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Pulmonary Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue Associated with Granulomatous Inflammation in a Child with Chromosome 22q11.2 Deletion Syndrome (DiGeorge Syndrome)

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Abstract

Patients with immunodeficiency disorders have an increased incidence of lymphoproliferative disorders; however, only 4 such patients with DiGeorge/chromosome 22q11.2 deletion syndrome have been reported. We report a case of a pulmonary Epstein-Barr virus–negative extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in a child with this syndrome.

The patient is a 15-year-old female with chromosome 22q11.2 deletion/DiGeorge syndrome diagnosed at age 9 years, documented by cytogenetic fluorescence in situ hybridization studies. She has cardiovascular defects with congenital ventricular septal defect, patent ductus arteriosus, and right-sided aortic arch, hypoparathyroidism, subtle dysmorphic facial features, immunodeficiency (including low peripheral $CD4^+$ T cell count, hypogammaglobulinemia, frequent recurrent pneumonias and other infections), and Evan syndrome diagnosed at the age of 3 years. She also has chronic eczema and lichen planus. Currently, she is maintained on amoxicillin and weekly to monthly gamma globulin.

Approximately 2 years ago, the patient presented with fever, chronic cough, and progressive respiratory symptoms. Chest radiograph revealed lung consolidation thought to represent pneumonia. Antibiotic therapy produced some improvement; however, follow-up chest radiograph remained abnormal, and a chest computed tomography (CT) scan showed consolidation involving the right lower lobe and multiple scattered bilateral pulmonary nodules. Pulmonary function testing revealed restrictive changes. Analysis of bronchoalveolar lavage fluid was nondiagnostic.

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Three months later, progressive enlargement of the pulmonary nodules was noted. The patient underwent thoracoscopic wedge biopsies, which were initially diagnosed as inflammation and granulomatous disease. Two months later, a repeat chest CT showed that the pulmonary nodules had increased in size. Pathological re-review of the more abnormal right lower lobe biopsy specimen revealed an extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma with plasmacytic differentiation (Figure 1, A–C). Elsewhere a patchier infiltrate, granulomas with negative acid-fast and Grocott staining, prominent intraalveolar macrophages, and some interstitial and pleural fibrosis were seen. Immunohistochemistry analysis identified many $CD20^+$ B cells in nodules; variable numbers of internodular $CD5^-$, $CD10^-$, $BCL6^-$, $CD43^-$, cyclin $D1^-$, and $BCL2^+$ B cells; IgM^+ λ light chain-restricted plasma cells in the main mass, and scattered $CD3^+$ T cells that were focally more numerous (CD4>CD8) (Figure 1, D–F). Elsewhere there were polytypic plasma cells and 2 small foci that appeared to be κ light chain-restricted (Figure 1, G and H). Epstein-Barr virus (EBV)-encoded RNA in situ hybridization for EBV and human herpesvirus 8 immunohistochemistry were negative. Polymerase chain reaction–based immunoglobulin heavy chain and T-cell receptor gene rearrangement analyses using BIOMED-2 protocols supported the presence of a monoclonal B-cell population but polyclonal T cells.[1] Staging of bone marrow, including flow cytometry studies, showed nonnecrotizing granuloma, but no evidence of lymphoma. Staging positron emission tomography (PET)/CT imaging showed extensive hypermetabolic lymphadenopathy and numerous hypermetabolic pulmonary nodules (Figure 2; available at www.jpeds.com).

The patient was treated with 6 cycles of rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone (R-CHOP), and achieved complete remission. Restaging bilateral bone marrow examinations were negative. Posttherapy skin biopsy analysis revealed only granulomas. Analysis of gastric biopsy specimens obtained at the time of the restaging because of high fluorodeoxyglucose activity detected on the initial PET/CT was unremarkable, with negative immunostaining for *Helicobacter pylori*.

