



Pediatric post-transplant lymphoproliferative disorder identified on random gastrointestinal biopsies shows non-mass-forming PTLD with clonal plasma cells: report of 2 cases

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Abstract

EBV-related lymphoproliferations in post-transplant settings range from non-destructive hyperplasia to polymorphic post-transplant lymphoproliferative disorder (PTLD) to overt lymphoma. Here we present two unusual cases of pediatric non-mass-forming gastrointestinal (GI) PTLDs with mixed pathologic features of non-destructive and polymorphic categories. Both patients were EBV naïve and presented within 1 year of transplant with non-specific gastrointestinal symptoms (diarrhea, abdominal pain, and food intolerance) with hypoalbuminemia, cytopenia, and EBV viremia. No mass lesions were found on imaging and endoscopy. Random GI biopsies showed a non-mass-forming, but polymorphic-appearing lymphoid infiltrate with EBV positivity, monotypic plasma cells, and clonal B cells. Cyclophosphamide, steroids, and rituximab treatment had good clinical response in all cases, including one case which had poor response initially with rituximab alone. Based on these cases, we conclude that GI PTLD in children can present with vague abdominal symptoms, cytopenia, and hypoalbuminemia, and can be non-mass-forming and non-destructive. A high level of suspicion with random GI biopsies and clinicopathologic and laboratory correlation are required. Since these patients have no mass lesions, evaluating symptomatic relief, EBV viral load, improvement in cytopenia(s), serum albumin levels, and/or resolution of other systemic symptoms may be needed to monitor response to therapy.

Keywords Pediatric · PTLD · Transplant · Gastrointestinal · Polymorphic

Introduction

Post-transplant lymphoproliferative disorders (PTLD) are lymphocytic and/or plasmacytic proliferations that develop as a consequence of immunosuppression in a recipient of a solid organ or stem cell allograft. This heterogeneous group of disorders range from non-destructive hyperplasia to polymorphic PTLD to overt lymphoma [1]. The current WHO classification of tumors of hematopoietic and lymphoid tissues classifies PTLD into non-destructive PTLD, polymorphic PTLD, monomorphic PTLD, and classic Hodgkin lymphoma PTLD based on morphology (the absence or presence and degree

of architectural distortion), cellular composition, immunophenotype, and clonality of the cells constituting the lesion. Non-destructive PTLDs typically arise as mass-forming lesions that do not cause architectural effacement of the involved tissue and consist of polyclonal B cells and/or plasma cells with admixed T cells. Majority of these cases are EBV-positive and are negative for clonally rearranged immunoglobulin (IG) genes. Polymorphic PTLDs present as mass lesions that cause architectural effacement of the involved tissue and are composed of a heterogeneous population of immunoblasts, plasma cells, and small and intermediate sized lymphocytes, with or without light chain restriction, and do not fulfill the criteria of any of the recognized types of lymphoma described in immunocompetent hosts [2]. Most cases of polymorphic PTLD are EBV-positive and demonstrate clonally rearranged IG genes [2, 3].

Here we present two unusual cases of pediatric non-mass-forming gastrointestinal (GI) PTLDs with pathologic features overlapping between non-destructive and polymorphic PTLD

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categories. Both cases were identified on random GI biopsies that were taken due to non-specific gastrointestinal symptoms (i.e., diarrhea, abdominal pain, and food intolerance) and also had hypoalbuminemia, cytopenia(s), and EBV viremia.

Materials and methods

An electronic search for pediatric PTLDs with GI involvement yielded two cases. Chart review for clinical and imaging findings was performed. Immunohistochemical stains and EBER in situ hybridization were performed on formalin-fixed paraffin-embedded tissue. Molecular studies for IGH and/or IGK gene rearrangements with BIOMED primers were performed in both cases. Flow cytometry on ascitic fluid was performed on one case.

