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Marginal Zone B-Cell Lymphoma in Children and Young Adults

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Abstract

We describe the clinicopathologic findings of 48 cases of marginal zone B-cell lymphoma (MZL) in children and young adults, a disease that has been recognized previously only rarely in this age group. Patients ranged in age from 2 to 29 years, with pediatric patients (< 18 years) comprising 52% of the cases. As in adults, both primary nodal (N) and extranodal (E) MZL were observed. However, primary NMZL comprised the majority of the cases (67%) and demonstrated distinctive clinical and histologic features. NMZL occurred most commonly in young males (median 16 years, male/female ratio 5.4:1), with no underlying disease, presenting as localized adenopathy (90% stage I), with excellent prognosis and low rate of recurrence. In contrast, EMZL were much less common, and patients were older (median 24.5 years), with only a slight male predominance (male/female ratio 1.2:1). Most patients had localized disease (73% stage I) with excellent prognosis and infrequent recurrences. In addition, an association with autoimmune disease was observed in 19% of the EMZL. Both primary NMZL and EMZL in young patients shared similar morphologic and immunophenotypic findings to those described in adults and were monoclonal B-cell proliferations with monoclonality demonstrated in 94% of the cases. A common morphologic feature in NMZL was disruption of residual follicles resembling progressive transformation of germinal centers (PTGC), observed in 66% of the cases. Although the precise relationship of primary NMZL and the PTGC-like changes is unclear, it is possible that NMZL arises in a background of PTGC, as florid PTGC often occurs in young males. We conclude that EMZL in children and young adults are similar to EMZL of mucosa-associated lymphoma tissue occurring in older patients. However, pediatric NMZL appear to have distinctive clinical and histologic features.

Keywords

Pediatric lymphoma; Marginal zone B-cell lymphoma; Extranodal MALT lymphoma; B-cell lymphoma; Autoimmune disease

Nodal (N) and extranodal (E) marginal zone lymphomas (MZL) are closely related forms of B-cell neoplasia thought to be derived from postgerminal center memory B cells.^{10,18,20} They occur in older patients with a median age at presentation ranging from 55 to 65 years, with females affected more commonly than males.^{1,4,23} EMZL is a well-established disease entity.¹³ The incidence is more than fourfold greater than primary NMZL.¹ The stomach is the most frequent site of involvement, followed by salivary glands, orbit, and lung.^{9,14} An association with autoimmune disease, including Sjogren's syndrome and more rarely systemic lupus erythematosus, has been shown in up to 30% of the patients.²³ EMZL tend to present as localized disease and have a good prognosis. Primary NMZL are much less common and, by definition, should be diagnosed in the absence of known extranodal disease.¹⁵ In 30-50% of patients with MZL involving lymph nodes, extranodal disease consistent with mucosa-associated lymphoma tissue (MALT) lymphoma is identified, sometimes many years before lymph node involvement, indicative of secondary spread.^{3,4,24} Some studies of primary NMZL have reported a high incidence of advanced-stage disease with generalized lymphadenopathy and bone marrow involvement.^{2,8,22}

Both NMZL and EMZL are extremely rare in children and young adults. There have been isolated reports of MALT lymphoma in pediatric patients with human immunodeficiency virus infection.^{16,30} In 1997 we identified two cases of NMZL in children without evidence of immunodeficiency.⁵ However, the true incidence of these lymphomas in young patients is not known, and there are few, if any, data regarding their clinicopathologic characteristics. We now report our experience with 48 cases of NMZL and EMZL in children and young adults, to define the clinicopathologic spectrum, diagnostic features, and similarities and differences with MZL in older adults.

MATERIALS AND METHODS

Case Selection and Clinical Data

The cases in this study were retrieved from the files of the Hematopathology Section of the Laboratory of Pathology, National Cancer Institute, National Institutes of Health from January 1995 to April 2002 based on a diagnosis of MZL and age <30 years at presentation. All cases were submitted in consultation from outside physicians. The hematoxylin and eosin-stained slides of both NMZL and EMZL were reviewed in 48 patients. Five of the cases (nodal case nos. 2-5 and extranodal case no. 6) were previously reported.^{3,5,31} Clinical data were obtained from referring clinicians. In particular, we solicited information regarding the extent of disease at presentation, presence or absence of bone marrow involvement, prior history of autoimmune disease or other immune disorder, and flow cytometry studies. We also obtained data regarding treatment instituted, clinical follow-up, and survival.

