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PTEN Hamartoma Syndrome in a Child Presenting With Malrotation, Panintestinal Polyps, Severe Anemia, and Protein-Losing Enteropathy

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Abstract: PTEN hamartoma syndrome (PTEN-HS) is a rare syndrome including neurologic, neurodevelopmental, integumentary, endocrine, and gastrointestinal manifestations. Eosinophilic disorders of the gastrointestinal system are diverse group of disorders reported to be more common in PTEN-HS. Our patient had malrotation and obstruction in infancy and subsequently developed macrocephaly and a lipoma. She presented at 4 years of age with both iron deficiency anemia and hypoalbuminemia from protein-losing enteropathy. She went on to endoscopy, colonoscopy, and video capsule endoscopy showing gastric, small intestinal, and colonic polyps but with histology including both a mixed histologic characterization of the polyps as expected with PTEN-HS, along with eosinophilic esophagitis, gastric, duodenal, colonic and polyp eosinophilia. She improved with enteral nutritional support and budesonide. Intestinal malrotation is a previously unrecognized feature of PTEN-HS, in our patient protein-losing enteropathy may have resulted from polyposis or eosinophilic gastrointestinal disorder. Albeit rare, PTEN-HS represents an elusive differential diagnosis with a broad spectrum including gastrointestinal symptomatology. Our case report illustrates the overlap of clinical, endoscopic, and histologic findings that can complicate PTEN-HS.

Key Words: pediatric, polyposis, PTEN, PTEN-HS, protein-losing enteropathy: hypoproteinemia, eosinophilic enteropathy: polyp, diarrhea, celiac disease

INTRODUCTION

Phosphatase and tensin homolog hamartoma syndrome (PTEN-HS) is a rare hereditary polyposis syndrome characterized by germline mutations in *PTEN* encoding gene on chromosome 10q23.3 resulting in hamartomatous lesions in the skin and gastrointestinal tract. It is associated with an increased risk of malignancy including thyroid and, in adults, breast, and colorectal cancer (1). PTEN-HS can present during childhood with gastrointestinal symptoms, macrocephaly, and developmental delays or autism (2). Symptomatic children can present with diarrhea, abdominal pain, and gastrointestinal bleeding (3) and may harbor polyps in the stomach, small intestine, and colorectum. PTEN-HS may be related to eosinophilic gastrointestinal disorders (EGIDs) presenting in the first decade of life, usually as eosinophilic esophagitis (EoE) with systemic eosinophilia and coexisting atopy (3). Herein we describe a 4-year-old female who presented initially with intestinal obstruction complicating malrotation and later developed severe malabsorption, iron deficiency, and protein-losing enteropathy (PLE) subsequently diagnosed with PTEN-HS.

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CASE REPORT

Our patient, a previously healthy Caucasian female initially presented at 4 years of age with pallor and decreased energy. She was found to have profound anemia and hypoalbuminemia and was referred for further evaluation. She had first presented in infancy with obstruction from volvulus complicating malrotation. She had macrocephaly, asthma treated with montelukast, and had undergone tonsillar adenoidectomy. Initial diagnostic workup included normal inflammatory markers, normal liver enzymes, and normal zinc level. A low total IgA negated celiac serology however stool for alpha-1 antitrypsin was elevated consistent with PLE. Urinalysis was negative for proteinuria. She was treated and responded to oral iron supplementation (ferrous sulfate). The family history was unknown on the father's side but negative for celiac disease, early colon cancer, and breast or thyroid cancer on the mother's side.

Longitudinal growth parameters were unremarkable with her weight and height tracking at the 50th and 25th percentile, respectively, throughout the period of time that she was followed. Her physical exam revealed a diffuse area of swelling on the right thigh consistent with a lipoma but otherwise unremarkable except for mild lower extremity pitting edema. Initial and subsequent abnormalities noted upon laboratory investigation are summarized in Table 1.

