A Case Series of Pediatric Intestinal Ganglioneuromatosis With Novel Phenotypic and Genotypic Profile

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Introduction: Intestinal ganglioneuromatosis (IGN) is a rare condition with enteric involvement. Herein, we report a case series of pediatric IGN with a novel phenotypic and genotypic profile.

Methods: The clinical presentation, histopathology, immunochemistry, molecular features, treatment, and prognosis of 3 cases of IGN were assessed.

Results: The cases involved 3 boys with an age range of 1 year and 4 months to 8 years, mimicking juvenile polyps or pseudomembranous enteritis. One patient carried a novel germline mutation in RTEL1 (c.296C>T/p.Pro99Leu) along with variants in F11 (c.1489C>T/p.Arg497Xaa), NBAS (c.1514delC/p.Pro505Hisfs*15), and FECH (c.315-48T>C/splicing), who died due to intractable inflammation. The other two patients underwent recurrence without significant signs of systemic syndrome or malignant progression.

Conclusion: This case series added to the phenotypic and genotypic spectrum of pediatric IGN, which requires the accumulation of more cases and research for in-depth understanding.

Keywords: intestinal ganglioneuromatosis, juvenile polyps, pseudomembranous enteritis, mutation, case series

INTRODUCTION

Ganglioneuroma (GN) is a well-differentiated benign tumor involving a combination of neuroblastoma (NB) and ganglioneuroblastoma (GNB) to compose a neuroblastic tumor (NT) according to the International Risk Group (INRG) (1). GN originates from the primitive neural crest, mostly the adrenal gland, followed by the retroperitoneum, mediastinum, neck, and pelvic sympathetic ganglia (2). In addition to a rare condition with enteric involvement, intestinal ganglioneuromatosis (IGN) is characterized by the proliferation of ganglion cells, Schwann stromal cells, and nerve fibers in the lamina propria, submucosa, and/or myenteric plexus of the intestinal wall. The disease can be divided into polyoid ganglioneuroma, ganglioneuromatous polyposis, and diffuse ganglioneuromatosis, depending on the number of lesions and growth pattern (3). The latter is usually associated with systemic disorders, including multiple endocrine neoplasia type 2B (MEN2B), neurofibromatosis type 1 (NF1), and Cowdom syndrome (4–6). Clinically, IGN often mimics Crohn’s disease (7) or gastrointestinal stromal tumor (GIST) (8). Death due to delayed diagnosis in a 6-year-old boy has been reported (9), rendering IGN a crucial threat to the health of children.
Herein, we reported 3 pediatric cases of IGN manifesting as recurrent bloody stools or watery diarrhea, with a preliminary diagnosis of juvenile polyps or pseudomembranous enteritis. The cases were finally diagnosed as IGN based on the proliferation of ganglion cells, Schwann stromal cells, and nerve fibers in the lamina propria, submucosa, and/or myenteric plexus by repeated biopsy or full-thickness resection. Whole-exome sequencing (WES) revealed a novel germline mutation in RETEL1 (c.296C > T/p.Pro99Leu), along with the potentially pathogenic variants in F11 (c.1489C > T/p.Arg497Xaa), NBAS (c.1514delC/p.Pro505Hisfs*15), and FECH (c.315-48T > C/splicing) in one patient, who died owing to intractable inflammation. The other two patients underwent recurrent polypectomy without significant signs of systemic syndrome or malignant progression. This work may enhance practitioners’ awareness and arouse further research.

This article is written in accordance with CARE Checklist (10), which is uploaded as Supplementary Material.

**MATERIALS AND METHODS**

**Patients**

The clinical data, histopathology, immunohistochemistry, treatment, and prognosis of two hospitalized patients and one consulted patient diagnosed with IGN were reviewed. In addition, one patient underwent molecular genetic analysis. This study conformed to the provisions of the institutional ethics committee and the Declaration of Helsinki (as revised in 2013). The patient’s parents shared all procedures, including treatment, and signed written informed consent. Written informed consent was obtained for the publication of any potentially identifiable images or data included in this article.

**Histopathology**

Specimens for all patients were obtained from endoscopic biopsy or surgical resection, fixed in 10% buffered formalin, dehydrated in graded concentrations of ethyl alcohol, and embedded in paraffin. Then, they underwent routine staining for hematoxylin and eosin (H&E).

