

MALT Lymphoma in Children: Case Report and Review of the Literature

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Received March 12, 2003; accepted October 3, 2003; published online July 15, 2004.

ABSTRACT

Mucosa-associated lymphoid tissue (MALT) lymphoma predominantly occurs in adults, and is rare in children. We report a case of MALT lymphoma involving minor salivary gland of the lip in an otherwise healthy 12-year-old boy. This is the second case report of MALT lymphoma of minor salivary gland in an immunocompetent child. Of 24 cases of MALT lymphomas in children reported in the English literature, parotid MALT lymphomas in human immunodeficiency virus (HIV) patients and *H. pylori* infection-associated gastric MALT lymphomas are the most common. As in adult cases, most MALT lymphomas in the pediatric age group are localized and follow an indolent clinical course, respond well to therapy, and have an excellent outcome.

Key words: *H. pylori* infection, HIV infection, MALT lymphoma

INTRODUCTION

Mucosa-associated lymphoid tissue (MALT) lymphoma, first described by Isaacson and Wright in 1983 [1], comprises 7–8% of all B-cell lymphomas [2]. The gastric MALT lymphoma is the most common and best studied. Other common sites are salivary gland, ocular adnexa, lung, thyroid, and

skin [3]. Most cases occur in adults with a median age of 60 and a slight female predominance [2]. Patients with certain autoimmune diseases, such as Sjögren syndrome or Hashimoto thyroiditis, and *Helicobacter pylori* (*H. pylori*) associated chronic gastritis, are at increased risk of developing MALT lymphoma. MALT lymphomas are exceedingly rare in children. We report an unusual case of MALT lymphoma involving minor salivary gland of the lip in an otherwise healthy 12-year-old boy. In reviewing the literature, we found this to be the second case report of MALT lymphoma of minor salivary gland in an immunocompetent child.

CASE REPORT

A 12-year-old Caucasian boy presented with a 6-month history of left lower lip mass. The patient had a history of a histologically confirmed mucocele removed from the site of the current lesion approximately 2 years previously. Lymphadenopathy, hepatosplenomegaly, and other abnormalities were absent on physical examination. Clinical and laboratory evaluation were negative for autoimmune disorders and infectious diseases. His past medical history was unremarkable. An excisional biopsy of