Given her initial presentation, the possibility of celiac disease, and evidence of PLE, she underwent endoscopy and colonoscopy. She was found to have extensive gastric, duodenal (Fig. 1A), and milder colonic polyposis. Polyp histology initially showed inflammatory, then hamartomatous polyposis along with significant tissue eosinophilia in biopsied polyp and nonpolyp mucosa in the esophagus, stomach and duodenum consistent with EGID. Initial duodenal mucosal histology did not show intraepithelial lymphocytes and although celiac serology has more recently turned positive (Table 1), synchronous duodenal mucosal biopsies on a regular diet were negative for celiac. Upon repeat endoscopy with polypectomy, colonoscopy, and wireless capsule endoscopy, we noted numerous sessile small intestinal polyps ranging in size from 3 to 5 mm and several pedunculated, predominantly proximal small intestinal polyps ranging from 0.8 to 1 cm (Fig. 1B). Enteroscopy with polypectomy was declined, and therefore, her guardian was counseled to be vigilant for symptoms of intestinal obstruction.

TABLE 1. Abnormal laboratory investigations/age

Age/y	2	4	5	6	7	9
Hgb, g/dL	10.6	6.6, 9.7, 10.0	11.5	10.0, 11.9	8.6	9.6
Platelet count, × 10^3/mcL	185	186, 217, 262	174	106		75
Eosinophil count, × 10^3/mcL		0.54, 0.52, 0.73	0.14	0.48, 0.85	0.43	0.48
MCV, fL	86.3	65.2, 86.7, 85.2	85.4	84.3, 83.5	68.1	71.9
MCH, pg	27.4	18.2, 26.8, 27.0	27.1	26.6, 27.3	18.8	25.2
RDW, %	12.5	17.5, 13.2, 13.9	13.6	13.3, 12.8	16.5	19.2
Protein total g/dL		4.2, 5.0	6.3	4.2, 5.1	4.8, 5.7	6.5
Albumin, g/dL		2.3, 2.9	3.8	3.0, 2.3	2.8, 3.4	4.0
Alkaline phosphatase, U/L		60				73
Ferritin, ng/mL	9	5, 62	36	25	5	
TTG IgA, U/mL		6.9*	13.8*		23.35*	<1†
Fecal α1AT, mg/mL		385				
Fecal calprotectin, μg/mg		544.1				
Stool reducing substances					Negative	

Hgb = hemoglobin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RDW = red cell distribution width; TTG IgA = anti-tissue transglutaminase IgA antibody.
TTG IgA reference range:
*0.0–19.99,
†<1 U/mL.

Initial and subsequent endoscopy and histology findings are summarized in Table 2.

Given evidence of extensive intestinal hamartomatous polyps, macrocephaly, and lipoma, she was evaluated through our multidisciplinary polyposis syndrome clinic. She satisfied clinical criteria for PTEN-HS (4) and, following genetic counseling, was tested for PTEN pathogenic variants. Targeted sequencing revealed heterozygosity for a known pathogenic variant (c.697 C>T, pArg-233Ter), which translates to premature termination of the messenger RNA transcript resulting in a truncated protein or messenger RNA decay.

The family declined further genetic testing, and the child received iron, multivitamin supplementation, and enteral nutrition support. Administration of oral budesonide on 2 separate occasions resulted in decreased edema but was discontinued after several months out of concern for possible adverse effects. She is currently asymptomatic with most recent growth parameters at the 42nd and 33rd percentile for weight and height, respectively. Serum protein and albumin are normal, but she has persistent iron deficiency anemia responsive to iron supplementation. Consent was obtained from the legal guardian for publication of the case details.

DISCUSSION

Our patient's earliest presentation was with intermittent intestinal obstruction from volvulus complicating malrotation. In a landmark paper describing the extraintestinal phenotype of juvenile polyposis syndrome, Desai et al (5) included 1 patient with intestinal malrotation. Given the phenotypic overlap between PTEN-HS and juvenile polyposis syndrome (6) and the fact that genetic analysis was not reported, the individual in question likely harbored PTEN mutation given that he was reported with Bannayan-Riley-Ruvalcaba syndrome and penile pigmentation (7,8). To date, an association