In addition, we retrospectively reviewed the hematoxylin and eosin and immunohistochemical stained slides of 16 cases of progressive transformation of germinal centers (PTGC) in pediatric and young adult patients diagnosed at our institution from 1999 to 2000 to identify distinguishing features of PTGC and NMZL.

Immunophenotypic and In Situ Hybridization Studies

Immunohistochemical studies were performed on fixed, paraffin-embedded tissue sections by use of antigen retrieval methods on an automated immunostainer (Ventana Medical System, Tucson, AZ, USA), according to the manufacturer's instruction as previously described.²⁸ The antibody panel included L26 (CD20), CD3, kappa, lambda, IgD, Bcl-2, Bcl-6, and p53 (Dako, Carpinteria, CA, USA), CD5 and CD10 (Novocastra, Newcastle upon Tyne, UK), MIB-1 (Coulter Immunology, Hialeah, FL, USA), and CD43 (Becton Dickinson, San Jose, CA, USA). MIB-1-positive nuclear stain was scored on a scale of 1 to 4 and interpreted as follows: low proliferative rate, <25% of the cells positive (1+/4); moderate, 25-50% positive (2+/4); moderate to high, 50-75% positive (3+/4); and high, >75% positive (4+/4). In 22 cases, flow cytometry data were obtained from the submitting institution.

In situ hybridization studies for Epstein-Barr virus were performed in a limited number of cases. In six cases the studies were performed at our institution on fixed paraffin-embedded sections using previously described methods.¹⁷ In two cases we reviewed the studies performed by the submitting institution.

Molecular Studies

In 43 cases genomic DNA was extracted from formalin-fixed, paraffin-embedded tissue blocks. In some cases DNA was extracted using standard phenol chloroform methods, whereas in other cases tissue samples were sectioned on charged slides, deparaffinized with xylene, and hydrated before being scraped into polymerase chain reaction (PCR) tubes with a single edge razor blade. The tissues were mixed with Gene Releaser resin (Bioventures, Murfreesboro, TN, USA) and preincubated in a Perkin Elmer 480 thermocycler (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's recommendations. To determine clonality of the immunoglobulin heavy chain (IgH) gene, PCR was performed as previously described.⁵ Briefly, consensus primers to the conserved framework three (FR3) and the JH alpha regions of the IgH gene were used in a Master Mix containing LD Taq DNA polymerase (Applied Biosystems) previously treated with Taq Start antibody (Clontech, Palo Alto, CA, USA). Additional seminested PCR amplification was performed using consensus primers to the conserved framework two (FR2) region of the IgH gene, according to the method of Ramasamy et al.²⁹ PCR products were analyzed using polyacrylamide gel electrophoresis as previously described.⁵

RESULTS

Clinical

Nodal Marginal Zone Lymphoma—Sixty-seven percent (32 of 48) of the patients were classified as primary NMZL (Table 1). The age range was 2-27 years (median 16 years); pediatric patients 18 years of age or younger comprised 66% (21 of 32) of the cases. There was a striking male predominance with a male/female ratio of 5.4:1. In the pediatric age group the male/female ratio was 20:1. Most patients presented with asymptomatic, isolated, peripheral adenopathy, ranging in duration from a few weeks to 2 years. Eighty-eight percent (28 of 32) had involvement of the head and neck region, with cervical lymph nodes being the most common site of involvement (50%, 16 of 32). None of the patients had any

evidence of immunodeficiency or underlying disease, and no patient manifested extranodal sites of involvement. Bone marrow examination was performed in 19 cases and was negative in all. Only one patient (case no. 8) had stage III disease with diffuse adenopathy involving supraclavicular, axillary, and mesenteric lymph nodes by computerized axial tomography scan. However, treatment and follow-up information were not available for this patient.

