Immature enteric ganglion cells were observed in a 13-year-old colon signet ring cell carcinoma patient

A case report and literature review

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Abstract

Rationale: All the enteric ganglion cells are fully mature by 2 to 5 years of age in human. No one had reported the presentation of immature enteric ganglion cells in elder ones. Colorectal carcinoma is also rare in the adolescent population. The coincidence of these 2 rare events in a 13-year-old boy has never been reported elsewhere, which may suggest some linkage between them.

Patient Concern: A 13-year-old boy presented with progressive abdominal pain and melena for 3 months. Computed tomography (CT) scan and endoscopic ultrasonography showed significant abnormality in the transverse colon characteristic of marked mural thickening. The biopsy results indicated signet ring cell carcinoma.

Diagnoses: A 13-year-old male patient with advanced colon signet ring cell carcinoma. In addition, immature but not mature ganglion cells could be observed in almost all of the slices of the resected nontumorous area of the specimen.

Interventions: The transverse colon tumor was resected and the subsequent histopathological examination confirmed the diagnosis of primary colon signet ring cell carcinoma. Then the patient received adjuvant chemotherapy and biological target therapies subsequently.

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HL, KH, and HW contributed equally to this work.

This work has been conducted according to the ethical standards, the Declaration of Helsinki, and national and international guidelines and has been approved by the authors’ institutional review board (Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China). After being informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal, guardians of the patient provided voluntary informed consent to participate in the study.

After being informed of the right to refuse to agree with publication without reprisal, guardians of the patient provided voluntary informed consent to consent for publication for this report.

All relevant data are within the paper. The authors confirm that all data underlying the findings are fully available without restriction. The data reported in the manuscript have been extracted from the papers cited in the references section.

Authorship: HL wrote the manuscript, performed patient follow-up, and took macroscopic photos. KH wrote the manuscript. HW designed the experiments and provided insightful discussion. LW designed the experiments and wrote the manuscript. MY performed the pathological experiments and took photos. LW performed the radiographic experiments and took photos. RL performed the endoscopic experiments and took photos. HL analyzed the data and provided insightful discussion. JG, XS, XL provided insightful discussion. KT performed the surgery and designed the experiments. GW and ZW conceived and designed the experiments, and wrote the manuscript.

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1. Introduction

Gastrointestinal malignancy occurs most commonly in the colorectal region, which represents approximately 12% of all cancers in China. While the incidence is relatively high (over 80%) in the elderly at the age of over 50, colorectal carcinoma (CRC) in children is extremely rare with the reported incidence of only 1.3 cases per million children, accounting for roughly 1% of the surgical patients with CRC.[3-5] Colon signet ring cell carcinoma (CSRCC) in children is an aggressive type of cancer known for its high incidence of metastasis with poor prognosis.[3-7] Unfortunately, CSRCC is often diagnosed at the very late stage, likely due to its low morbidity and nonspecific clinical manifestations,[3,5] which may result in insufficient medical awareness of CSRCC. Usually, the maturity of the enteric ganglion cells in the nonumbrous area was mostly ignored in pathological examination of colorectal tumor specimen. At 24 weeks of gestation, most of the enteric ganglion cells are very small and immature. By birth, there is a combination of fully mature (large) and immature (small) ganglion cells. By 2 to 5 years of age, all the enteric ganglion cells are fully mature.[8,9] No one had reported the presentation of immature ganglion cells in adolescent or adult population. With this in mind, we report a case of 13-year-old boy with both CSRCC and immature enteric ganglion cells, which may suggest some relationship between these 2 events, in hope of providing more insight toward improving CSRCC detection and treatment.

2. Case presentation

In January 2015, a 13-year-old boy presented with progressive abdominal pain for 3 months with melena and acratic but without nausea, vomiting, constipation, fever, diarrhea, palpitation, or dyspnea. The patient was admitted to a local hospital where a colonoscopy showed a cauliflower-shaped neoplasm in the transverse colon. The patient did not receive any treatment and then was referred to our hospital for further examination and treatment on January 21, 2015.

Upon admission, the direct questioning revealed that he had no history of smoking, alcoholism, drug abuse, foreign travel, and occupational or residential exposure. He reported a medical history of pneumonia. The physical examination showed the blood pressure (107/61 mm Hg), the regular heartbeat rate (88/min), the normal respiration rate (20/min), the normal body temperature (37°C), and the body mass index (BMI, 17.9). No edema was observed. The chest auscultation revealed clear lung and normal heart sounds. The abdomen auscultation revealed mild hyperactive bowel sounds. A suspicious lump with a diameter of approximately 10 cm was palpated at the lower abdomen.