**Immunohistochemistry**

Additional 4 μm sections were deparaffinized, rehydrated, and pretreated with 3% H2O2 to eliminate endogenous peroxidase activity. Moreover, they were treated with ethylenediaminetetraacetic acid (EDTA) (pH 9) or citrate buffer (pH 6) for heat-mediated antigen retrieval before commencing with the immunohistochemical (IHC) staining protocol. The primary antibodies used included S-100 (clone 3-3-C, ready-to-use solution), neuron-specific enolase (NSE) (clone MX006, ready-to-use solution), CD117 (clone YR145, ready-to-use solution), CD34 (clone QBCEnd/10, ready-to-use solution), and CD163 (clone MX081, ready-to-use solution), which were purchased from http://www.maxim.com.cn (Fuzhou, China) and http://www.gzlb.com (Guangzhou, China). The sections were incubated at 4°C, followed by incubating with a general secondary antibody for 1 h at room temperature. Finally, the sections were developed with diaminobenzidine (DAB) and counterstained with hematoxylin. Omitting the first antibody was prepared as the negative control.

**Molecular Genetic Analysis**

The EDTA-anticoagulated whole blood samples were collected from one patient and his parents. Trio-WES was performed by MyGenostics (a commercial genetic testing company) using the Illumina HiSeq X ten platform. DNA libraries were prepared with TruSeq DNA Library Preparation Kit following the manufacturer’s instructions. The raw reads were mapped to the reference human genome (GRCh37/hg19). Genome Analysis Toolkit (GATK)1 was applied for variation calling to summarize single nucleotide variants (SNVs) and indels. The ANNOVAR software and Enliven2 Variants Annotation Interpretation System were employed for annotation and interpretation. Data were filtered in 1,000 Genome,3 NHLBI Exome Sequencing Project (ESP6500),3 Genome Aggregation Database (gnomAD),4 dbSNP152,5 and Exome Aggregation Consortium (ExAC),6 Damage prediction of the genetic variants was conducted by Combined Annotation Dependent Depletion (CADD)7 for scoring and Mutation Significance Cutoff (MSC)8 for further comparing. The MSC server was applied to CADD, PolyPhen 2,9 and SIFT,10 with a 99% confidence interval and database source of HGMD and ClinVar.11 Genomics England PanelApp,12 a crowdsourcing tool, was utilized for analysis based on the variant-disease and gene-disease associations. Human Phenotype Ontology (HPO),13 Online Mendelian Inheritance in Man (OMIM),14 and HGMD database were used to match phenotype descriptions with variant and gene prioritization results. According to the American College of Medical Genetics and Genomics (ACMG) guidelines, genetic variants were classified as pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign, and benign. The pathogenicity

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1https://gatk.broadinstitute.org
2www.1000genomes.org
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4https://gnomad.broadinstitute.org
5https://www.ncbi.nlm.nih.gov/snp
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11https://www.ncbi.nlm.nih.gov/clinvar
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of filtered-out variants was predicted by MutationTaster as well. We conducted protein modeling of RTEL1 by SWISS-model with a UniProtKB code Q9NZ71, and the mutated structure was analyzed and visualized using PyMol. In addition, a total of 647 colorectal cancer samples and 51 normal controls from TCGA COADREAD were selected. The differential expression of RTEL1 mRNA was analyzed by the Wilcoxon rank-sum test and visualized by ggplot2 (3.3.3 version). The protein expression of RTEL1 in Caco-2 cells was displayed by The Human Protein Atlas (HPA), using an antibody coded HPA078328.