The patient subsequently developed new lymphadenopathy; however, biopsy demonstrated only granulomas and florid follicular hyperplasia. At the time of this report, she has received 4 weekly doses of rituximab, with a plan to begin azathioprine once her platelet count is stable. The cause of the granulomas remains uncertain. Although sarcoidosis remains a possibility, the lack of progression with such extensive granulomatous disease does not favor that diagnosis, even recognizing that the patient received steroids and chemotherapy. Although an angiotensin-converting enzyme test was requested, it was not performed. The patient is currently receiving calcium supplementation because of her hypoparathyroidism and hypocalcemia.

Discussion

Many patients with a primary immunodeficiency disorder are at increased risk for lymphoproliferative disorders (LPDs), often EBV-associated aggressive B-cell neoplasms, although both T-cell and indolent B-cell lymphomas have been reported as well.[2] However, despite a suggested increased incidence of malignancies in patients with DiGeorge syndrome,[3] few cases of LPD have been reported to date. In addition to 1 patient with B-lineage lymphoblastic lymphoma, [3] 4 patients with DiGeorge syndrome who developed an LPD have been reported (Table).[4–7] The patient reported herein had a documented autoimmune disorder, a feature also reported in DiGeorge syndrome.[8] We did not identify prior reports of MALT or any other type of low-grade lymphomas occurring in patients with DiGeorge syndrome. It is possible that other patients with indolent MALT lymphomas have gone unrecognized, given that many of the changes and the association with more extensive

granulomatous and other inflammatory diseases (as seen in the present case) may be interpreted as reactive changes. Only after her progressively growing pulmonary nodules were identified was our patient diagnosed with an LPD.

The present case is also unusual in the sense that MALT lymphomas usually occur in immunocompetent adults, with children affected only rarely.[9, 10] Moreover, they are reported only infrequently in association with immunodeficiency, with most cases EBV^-, although EBV^+ MALT lymphomas have been described in the posttransplantation setting.[2,11–13] Pulmonary MALT lymphomas, like other MALT lymphomas, have an indolent clinical course.[9] MALT lymphomas arise in the setting of acquired MALT, related to infection, autoimmune disorders, or sometimes unknown factors.[14] Pulmonary MALT lymphomas have been associated with autoimmune disorders, as well as with chronic inflammatory diseases.[9,15] Perhaps this patient's immunodeficiency with resulting chronic infections led to the acquired pulmonary MALT that ultimately developed into a MALT lymphoma. The development of lymphoma also might have been fostered by a lack of immune regulation related to the patient's chromosome 22q11.2 deletion/DiGeorge syndrome. There are also rare reports of MALT lymphomas arising in patients with sarcoidosis,[16–18] although the incidence must be extremely low, given that a large population-based study identified no such cases.[19] In addition, the most recent large population-based studies have not confirmed an increased incidence of lymphoma in patients with sarcoidosis.[20] Finally, clinically it is not likely that this patient has sarcoidosis, given that there have been only several reports of sarcoidosis or possible sarcoidosis in patients with DiGeorge syndrome (1 with mediastinal adenopathy, [21] 1 with "sarcoid dermatitis" after isoniazid therapy with a negative "sarcoidosis workup,"[22] and 1 "suggestive of ocular sarcoidosis"[23]).

In summary, this case expands the type of LPDs that may be seen in the setting of the chromosome 22q11.2 deletion/DiGeorge syndrome, and illustrates the difficulty in diagnosing MALT lymphomas in the setting of a chronic inflammatory disorder. Although this patient was apparently treated effectively with R-CHOP, the optimal therapy for MALT lymphomas in this setting remains to be established.

Glossary

CT	Computed tomography
EBV	Epstein-Barr virus
LPD	Lymphoproliferative disorder
MALT	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
PET	Positron emission tomography
R-CHOP	Rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone

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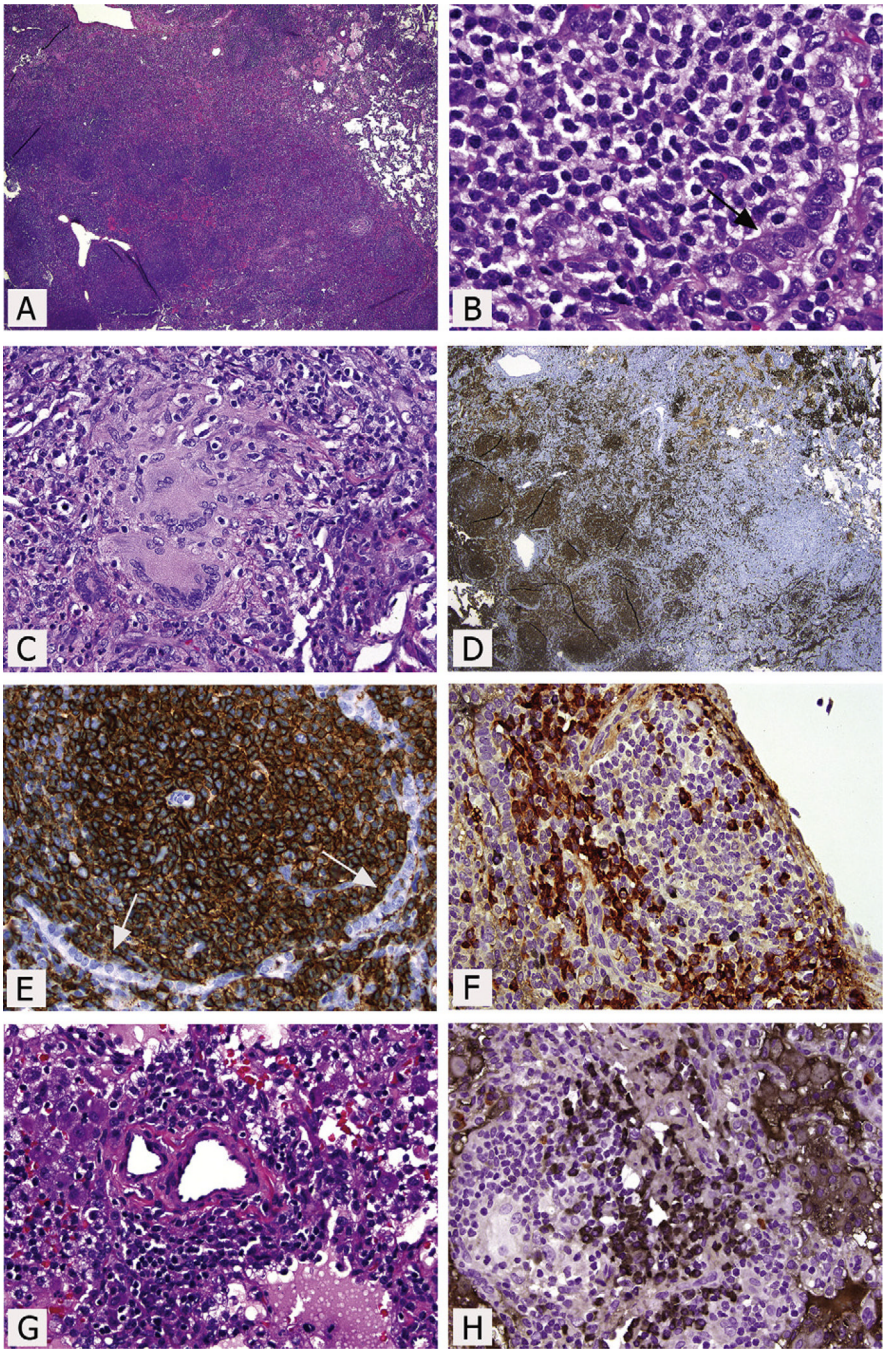

Figure 1.

Pulmonary wedge excision of the right lower lobe. **A,** Mass-like dense infiltrate with scattered follicular-type structures. **B,** Predominantly small lymphoid cells, including some with monocytoid and plasmacytoid features, infiltrating the epithelium. Note the residual epithelial remnants (*arrow*). Other focal areas show numerous plasma cells. **C,** Epithelioid granulomas with Langhans giant cells. **D,** Numerous $CD20^{+}$ cells in the follicles and a moderate number in the interfollicular regions. **E,** At higher magnification, numerous $CD20^{+}$ small lymphocytes in and around the follicle, also surrounding the residual $CD20^{-}$ epithelial cells (*arrows*). **F,** Double immunostaining for κ and λ immunoglobulin light

