DOI: 10.7860/JCDR/2021/48101.14848

Case Report

Pathology Section

A Rare Case of Diffuse Intestinal Ganglioneuromatosis in a Child Presenting with Intussusception

ANURADHA SEKARAN[1], AMRUTA PATIL[2], MAHESH SHETTY[3], GUDURU VENKAT RAO[4], DUVVUR NAGESHWAR REDDY[5]

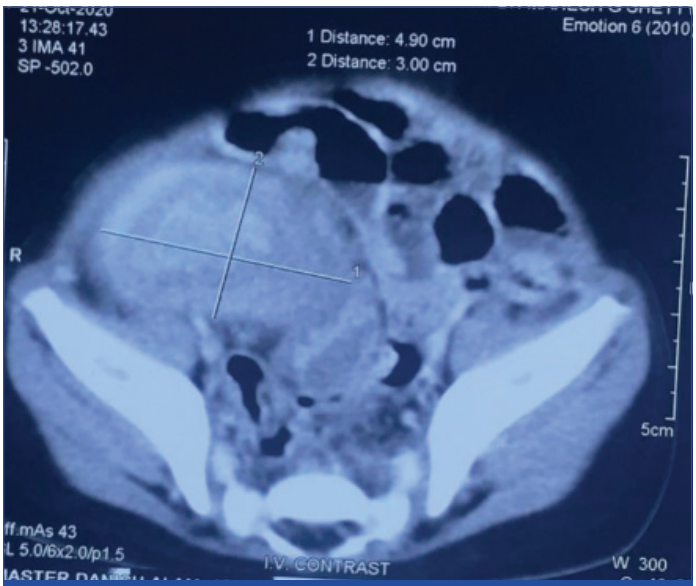
ABSTRACT

Ganglioneuromas are benign neurogenic neoplasms commonly seen in children which are originating from neural crest cells of sympathetic ganglia or adrenal medulla. Rarely, they may arise from the visceral organs like intestine. Diffuse intestinal ganglioneuromatosis is a rare disease, caused due to abnormal proliferation of ganglion cells, nerve fibres and schwann cells in the wall of intestine. Author hereby present a case of diffuse intestinal ganglioneuromatosis in an 18-month-old male child who presented with symptoms of small bowel obstruction. Resected segment of ileocecal junction revealed ulcero-nodular areas which on microscopy showed diffuse hyperplasia of nerve bundles and ganglion cells with immunohistochemistry confirmation. Intestinal ganglioneuromatosis is a rare condition having syndromic association with MEN-2B, Neurofibromatosis-1 and Cowden syndrome. As this disease has a low clinical suspicion, very nonspecific symptoms and radiological findings, histopathological examination becomes mainstay in diagnosis. Further workup is essential to rule out presence of associated syndromes. Surgical excision is the ultimate treatment with screening for genetic abnormalities.