Results

Case 1

The patient is an 18-month-old EBV naïve Hispanic girl who presented with severe diarrhea 5 months post liver transplant for biliary atresia, maintained on Prograf for immunosuppression. Laboratory studies showed new onset pancytopenia—WBCs 2.41 K/mcL (6.00–13.50 K/mcL), RBCs 3.04 M/mcL (3.97–5.01 M/mcL), hemoglobin 8.5 g/dL (10.2–12.7 g/dL), platelets 128 K/mcL (206–459 K/mcL); hypoalbuminemia—serum albumin 2.9 g/dL (3.2–5.0 g/dL); and EBV viremia—2529 copies/mL (<200 copies/mL). CT scans of the chest, abdomen, pelvis, and neck failed to reveal any concerning masses. Colonoscopy and upper GI endoscopy exams were normal and did not reveal any suspicious mass lesions or ulcers. Random biopsies of the colon, duodenum, and stomach were obtained to evaluate for the cause of diarrhea.

A random duodenal biopsy showed a non-destructive atypical lymphoid aggregate in the lamina propria composed of small and intermediate sized lymphoid cells, immunoblasts, and plasma cells (Fig. 1a, b). No lymphoepithelial lesions were seen; however, there was focal villous blunting. Immunohistochemistry showed numerous small, intermediate, and large CD20 positive B cells with admixed small CD3 positive T cells (Fig. 1c, d). EBER ISH stain showed many positive small and intermediate sized cells within and around the aggregate (Fig. 1f). Kappa and Lambda IHC stains showed polytypic plasma cells in most of the submucosal plasma cells but showed kappa light chain restriction in the plasma cells at the periphery of the lymphoid aggregate (Fig. 1g, h). Rare large atypical CD30 positive cells were also seen (Fig. 1e). No tissue was procured for flow cytometry. Molecular studies were positive for clonal rearrangement of the IGH gene in a polyclonal background. Subsequent bone

marrow biopsy showed no evidence of PTLD. Following a diagnosis of PTLD, the patient was treated with reduction of immunosuppression and six cycles of rituximab, cyclophosphamide, and steroids (protocol ANHL0221) that resulted in resolution of pancytopenia, hypoalbuminemia, EBV viremia, and diarrhea. She remains asymptomatic and clinically stable 20 months following the diagnosis of PTLD with detectable, but non-quantifiable EBV levels.

Case 2

A 23-month-old EBV naïve Hispanic boy presented with diarrhea, weight loss, ascites, and lethargy 4 months post liver transplant for biliary atresia. He was maintained on Prograf for immunosuppression. Laboratory studies showed new onset pancytopenia—WBCs 2.16 K/mcL (6.00–13.50 K/mcL), RBCs 2.80 M/mcL (3.97–5.01 M/mcL), hemoglobin 7.3 g/dL (10.2–12.7 g/dL), platelets 81 K/mcL (206–459 K/mcL); hypoalbuminemia—serum albumin 2.4 g/dL (3.2–5.0 g/dL); and EBV viremia—722,406 copies/mL (<200 copies/mL). Imaging, colonoscopy, and upper GI endoscopy were negative for mass lesions or suspicious findings similar to the first case. Random biopsies of the colon, duodenum, and stomach were obtained to evaluate for the cause of GI distress.

A random duodenal biopsy showed a small infiltrate consisting of small to medium mature lymphocytes, immunoblasts, plasma cells, histiocytes, and occasional eosinophils causing mild architectural distortion (Fig. 2a–b). CD20 highlighted increased numbers of polymorphic appearing B cells in a background of CD3+ T cells (Fig. 2c, d). CD30 positivity was observed in a few large cells (Fig. 2e). EBV by EBER ISH was positive in several small, medium, and large lymphocytes in this infiltrate (Fig. 2f). Immunohistochemistry for Kappa and Lambda could not be performed due to lack of sufficient tissue; however, flow cytometry on the ascitic fluid revealed a small abnormal lambda-restricted CD138+ plasma cell population (Fig. 2g, h). Molecular studies were positive for clonal rearrangement of the IGK gene in a polyclonal background. No clonal IGH gene rearrangement was detected. Subsequent bone marrow biopsy also showed involvement by PTLD and monotypic plasma cells. Clonal IGH and IGK gene rearrangements were detected in the bone marrow; however, the clonal IGK peak was different from that detected in the duodenum biopsy. After an incomplete clinical response to reduction of immunosuppression and rituximab alone for a month, the patient was treated with six cycles of rituximab in combination with cyclophosphamide and steroids (protocol ANHL0221) that resulted in resolution of anemia, leukopenia, hypoalbuminemia, EBV viremia, and diarrhea. He remains asymptomatic and clinically stable 22 months since the diagnosis with undetectable EBV levels.