RESULTS

Patient 1

A 6-year-old boy with anal masses and bloody stools for 2 years was admitted to our hospital. The patient was born to healthy non-consanguineous parents as the second child in the family, and the sibling was healthy. No family members had similar symptoms. Physical examination on admission showed normal growth and development, with a height of 122 cm and a weight of 25.5 kg. There was no tenderness and no palpable mass in the abdomen. By finger examination, many spherical masses with diameters of 0.2–0.5 cm were palpable in the rectum, protruding from the surface of the rectal mucosa. Except for a reduction in hemoglobin (101 g/L) and red blood cell count (3.96 × 10¹²/L), other routine blood test indicators were in the normal range. Liver and kidney function and coagulation parameters were unremarkable. Colonoscopy revealed multiple polyps with paving stone-like changes in the descending colon (Figure 1A) of 10 cm from the anal orifice, extending outward to the dentate line and partly located in the rectal fold. The polyps were removed by electrocoagulation and cauterization. Gland hyperplasia, cavity expansion, interstitial blood vessel hyperplasia, necrosis, neutrophil infiltration, and hemosiderin deposits were observed in the lesions under microscopy (Figure 1B). The preliminary impression was juvenile polyps. In addition, there was a proliferation of the nerve plexus in the lamina propria and submucosa, consisting of nerve fibers, Schwann cells, and scattered ganglion cells (Figure 1C). IHC staining showed that the neoplastic hyperplasia was positive for S-100, PGP9.5, and Syn, but negative for PHOX2B. The Ki67 index was 5% approximately. Based on the findings, a diagnosis of IGN (ganglioneuromatous polyposis subtype) was made. To investigate systemic disorders correlating with IGN, an additional examination was performed. Cutaneous café-au-lait spots and neurofibromas, thyroid and adrenal lumps, or trichilemmomas and “cobblestone” tongue lesions were all absent, and serum calcitonin and urine catecholamine levels were normal. However, due to the unavailability of genetic testing in this patient, NF1, MEN2B, and Cowden syndrome cannot be ruled out. The mutations in NF1, RET, and PTEN are pending to be detected. During the 3-year follow-up, the patient had multiple recurrences but with no malignant transformation.

Patient 2

A boy aged 1 year and 4 months with recurrent diarrhea for 2 months was referred to our hospital. Prior to admission, the patient had been hospitalized in the intensive care unit (ICU) of another hospital for 77 days due to severe pneumonia. After anti-infective therapy and invasive ventilator-assisted ventilation, the patient’s pneumonia improved. Subsequently, the patient repeatedly developed rashes and loose stools, which resembled a dilute water sample, more than 20 times a day. The boy was delivered by a full-term cesarean section and he weighed 4.1 kg at birth and was assessed as having macrosomia. The parents both claimed to be in good health, though his mother had a miscarriage in the third month of her first pregnancy for unknown reasons. No family members had similar symptoms. Compared with his peers, the patient’s growth and development were normal, with a height of 79.5 cm and a weight of 8.9 kg on physical examination at admission. Routine blood tests revealed elevated C-reactive protein (51.8 mg/L), neutrophil percentage (66.9%), and white blood cell count (8.4 × 10⁹/L), and decreased lymphocyte percentage (27.1%). Albumin (22.90 g/L), alanine aminotransferase (7.0 U/L), and lactate dehydrogenase (361 U/L) were at low levels. Routine stool examination displayed 3–5 white blood cells per high-power field (HPF), without pathogens. Metagenome sequencing screened out human cytomegalovirus (HHV-5) with high confidence. However, no nucleotide sequences of other pathogens were detected, such as Clostridium difficile. Abdominal computed tomography (CT) showed that the liver was slightly enlarged, with a reduced density. The rectum, sigmoid colon, and partial small intestine were dilated and effused, and the colon wall was slightly thickened. In addition, enlargement of multiple mesenteric lymph nodes and minimal ascites was noted. Although colonoscopy during the patient’s previous hospitalization showed erosive colitis with superficial ulcers and granulation tissue formation, our surgeon performed another colonoscopy to confirm the intestinal manifestation, when the colonoscope explored the transverse colon, a change to laparotomy was required due to difficulty in entering the region. In the surgical view, there was a moderate amount of clear ascites in the abdominal cavity. Starting from 15 cm of the flexor ligament, the small intestine exhibited multiple segmental stenoses and dilatations, with poor peristaltic function. The entire small intestinal mucosa presented pseudomembranous changes, raising suspicion of pseudomembranous enteritis. After clearing the necrotic mucosa, the entire thickness of the intestinal sample was taken and sent for pathological examination, followed by enterotomy. Histologically, significant inflammatory exudation and necrosis of the mucosal layer of the intestinal wall with ulcer formation, as well as eosinophils and histiocyte-like cells, were detected (Figure 1E). The nerve plexus in the submucosa and myenteria was significantly proliferated and enlarged, including ganglion cells, nerve fibers, and Schwann matrix (Figures 1F,G). Histiocyte-like cells in the necrotic region were
immunoreactive for CD163, and neural elements were positive for Syn (Figure 1H) and PGP9.5. Hence, he was diagnosed with IGN (diffuse ganglioneuromatosis). The patient received symptomatic and supportive treatment of anti-infection and albumin supplementation. Because of severe and uncontrollable inflammation, the patient’s condition gradually deteriorated, and he unfortunately died 3 months after surgery.