chains showing numerous λ^+ plasma cells (*red/brown*), but only rare κ^+ plasma cells (*black*). The λ restriction was confirmed by κ and λ single immunostains and in situ hybridization stains. The plasma cells were IgG^-, IgA^-, IgM^+, and IgD^-. **G,** Small aggregates of small lymphocytes and plasma cells away from the main mass. **H,** In contrast to the main mass, the plasma cells here show κ light chain restriction in this double-immunohistochemical stain. (**A, B, C,** and **G,** hematoxylin and eosin staining; **D** and **E,** immunoperoxidase staining for CD20; **F** and **H,** double-immunoperoxidase staining for κ and λ immunoglobulin light chains).

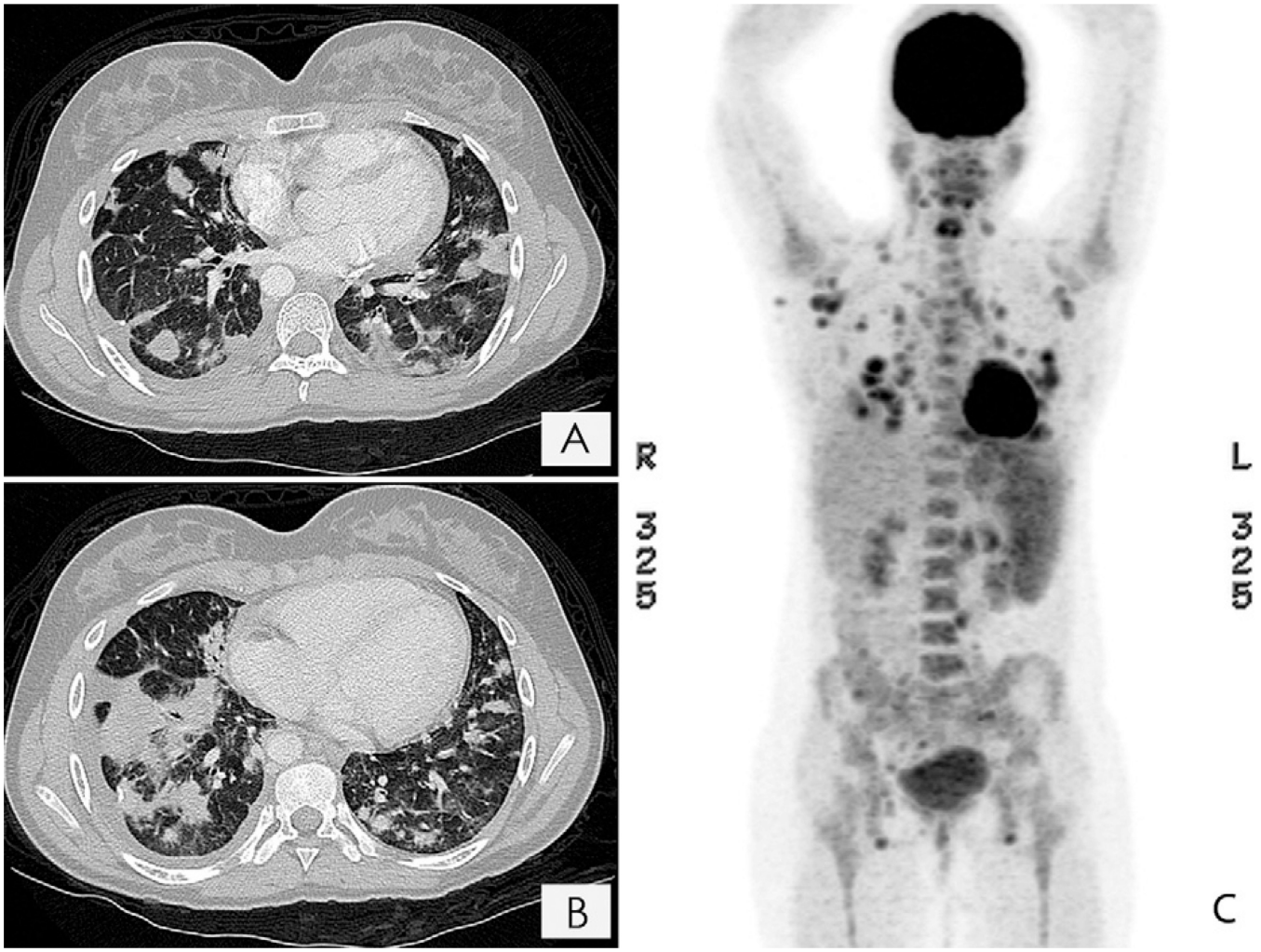

Figure 2.