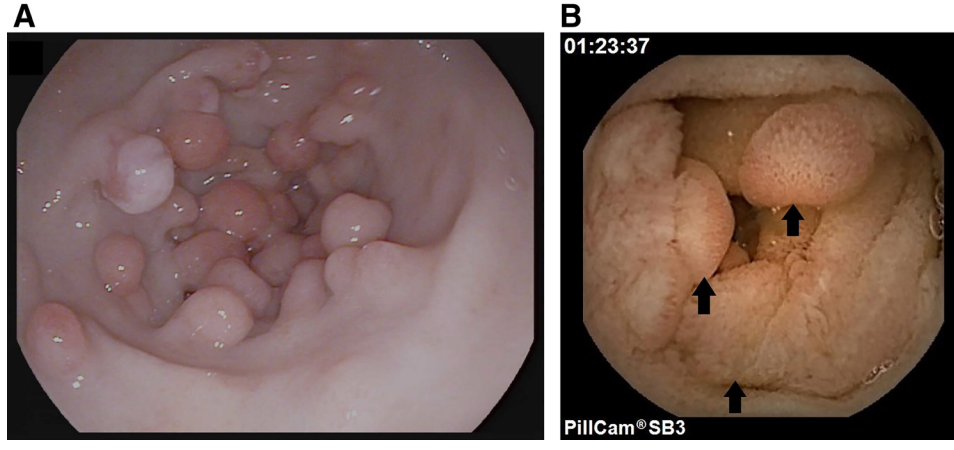

FIGURE 1. Endoscopic findings at 4 y of age. A) Esophagogastroduodenoscopy showing profuse gastric antral polyps and (B) Small bowel capsule showing jejunal polyps.

TABLE 2. Procedure findings, gross, and histopathology reported findings

Age	Procedure	Gross findings	Histology
4	EGD	Several (>10) polyps 5–9 mm in size in the antrum, duodenal bulb, and second portion (Fig. 1A)	Esophagus: Esophagitis with increased intraepithelial lymphocytes, infiltration by eosinophils (up to 10/HPF), basal cell hyperplasia, submucosal fibrosis, and subepithelial infiltration by eosinophils
			Stomach polyp: Chronic gastritis with mixed inflammatory infiltrate with increased lymphocytes, plasma cells, neutrophils, and eosinophils (>20/HPF), associated with inter-glandular fibrosis, suggestive of eosinophil-rich inflammatory polyp
			Duodenal mucosal biopsies: Chronic duodenitis with slightly shortened mucosal villi, increased lamina propria lymphocytes, and plasma cells. No evidence of increased numbers of intraepithelial lymphocytes
			Duodenal polyp biopsies: Increased lamina propria lymphocytes, plasma cells, and eosinophils associated with regenerative changes and stromal fibrosis, suggestive of eosinophil-rich inflammatory polyp
	Colonoscopy	Several (>10) pan-colonic sessile polyps; 3–5 mm diameter	Colon (mucosal and polyp biopsies): Hyperplastic lymphoid aggregates
	SBC (Fig. 1B)	• Numerous SI polyps ranging in size from 3 to 5 mm sessile to 0.8–1 cm pedunculated • Proximal > distal SI distribution • Mucosal inflammatory changes in several polyps	
5	EGD	Multiple sessile antral polyps 5–9 mm in diameter Multiple sessile polyps (3–7 mm in diameter) noted throughout the duodenum	(Polypectomy tissue) Hamartomatous and hyperplastic polyps: Gastric mucosa with cystically dilated glands and marked stromal infiltration by chronic inflammatory cells, predominantly eosinophils. Noted eosinophil pit abscesses, foveolar hyperplasia, and lamina propria smooth muscle proliferation
	Colonoscopy	Multiple polyps noted throughout the colon, poor prep	
6	EGD	Antrum: Multiple polyps 5–9 mm diameter gastric corpus; numerous sessile polyps 3–5 mm diameter	Esophagitis: Mild focal basal cell hyperplasia, spongiosis, and upward migration of the vascular papillae; maximum eosinophil density 5/HPF
		Duodenum: Multiple polyps 3–5 mm in size throughout	(Polypectomy tissue—stomach, duodenum) (multiple) polypoid fragments of tissue composed of cystically dilated glands lined by mature epithelium and separated by prominent stroma with a mixed inflammatory infiltrate with many eosinophils; surface focally eroded and lined by inflamed granulation tissue; juvenile/inflammatory polyp
			Normal duodenal mucosal biopsies without villous abnormality or IEL (distal) duodenal polypectomy tissue slight blunting of mucosal villi, no IEL, increased lamina propria cellularity; lymphocytes, plasma cells, and eosinophils (>26/HPF)
	Colonoscopy	Several (>10) pan-colonic, 3–5 mm diameter sessile polyps	Colon polyp tissue and mucosal biopsies; no distinctive architectural or inflammatory alterations; cellularity of the lamina propria within normal limits
			Terminal ileum mucosal biopsies with increase in mucosal eosinophils (>48/HPF)
8	EGD	Several (>10) sessile and pedunculated polyps 3–8 mm in antrum	Gastric polyp tissue; hamartomatous polyps
		Several (>10) sessile duodenal (1st and 2nd part) polyps	Duodenal polyp tissue; hamartomatous polyps
			Polyp core supported by broad bands of muscularis mucosa smooth muscle, thicker centrally with Christmas tree appearance at low power; single-layer columnar and goblet cells are at the surface, stromal component is infiltrated by inflammatory cells
			Ki67 expressed at the base of the crypts and not expressed at the surface of the lesion, smooth muscle actin highlight smooth muscle fibers
			Duodenal mucosal biopsies; mucosal villi are tall and slender and the villous/crypt height ratio is within normal limits. The cellularity of the lamina propria is within normal limits
	Colonoscopy	Several (>10) pan-colonic sessile polyps	Colon polyp tissue; no distinctive architectural or inflammatory alterations; cellularity of the lamina propria within normal limits