**Patient 3**

Case 3, a consultation case, involved an 8-year-old boy who had a history of bloody stools for 3 months. No family members had similar symptoms. The patient had been hospitalized in a local hospital. Routine stool examination revealed occult blood positivity, though routine blood examination and coagulation function were normal. Electronic colonoscopy revealed multiple colorectal polyps. Two sigmoid colon and rectal polyps were removed, with a pathological diagnosis of juvenile polyps. Subsequently, intestinal endoscopic submucosal dissection (ESD) was performed, and 17 sigmoid colon polyps were excised. Then, the patient’s pathological slides were transferred to our Department of Pathology for consultation. Histologically, there were many acute and chronic inflammatory cell infiltrations in the intestinal mucosa, and hyperplastic nerve plexuses were seen in the lamina propria and submucosa, in which several ganglion cells were surrounded by nerve fibers and Schwann cells. The cells were positive for Vimentin, NF, NSE, S-100, SOX10, and Syn but negative for NeuN, CD117, and CD34. Therefore, the result of the consultation was IGN (ganglioneuromatous polyposis subtype). Because it was a consultation case, no more clinical examination information was obtained. The patient’s subsequent follow-up indicated recurrence. During the 2-year follow-up, there were still more than ten broad-based polypoid lesions in the descending colon, sigmoid colon, and rectum, which all indicated IGN.

The main manifestations of the 3 patients are provided in Table 1.

### Genetic Findings

In Patient 2, a germline heterozygous variation, c.296C>T, was found in RETEL1 with the transcript of NM_032957 by WES. The variant was inherited from the healthy father, leading to a change of proline to leucine at the amino acid position 99 (p.Pro99Leu) in the domain of helicase ATP-binding (Figure 2A), which was not reported in the HGMD. The amino acid residue of the base substitution (p.Pro99Leu) was not conserved across various species (Figure 2B). The CADD score of c.296C>T was 12.030, predicted as an uncertain impact by MSC. Comprehensively, c.296C>T (absent from controls PM2 + insufficient evidence in silico BP4) was evaluated to be VUS according to the guideline of the ACMG, which need further study to confirm the association between the variant and phenotype. The nomenclature of variants was based on the recommendations of the Human Genome Variation Society (HGVS).\(^{19}\) Wild-type and mutated RETEL1 were modeled by PyMol (see text footnote 17) that showed no effect of Pro99Leu residue change on polar contact with the amino acids Gly97 and Ala101 (Figure 2C). In the TCGA database, the differential expression of RETEL1 mRNA in colorectal cancer was higher than normal control with statistical significance (p < 0.001) (Figure 2D). The protein expression of RETEL1 in Caco-2 cells was exhibited by data from HPA (Figure 2E). There were

\(^{19}\)http://www.hgvs.org/varnomen
The age, sex, and clinical and endoscopic findings of our case series are consistent with those reported previously, but there were no signs of systemic disorders, which need further surveillance and validation. Patient 2 presented with severe lung and intestinal inflammation, and notable intestinal mucosal necrosis mimicked pseudomembranous enteritis, which is not reported previously. With no positive findings based on multiple mucosal biopsies, a definitive diagnosis was delayed, illustrating the importance of full-thickness biopsy.

Histologically, IGN is defined by the abnormal proliferation of ganglion cells, nerve fibers, and Schwann cells in the enteric nervous system. IGN can be divided into polypoid GN, ganglioneuromatous polyposis, and diffuse ganglioneuromatosis (3). Polypoid ganglioneuroma is a small, single polypoid lesion ≤ 2 cm in size composed of hyperplastic Schwann cells and scattered ganglion cells involving the mucosa and submucosa (17). Ganglioneuromatous polyposis presents as multiple intestinal polyps, often > 20 in quantity and ≤ 2.2 cm in diameter, endoscopically similar to familial adenomatous polyposis (FAP) or juvenile polyposis, which may lead to misdiagnosis (23). The tumor cells of diffuse ganglioneuromatosis are nodular or diffusely proliferating, and they invade the intestinal wall and may be accompanied by the proliferation of the submucosa, myenteric nerve plexus, or even mesenteric nerve plexus (4, 6–8, 24–26). On IHC staining, Schwann cells express CD56, SOX10, and S-100, and ganglion cells express NSE, CD56, Syn, Calretinin, NeuN, and S-100 (6, 8, 12, 19, 20, 25–27). According to the above criteria, 2 of our cases showed multiple colorectal polyps (> 20), and neurofibril and ganglion cell hyperplasia was detected in the juvenile polyps under the microscope; thus, they were diagnosed as ganglioneuromatous polyposis. Another case showed significant pseudomembranous inflammation and stenosis changes in the entire small intestine wall. In addition to inflammation and necrosis by microscopy, the nerve plexus in