A and **B,** Chest CT scans showing multiple nodules throughout the lung parenchyma. **C,** Fluorodeoxyglucose PET showing extensive hypermetabolic cervical, axillary, mediastinal, abdominal, and pelvic lymphadenopathy, along with diffusely increased bone marrow, splenic, and gastric activity.

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Table

Reported patients with DiGeorge syndrome and an LPD

	Ramos et al[5]	Sato et al[6]	Hong et al[7]	Itoh et al[4]	Present case
Age at LPD diagnosis/sex	23 months/female	7 months/male	14 years/female	25 years/male	15 years/female
Cytogenetics	Not done	Not done	Equivocal chromosome 22q11.2 deletion (method not specified)	Hemizygous chromosome 22q11.2 deletion (FISH)	Hemizygous chromosome 22q11.2 deletion (FISH)
DiGeorge syndrome features	Thymic and parathyroid aplasia; no cardiac anormaly	Dysmorphic face, hypothyroidism, TOF, thymic and parathyroid aplasia	TOF, undetectable parathyroid hormone, thymic hypoplasia	Dysmorphic face, TOF, major aortopulmonary collateral artery, VSD, markedly hypoplastic thymus and parathyroid glands	Dysmorphic face, hypoparathyroidism, VSD, PDA, right-sided aortic arch
Evidence of immunodeficiency	Low peripheral T-cell counts, several episodes of thrush and otitis media	Low peripheral T-cell counts, hypogammaglobulinemia	Low peripheral T-cell counts, recurrent otitis media and sinopulmonary infection (led to bronchiectasis)	Recurrent fever and diarrhea for several months	Low peripheral $CD4^+$ T-cell counts, recurrent sinusitis and pneumonia, hypogammaglobulinemia
Autoimmune phenomenon	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Evans syndrome
Major complications	Not mentioned	Not mentioned	None	Hemophagocytic syndrome, DIC, multiorgan failure	None
Nature of LPD	EBV^+ DLBCL involving mediastinal lymph nodes, brain, liver, and kidneys	EBV^+ DLBCL involving mediastinal and mesenteric lymph nodes, lung, trachea, larynx, small intestine, and liver	EBV^+ DLBCL manifested with generalized lymphadenopathy	EBV^+ peripheral T-cell lymphoma ($CD3^+$, $CD5^+$, $CD8^+$, $CD56^-$, $TIA1^+$), involving mediastinal, para-aortic, and inguinal lymph nodes	MALT lymphoma (EBV^-) involving lungs and presumptive cervical, axillary, mediastinal, abdominal, and pelvic lymph nodes (no pretreatment lymph node biopsy results to document lymphoma)
Therapy for LPD	Refused therapy for malignancy	Not mentioned	Chemotherapy (modified French LMB 89), thymus transplantation at 8 months after complete course of chemotherapy, autologous anti-EBV cytotoxic T-cell infusion (for relapsed disease)	None	Immunochemotherapy (6 cycles of R-CHOP)
Outcome *	Died 1 month after diagnosis of LPD	Died 1 month after diagnosis of LPD	Relapsed 16 months after thymus transplantation but later achieved remission for at least 29 months	Died at 12 hours after admission	In complete remission at least 22 months after diagnosis of LPD, lymph node biopsy at 17 months showed only granulomas.

DIC, disseminated intravascular coagulation; *DLBCL*, diffuse large B-cell lymphoma; *FISH*, fluorescence in situ hybridization; *PDA*, patent ductus arteriosus; *TOF*, tetralogy of Fallot; *VSD*, ventricular septal defect.

*All patients who died underwent autopsy.