Keywords: Ganglioneuroma, Paediatrics, Syndrome

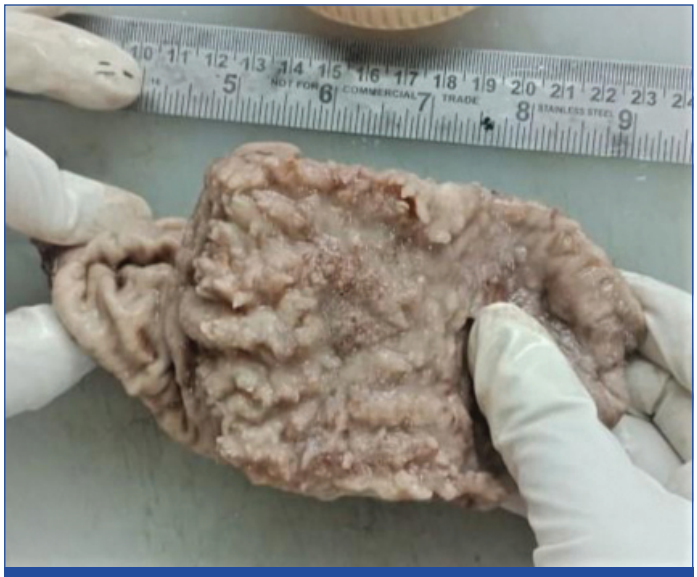
CASE REPORT

An 18-month-old male child presented with history of recurrent vomiting since eight months associated with abdominal distension and failure to thrive. No history of fever, jaundice, loss of appetite and gastrointestinal (GI) bleed was noted. All haematological and biochemical investigations were within normal limits. Ultrasound examination revealed small bowel intussuseption with features of small bowel obstruction. CT abdomen showed diffuse circumferential long segment thickening on terminal ileum measuring 7 cm in length and 1.5 cm in thickness with bowel within bowel appearance in its distal end suggesting intussuseption with grossly dilated small bowel [Table/Fig-1]. Multiple mesenteric lymph nodes were noted. Based on clinical and radiological findings diagnosis of subacute intestinal obstruction with intussuseption was made and laparotomy was done.



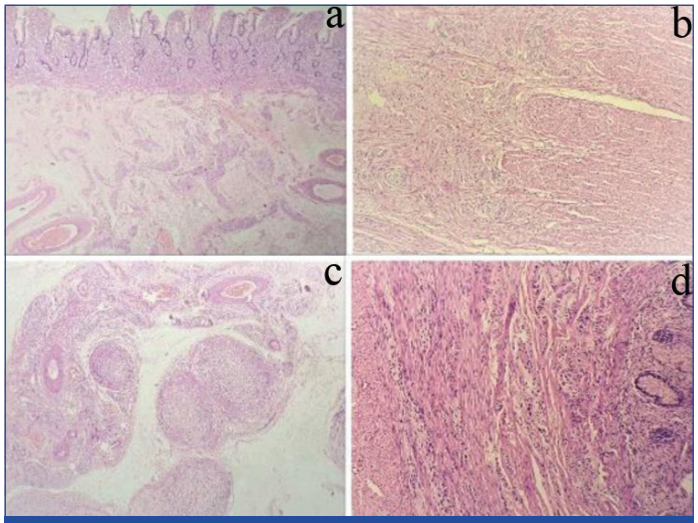
[Table/Fig-1]: CT abdomen showing diffuse circumferential long segment thickening on terminal ileum.

Intraoperatively there was thickened ileocecal region causing luminal compromise and upstream dilatation of small bowel with circumferentially thickened ileocecal region with mucosal nodularity and linear mucosal ulcers visible on luminal surface, clinically thought to be inflammatory or neoplastic lesion. In view of clinical and radiological diagnosis of intussusception and intestinal obstruction, laparotomy with resection of ileocecal junction was done. We received an ileocecal resection specimen measuring 15 cm in length which on cut surface showed ulcero-nodular areas with irregular mucosa near ileo-cecal junction and ileum in a length of 7 cm [Table/Fig-2]. The appendix was 5.5 cm in length and was unremarkable on gross examination. Microscopic examination from ulcero-nodular areas in ileo-cacal region, colon and appendix showed mucsularis mucosa, submucosa, muscularis propria and serosa with diffuse hyperplasia of nerve bundles and ganglion cells [Table/Fig-3]. Focal areas of ganglion cells in clusters (5-20/cluster) with thickening of muscularis mucosa were also seen. With these histological features, differential diagnosis of diffuse ganglioneuromatosis, neurofibromatosis and intestinal neuronal dysplasia involving ileum, ileocecal junction, ascending colon and appendix were considered. On immunohistochemistry,

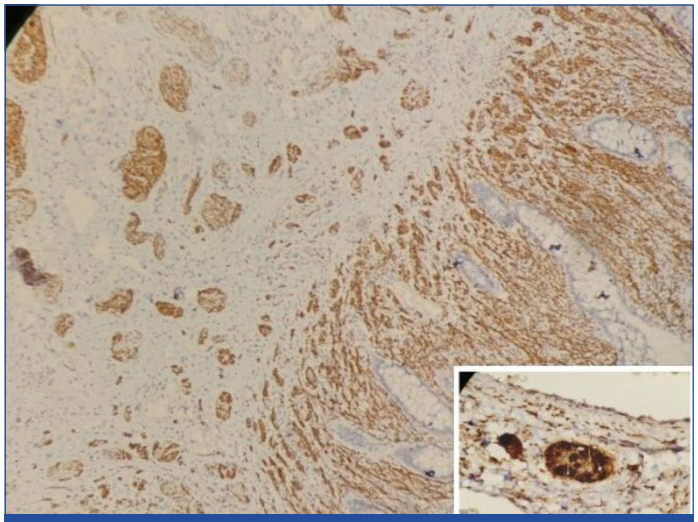


[Table/Fig-2]: Ulcero-nodular areas with irregular mucosa near ileo-cecal junction.