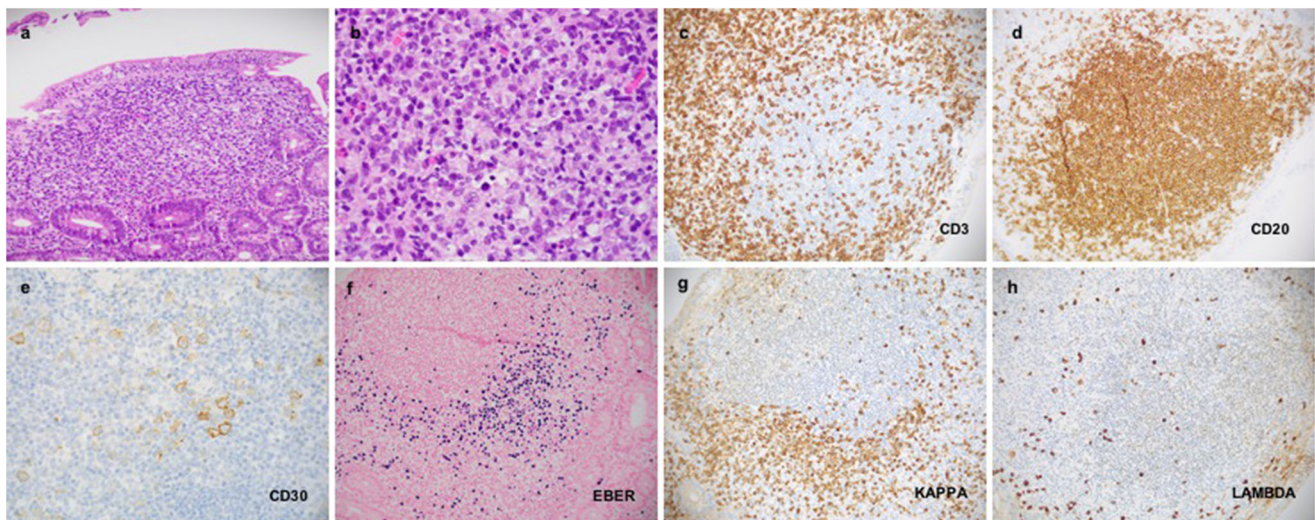


Fig. 1 Histopathologic findings in Case 1. **a** Low power view showing an atypical lymphoid infiltrate in the duodenal mucosa (H&E stain, × 10). **b** Higher power shows polymorphic morphology of the lymphoid cells with mixture of small, intermediate, and larger lymphocytes with admixed immunoblasts, histiocytes, and plasma cells (H&E stain, × 60). The

lymphocytes are predominantly CD20+ B cells (**d**) admixed with fewer CD3+ T cells (**c**). **e** CD30 stain highlights scattered immunoblasts. **f** Numerous EBV-positive cells are detected on EBER ISH. **g** The plasma cells appear monotypic for kappa light chain. **h** Rare scattered lambda light chain expressing plasma cells are seen

Summarized features of 2 cases

Both children were under 2 years old, EBV naïve, and presented within 1 year of transplant with non-specific abdominal symptoms (diarrhea in 2 of 2 cases and ascites, lethargy, and weight loss in 1 of 2 cases). Clinical findings included cytopenia(s) (2 of 2 cases), hypoalbuminemia (2 of 2 cases), and EBV viremia (2 of 2 cases). Radiologic imaging studies and upper and lower GI endoscopies did not reveal any mass lesions. A focal non-destructive polymorphic lymphoid infiltrate was

identified on random GI biopsies. Both cases showed a polymorphic lymphoid infiltrate admixed with plasma cells and many EBV-positive cells. EBV-positive cells within both lesions were present in significant numbers (>30/high power field) and were clearly greater than that expected in latent EBV infections. Plasma cells in the GI biopsy were light chain restricted by IHC in one case and the other case showed involvement of ascitic fluid and bone marrow with light chain restricted plasma cells detected by flow cytometry. Treatment with cyclophosphamide, steroids, and rituximab had good