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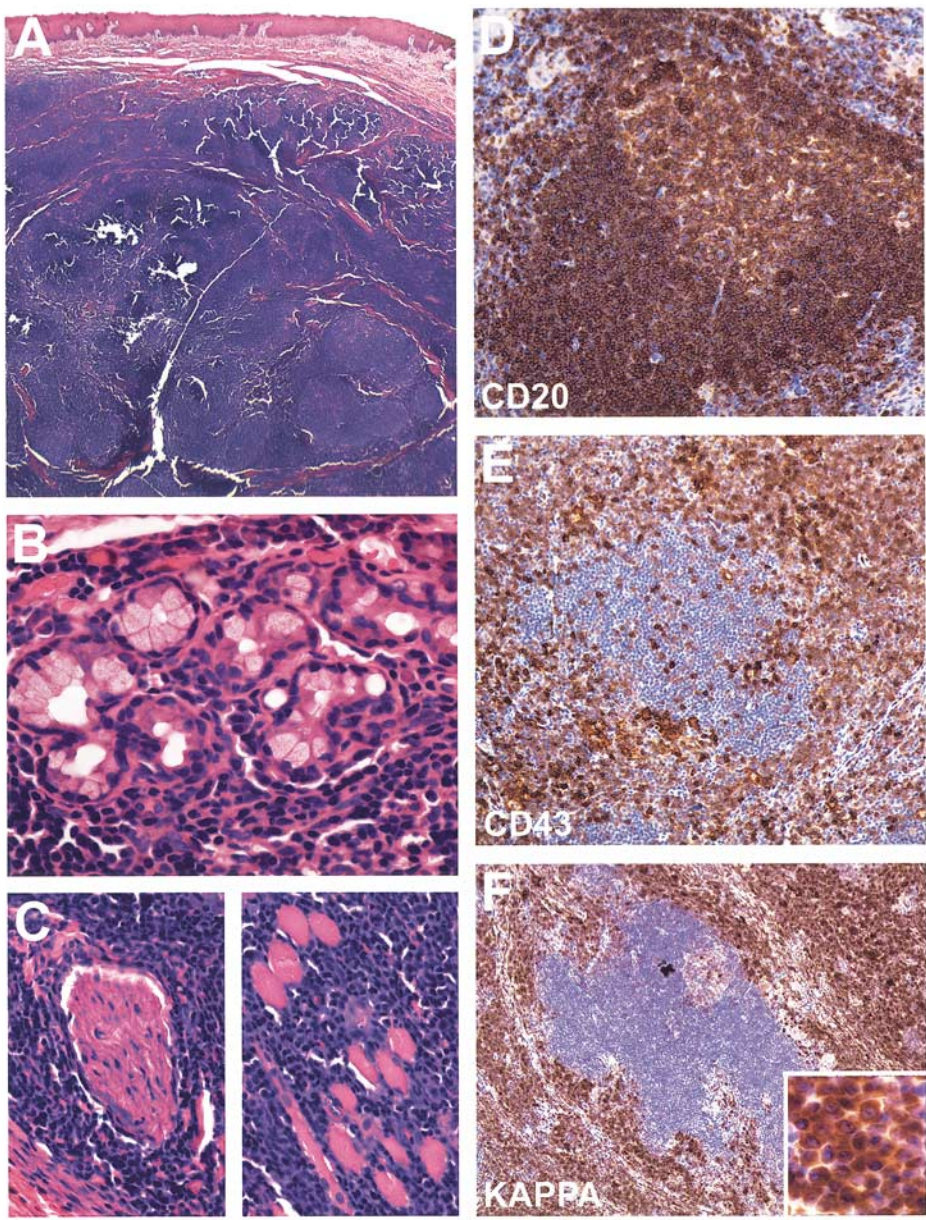


Figure 1. Mucosa-associated lymphoid tissue (MALT) lymphoma involving minor salivary gland of the lip. **A.** A vaguely nodular appearance in low-power view. **B.** Lymphocyte invasion of adjacent minor salivary gland. **C.** Perineural invasion (left) and skeletal muscle infiltrate (right). **D.** Tumor cells in marginal zone are positive for CD20 by immunohistochemical stain. **E.** Tumor cells in marginal zone are positive for CD43 by immunohistochemical stain. **F.** Tumor cells in marginal zone exhibit Kappa light chain restriction by immunohistochemical stain and a plasma cell/plasmacytoid appearance (**inset**). Original magnifications: A, $\times 5$; B, $\times 120$; C, $\times 100$; D, $\times 30$; E, $\times 20$; F, $\times 20$; inset, $\times 250$.

the lip mass was performed. Upper gastrointestinal endoscopic exam and histological evaluation were normal. Steiner staining performed on biopsy specimens of gastric and duodenal mucosa failed to reveal evidence of *H. pylori* infection. Whole body computed tomography (CT) and other imaging studies, as well as bone marrow biopsy, were also normal. Due to lack of a standard protocol for treatment of MALT lymphoma in pediatric patient, our patient was given six cycles of maintenance-type chemotherapy (cytotoxin, vincristine, methotrexate, and prednisone). The patient is well with no evidence of recurrence 1 year after excision.