Clinical management consisted of excision and close follow-up in 68% (19 of 28), local radiation in 18% (5 of 28), and chemotherapy in 11% (3 of 28) of the cases, whereas one patient received combined radiation and chemotherapy. There was no evidence of recurrence, regardless of treatment modality, in the vast majority of the patients with follow-up ranging from 1 months to 5 years (median 6 months). One patient (case no. 2), who was initially treated with antibiotics and excision, recurred at the same site 1 year after excision. He was subsequently treated with chemotherapy and has no evidence of recurrence with a 4-year follow-up. Another patient (case no. 7) had recurrent adenopathy at the same site 1 year after excision. However, morphologically the recurrent node was felt to be atypical, with no definitive histologic evidence of lymphoma.

Extranodal Marginal Zone Lymphoma—Thirty-three percent (16 of 48) of the patients were diagnosed as EMZL (Table 2). The age range was 9-29 years (median 24.5 years); pediatric cases comprised 25% (4 of 16) of the cases. The male/female ratio was 1.2:1 with an equal number of males and females in patients 18 years of age and younger. Most patients presented with an asymptomatic mass most commonly involving the ocular adnexa (31%, 5 of 16), salivary glands (25%, 4 of 16), and skin (19%, 3 of 16). Only one patient had gastric involvement. Most patients had no evidence of any underlying disease. However, three of the patients with salivary gland involvement (two females and one male) had a history of autoimmune disease: Sjogren's syndrome in two (case nos. 3 and 16) and systemic lupus erythematosus in the other (case no. 7). In addition, the single patient with gastric MALT lymphoma (case no. 14) had a history of *Helicobacter pylori* gastritis and gastric ulcers that were refractory to antibiotic treatment. Seventy-three percent of evaluable patients had stage I disease. Concomitant regional lymph node involvement was present in two cases, but dissemination to other nodal or extranodal sites was not observed. Bone marrow examination was performed in five cases, and all were reported negative.

Fifty-six percent (5 of 9) of the patients were treated with local radiation, 22% (2 of 9) were managed with excision and close follow-up, and 22% (2 of 9) received chemotherapy. Most patients had no evidence of recurrence with follow-up ranging from 1 to 24 months (median 3 months). One patient (case no. 2) had a large conjunctival mass (Fig. 1) that was excised and recurred rapidly, but no further information was available as the patient was lost to follow-up. Another patient (case no. 13), on whom we made a diagnosis of EMZL on a skin biopsy, was reported to have a prior lesion excised at the same site, but neither that material nor the histologic diagnosis was available for review. The patient subsequently received local radiation without evidence of recurrence posttherapy.

The pertinent clinical findings with a comparison between NMZL and EMZL are summarized in Table 3 and highlight the differences and similarities between these two entities.

Morphologic Features

In NMZL the lymph node architecture was partially to totally effaced with obliteration of the sinuses. The atypical cells showed a predominantly interfollicular distribution with marked expansion of the marginal zones (Fig. 2A). The infiltrate was composed of a polymorphic population of small- to medium-sized cells, with some cells having round nuclear contours and moderate cytoplasm, whereas others were centrocyte-like with scant cytoplasm and irregular nuclei (Fig. 2B). Scattered plasma cells and larger transformed cells were usually present, although blast cells were few in number, no more than 2-3 per high power field. Occasionally, the number of larger cells was increased but they did not form sheets.

In 66% (21 of 32) of the cases, the majority of the follicles showed features resembling PTGC. The follicles were increased in diameter with marked expansion of marginal zones. As is typical of PTGC, the mantle cells often infiltrated the remaining germinal center, leading to fragmentation (Fig. 2D). However, in these cases, in contrast to typical PTGC, the peripheral rim of the follicle was irregular and disrupted by the atypical proliferation in the marginal zone. The mantle was often difficult to discern in the absence of immunohistochemical stains and was highlighted by IgD staining (Fig. 2E). In other areas of the lymph node, scattered residual reactive follicles were present with preserved mantle zones. In a few cases (4 of 32), the mantle was greatly attenuated and focally absent, and the atypical cells in the marginal zone blended with the residual germinal centers, imparting a vaguely nodular growth appearance on low power (Fig. 2C). In one case the growth pattern was frankly nodular mimicking follicular lymphoma. However, the nodules were composed of a proliferation of monocytoid cells and showed evidence of follicular colonization. The existence of follicular colonization in these cases was confirmed by germinal center cell markers that were positive only in the small residual germinal centers while the infiltrating tumor cells were negative. Moreover, intra- follicular light chain restricted cells similar to those seen in the interfollicular areas highlighted the follicular colonization.