The laboratory tests indicated a hemoglobin level of 67 g/L, a normal white blood cell count with normal differentials and values for platelets, electrolytes, and normal liver-function-associated enzymes. The test on tumor markers using the patient’s blood sample revealed the elevated levels for CEA (carcinoembryonic antigen: 9.4 μg/L), CA-125 (carbohydrate antigen 125: 72.2 U/mL), NSE (neuron-specific enolase: 17.66 μg/L), and CA15-3 (carbohydrate antigen 153: 14.8 U/mL), CA199 (carbohydrate antigen 199: <2.0 U/mL), AFP (alpha fetal protein: 1.3 μg/L), SCC (squamous cell carcinoma antigen: 0.8 ng/mL), and CYFRA21–1 (cytokeratin 19 fragments: 0.86 ng/mL), were within their normal ranges.

To further determine the property and origination of the mass, and the occurrence of lymphatic or organ metastasis, a contrast-enhanced computed tomography (CT) of the chest was carried out. The CT scan revealed the significantly thickened transverse colon wall with the maximal thickness 2.8 cm, where a 12-cm-diameter mass was detected (Fig. 1A, B). The mass is located in the mid-transverse colon and dragged the transverse colon down to the pelvic cavity. No obviously enlarged lymph nodes were observed in the pelvic cavity or the retroperitoneal region. No abnormalities were detected in liver, cholecyst, spleen, pancreas, kidneys, prostate, and seminal vesicle. The colonoscopy revealed a large circumferential neoplasm along the lumen wall of the colon that was distorted and narrowed (Fig. 1C). Consistent with the CT scan, the endoscopic ultrasonography showed the circumferentially thickened colonic wall with a maximal thickness 2.8 cm, and the layers within the colonic wall were disappeared (Fig. 1D). Combined with the above results, the diagnosis of the mid-transverse colon malignant tumor was thus made.

The surgical operation for this patient was scheduled immediately. The exploratory laparoscopy detected a solid mass at the mid-transverse colon, as suggested by CT imaging. We then proceeded to the laparotomy to resect this transverse colon.
tumor. The resected specimen consisted of a 23-cm long segment of the transverse colon, containing a circumferentially growing 11 cm long, hollow mass, 5 and 7 cm away from the proximal and distal resection margins, respectively (Fig. 1E–H). There were several macroscopic enlarged lymph nodes and tumor nodules in the mesentery and greater omentum. No polyp-like lesion was observed in the resected specimen, thereby excluding polyposis syndromes.

Figure 1. CT scan of the abdomen (A and B). (A) The thickened transverse colonic wall forms a round and hollow mass (arrows marked). (B) The proximal and distal intestinal lumen (arrows) within the mass is interconnected. Endoscopic view (C and D). (C) The circumferential neoplasma is observed with the lumen colon distorted and narrowed. The stenotic lesion is in front of the endoscope. (D) The ultrasound scan shows the circumferentially thickened colonic wall with the maximal thickness 2.8 cm (the dotted yellow line). The layers of the colonic wall were disappeared. Macroscopic features (E–H). (E) The tumor with a 12 cm diameter is removed by radical resection from the transverse colon. It is rubbery, jellylike, and spherical. (F) A close-up for the tumor shows its granular, jellylike, and semi-transparent appearance. (G) Opened lengthwise, featuring a hollowed, interconnected with the proximal and distal colonic lumen. (H) The mucosa is granular, the serosa puckered, and the mesocolic/pericolic fat indurated.
The histopathological examination on the resected tumor showed the features of the poorly differentiated mucin-secreting adenocarcinoma with the presence of typical signet ring cells (Fig. 2A–D). The resection margins were free of tumor cells. The sections from the nontumorous areas of the specimen showed the normal histology without any evidence of inflammatory bowel disease or familial polyposis coli. The cancerous tissue diffusely infiltrated into the entire colonic wall and the adipose tissue surrounding the serous coat. The tumor nodules were found in the mesentery. Vascular cancer emboli and lymph nodes with