The specimen was a $1.7 \times 1.0 \times 0.8$ -cm tan-gray soft nodule. Sections revealed unremarkable squamous epithelial mucosa, a small component of minor salivary gland, and a partially circumscribed submucosal mass composed of dense lymphocytes. The lymphocytes proliferated around variably well-defined germinal centers with a marginal zone and interfollicular distribution, creating a vaguely nodular growth pattern (Fig. 1A). Lymphocytes infiltrated an adjacent minor salivary gland (lymphoepithelial lesion, Fig. 1B) and skeletal muscle, and also showed perineural invasion (Fig. 1C). The “centrocyte-like” lymphocytes were

monomorphic, small to medium in size with moderate amounts of pale cytoplasm and slightly irregular nuclei with inconspicuous nucleoli, resembling germinal center centrocytes. Some of the nodules contained clusters of epithelioid histiocytes, which were also seen in other areas. Interspersed between nodules and follicles there were numerous plasma cells or plasmacytoid cells with relatively abundant, pale cytoplasm and eccentrically placed nuclei (Fig. 1F, inset). A few scattered large transformed cells were present. The cells surrounding germinal centers and between the nodular areas were CD20+ (Fig. 1D), CD43+ (Fig. 1E), CD79a+, CD5-, CD10-, and CD23- using immunohistochemical stains, and also demonstrated Kappa light chain class restriction by in situ hybridization (Fig. 1F). Based on these findings, this lip mass was interpreted as an extranodal marginal zone B-cell lymphoma of MALT with plasmacytic differentiation. There was no histological evidence of *H. pylori* infection and no viral inclusions or viral cytopathy in the specimen submitted.

DISCUSSION

Extranodal marginal zone B-cell lymphomas of MALT are defined as extranodal lymphomas composed of morphologically heterogeneous small B-cells and sometimes plasma cells growing in marginal zones and interfollicular areas [4]. MALT often may develop in the context of a preexisting inflammatory response due to infection or autoimmune disorder. Progression from reactive lymphoid tissue to MALT lymphoma is believed to depend on immune stimuli for clonal expansion. Current knowledge of MALT lymphoma is largely based upon studies in adults. MALT lymphoma is rare in children, consisting mostly of isolated case reports except for one series of 10 cases [5]. We summarize MALT lymphomas reported in children in Table 1 (only patients 18 years old or less, and papers published in English, are included).

Of the 24 tabulated cases, salivary glands and stomach were the most common sites; lung was much less common. The youngest patient was a 5-year-old boy. In common with adult MALT lymphomas, there was a slight female predominance. Except for case 6 and the case we present here, all others were associated with predisposing conditions. The details of morphologic features were

lacking in many cases, but were well described in other cases, and were similar to features in adult MALT lymphomas. Typically, the neoplastic lymphocytes infiltrated around the reactive follicles in a marginal zone distribution and expanded between follicles. Characteristic lymphoepithelial lesions are present. The tumor cells had a monocytoid appearance with abundant pale cytoplasm and often exhibited plasma cell differentiation. Available data indicated that the most common immunophenotype of pediatric MALT lymphomas is CD20+, CD79a+, CD5-, CD10-, CD23-, and CD43+ with light chain class restriction. As in adult cases, most MALT lymphomas in the pediatric age group were localized and had an indolent clinical course. Involvement of regional lymph nodes was rare, and bone marrow was uninvolved. Pediatric MALT lymphomas responded well to a variety of therapies, and the prognosis was excellent.

Thirteen MALT lymphomas occurred in the parotid region of patients with human immunodeficiency virus (HIV) infection [5-7], whereas two, including our case, arose in minor salivary glands (lip) of immunocompetent children [8]. Notably, nodal marginal zone B-cell lymphoma has been previously reported in two pediatric patients without immunodeficiency [9]. In 13 patients with HIV infection, parotid gland swelling, mostly bilateral, was the presenting manifestation of MALT lymphoma. In addition, two pulmonary MALT lymphomas occurred in HIV-infected children [10,11]. Because MALT lymphomas are part of the spectrum of neoplasms associated with HIV infection in children, immune deficiency/dysregulation following HIV infection is a major-risk factor for their development.