In extranodal MZL the relevant site contained a dense lymphoid infiltrate composed of broad sheets of mono- cytoid cells and or centrocyte-like cells with glandular destruction and architectural distortion. Extension into adjacent soft tissue structures was seen. As in nodal MZL, residual reactive follicles were usually seen. However, PTGC-like changes of follicles were seen in only 2 of 16 cases (12.5%), involving the parotid and lacrimal glands (case nos. 5 and 7). Lymphoepithelial lesions were most prominent in the salivary gland (Fig. 3A) but also identified in thyroid and stomach. The skin contained dense dermal perivascular and periadnexal lymphoid infiltrates, with extension into the subcutaneous tissue but sparing of the epidermis. In two cases with regional node involvement, lymph nodes showed partial effacement of the architecture with numerous clusters of intrasinusoidal and perifollicular monocytoid B cells (Fig. 3B, C). In comparison with NMZL, plasmacytic differentiation (Fig. 3D) was more conspicuous, and clusters of monocytoid cells were usually present.

Immunophenotypic Features

The immunohistochemical findings were similar in both NMZL and EMZL (Table 4). The neoplastic cells had a B-cell phenotype positive for CD20 (Fig. 2F) with CD43 coexpression

observed in 70% (30 of 43) of the cases. Immunoglobulin light chain restriction, detectable by paraffin section immunohistochemistry (Fig. 3F), was present in 48% (22 of 46) of the cases. IgD positivity, ranging from weak to moderate in intensity, was present in the neoplastic cells in 24% (8 of 33). In addition, IgD highlighted the PTGC-like changes and the fragmented remnants of the mantle zones. Bcl-2 was positive in 42% (13 of 31) and was weak to moderate in intensity of staining, whereas in the remaining cases, it was either clearly negative or difficult to interpret because of numerous admixed CD3-positive T cells. CD10 and Bcl-6 were negative in the tumor cells but highlighted residual germinal centers, which showed negative staining for Bcl-2. Only one case of NMZL showed positive staining for CD10 in interfollicular B cells. However, the cells were negative for Bcl-6, which highlighted only the residual Bcl-2-negative germinal centers. In the majority of the cases, the proliferative rate, with MIB-1 staining, was low in the interfollicular areas, whereas the residual germinal centers showed a high proliferative rate. In all cases tested, the neoplastic cells were negative for CD3, CD5, CD23, and p53.

Information from flow cytometry studies was available in 22 cases of which 59% (13 of 22) showed a monoclonal B-cell population. Five cases had identical light chain restriction by flow and immunohistochemistry, whereas the other eight cases were noncontributory by immunohistochemistry. In situ hybridization studies for Epstein-Barr virus were negative in all eight cases tested with adequate controls.

Molecular Studies and Clinical Correlations

Monoclonal IgH gene rearrangement was identified in 84% (36 of 43) of the cases. A dominant clonal band was identified by IgH FR3 and FR2 PCR performed at our institution in 72% (31 of 43) of the cases. VJ-PCR was positive in one additional case as determined by the referring laboratory. Four cases were reported to be positive by Southern blot hybridization by the referring institution (data not shown). In one patient with gastric EMZL (case no. 14), bands of identical molecular weight were detected from three separate gastric biopsies taken 1 month apart (Fig. 4). In 50% (21 of 42) of the cases monoclonality was demonstrated only by molecular studies with immunohistochemical stains for light chains being noncontributory. In contrast, only 9.5% (4 of 42) of the cases showed light chain restriction by immunohistochemistry without demonstrable monoclonality by molecular analysis. In one case material was not available for molecular or immunophenotypic studies.