Figure 2. HE staining of the resected tumor specimen. (A, B) Transverse colon mucosa with signet ring cells infiltrating the lamina propria. Representative photographs taken at ×40 magnification (A) and ×100 magnification (B). The inset in B represents a typical signet ring cell. (C) Muco-secreting adenocarcinoma with a nested pattern. (D) Signet-ring cell adenocarcinoma with a diffuse pattern. (E, F) Lamina propria with tumor involvement and vascular cancer emboli. Representative photographs taken at ×40 and magnification (E) ×100 magnification (F). The inset in E represents a typical vascular cancer embolus. The inset in F represents typical signet ring cells within a blood vessel. (G, H) A lymph node with subcapsular metastatic deposit. Representative photographs taken at ×40 magnification (G) and ×100 magnification (H). The insets in G and H represent typical subcapsular metastatic signet ring cells.
subcapsular metastatic deposit were also observed (Fig. 2E–H). Twelve of 32 transverse mesenteric lymph nodes contained the metastatic deposits of signet ring cells. Collectively, the pathological staging was given, T4bN2bM0, Stage Duke C, Astler–Coller C3. While the tumor specimen was cytoplasmically stained positive for E-cadherin and β-catenin (Fig. 3A, B), the staining for the mismatch repair genes complex (MLH1, MSH2, MSH6, and PMS2) using a 4-antibody panel did not detect differences from the noncancerous tissue (Fig. 3C–F). The genotyping test did not identify the mutations in BRAF and K-RAS genes. Surprisingly, immature ganglion cells were observed in almost all the enteric ganglions in the nontumorous areas of the specimen given that the enteric immature ganglion cells were reportedly observed in neonatal functional intestinal obstruction or Hirschsprung disease[10,11] (Fig. 4). No family history of CRC in the first- or second-degree relatives was found.

Three days after the surgery, the patient’s hemoglobin level rose to 103 g/L. The patient was discharged 11 days after the surgery. The follow-up a year after the surgery showed that the patient had received 6 cycles of adjuvant chemotherapy (FOLFOX, no exact details) and biological target therapies (no exact details) in another hospital since a month after the surgery. The detailed chemotherapy regimens were unclear. Eleven months after the surgery, the metastasis in liver was detected through a CT scan, suggesting poor responses to chemotherapy and biological target therapy. The patient subsequently received radiotherapy elsewhere.

3. Discussion and literature review
Colorectal cancer (CRC) is rare in pediatric or adolescent population. A review of the published cases (under 20-year-old) in the last 5 decades is presented in Table 1, which showed the relatively high incidence of mucinous adenocarcinoma or signet ring cell carcinoma and the poor prognosis of CRC in children or teenagers.[12–28] Consistently, the review on the records of CRC patients admitted in our hospital (30 years, 1986–2015) showed that the pediatric and adolescent patients (≤18-year-old) with CRC account for merely 0.74% (36/4875) of the total cases. Similar to most of the pediatric and adolescent cases that appeared to be sporadic with no obvious predisposing factors,[15,16,29] the case presented here was also sporadic. As the diagnosis was often made at the advanced stages,[16] these young patients often had dismal prognosis.[23] Our case was also diagnosed at the late stage (T4bN2bM0, Stage Duke C, Astler–Coller C3) with metastasis detected within a year.

Colorectal primary signet ring cell carcinoma only accounts for nearly 1% of all CRCs. While adult colorectal adenocarcinoma
usually shows tubular differentiation, pediatric or adolescent colorectal adenocarcinoma often tend to be mucinous or signet-ring-cell-rich. Thus far, this age-associated pathological difference remains unclear. In this case, we observed immature ganglion cells in almost all of the enteric ganglions, which were never reported in normal adolescent or adult population. Despite unconfirmed correlation with CRC tumorigenesis in young patients, this represents the first observational report. A review of the published cases with immature enteric ganglion cells is presented in Table 2, which are all under 5 years of age. The immature enteric ganglion cells were reportedly observed in either term or pre-term neonates with neonatal functional intestinal obstruction and Hirschsprung disease. Venugopal et al. did punch biopsies in 100 neonates, infants, and children, who had died of nonintestinal causes. They found immature ganglion cells from birth to 2 years of age, but not in ones elder than 2 years. The presence of immature ganglion cells in colon or rectum of neonates was thought to indicate transient functional immaturity of the intestine. However, the patient in this case did not present any symptoms related with transient intestine dysfunction and had no history of neonatal functional intestinal obstruction or habitual constipation during his neonatal period. This raises the possibility that the immature neurons may suggest some genetic defects in the development of ganglion cells, which might be related to the tumorigenesis of CSRCC. It is possible that some of the patients with CSRCC may have immature enteric ganglion cells, but are not commented on. Even if the immaturity is commented on, the observation is often not reported. However, the fact needs to be clarified. Given that dysregulation of development genes is often associated with tumorigenesis, the relationship between the immature ganglion cells and CSRCC is worth further investigation. For example, colorectal biopsy and long-term follow-up of the children with neonatal functional intestinal obstruction or Hirschsprung disease, and histopathological examination of the nontumorous areas from young patients with CSRCC, may reveal correlations between the presence of immature enteric ganglion cells and the onset of CSRCC in young patients.
The abundance of signet ring cells with CRC was reported to be an independent prognostic factor associated with an unfavorable outcome.\textsuperscript{[43]} Its aggressiveness is mainly due to its unique epidemiology, oncogenesis, and intrinsic tumor biology that cause immune evasion and chemoresistance.\textsuperscript{[139–141]} This case received 6 cycles of adjuvant chemotherapy and molecular targeted therapies, which however did not prevent liver metastasis. Therefore, high awareness and early diagnosis are especially important. Early-stage signet ring cell carcinoma that can be completely resected endoscopically has a reportedly better outcome than nonsignet ring cell carcinoma.\textsuperscript{[41]} However, the complete resection is merely possible in less than 40% of pediatric or adolescent cases due to a high percentage of patients at advanced stages when medical attention was sought.\textsuperscript{[16]} The case here was also an incomplete resection due to the advanced stage.