The etiology and pathogenesis of MALT lymphoma in HIV-infected children is currently obscure. Epstein-Barr virus (EBV), a common infection in HIV patients, has been implicated in the pathogenesis of many HIV-related high-grade lymphomas. Among the 15 MALT lymphomas in patients who were HIV-positive, only a few tumors were evaluated for EBV, and these were negative. In case 9, the EBV genome copy number was very high in bone marrow and peripheral blood, but was very low in the tumor [7]. This experience does not suggest a direct pathogenic role for EBV in

Table 1. Low-grade MALT lymphomas reported in children

Case no.	Reference	Age (years)	Sex	Clinical features/associated conditions	Site	Treatment	Outcome
1	Isaacson and Wright, 1984 [15]	18	M	Epigastric pain, ? <i>H. pylori</i> gastritis	Stomach	Total gastrectomy	Disease free, 3 months FU
2	Ashorn et al., 1994 [16]	11	M	<i>H. pylori</i> gastritis	Stomach	Antibiotics + chemotherapy	CR
3	Horstmann et al., 1994 [17]	16	F	<i>H. pylori</i> gastritis	Stomach	Antibiotics + chemotherapy + radiation therapy	CR with 3 months FU
4	Blecker et al., 1995 [18]	14	F	<i>H. pylori</i> gastritis	Stomach	Antibiotics only	CR with 7 years FU
5	Kurugoglu et al., 2002 [20]	11	F	<i>H. pylori</i> gastritis	Stomach	Antibiotics only	CR
6	Kurugoglu et al., 2002 [20]	5	M	Negative for <i>H. pylori</i> ; no predisposing factor	Stomach	Chemotherapy	CR with 10 months FU
7	Kurugoglu et al., 2002 [20]	16	M	<i>H. pylori</i> gastritis with perforation	Stomach	Total gastrectomy + chemotherapy	Disease free
8	Chetty, 1996 [6]	5	M	HIV(+), parotid swelling lymphadenopathy	Parotid	NA	NA
9	Joshi et al., 1997 [7]	9	F	HIV(+), parotid swelling lymphadenopathy	Parotid	Alpha-interferon	Partial (75%) response
10	Joshi et al., 1997 [7]	17	F	HIV(+), parotid swelling	Parotid	No specific therapy	6 months FU
11–20 ^a	Corr et al., 1997 [5]	1–8 ^b	NA	HIV(+), parotid swelling	Parotid	Single drug chemotherapy	CR
21	Teruya-Feldstein et al., 1995 [10]	7	F	HIV(+), lung mass	Lung	Resection	CR with 4 months FU
22	Teruya-Feldstein et al., 2001 [11]	15	M	HIV(+), lung mass	Lung	? Resection + chemotherapy	CR
23	Berrebi et al., 1998 [8]	10	M	<i>H. pylori</i> gastritis	Lip	Antibiotics only	CR with 1 year FU
24	Present case	12	M	History of mucocele	Lip	Excisional biopsy + chemotherapy	CR

MALT, mucosa-associated lymphoid tissue; HIV, human immunodeficiency virus; *H. pylori*, *Helicobacter pylori*; NA, not available; CR, complete remission; FU, follow-up.

^aA series of 10 cases.

^bPatients age range, 1 to 8 years old, with a mean years old.

MALT lymphoma in HIV-positive children, but EBV may play a role in the transformation of a MALT lymphoma to a high-grade diffuse large B-cell lymphoma. Tao et al. [12] reported a very atypical case of MALT lymphoma in a 9-year-old child with congenital endocrine disorders (not included in Table 1). The patient had MALT lymphomas involving the lungs, kidneys, and axillary lymph nodes. The tumor rapidly progressed to a "high-grade MALT lymphoma." EBV genome was demonstrated in both the low- and high-grade components of the lymphoma. In other circumstances, transformation from a low-grade to diffuse large B-cell lymphoma was not always associated with EBV [7], suggesting other possible mechanism of progression.

MALT lymphomas of salivary gland are more common in adult patients with Sjögren syndrome [13]. However, none of the 15 children with salivary gland MALT lymphomas had Sjögren syndrome, or other autoimmune disorders based on the information provided in the reports.