S-100 protein, synaptophysin and Neuron Specific Enolase (NSE), the ganglion cells and hyperplastic nerve bundles were highlighted [Table/Fig-4] which further confirmed the diagnosis of diffuse ganglioneuromatosis. On three months follow-up patient is doing well with no evidence of recurrence.



[Table/Fig-3]: a) The submucosa with diffuse hyperplasia of nerve bundles and ganglion cells (H&E, 10 x); b) The muscularis propria with diffuse hyperplasia of nerve bundles and ganglion cells (H&E, 10 x); c) The serosa with diffuse hyperplasia of nerve bundles and ganglion cells (H&E, 10x); d) The submucosa with diffuse hyperplasia ganglion cells (H&E, 40 x).



[Table/Fig-4]: a) S-100 protein, synaptophysin and Neuron Specific Enolase (NSE) highlighting the ganglion cells and hyperplastic nerve bundles (20x); Inset picture Neuron Specific Enolase (NSE) highlights the ganglion cells (IHC for NSE, 40x).

DISCUSSION

Intestinal ganglioneuromatosis is a rare benign neurogenic neoplasm, defined by an abnormal proliferation of ganglion cells, nerve fibres and schwann cells in the wall of intestine [1]. Ganglioneuromas are commonly seen in children which are originating from neural crest cells of sympathetic ganglia or adrenal medulla. Rarely, they may arise from the visceral organs like intestine. In the younger children presenting with intestinal obstruction, aetiology could vary from functional causes like Hirschprung disease which is caused due to defective migration and implantation of neural crest cells to mechanical causes like intestinal atresia [2].

In diffuse intestinal ganglioneuromatosis, wall of intestine shows proliferation of nerve fibers along with ganglion cells and supporting enteric nervous system cells. Intestinal ganglioneuromatosis was classified into 3 types: 1) Polypoidganglioneuroma; 2) Ganglioneuromatous polyposis; 3) Diffuse ganglioneuromatosis by Shekita KM and Sobin LH [1]. The polypoidganglioneuroma presents as solitary polyp or a few small polyps which may be sessile or pedunculated in nature present in the colonic mucosa or submucosa. Unlike other forms they have no association with NF1, MEN2b or other genetic syndromes. The ganglioneuromatous polyposis is characterised by numerous (>20) sessile or pedunculated mucosal and/or submucosal polyps in the colon and terminal ileum which shows association with syndromes like MEN2B, NF1, Cowden disease, nonfamilial colic polyposis or juvenile polyposis [2,3]. The diffuse ganglioneuromatosis is a disseminated form of disease characterised by intramural or transmural hyperplasia of the myenteric plexus including ganglion cells and nerve fibres which also shows syndromic association. Diffuse ganglioneuromatosis again has two forms, mucosal or transmural. Both these variants can be seen in children and they have syndromic association with RET-proto-oncogene. Diffuse ganglioneuromatosis can be seen in adults and adolescents which commonly involves the mucosa with less common genetic abnormalities [1]. The present case has a diffuse transmural involvement of ileo-cecal junction, colon and appendix. There was none of the pathognomonic clinical signs like mucosal neuromas, marphanoid habitus, café-au-lait spots, macrocephaly, musculo-skeletal abnormality or biochemical evidence like increased calcitonin, serum calcium and parathyroid hormone pathognomic of MEN, PTEN Hamartoma Tumour Syndrome or NF1 noted in this particular case.

Clinically, the intestinal ganglioneuromatosis commonly present with abdominal pain, constipation or diarrhoea, bleeding, changes in bowel habits, and intestinal obstruction due to stricture formation. Although the signs and symptoms could vary depending on the location and extent of the lesion. In case of syndromic associations, intestinal ganglioneuromatosis could be the first presentation of syndrome [4].