In three cases monoclonality could not be demonstrated by either immunohistochemistry or PCR. The PCR technique used in our laboratory has an overall false-negative rate of 30%; therefore, a negative result does not rule out a clonal process.²⁹ All three cases that could not be proven to be monoclonal by immunophenotypic or molecular studies had evidence of lymphoma by other clinical or pathologic criteria. Nodal case no. 9 presented with a tonsillar mass that showed extensive infiltration by a CD43-positive B-cell population that expanded and replaced the marginal zone. The patient was treated with chemotherapy and did not develop recurrent disease. Nodal case no. 21 also exhibited immunophenotypic abnormalities suggestive of lymphoma. The atypical cells greatly expanded the marginal zone, leaving small residual germinal centers, and were CD10 positive but BCL-6 negative. The residual diminutive germinal centers were BCL-2 negative but BCL-6 positive.

Extranodal case no. 2 exhibited a large conjunctival mass that recurred after original resection (Fig 1). The neoplastic B cells coexpressed CD43 and IgD. The patient was subsequently treated with radiation therapy.

PTGC

Sixteen cases of PTGC were reviewed with an age range of 3-22 years (median 15 years). The male/female ratio was 4:1. These lymph nodes showed changes of reactive lymphadenopathy with scattered, well- circumscribed follicles of PTGC in a background of well-preserved cortical and paracortical areas. Two cases showed a focal increase in interfollicular B cells, but there was no evidence of monotypic light chain expression or CD43 coexpression. IgH PCR was negative in all cases studied.

DISCUSSION

We identified 48 cases of NMZL and EMZL occurring in children and young adults. In contrast to MZL in adults, primary NMZL were more common than EMZL, representing 67% of the cases in our study. These incidence figures contrast with the more than fourfold greater prevalence of EMZL over NMZL in adults.¹ The clinical features of NMZL also contrasted with those of EMZL. The patients were younger (median age 16 years) than patients with EMZL (median age 24.5 years). NMZL also showed a striking male predominance (5.4:1), especially in children 18 years of age and younger (20:1).

The most common presentation of NMZL was asymptomatic lymphadenopathy involving head and neck region, most commonly cervical nodes. The majority of the patients had localized stage I disease and showed a low rate of recurrence after conservative treatment. This clinical behavior contrasts with NMZL in adults, which show a slight female predominance and more often present with advanced stage disease, propensity for bone marrow involvement, and shorter survival.²²

NMZL also manifested distinctive histologic features. Sixty-six percent of the cases were associated with PTGC-like changes involving residual germinal centers. PTGC is seen in approximately 10% of lymph nodes showing marked reactive follicular hyperplasia and may be diagnosed in pediatric patients presenting with solitary asymptomatic cervical adenopathy. Like NMZL, florid PTGC occurs commonly in young males,^{6,25} whereas sporadic isolated PTGC occurs in many clinical settings.¹¹ However, both in the cases analyzed in our study and in the literature, uncomplicated PTGC is a reactive polyclonal proliferation without immunophenotypic aberration. We think it is possible that NMZL arose in a background of PTGC in our patients or that the infiltrating marginal zone cells disrupt the residual follicles in a manner similar to PTGC. It is unclear whether children with PTGC are at an increased risk of developing NMZL, and the true incidence of NMZL in young patients is not known. Although an association between PTGC and nodular lymphocyte predominant Hodgkin's lymphoma also has been shown,^{11,27} PTGC occurs in most pediatric patients without antecedent or subsequent evidence of NLPHL.^{6,25}

Histologic, immunophenotypic, and molecular features help discriminate NMZL with PTGC-like changes from uncomplicated PTGC. Features that favor NMZL over a reactive

process include expansion of the inter-follicular region and destruction of follicular structures, at least focally. Immunophenotypically, all cases showed an increase in interfollicular B cells. Monoclonality was demonstrated by paraffin section immunohistochemistry and/or IgH gene rearrangement studies in 94% of nodal and 94% of all cases studied. In 50% of these cases, monoclonality was demonstrated by molecular means but not by immunohistochemistry, whereas the reverse was true in only 9.5% of the cases, highlighting the diagnostic importance of gene rearrangement analysis. In the three cases in which immunohistochemical and molecular studies failed to reveal monoclonality, an aberrant immunophenotype with coexpression of CD43 or CD10 by the B cells was helpful in establishing the diagnosis. These immunophenotypic and molecular features contrast with those reported in atypical reactive hyperplasia with marginal zone expansion. In the study from Hunt et al., only one case showed a clonal Ig gene rearrangement, and this single patient subsequently was diagnosed with MZL.¹²

IgD positivity, which had been previously reported in adult nodal MZL,³ was uncommonly expressed (24% of cases). It was seen with equal frequency in NMZL and EMZL cases, but positive cases did not demonstrate distinctive clinical or morphologic features. In particular, none of the MZL encountered in children or young adults resembled splenic MZL. Splenic MZL is consistently positive for IgD, a feature that highlights its distinction from other B-cell lymphomas in the marginal zone family.

