

A Single-Center Retrospective Review of Pediatric Cases of Progressive Transformation of Germinal Centers

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November 7, 2022

Abstract

Background Progressive transformation of germinal centers (PTGC) is a rare diagnosis characterized by asymptomatic lymph node enlargement. It has previously been associated with lymphoma, autoimmune conditions, and lymphoproliferative diseases in small pediatric case series. **Procedures** We conducted a single-center retrospective review of pediatric cases of PTGC diagnosed at our institution by hematopathologists from 2000 - 2020. **Results** We identified 57 primary cases and 3 recurrent cases of PTGC. There was a male predominance in cases (32/57), with median age at diagnosis of 11 years. Head and neck lymph nodes were the most commonly involved and biopsied sites. Laboratory and imaging evaluations were obtained inconsistently. Only 16% of patients saw a pediatric hematology/oncology (PHO) specialist prior to diagnosis and 37% had follow-up with PHO after diagnosis. Six patients (10%) had a preceding or concurrent diagnosis of lymphoma and 5% of patients returned with recurrent PTGC. **Conclusions** Patients with PTGC had similar characteristics to those from previous case series. Fewer patients underwent recurrent lymph node biopsy than previously described. PTGC has been linked to certain types of lymphoma, although never definitively associated with lymphoma. Follow-up with a PHO provider is indicated to ensure that close surveillance is performed.

Introduction

Pediatric lymphadenopathy has a broad differential, one of which is progressive transformation of germinal centers (PTGC). PTGC is characterized histologically by the expansion of mantle zone lymphocytes, follicular dendritic cells, and T-cell lymphocytes into germinal centers, resulting in germinal center enlargement and disruption of architectural differentiation in the lymph node (LN).¹ The expansion of LN follicles causes clinically apparent LN enlargement. Affected LN may contain epithelioid histiocytes and other cells consistent with infection or granulomatous reactions;¹ however, patients with PTGC may have no symptoms other than LN enlargement.² Nodes affected by PTGC can recur after excisional surgeries. Interestingly, PTGC can precede, occur synchronously, or occur after the diagnosis of lymphomas,³⁻⁵ although the association between lymphomas and PTGC remains unclear. While PTGC is a rare diagnosis overall, it has been better described in adults and shows a predominance among young adult males.⁴ Given that literature describing the clinical and diagnostic features of PTGC in pediatric patients remains limited to small case series,^{2,6-8} we reviewed pediatric cases of PTGC at our institution across 20 years to add to the data surrounding this diagnostic mystery.

Methods

With Institutional Review Board approval from Children's Healthcare of Atlanta, the electronic anatomic pathology database was queried for cases of PTGC that were diagnosed between January 1, 2000 through December 31, 2020. Data included age and sex at diagnosis as well as location of involved lymph nodes.

Blood test results, radiologic imaging, and duration of follow-up evaluation were extracted from the electronic medical record (EMR). Microsoft Excel (v16.62, 2022) was used for database management, and GraphPad Prism (v9.3.1, 2022) was used for statistical analyses.

Results

Patient Characteristics

Sixty cases of PTGC were found on histopathology during the study period, with 57 discrete patients. Three patients had recurrent excisional LN biopsies due to persistent lymphadenopathy, all of whom received repeated diagnoses of PTGC.

Of the 57 patients, 32 were male (56%) and 25 were female (44%) at diagnosis. Median age was 11 years at diagnosis (range 1-20 years). The most common location of involvement were head and neck LNs (n=44), although some patients were noted to have additional sites of adenopathy on physical exam prior to LN biopsy. Five patients underwent biopsies of axillary nodes, and eight patients underwent biopsies of abdominopelvic nodes, including one patient who had PTGC found in a gastrointestinal lymph node in the terminal ileum.

Clinical Presentation

Patients presented with slow-growing lymphadenopathy preceding biopsy for durations ranging from one month to “several years” on history; this was not often specified in the EMR. The majority of cases were diagnosed after initial presentation to an otolaryngologist or general surgeon resulted in biopsy, with only 9 patients (16%) seen by a pediatric hematology/oncology (PHO) specialist prior to biopsy. One patient presented with a two-week history of fevers. No patients reported weight loss or night sweats. Of the 57 patients, 38 underwent radiologic imaging prior to LN biopsy; two of the three patients who received PET scans had concurrent diagnoses of lymphoma (Fig. 1).

