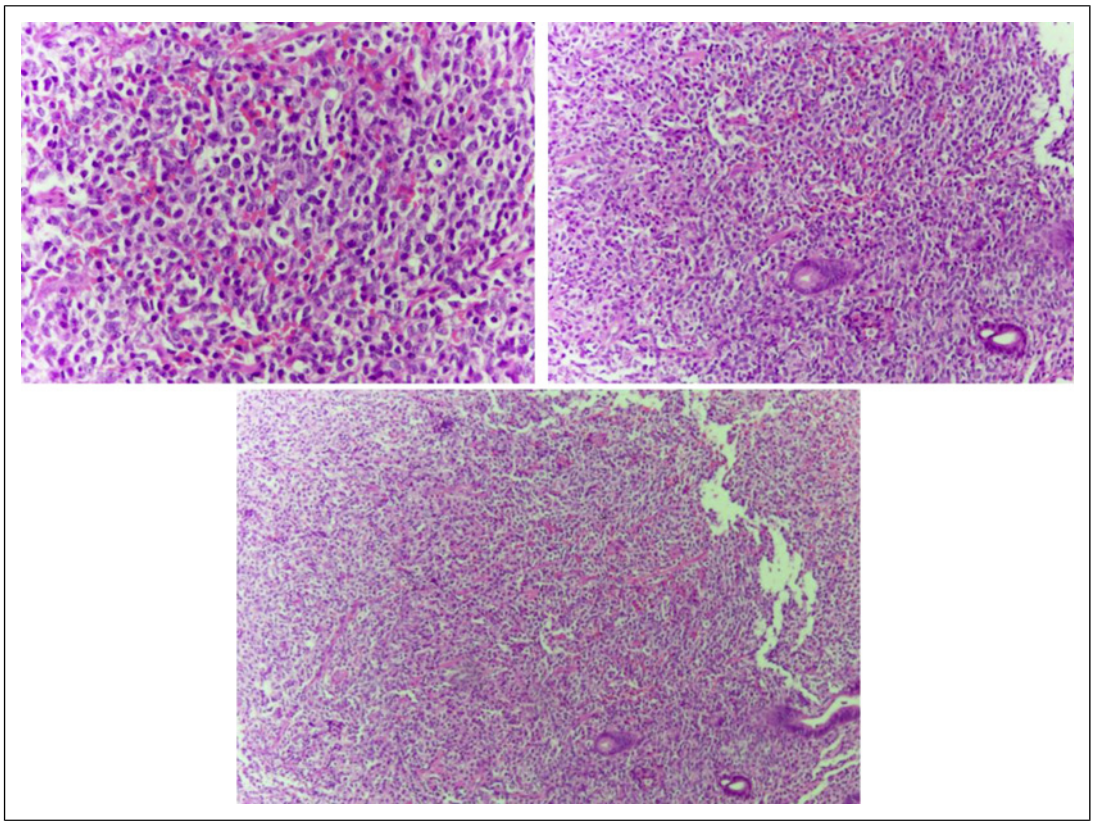

Fig. 2. Histopathology.

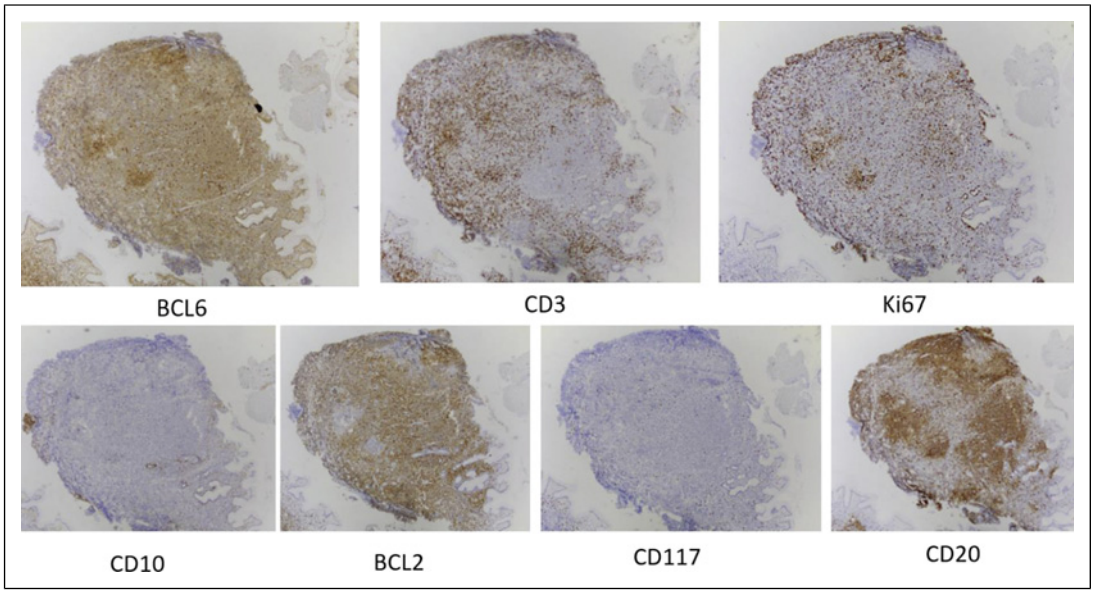

Fig. 3. IHC.