EGD = esophagogastroduodenoscopy; HPF = high-power field; IEL = intra-epithelial lymphocytes; SBC = small bowel capsule; SI = small intestine.

between PTEN-HS and malrotation has not been recognized, and we could not identify other cases in the literature, this may however reflect the rarity and relatively elusive diagnosis of both conditions. If malrotation is in fact associated with PTEN, this would have important implications in counseling the parents and monitoring diagnosed or at-risk patients.

Hypoproteinemia is characteristic of several gastrointestinal pathologies. It may reflect decreased synthesis consequent to malnutrition, malabsorption, or advanced liver disease. Alternatively, an exudative hypoproteinemia may occur from an inflammatory process such as EGID that results in protein loss in the stool, hence PLE. PLE has also been described in severe juvenile polyposis phenotypes

including the severe infantile phenotype and with SMAD4 mutation. It has also been reported in adenomatous polyposis and Cronkhite-Canada syndrome in adults suggesting a relationship to polyp burden more so than histology (9).

PTEN-HS in children often presents with macrocephaly, developmental delay, and neurologic and behavioral abnormalities. Children may exhibit growth abnormalities including short stature and obesity (10). Characteristic skin manifestations including pigmented macules on the glans penis may present as early as infancy. Thyroid involvement including follicular adenomas and thyroid cancer has been reported as early as at 6 years of age (11). Additional risk for colorectal and extraintestinal malignancy is of concern in adulthood.

Intestinal polyposis is one of the most penetrant characteristics of PTEN-HS in childhood with panintestinal (stomach to colon) distribution and mixed histologic presentation including inflammatory, hamartomatous, tubular adenomatous types, and, less frequently, lipomas and ganglioneuromas (12). Often, children with PTEN-HS will present with constipation potentially related to coexisting neurodevelopmental disability or dysmotility.

Henderson et al (3) reported eosinophilic gastrointestinal disorders (EGID) to be more prevalent in patients with PTEN-HS, in their series, as in our patient, the diagnosis of PTEN-HS trailed that of EGID (8.0, 7.6 y; P = non-significant). The prevalent EGID phenotype was EoE (6/8) followed by eosinophilic gastritis (3/8) and eosinophilic colitis (1/8). Most patients (6/8) had atopic illness. Gastric, followed by duodenal and colonic polyps were the most common distribution with most (6/8) involving multiple sites as noted in our patient. Histologic manifestations in these patients include eosinophil-rich gastrointestinal polyposis including hamartomatous and inflammatory polyps overlapping with eosinophil-rich inflammatory pseudopolyps occasionally reported in EGID (13). PLE, in turn, has been noted in isolated case reports of eosinophilic gastritis or gastroenteritis but not with PTEN-HS. PLE in EGID may be responsive to low-dose or topical corticosteroids (14).

Our patient presented several interesting clinical features related to PTEN-HS including the speculative association with malrotation. The coexistence of a large polyp burden and simultaneous eosinophilic inflammatory process render the precise etiology of the observed PLE ambiguous. Our patient harbored hyperplastic, hamartomatous, and inflammatory polyps, diffuse mucosal eosinophilia including EoE, duodenitis, and nonspecific gastritis illustrating the potentially complex gastrointestinal involvement in pediatric patients with PTEN-HS. Our report underscores the need for clinical vigilance for a rare hereditable disorder that may coexist with EGID and may include spectrum of gastrointestinal and extraintestinal manifestations, often without family history.

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