Lymphocytic interstitial pneumonia (LIP) is a frequent pulmonary complication of HIV-infected children [14]. In one case (case 21), the patient had concurrent LIP and pulmonary MALT lymphoma. Immunoglobulin heavy-chain gene rearrangement using polymerase chain reaction (PCR) on lung tissue with LIP revealed a band of increased intensity on a background of polyclonal ladder pattern; this band was identical in size to the monoclonal band in the concurrent MALT lymphoma specimen [11]. The author suggested that LIP might represent an early stage or a precursor lesion of pulmonary MALT lymphoma in children.

The stomach is a common site for MALT lymphomas in both adults and children. Of seven pediatric gastric MALT lymphomas [15–20], five cases were associated with *H. pylori* gastritis. The status of *H. pylori* infection in case 1 was unknown. Case 6 lacked evidence of *H. pylori* infection by morphological and serological studies. Due to the lack of experience in pediatric MALT lymphomas, treatment modalities were not uniform. Eradication of *H. pylori* by antibiotics alone led to complete remission in two patients (cases 4 and 5). In case 3, the gastric MALT lymphoma relapsed after initial antibiotic treatment, but eventually regressed with combination of chemotherapy and

radiation therapy. The disparities between treatment modalities did not affect the outcome of the tumor. All patients achieved complete resolution of the tumor or disease-free status clinically with a follow-up time varying from 3 months to 7 years.

In the adult, more than 90% of gastric MALT lymphomas are associated with *H. pylori* infection [21], and *H. pylori* eradication by antibiotic treatment alone leads to complete remission of approximately 30–80% of gastric MALT lymphomas [22,23]. Recent studies suggest that chromosomal translocation t (11; 18) (q21; q21) and nuclear bcl-10 expression are associated with failure to respond to antibiotic treatment in those patients [24–26]. Moreover, the frequency of both t (11; 18) (q21; q21) and nuclear bcl-10 expression is significantly higher in tumors that have disseminated beyond the stomach compared to those confined to the stomach [27]. To better understand the biologic behavior of gastric MALT lymphoma in children, cytogenetic study may be important.

One recently reported patient (case 23) [8] resembles our patient. A MALT lymphoma in the lip of an immunocompetent 10-year-old boy with gastric *H. pylori* infection dramatically regressed after treatment with antibiotics alone, despite the absence of *H. pylori* organisms in the biopsy of the lip mass. There has been no recurrence after 1 year of clinical follow-up. Following *H. pylori* eradication, regression of MALT lymphomas in parotid gland [28], small intestine [29,30], and rectum [31] have been reported. *H. pylori* organisms were found in the saliva in 75% of patients with gastric *H. pylori* infection in one study [32], supporting linkage of the stomach to the oral cavity by infection. In another report, a patient with gastric MALT lymphoma and Sjögren syndrome showed clonal identity between the gastric lymphoma cells and lymphocytes from salivary gland tissue, which did not contain lymphoma [33]. Despite those anecdotal reports, the concept that extragastric MALT lymphoma might be related to *H. pylori* infection remains controversial [34]. In our case, extensive work-up failed to reveal evidence of *H. pylori* infection.

Mucocele is a relatively common lesion of the lip in children. The resected specimen of mucocele in our patient showed a typical histology for mucocele. A few scattered small mature lymphocytes

were heterogeneous for T- and B-cell markers and failed to reveal light-chain restriction using immunohistochemical stains. No *H. pylori* infection was evident using the Steiner stain. The significance of the antecedent mucocele in the present case is unknown.

In summary, our case is the second example of MALT lymphoma in minor salivary gland in an immunocompetent child. Our patient had no evidence of known predisposing conditions but did have previous surgery at the site of the MALT lymphoma. We have reviewed MALT lymphomas reported in children with brief discussions of location, etiology, pathogenesis, clinical behavior, and prognosis. Because data in pediatric MALT lymphomas is scant, it is important to document, recognize, and further define this category of disease to determine optimal therapy, the relationship, if any, to infection with *H. pylori*, and the relationship to both MALT lymphoma in adults and to diffuse large B-cell lymphomas associated with MALT.

ACKNOWLEDGMENTS

We thank Jay Card and Chris Woods for their graphic technical support.

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