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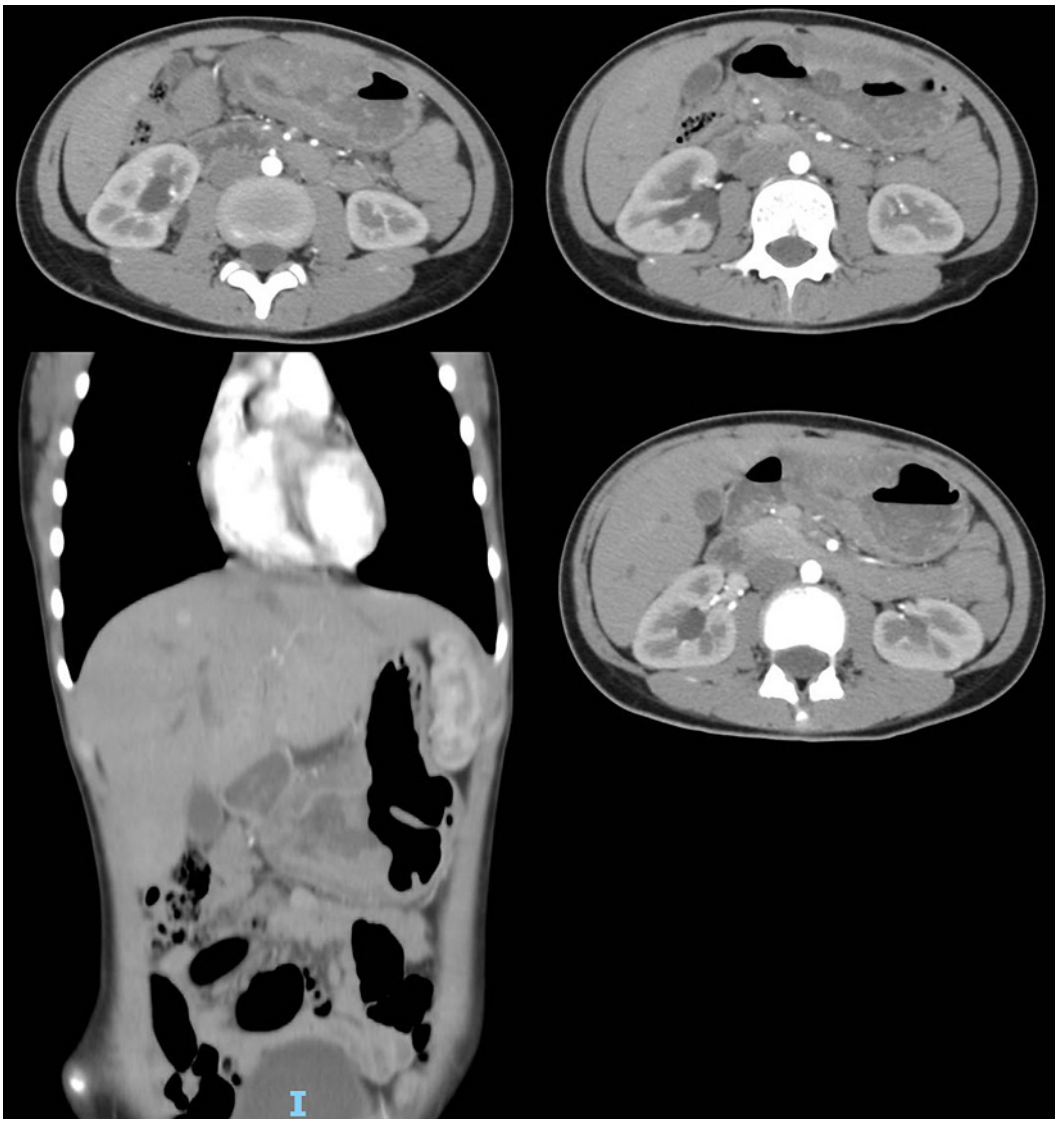

Fig. 4. CT-scan images at diagnostic time.

Outcomes

Endoscopy of the stomach after finishing irradiation therapy 1 and 3 months and 6 months: There were small scars with slight constriction near the pylorus and no signs of bleeding with negative CLO test result (Fig. 5). The patient will have a follow-up at intervals of 3 months. 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/10.1159/000535999).