| TABLE 1 | The main manifestations of the case series. |
|-----------------------------------------------|
| **Gender** | Patient 1 | Patient 2 | Patient 3 |
| Male | Male | Male |
| Age (years) | 6 | 1.3 | 8 |
| Bloody stools | Present | Absent | Present |
| Diarrhea | Absent | Absent | Absent |
| Constipation | Absent | Absent | Absent |
| Growth and development | Normal | Normal | Normal |
| Systemic disorders | None | None | None |
| Family history | None | None | None |
| Disease location | Descending colon | Small intestine | Sigmoid colon and rectum |
| Mimicry | Juvenile polyps | Pseudomembranous enteritis | Juvenile polyps |
| Pathological subtype | Ganglioneuromatous polyposis | Diffuse ganglioneuromatosis | Ganglioneuromatous polyposis |
| Genetic findings by WES | Not available | Not available | Not available |
| Mutations in RET, NF1, and PTEN | Not available | Not detected | Not available |
| Treatment | Polypectomy | Surgical resection | Polypectomy |
| Outcome | Relapsed during 3-year follow-up | Died 3 months after surgery | Relapsed during 2-year follow-up |

DISCUSSION

The IGN occurs in both children and adults, mostly in children younger than 15 years. The pediatric patients aged from 2 days to 14 years, with a median age of 6 years, and with a slightly higher incidence in males. The most common location is the colorectum, followed by the terminal ileum and the entire intestine. The stomach or pancreatic head may be involved simultaneously (11, 12), and a few occurrences in the gallbladder or bladder have been reported (13, 14). Usually, patients present with abdominal pain, diarrhea, vomiting, bloody stools, constipation, and obstruction, which in some cases is accompanied by iron-deficiency anemia, elevated serum vasoactive intestinal peptide and hypokalemia, and growth and motor development retardation (15–20). Many patients have systemic disorders, predominantly MEN2B, followed by Cowden syndrome and NF1, presenting thyroid and adrenal tumors, trichilemmomas and “cobblestone” tongue lesions, or cutaneous café-au-lait spots and neurofibromas (4–6, 16, 17, 21–24). Endoscopically, pedunculated or sessile polyps are common, ranging from single to numerous, with a diameter of 0.1–17 cm, and may be misdiagnosed as juvenile polyps or GIST (8, 17). Non-polyposis lesions manifest as intestinal stenosis or inflammatory lesions of mucosal ulcers, leading to misdiagnosis with Hirschsprung’s disease or Crohn’s disease (7, 9, 16, 20, 21). The age, sex, and clinical and endoscopic findings of our case series are consistent with those reported previously, but there were no signs of systemic disorders, which need further surveillance and validation. Patient 2 presented with severe lung and intestinal inflammation, and notable intestinal mucosal necrosis mimicked pseudomembranous enteritis, which is not reported previously. With no positive findings based on multiple mucosal biopsies, a definitive diagnosis was delayed, illustrating the importance of full-thickness biopsy.
FIGURE 2 | Bioinformatics analysis results of RTEL1. (A) The location of variant c.296C > T (p.Pro99Leu) in gene and protein. (B) Conservation status of amino acid residue of the mutation site across various species. (C) Wild and mutated type of the p.Pro99Leu variant compared by PyMol. (D) The differential expression of RTEL1 mRNA in colorectal cancer (n = 647) and normal control (n = 51) in TCGA. (E) The protein expression of RTEL1 in colorectal adenocarcinoma cell line Caco2 in the Human Protein Atlas.
the submucosa and myenteric plexus was significantly proliferated and enlarged, with ganglion cells, nerve fibers, and Schwann matrix, in line with the diagnosis of diffuse ganglioneuromatosis. IHC staining showed that the neoplastic hyperplasia was positive for S-100, PGP9.5, and Syn, which further supported the diagnosis. However, due to the uncommon nature of IGN and the possibility of coexistence with juvenile polyps, neurofibromas, or schwannoma, it is still challenging to reach timely and correct judgment in daily work.