Laboratory evaluation of patients with PTGC was variable. Of the 57 patients, 28 had no perioperative blood tests sent at all, and 3 additional patients had blood tests that were reportedly normal per comment in the chart but not specified in the EMR. The most frequently ordered labs were complete blood counts with differentials (CBC), complete metabolic panels (CMP), erythrocyte sedimentation rates (ESR), lactate dehydrogenase (LDH), and uric acid (Fig. 2). Three patients had leukopenia noted on their CBC and one patient had leukocytosis. One patient had notable anemia with a hemoglobin of 7.2 g/dL, but also had sickle cell disease, for which she was followed by PHO. No patients had thrombocytopenia at time of diagnosis. CMPs collected were all within normal range except for four patients who had mild elevations in total protein. One patient had an elevated ESR, one patient had an elevated LDH, and no patients had elevated uric acid levels based on our laboratory’s normal values.

Hematopathologic Characteristics

Thirty-eight of the 57 patients had flow cytometry performed on their LN samples, and all were negative for malignancy by immunophenotyping. This included three patients who had concurrent diagnoses of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Two of these three had PTGC in one biopsied LN with NLPHL present in a different excised LN, while the third had both NLPHL and PTGC present in the same LN concurrently. Two of the 38 patients who had flow cytometry performed on their LN samples had elevated percentages of double negative T-cells, concerning for autoimmune lymphoproliferative syndrome (ALPS).

Surveillance

Of the 57 patients, 36/57 (63%) had no follow-up visits with PHO. All nine of the patients who saw PHO prior to diagnosis had at least one follow-up visit with a PHO provider. Duration of follow-up with PHO ranged from one week after the biopsy to 5 years, which includes patients with concurrent NLPHL who continue to be followed by our survivorship program at time of writing. Most commonly, the 21 patients who had PHO follow-up were seen for one visit prior to discharge from PHO clinic.

Outcomes

Three of the 57 patients (5%) had concurrent diagnoses of NLPHL; all three were treated with chemotherapy. Another three patients (5%) had completed therapy for prior history of malignancy two or more years prior to PTGC diagnosis; one with recurrent NLPHL, one with classic Hodgkin lymphoma (CHL), and one with T-cell/histiocyte-rich large B-cell lymphoma. No patients went on to be diagnosed with a subsequent malignancy during the study period, but 3/57 (5%) patients had recurrent PTGC. Repeat LN biopsy for these three individuals was performed at intervals of three months, four months, and six years from the first biopsy.

One patient had prior history of common variable immunodeficiency (CVID) managed at an outside center and one had history of refractory Evans syndrome treated with steroids and rituximab; due to history of bulky lymphadenopathy, this patient was being evaluated for ALPS. An additional patient developed a subsequent diagnosis of Type 1 diabetes mellitus during the inclusion period. No other immune-mediated or lymphoproliferative conditions were documented in these patients during the inclusion period.

Discussion

The median age (11 years) and location of common LN involvement (head and neck) in our patients is comparable to previous studies. The male predominance of cases was not as dramatic as other case series, which have found a nearly 2:1 ratio.^{2,8} Compared to the prior single-center review of PTGC from Shaikh, et al (2013), our patients underwent fewer recurrent lymph node biopsies (5% versus 52%).² The larger sample size and longer duration of follow-up for the current report suggest that repeated biopsies are less common than previously reported.

The percent of patients with preceding or concurrent diagnosis of lymphoma was similar to that previously found (10% versus 14%) in the Shaikh, et al study (2013).² Our study reiterates the reported association of PTGC with lymphoma;⁵ however, it does not argue against the more likely view that PTGC is a vigorous reactive process. Antecedence or concurrence with lymphoma can also be said of established reactive processes such as follicular hyperplasia, which is concurrently identified in virtually all LNs with PTGC. An interesting histopathologic study by Chang, et al (2003) suggested that follicular hyperplasia and PTGC constitute an evolutionary spectrum in resolution of lymphoid hyperplasia with sequential ingression of T-cells followed by mantle B-cells.⁹ More recently, Gars, et al (2020) employed a multitude of immunohistochemical stains to study the immunoarchitecture of lymphoid follicles and pointed out that PTGC is a conceivable stage in the life cycle of a reactive germinal center.¹⁰ It is notable that no patient with PTGC in our cohort went on to develop a new malignancy within the time frame of follow-up. Our hospital system allowed for the treatment of patients until the age of 21 years during the time of this study, and all 26 of the patients who would have “graduated” from pediatric care by 2020 had been diagnosed a minimum of 7 years prior to the end of the inclusion period.