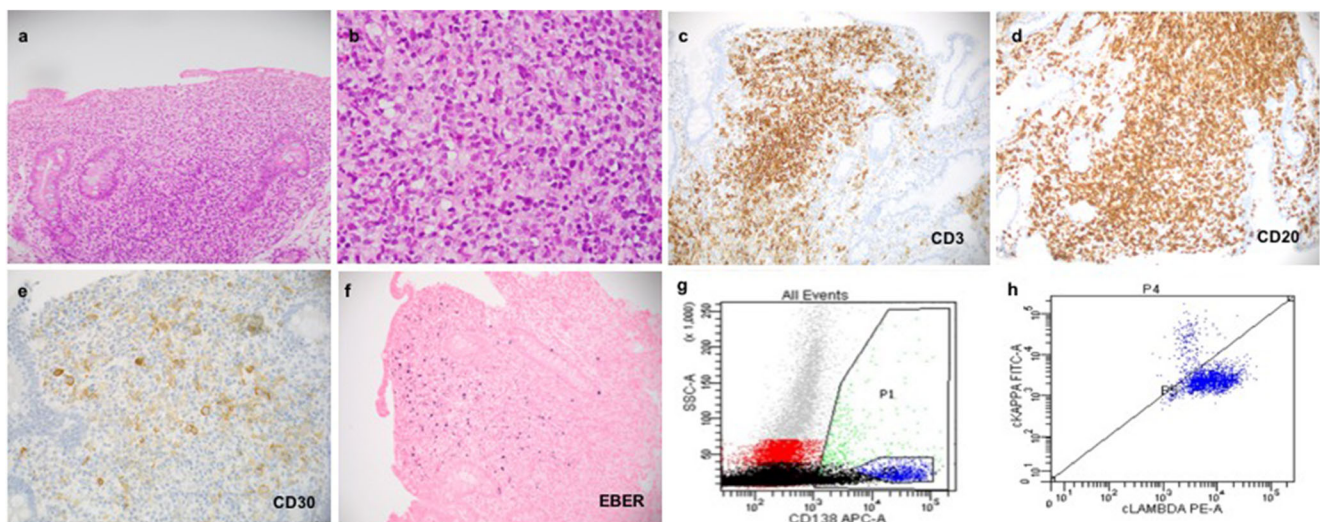


Fig. 2 Histopathologic findings in Case 2. **a** An atypical lymphoid infiltrate is noted in the duodenal mucosa on low power (H&E stain, × 10). **b** Higher power shows polymorphic lymphoid infiltrate with mixture of small, intermediate and larger lymphocytes with admixed immunoblasts and plasma cells (H&E stain, × 60); The lymphocytes are

a mixture of CD3+ T cells (**c**) and CD20+ B cells (**d**). **e** CD30 stain highlights scattered immunoblasts. **f** Numerous EBV-positive cells are detected on EBER ISH. **g** Flow cytometry on ascitic fluid detects increased CD138 positive plasma cells. **h** Plasma cells appear to be lambda light chain restricted by flow cytometry

Table 1 Summary of findings in the two cases of pediatric GI PTLD

	Case 1	Case 2
Age and ethnicity	18 months, Hispanic	23 months, Hispanic
Transplant history	Liver transplant for biliary atresia	Liver transplant for biliary atresia
Clinical findings	Diarrhea, low albumin, pancytopenia	Diarrhea, ascites, low albumin, pancytopenia
Serum EBV	2529 copies/mL	722,406 copies/mL
Endoscopic findings	No lesions	No lesions
Site of PTLD	Duodenum	Duodenum
Morphology	Mild architectural distortion with polymorphic infiltrate	Mild architectural distortion with polymorphic infiltrate
IHC/flow cytometry	Kappa-restricted plasma cells	Lambda-restricted plasma cells
Bone marrow involvement	Not identified	Present with lambda-restricted plasma cells
Molecular studies	Positive for clonal IGH gene rearrangement	Positive for clonal IGH (bone marrow) and IGK gene rearrangements (duodenum and bone marrow)

clinical response in both cases, including one case which had incomplete response with Rituximab alone (Table 1).