The differential diagnosis of NMZL includes other low-grade B-cell lymphomas, especially follicular lymphomas with marginal zone differentiation.²¹ Follicular lymphoma is extremely rare in the pediatric age group, and most cases are of high histologic grade. Interestingly, follicular lymphomas in young patients are also more common in males, present with localized disease, with a predilection for head and neck sites and show good response to therapy.^{7,26} The presence of follicular colonization and nodular growth pattern in NMZL may simulate follicular lymphoma. However, marginal zone differentiation in pediatric follicular lymphoma has not been described. Follicular colonization was seen in eight cases in our study. Immunophenotypic studies are very useful in this differential diagnosis. NMZL lack the germinal center-associated markers Bcl-6 and CD10, and coexpression of CD43 is not a feature of follicular lymphoma. In our study only one case of NMZL was positive for CD10, but the cells were negative for Bcl-6. Moreover, CD10 expression has been reported rarely in MZL in previous studies.¹⁹ Bcl-2 protein may be expressed in NMZL but is generally weak. Bcl-2 protein is positive in most small B-cell lymphomas, including chronic lymphocytic leukemia and mantle cell lymphoma. As such, this marker is generally not useful in further subclassification of small B-cell malignancies.

In contrast with NMZL, cases of EMZL closely resembled MALT lymphomas occurring in the older adult population. The median age in our series was 24.5 years, with only a slight male predominance. Most patients presented with localized disease without predisposing risk factors. Salivary gland involvement and association with autoimmune disease were seen in three patients (19%), two of whom were women. However, an association with *Helicobacter pylori* was rarely identified; we encountered only a single case of gastric MALT lymphoma diagnosed in a 23-year-old man. EMZL had previously been reported in pediatric patients with human immunodeficiency virus infection.³⁰ However, none of the

patients in our study had evidence of immunodeficiency, and we did not include patients reported in our earlier study of human immunodeficiency virus-associated MALT lymphoma. Histologically, EMZL in children and young adults were indistinguishable from those in older individuals and were characterized by frequent lymphoepithelial lesions, monocytoid B cells, and plasmacytic differentiation.

Our study has shown the occurrence of both NMZL and EMZL in children and young adults. Because low-grade B-cell lymphomas are rare in this age group, it is important for pathologists and clinicians to be aware of these cases. Indeed, based on the large number of cases (n = 48) diagnosed over a <10-year period, these cases are not rare. Nevertheless, it is likely that selection bias has occurred. Nearly all cases were referred in consultation, perhaps based in part on our prior publications on this subject. For patients presenting with localized stage I disease, we recommend a conservative management approach, as relapse or progression was rarely encountered. Nevertheless, the follow-up period in our study was relatively short, and long-term follow-up is necessary to determine whether these lymphomas recur later in life.

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FIG. 1. Clinical manifestations of extranodal marginal zone lymphoma (EMZL) in a 22-year-old man with enlarging conjunctival mass of 6 months' duration that was excised but recurred rapidly (case no. 2).

FIG. 2.

Histologic and immunophenotypic features of nodal marginal zone lymphoma (NMZL). **(A)** Lymph node showing partial architectural effacement by marginal zone expansion. Residual follicles are present with small germinal centers and preserved mantle zones. **(B)** The cells are composed of a polymorphic population of centrocyte-like cells, plasma cells, and scattered larger cells. **(C)** Hyperplastic follicles with attenuated to absent mantle zones blend imperceptibly with expanded marginal zones. **(D)** Expanded residual follicles showing PTGC-like changes. **(E)** IgD immunohistochemical stain highlights disrupted mantle zones

resembling PTGC. (F) Immunohistochemical stain with CD20 stains residual follicles and sheets of B cells in the interfollicular areas (E and F, ABC immunoperoxidase, hematoxylin counterstain).