Fewer patients at our center had immune-mediated conditions associated with PTGC compared to the prior review (5% versus 24% in Shaikh et al, study). ALPS, CVID, Castleman disease, systemic lupus erythematosus (SLE), and autoimmune cytopenias have all been previously described in patients with PTGC.^{2,11,12} Two of the patients in our cohort had increased double-negative T-cells on LN flow cytometry, but neither patient had confirmatory testing for ALPS within our center, and one had a pre-existing diagnosis of CVID. Our patient with Evans syndrome (immune-mediated anemia and thrombocytopenia) who developed PTGC had previously been evaluated for ALPS but did not have increased double-negative T-cells; due to persistent bulky lymphadenopathy and development of neutropenia, repeat flow cytometry and FAS gene mutation analysis were sent, both of which returned negative. He was noted to have low IgM and elevated IgG, with increased transitional B cells in his immune cell subsets (CD21 low, CD19 high), concerning for a developing immunologic defect, but unfortunately was lost to follow-up.

Only one of the patients in our study presented with fever. This patient did not have evidence of infection on physical exam or by extensive laboratory evaluation, although she did have evidence of systemic inflammation as demonstrated by elevated ESR and CRP values. PTGC has been reported in patients with HIV and upper

respiratory tract infections; infection screening is recommended based on exposure history.¹³

Our review adds to the literature about the diagnostic evaluation and referral patterns for pediatric patients with PTGC. Of our 57 patients, only nine were seen by a PHO specialist prior to biopsy; one was seen by an infectious disease specialist prior to biopsy. The rest were diagnosed after referral to a pediatric otolaryngologist or general surgeon at our pediatric hospital. All nine patients seen by PHO had a follow-up visit to discuss biopsy results, while 12 patients were referred to PHO for follow-up after biopsies resulted. These 21 patients all had some subset of laboratory evaluations sent, as described above, and were followed for anywhere from 1 week to 5 years after initial biopsy. Although most of these 21 patients only had one visit with PHO, patients who had prior or concurrent history of lymphoma were followed for longer, and one patient whose brother had a history of relapsed CHL was followed for over 2.5 years. Of the 36 patients who did not see PHO at all, only 9 (25%) had any blood tests sent. These 36 patients did not have in-person follow-up with any of our children's hospital providers, and if counseling occurred on the telephone regarding the potential for recurrence, increased risk of lymphoma, and association with autoimmune or lymphoproliferative conditions, this was not documented in our EMR.

Given the association of PTGC with lymphoma and lymphoproliferative conditions, we propose that a PHO specialist should see and examine patients diagnosed with PTGC at least once following their diagnostic biopsy, if they have not yet been involved in their care. Given that laboratory evaluations may not be performed by the provider performing the biopsy, a PHO specialist would have the expertise to draw labs tailored to the patient's presentation and counsel patients and families on close monitoring. Yan, et al (2022) proposed standardized Tier 1 investigations recommended for all patients with isolated PTGC.¹³ Additional visits to PHO may be necessary depending on recurrence of lymphadenopathy, abnormal lab values, family history, and patient needs.

Conflict of Interest Statement

None of the authors have any disclosures to make.

Acknowledgements

We gratefully acknowledge the support of the leukemia and lymphoma division of the Aflac Cancer and Blood Disorders Center.

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Legends

FIGURE 1 Imaging modalities used in patients diagnosed with PTGC. Chest X-ray, chest radiograph. Ultrasound, of affected area. PET/CT, positron emission tomography/computed tomography (whole body; skull base to feet). CT, computed tomography, of noted area.

FIGURE 2 Laboratory evaluations in patients diagnosed with PTGC. CBCd, complete blood count with differential. CMP, complete metabolic panel. ESR, erythrocyte sedimentation rate. LDH, lactate dehydrogenase. EBV IgM/IgG, Epstein-Barr viral antibody titers. CMV IgM/IgG, Cytomegalovirus antibody titers. Ig panel, Immunoglobulins G, A, M. Cat scratch, Bartonella serologies. CRP, C-reactive protein. HIV, human immunodeficiency virus.

Figures

Figure 1

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Figure 2

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