Discussion

Post-transplant lymphoproliferative disorders (PTLDs) are a group of hematolymphoid diseases that develop as a consequence of immunosuppression in a recipient of a solid organ or stem cell allograft [4, 5]. The pathogenesis of PTLT is considered to be multifactorial, but the role of EBV has been established to play a central role in driving the proliferation of EBV-infected B cells that leads to subsequent development of the lymphoproliferative disorder [6]. The incidence of PTLT depends on the type of organ transplanted, the respective intensity of immunosuppression, and the recipient's viral status (EBV and CMV seronegativity) prior to transplantation. The incidence has been steadily increasing over the years, most likely reflecting the increasing number of transplants, increasing awareness, and improved diagnostic techniques [7, 8]. Children are more prone to developing PTLTs as they are usually naive for Epstein-Barr virus (EBV) infection [9] and cytomegalovirus infection (CMV), although the effect of CMV is not as strong as for EBV and less consistent [10, 11]. The overall incidences for PTLT among pediatric patients are lowest in renal transplant recipients with 1–3% at 5 years post transplantation [12, 13] while PTLT incidence after pediatric liver transplant has an overall incidence between 5 and 10% [14–16] with the time from transplantation ranging from 1 to 84 months [16]. PTLT is most frequent in pediatric lung transplant recipients (overall PTLT incidences of approximately 15%) [17, 18] and recipients of intestinal grafts (predicted incidence 20% ± 5%) [19].

The most frequent sites for PTLT in children are tonsillar/adenoidal tissue (34%) followed by gastrointestinal (32%) [20]. Other organs such as the central nervous system, bone marrow, spleen, lung, small intestine, liver, and kidney may also be affected. The clinical manifestations of PTLT in children include non-specific symptoms in the form of fever, sweats, malaise, and weight loss and mass-forming lesion/s in the involved organ [9, 21].

The current WHO classification of tumors of hematopoietic and lymphoid tissues classifies PTLT into non-destructive PTLT, polymorphic PTLT, monomorphic PTLT, and classic Hodgkin lymphoma PTLT based on morphology, cellular composition, immunophenotype, and clonality of the cells constituting the lesion [2]. Non-destructive PTLTs are characterized by architectural preservation of the involved tissue, but in most cases, they do present as mass lesions. To this point, the three WHO-recognized subtypes of non-destructive PTLT, plasma cell hyperplasia, florid follicular hyperplasia, and infectious mononucleosis PTLT, all require the formation of a mass lesion and/or significant EBV positivity. Immunophenotypic studies show an admixture of polyclonal B cells, plasma cells, and T cells without phenotypic aberrancy. Clonally rearranged IG genes are not expected, and most cases regress spontaneously with reduction in immunosuppression alone or may be successfully treated by surgical excision [22]. The histologic differential diagnosis in our cases include active EBV infection, including infectious mononucleosis-like PTLT (IM-like PTLT), which is a form of early/non-destructive PTLT lesion [2]. Both lesions show marked immunoblastic proliferation, often with foci of necrosis. The histology of our two cases is not typical of IM-like PTLT and instead shows a polymorphic lymphoid infiltrate with only rare, scattered immunoblasts and no necrosis. In addition, light chain restriction of B cells or plasma cells and

B cell clones detected by molecular studies are rare in mononucleosis or IM-like PTLD. Oligoclonal populations may be detected on molecular studies in IM-like PTLD [23].