Intestinal ganglioneuromatosis can affect any portion of the gastrointestinal tract, but the ileum, colon and appendix are most frequently involved [2]. As diffuse intestinal ganglioneuromatosis has unspecific clinical presentations and imaging findings, the clinical diagnosis of the same becomes difficult. Clinically, intestinal tuberculosis, Crohn disease, intestinal tumours (adenocarcinoma, GIST, leiomyoma, lymphoma, neurofibroma, schwannoma), cytomegalovirus infection, NSAIDs enteropathy and amyloidosis can be considered as differential diagnosis [5].

Crohn disease is clinical and histopathological differential diagnosis of diffuse intestinal ganglioneuromatosis, which will have transmural involvement with neuronal hyperplasia but can be associated with inflammation unlike in present case. Intestinal ganglioneuromatosis needs to be distinguished from intestinal neuronal dysplasia (Type B) which is a controversial entity showing increase in the ganglion cell with giant ganglion with no mural thickening. Neurofibromatosis involving digestive tract can show nodular or diffuse submucosal proliferation of spindle cell bundles especially in NF1 syndrome but shows no ganglion cells [2].

Intestinal ganglioneuromatosis is often found in patients with MEN 2B, a rare, autosomal dominant syndrome associated with Medullary Thyroid Carcinoma (MTC) in young children with several case reports stating the same [6]. Gfroerer S et al., concluded that in children with gastrointestinal tract problems, appropriate clinical examination with rectal biopsy would help in early diagnosis of intestinal ganlioneuromatosis and the associated syndromes like MEN2B [7].

Its association with NF1 is infrequent and typically identified in the adults. Lu C et al., reported a case of diffuse ganglioneuromatosis with mutiple intestinal subserosal schwannoma in a middle aged male [8]. Another disease associated with intestinal ganglioneuromatosis is Cowden syndrome [1]. Rosenfeld EH et al., reported a six-year-old girl with PTEN hamartoma tumour syndrome and secondary chronic intestinal pseudo-obstruction associated with diffuse ganglioneuromatosis suggesting its genetic association to the syndrome [9]. On the review of last ten years English literature, we found five cases of ganglioneuromatosis of gastrointestinal tract in

Author, Year, [Reference]	Age	Sex	Site of involvement	Associated genetic abnormality, if any	Treatment	Follow-up
Matthews MA et al., 2014 [10]	7 year	Male	Ileum, caecum, ascending colon, anastomotic site	Congenital neutropenia	Right hemicolectomy followed by ileocolic anastomosis resection after 7 months	No recurrence
Mitra S et al, 2016 [11]	11 year	Male	Distal ileum, ileocecal junction	Nil	Distal ileum, ileocecal junction res ection	1 month, No recurrence
Williams AJ et al., 2018 [12]	9 year	Female	Stomach	Novel frameshift mutation in PTEN gene	Partial gastrectomy	Not available
Rosenfeld EH et al., 2019 [9]	6 year	Female	Colon, ileum	PTEN Hamartoma syndrome	Total colectomy	Not available
Present case	18 months	Male	Ileum, caecum, appendix	Nil	Surgical excision- Right hemicolectomy	3 months, No recurrence

[Table/Fig-5]: Summary of reported cases of diffuse ganglioneuromatosis of gastrointestinal tract in paediatric population in last 10 years [9-12].

paediatric population including the present case. The demographic details, clinical presentation, site of involvement, and associated genetic abnormality along with follow-up of the case are been presented in the tabular form in [Table/Fig-5] [9-12].

Diffuse intestinal ganglioneuromatosis is treated with complete surgical excision. Screening for clinical features of associated syndromes like NF1, Cowden syndrome or MEN2B like external stigmata, multiple café-au-lait spots, skin nodule and tumours at other sites such as breast, uterus, thyroid and colon are recommended. In case of diagnosed MEN2B, early thyroidectomy is preferred to prevent occurrence of MTC. For patients with NF-1 mutation, symptomatic treatment is sufficient. In patients with PTEN mutation with Cowden syndrome it is advised to increase the cancer surveillance [10]. However, to have a definitive treatment guideline, large cohort study is essential.

CONCLUSION(S)

Authors reported ganglioneuromatosis, which is a rare condition affecting paediatric population. Clinical and radiological suspicion of this condition is low due to nonspecific symptoms and unspecified radiological findings. Histopathology is the only mainstay in diagnosis. Complete surgical resection is essential. The diagnosis of diffuse intestinal ganglioneuromatosis necessitates further work-up for the presence of associated syndromes. Future studies with large cohort of cases will be needed for the definitive guidelines with medical and surgical management of children with this disorder which may include early genetic identification, development of targeted therapies and specifically directed management.