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FIG. 3.

Histologic and immunophenotypic features of extranodal marginal zone lymphoma (EMZL).

(A) Section of parotid gland showing lymphoepithelial lesion. The epithelium is infiltrated by monocytoid cells. (B) Secondary lymph node involvement by EMZL with multiple clusters of monocytoid cells within dilated sinusoids. (C) The monocytoid cells are composed of medium-sized cells with abundant cytoplasm and indented nuclei. (D) Section of orbital mass with expansion of the marginal zone and infiltration into muscle. The cells show marked plasmacytic differentiation (inset). (E) CD20 highlights a residual germinal

center with the plasmacytoid cells showing light chain restriction with lambda stain (**F**) (**E** and **F**, ABC immunoperoxidase, hematoxylin counterstain).

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FIG. 4. Polyacrylamide gel electrophoresis of FR3-IgH PCR showing three bands of similar molecular weight in three separate biopsies of the gastric EMZL (case no. 14). P, patient; MW, molecular weight.

TABLE 1.
Nodal marginal zone lymphoma (NMZL) in children and young adults: clinical characteristics and clonality

Case no.	Age (y)/sex	Biopsy site lymph node	Stage	Flow	Clonality			Treatment	DFS (mo)
					IHC	Mol			
1	22/M	Cervical	I	NA	ND	ND	CT	CT	24
2 [†]	6/M	Cervical	I	Clonal	NC	Clonal	CT	CT	48
3 [*]	18/M	Submandibular	I	Poly	NC	Clonal	RT	RT	60
4 [*]	15/M	Submandibular	I	NA	NC	Clonal	Excision	Excision	36
5 [*]	23/F	Cervical	I	Poly	NC	Clonal	RT	RT	30
6	16/M	Cervical	I	NA	L	Clonal	RT	RT	24
7	15/M	Inguinal	I	NA	K	Clonal	CT + RT	CT + RT	12
8	23/M	Multiple	III	NA	L	Clonal	NA	NA	NA
9	12/M	Tonsil	I	NA	NC	Poly	CT	CT	12
10	24/F	Inguinal	II	NA	K	Clonal	Excision	Excision	15
11	17/M	Chest	I	NA	K	Clonal	Excision	Excision	12
12	14/M	Periparotid	NA	NA	NC	Clonal	Excision	Excision	9
13	16/M	Cervical	NA	NA	NC	Clonal	NA	NA	NA
14	16/M	Cervical	I	NA	K	Clonal	Excision	Excision	3
15	16/M	Periparotid	I	Equi	K	Clonal	Excision	Excision	4
16	6/M	Cervical	I	Clonal	NC	Clonal	Excision	Excision	3
17	16/M	Cervical	I	Clonal	NC	Clonal	RT	RT	2
18	14/M	Cervical	I	NA	NC	Clonal	Excision	Excision	5
19	25/M	Submental	I	Clonal	K	Poly	RT	RT	6
20	16/M	Periparotid	I	Poly	K	Clonal	Excision	Excision	2
21	26/F	Cervical	I	Poly	NC	Poly	Excision	Excision	9
22	17/M	Submental	I	NA	NC	Clonal	Excision	Excision	12
23	22/M	Cervical	I	Poly	NC	Clonal	Excision	Excision	6
24	12/M	Cervical	I	NA	NC	Clonal	NA	NA	NA
25	27/M	Cervical	II	Poly	L	ND	Excision	Excision	1
26	26/F	Breast	NA	NA	K	Clonal	NA	NA	NA

Case no.	Age (y)/sex	Biopsy site lymph node	Stage	Flow	Clonality		Treatment	DFS (mo)
					IHC	Mol		
27	16/M	Cervical	I	Clonal	L	Clonal	NA	NA
28	14/M	Cervical	I	Clonal	NC	Clonal	NA	NA
29	20/M	Pre-auricular	I	Clonal	NC	Clonal	Excision	3
30	19/M	Cervical	I	Clonal	K	Clonal	Excision	3
31	8/F	Adenoid	I	NA	L	ND	Excision	2
32	2/M	Tonsil	I	Clonal	L	Poly	Excision	5

* Cases previously published.