In contrast, polymorphic PTLDs present as mass lesions that cause architectural effacement of the involved tissue. They are composed of a heterogeneous population of immunoblasts, plasma cells, and small and intermediate sized B cells and T cells. Light chain class restriction in B cells is variable in polymorphic PTLDs but does not exclude the diagnosis. These PTLDs usually demonstrate clonally rearranged IG genes and usually require chemotherapy in addition to reduction in immunosuppression for successful treatment [24–26]. Our cases have features of polymorphic PTLD (morphology of infiltrate, light chain restricted plasma cells, and clonal B-cells), except that they presented without mass lesions or destructive architecture.

The gastrointestinal tract with its extensive mucosa-associated lymphoid tissue is not an unexpected site for PTLD. However, isolated PTLD of the GI tract is rare. There is also limited literature regarding the pathologic findings of pediatric GI PTLD. An early study by Nalesnik [27] reported 12 cases of GI PTLD with histologic appearance ranging from polymorphic to monomorphic and some showing clonal B cells in a non-clonal background. Cao et al. [28] subsequently reported that at 1-year follow-up after liver transplant, 31% of children developed symptomatic EBV infections, and 12% affected the GI tract. Of the 2 patients in their cohort with biopsy-proven GI PTLD, endoscopy revealed ulceration and nodularity of the GI tract. Younes et al. [29] reported 9 cases of pediatric GI PTLD post liver transplant, with majority occurring in children younger than 5 years old. The endoscopy findings range from almost normal appearing mucosa to erythematous nodularity to ulceration and perforations. O'Connor et al. [30] described 6 pediatric post liver transplant cases who presented with non-specific GI symptoms with endoscopy revealing rubbery, raised, and ulcerated lesions which were histologically confirmed to be PTLD. The colon and stomach were the most common sites involved. Two additional pediatric case reports describe GI bleeding as the presenting symptom with endoscopic findings of ulcerations in the small intestine that were confirmed histologically as PTLD [31, 32]. In a retrospective study involving 34 patients with GI PTLD conducted by Dziegielewski et al. [33], 15 (44%) patients had monomorphic disease, 12 (35%) patients had polymorphic disease, 6 (18%) had early lesions, and 1 (3%) patient had mixed monomorphic and polymorphic. The endoscopic findings on the cases are not reported in the study. Majority of patients presented with non-specific GI symptoms, and association with EBV was identified in 65% cases, and 53% cases developed GI PTLD in the first 2 years post-transplant. EBV-negative cases appeared to have a significantly later

onset of GI PTLD (median 68 months) compared to EBV positive cases.

We present two unusual cases of pediatric gastrointestinal (GI) PTLDs with pathologic features overlapping between non-destructive and polymorphic categories. Grossly and/or histologically, these cases show no mass lesions or significant architectural effacement as required for polymorphic PTLD and show evidence of clonal plasma cells and/or B cells that are not typical for the 3 recognized WHO subtypes of non-destructive PTLD. Both cases were identified on random GI biopsies that were taken due to non-specific gastrointestinal symptoms (diarrhea, abdominal pain, and food intolerance) in patients who also had hypoalbuminemia, EBV viremia, cytopenias, and in one case ascites. Both cases showed response to a combination regimen of cyclophosphamide, steroids and rituximab while one case showed incomplete response to an initial trial of rituximab alone.

One potential limitation of this conclusion is that it is difficult to entirely exclude the possibility of a “mass-forming” or other lesion with architectural effacement on histology that could be present in the portions of small intestine that could not be visualized via standard endoscopy procedures. Even if a non-visualized mass lesion is present, random GI biopsies may still be useful to diagnose PTLD in these patients.

Conclusion

These cases illustrate that some post-transplant EBV-related lesions may not fit cleanly within our current WHO PTLD categories, and clinicopathologic correlation is necessary to determine appropriate therapy. Pediatric GI PTLD can present within 1 year of transplant with vague abdominal symptoms, cytopenia, and hypoalbuminemia, without mass lesions. A high level of suspicion with random GI biopsies is recommended. Since these patients have no mass lesions, relief of GI symptoms, EBV viral load, and improvement in cytopenia and serum albumin levels may be used to monitor response to therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have conflicts of interest.

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