REFERENCES

[1] Shekitka KM, Sobin LH. Ganglioneuromas of the gastrointestinal tract. Relation to von Recklinghausen disease and other multiple tumour syndromes. Am J Surg Pathol.1994;18:250-57.
[2] Schäppi MG, Staiano A, Milla PJ, Smith VV, Dias JA, Heuschkel R, et al. A practical guide for the diagnosis of primary enteric nervous system disorders. J Pediatr Gastroenterol Nutr. 2013;57:677-86.
[3] Haggitt RC, Reid BJ. Hereditary gastrointestinal polyposis syndromes. Am J Surg Pathol. 1986;10(12):871-87.
[4] Leunbach TL, Madsen M, Nielsen RG, Hansen D, Mathiesen JS. Intestinal ganglioneuromatosis as first manifestation of multiple endocrine neoplasia 2B in a premature girl. Hormone Research in Paediatrics. 2019;91(Suppl. 1):460.
[5] Fernandes A, Ferreira AM, Serra P, Carvalho L. Intestinal ganglioneuromatosis: An unusual aetiology for occult gastrointestinal bleeding. BMJ Case Rep. 2015;2015(pii):bcr-2015-211764.
[6] Yin M, King SK, Hutson JM, Chow CW. Multiple endocrine neoplasia type 2B diagnosed on suction rectal biopsy in infancy: A report of 2 cases. Pediatr Dev Pathol. 2006;9:56-60.
[7] Gfroerer S, Theilen TM, Fiegel H, Harter PN, Mittelbronn M, Rolle U. Identification of intestinal ganglioneuromatosis leads to early diagnosis of MEN2B: Role of rectal biopsy. J Pediatr Surg. 2017;52(7):1161-65.
[8] Lu C, Qiu Y, Lu X, Li G, Bu H. Synchronous diffuse ganglioneuromatosis and multiple schwannomas of the colon: A case report and literature review. Exp Ther Med. 2015;9(3):733-36.
[9] Rosenfeld EH, Chumpitazi BP, Castro E, Naik-Mathuria B. Diffuse intestinal ganglioneuromatosis causing severe intestinal dysmotility in a child with a PTEN mutation. J Pediatr Gastroenterol Nutr. 2019;68(2):e35-37.
[10] Matthews MA, Adler BH, Arnold MA, Kumar S, Carvalho R, Besner GE. Diffuse intestinal ganglioneuromatosis in a child. J Pediatr Surg. 2013;48(5):1129-33.
[11] Mitra S, Mukherjee S, Chakraborty H. Isolated ilealganglioneuromatosis in an 11-year-old boy: Case report and review of literature. Indian J Pathol Microbiol. 2016;59:365-67.
[12] Williams AJ, Doherty ES, Hart MH, Grider DJ. Diffuse gastric ganglioneuromatosis: Novel presentation of *PTEN* hamartoma syndrome-case report and review of gastric ganglioneuromatous proliferations and a novel *PTEN* Gene mutation. Case Rep Med. 2018;2018:4319818.

PARTICULARS OF CONTRIBUTORS:
1. Director and Chief Pathologist, Department of Pathology, AIG Hospitals, Hyderabad, Telangana, India.
2. Pathologist, Department of Pathology, AIG Hospitals, Hyderabad, Telangana, India.
3. Surgical Gastroenterologist, Department of Surgery, AIG Hospitals, Hyderabad, Telangana, India.
4. Chief of Surgical Gastroenterology and Minimally Invasive Surgery, Department of Surgical Gastroenterology, AIG Hospitals, Hyderabad, Telangana, India.
5. Chairman and Chief of Gastroenterology, Department of Medical Gastroenterology, AIG Hospitals, Hyderabad, Telangana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Anuradha Sekaran,
Mindspace Road, Gachibowli, Hyderabad, Telangana, India.
E-mail: dr.sanuradha@aighospitals.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Dec 17, 2020
- Manual Googling: Feb 05, 2021
- iThenticate Software: Mar 22, 2021 (11%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Dec 11, 2020**
Date of Peer Review: **Jan 09, 2021**
Date of Acceptance: **Feb 17, 2021**
Date of Publishing: **May 01, 2021**