[†] Recurred 1 year after excision, no recurrence after CT.

Flow, flow cytometry; IHC, immunohistochemistry; Mol, molecular; NA, not available; ND, not done; NC, noncontributory; Poly, polyclonal; Equi, equivocal; RT, radiation therapy; CT, chemotherapy; DFS, disease-free survival.

TABLE 2.
Extranodal marginal zone lymphoma (EMZL) in children and young adults: clinical characteristics and clonality

Case no.	Age (y)/sex	Biopsy site	Stage	Flow	Clonality			DFS (mo)
					IHC	Mol	Treatment	
1	23/M	Cheek	I	Clonal	K	Clonal	RT	12
2 [†]	22/M	Conjunctiva	I	NA	NC	Poly	NA	NA
3 [*]	17/F	Submandibular	II	Clonal	NC	Clonal	Excision	12
4	29/F	Parotid	III	Poly	K	Clonal	NA	NA
5	10/M	Lacrimal	I	Clonal	NC	Clonal	CT	2
6 [‡]	25/F	Larynx	I	NA	ND	Clonal	RT	24
7 [*]	28/F	Parotid	II	NA	NC	Clonal	RT	7
8	25/M	Orbital	I	Poly	L	ND	RT	1
9	24/F	Skin	NA	NA	NC	Clonal	NA	NA
10	27/F	Skin	I	NA	K	Poly	Excision	1
11	25/M	Thyroid	NA	Clonal	NC	Clonal	NA	NA
12	9/F	Orbital	I	NA	NC	Clonal	NA	NA
13	29/M	Skin	I	NA	K	ND	RT	3
14	23/M	Gastric	NA	NA	NC	Clonal	CT	1
15	18/M	Orbital	NA	NA	L	Equi	NA	NA
16 [*]	29/M	Parotid	NA	NA	K	Clonal	NA	NA

^{*}Patients with history of autoimmune disease.

[†]Recurred 1 month after excision, lost to follow up.

[‡]Case previously published.

Flow, flow cytometry; IHC, immunohistochemistry; Mol, molecular; NA, not available; NC, not contributory; ND, not done; Equi, equivocal; RT, radiation therapy; CT, chemotherapy; DFS, disease-free survival.

TABLE 3.

Summary and comparison of clinical characteristics of nodal marginal zone lymphoma (NMZL) and extranodal marginal zone lymphoma (EMZL) in children and young adults

	NMZL	EMZL
Incidence	67% (32/48)	33% (16/48)
Median age	16 (2-27)	25 (9-29)
Cases < 18 yrs	66% (21/32)	25% (4/16)
Overall M:F	5.4:1	1.2:1
M:F < 18 yrs	20:1	1:1
Common site	Cervical	Ocular adnexa
Autoimmune disease	None	19% (3/16)
Monoclonality *	94% (29/31)	94% (15/16)
Stage I	90% (26/29)	73% (8/11)
Excision	68% (5/28)	22% (2/9)
Local radiation	18% (5/28)	56% (5/9)
Chemotherapy	11% (3/28)	22% (2/9)
Median follow up	6 months (1 –60)	3 months (1-24)

* Light chain restriction by immunohistochemistry and/or immunoglobulin heavy chain gene rearrangement by PCR.

TABLE 4.

Immunohistochemical findings of NMZL and EMZL in children and young adults

	n-MZL	e-MZL	Total
CD20	97% (30/31)	94% (15/16)	96% (45/47)
CD3	0% (0/31)	0% (0/16)	0% (0/47)
CD5	0% (0/24)	0% (0/10)	0% (0/34)
CD10	4% (1/26)	0% (0/10)	3% (1/36)
CD43	70% (21/30)	69% (9/13)	70% (30/43)
Mono Ig	48% (15/31)	47% (7/15)	48% (22/46)
IgD	26% (6/23)	20% (2/10)	24% (8/33)
BCL2	43% (9/21)	40% (4/10)	42% (13/31)
BCL6	0% (0/20)	0% (0/9)	0% (0/29)