Due to close relationship between IGN and hereditary tumor syndromes, diagnosis of IGN usually triggers genetic testing. RET, PTEN, or NF1 mutations were detected to screen for MEN2B, Cowden syndrome, or NF1, respectively. Animal model studies have found that RET-activated mutations and PTEN deletion mutations can generate GN in mice through the PI3K/PTEN-AKT-S6K signaling pathway (28, 29). Whether the pathogenesis of IGN is consistent with the mechanism remains to be confirmed by more experiments. In our series, genetic testing for RET, PTEN, or NF1 was not available in Patient 1 and Patient 3, and further work is required to rule out systemic disorders. Patient 2 underwent WES to investigate possible genetic syndromes, and a heterozygous RTEL1 mutation (c.296C > T/p.Pro99Leu) was detected rather than a mutation in RET, PTEN, or NF1. Therefore, MEN2B, Cowden syndrome, and NF1 were excluded. RTEL1 (regulator of telomere elongation helicase 1) (NM_032957, ENST00000508582) is located on chromosome 20 (chr20: 63,658,312-63,696,245), containing 35 exons encoding a protein of 1,243 amino acids, which functions in the stability, protection, and elongation of telomeres and interacts with proteins in the shelterin complex known to protect telomeres during DNA replication (30). RTEL1 mutations have been associated with dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome (31, 32). Ziv et al. (33) found that C.3791G > A in RTEL1 was linked to infantile-onset ulcerative colitis and severe immunodeficiency, which is likely the result of aberrant telomere function in both immune and epithelial cells. Patient 2 harbored the novel c.296C > T in RTEL1, resulting in the change of proline to leucine at the amino acid position 99 (p.Pro99Leu) in the domain of helicase ATP-binding. Whether the mutation led to unstable telomere maintenance and drove the occurrence of IGN in patient 2 needs further analysis.

Additional mutations in F11, NBAS, and FECH were screened out in Patient 2, predicted as pathogenic or likely pathogenic. F11 (coagulation factor XI) encodes coagulation factor XI of the blood coagulation cascade. The variant of c.1489C > T/p.Arg497Xaa has been found in factor XI deficiency (34). NBAS (NB-amplified sequence) encodes a protein with two leucine zipper domains, a ribosomal protein S14 signature domain and a Sec39-like domain. The protein is thought to be involved in Golgi-to-ER transport. Mutations in this gene are associated with short stature, optic nerve atrophy, and Pelger-Huet anomaly. The frameshift mutation (c.1514delC/p.Pro505Hisfs*15) in Patient 2 caused the amino acid at position 505 to be shifted 15 positions back and then terminated early, which is unique according to references. The protein encoded by FECH (ferrochelatase) is localized to the mitochondrion, where it catalyzes the insertion of the ferrous form of iron into protoporphyrin IX in the heme synthesis pathway. The c.315–487T > C/splicing has been reported to be associated with erythropoietic protoporphyria (36). However, the variants are not highly correlated with the phenotype of Patient 2 and the evidence for pathogenicity was insufficient.

Patients with IGN are usually treated with surgery. For polyp lesions, polypectomy alone is sufficient. If the lesions are too large or the intestinal stenosis is obvious, bowel resection should be performed. Although IGN is a benign tumor, many patients experience recurrence. There are 2 reported cases of IGN with concomitant adenocarcinoma or adenocarcinoma development at 12 years after diagnosis (37, 38). The significant differential expression of RTEL1 in colorectal cancer and normal control in TCGA indicates that RTEL1 may play a role in the progression of malignancy, while its contribution to IGN or adenocarcinoma that developed from IGN is unclear and worth investigating. Our case series involved polypectomy and surgical resection. After 3 months to 3 years follow-up, 2 cases of ganglioneuromatous polyposis recurred repeatedly, despite multiple polypectomy procedures. Intestinal resection should be considered in the future. Unfortunately, the excessive inflammatory response in another case of diffuse ganglioneuromatosis was not corrected, resulting in multiple organ dysfunction and death. These results demonstrate that seemingly benign IGN has a poor disease course, which should arouse the attention of clinicians.

### CONCLUSION

As a rare condition with enteric involvement, our case series expands the phenotypic and genotypic spectrum of pediatric IGN by mimicking pseudomembranous enteritis and carrying a novel germline mutation in RTEL1 along with additional variants. The patients experience relapses or death. The unclear pathogenesis and unfavorable prognosis require more awareness and research.
AUTHOR CONTRIBUTIONS

YF and YZ drafted and revised the manuscript. RD and Y-ZW collected and analyzed the data. LC and GC designed the work and approved the final version to be published. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.883958/full#supplementary-material
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