Discussion

This is the first successfully diagnosed and treated case of gastric MALT lymphoma in children in Vietnam, at Hue Central Hospital. MALT lymphomas are exceedingly rare in children [7]. The stomach is by far the most common site for MALT lymphomas, comprising

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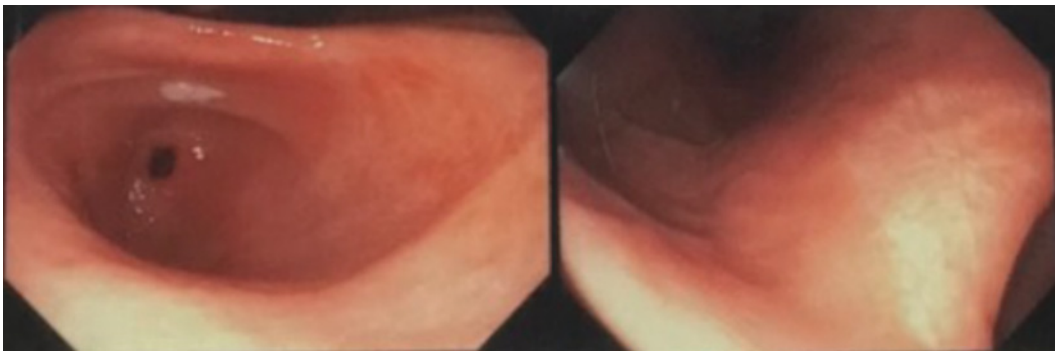

Fig. 5. Endoscopy after treatment.

70% of the total [9]. However, only 10% of these also tested negative for *H. pylori* [10]. Additionally, there is no concurrent immunosuppression observed in this patient. The diagnosed case displays the usual clinical and histopathological characteristics. There have been no documented cases of diagnosing pediatric gastric MALT lymphoma in children within Vietnam.

In the English literature, there were only 22 reported cases of MALT lymphoma in children, and among them, only 5 cases were gastric lymphomas, with only 1 case testing negative for *H. pylori* [7]. Only four children identified with MALT lymphomas (three in trial NHLBFM-95 and one in trial NHL-BFM-90) in a cohort of 2,703 patients registered in the consecutive treatment studies (0.1%) and only 1 case gastric Malt lymphoma among them. One possible cause for the rarity of MALT lymphomas in childhood may be attributed to the rather long prephase of this lymphoma type [4].

The clinical manifestations are similar to gastric ulcers, including epigastric pain, persistent vomiting, unintended weight loss, malaise, and iron deficiency anemia, without classic B symptoms (fever, night sweats, weight loss). However, during endoscopy, it appears as a distinct malignant lesion such as a giant ulcer or a vegetant mass. The definitive diagnosis is established based on histopathology and immune markers.

Our approach for this case is in line with that of the European Society of Medical Oncologists (ESMO). We initiated treatment by implementing *H. pylori* eradication therapy, despite the negative CLO test result. Encouragingly, the patient exhibited positive clinical and endoscopic responses to this approach.

This allows us to suspect the presence of *H. pylori* in the stomach and the potential false negatives, as per ESMO recommendations. However, the recurrence of lesions on the stomach and acute pain within 1 month after treatment ended, initially attributed to high-grade epithelial dysplasia aligning with ESMO guidelines, not excluding the possibility of *H. pylori* reinfection due to intra-family transmission in family dining settings. Also, it could not be ruled out the possibility that the child self-treated with PPIs initially, which is a common phenomenon in Vietnam, leading to incorrect CLO test results.

Pediatric MALT lymphomas respond well to a variety of therapies, and the prognosis is excellent [7]. However, we opted for radiotherapy after the failure of internal medicine treatment. Though either chemotherapy or radiotherapy is suggested as first-line anti-tumor treatment, the remission rate following radiotherapy was higher than that of chemotherapy (97.8% vs. 85.9%) and was similar to that of surgery. Moreover, radiotherapy preserves the stomach and its functions, without the possible long-term complications of gastric surgery, which include cancer risk on the remnant stomach [3].

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In another study, the superiority of radiation therapy was also demonstrated. For localized gastric lymphomas, exclusive RT in the case of failure of *H. pylori* eradication gives very good results with a complete remission rate of 96–100% for a median follow-up of between 1.3 and 4.1 years without long-term side effects. The local tumor control is excellent after exclusive RT with fewer than 5% of patients experiencing local relapse after treatment. Gastric RT is well tolerated with hardly any severe (G3+) acute or late toxicities. Some studies have reported only mild (G1-2) and transient acute gastro-intestinal toxicities [11]. And the relapses are rarely seen.

Conclusion

A comprehensive evaluation for staging is essential for the initial approach, including multiple biopsies taken, tests for HP, bone marrow involvement, endoscopic ultrasound, and whole body FDG PET/CT should be performed if possible. Tests for trisomy 3, BCL10 gene mutation, and/or t(11;18) translocation should be conducted if possible. *Helicobacter pylori* eradication therapy should be given to all patients with gastric MZL regardless of the detection of the pathogen. Radiotherapy is a preferred option over other managements for localized disease due to various advantages.

Statement of Ethics

The study was reviewed and approved by the Ethical Committee of the Hue Central Hospital (reference number 2260/BVH, dated October 18, 2023). Written informed consent was obtained from the parents of the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors were involved in the preparation of this manuscript. Dang A. collected the data and wrote the manuscript. Pham N.H., Phan C.D., Dang A., Chau V.H., Nguyen T.K.H., Nguyen T.M.L., Dang T.T., and Nguyen L.G. treated this patient. Pham N.H. and Tran K.H. made substantial contributions to the study design and revised the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding authors.

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