### 4. Conclusions

The clinical presentations of CRC in pediatric or adolescent population can be variant, including melena, abdominal pain, altered bowel pattern, weakness, increasing fatigue, unexplained weight loss, and intestinal obstruction. The nonspecific nature of these symptoms is thought to be one of the main reasons that delay the precise diagnosis, in particular, in CSRCC young patients. Melena along with weight loss was reported to be strongly suggestive of tumorous lesions in gastrointestinal tract for pediatric or adolescent patients\textsuperscript{[23]} which was the case for our patient. Thus, the presence of such symptoms in pediatric or adolescent patients should be given high medical alert. Pediatric or adolescent patients are a special social group. They cannot clearly describe their feelings and do not have the sufficient awareness of diseases. A lack of effective communication between young patients and their parents during their rebellious period could be a contributing factor affecting the timely diagnosis. In some cases, they would not complain to their parents until the very late stages with melena or intestinal obstruction. Some parents are not aware of tumorous disease associated signs and symptoms, such as abdominal pain and altered bowel habits. High suspicion should be given to a child who complains progressive abdominal pain, altered bowel habits, or melena. Careful clinical and rectal examination along with colonoscopic evaluation may lead to early diagnosis. In addition, the education

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**Table 1**

| Literature                        | Age, y | Gender | Location | Pathological type | Outcome |
|-----------------------------------|--------|--------|----------|-------------------|---------|
| Oncol Lett. 2015                  | 9      | M      | TC       | SR                | Died 1–12 mo |
| Adv Anat Pathol. 2015             | 14     | F      | TC       | A                 | 18 mo after diagnosis, bulky abdominopelvic peritoneal tumor recurrence. Twenty-four months after diagnosis, the patient is alive with disease. |
| Case Rep Oncol Med. 2013          | 19     | M      | SC       | SR                | Still underwent chemotherapy after palliative colostomy |
| J Cancer Res Ther. 2012           | 10     | F      | DC       | MA/SR             | No evidence of recurrence 8 mo after surgery |
| Pediatr Surg Int. 2005            | 12     | F      | SC       | A                 | One year later, a local recurrence and hepatic metastases were diagnosed and she underwent chemotherapy and surgical resection. Twenty-six months from initial diagnosis, she is alive with evidence of disease |
| Eur J Pediatr Surg. 2003          | 10–16  | 3M: 5F | 4AC: 1DC: 3SC | 2MA: 6A | Died 1–12 mo |
| J Pediatr Surg. 1999              | 7–16   | 12M: 8F | 1CC: 2AC: 3TC: 1DC: 5SC: 8RC | 16MA: 4A | 13 died of disease 1 d to 1 y after surgery, 3 were alive for 2–4 y postoperatively, 4 unknown |
| Pediatr Surg Int. 1997            | 16–19  | 1M: 2F | 2SC: CC  | MA: 2A           | 2 survived 14 and 20 y without evidence of disease, respectively, 1 died 3 mo after surgery |
| Yonsei Med J. 1993                | 12     | M      | TC       | A                | Survived more than 6 y without evidence of disease |
| J Postgrad Med. 1993              | 11     | F      | RC       | CA               | Entire bowel and peritoneal metastasis was found 3 mo after surgery |
| J Pediatr Surg. 1992              | 10–15  | 4M: 3F | 3AC: 1DC: 1SC: 2RC | 3MA: 2MA/SR: 2A | All 7 died on average 11 mo after diagnosis |
| J Pediatr Surg. 1976              | 13–16  | 6M     | 2AC: 1TC: 2DC: 1SC | 3MA: 3A | Died 16 mo/10 mo/3 dy/1 mo/15 mo/46 mo after surgery, respectively |
| Cancer. 1985                      | 8–25   | 17M: 13F | 6CC: 4AC: 5TC: 6SC: 4RC | 25MA: 5A | Survival: only biopsy (1–15 mo), palliative segmental resection (6–36 mo), complete resection (7 mo to 14 y) |
| Surgery. 1983                     | 11–20  | 1M: 6F | 3MT: 1DC: 1SC: 2RC | MA: 6A | 4 died 2–14 mo after diagnosis, 3 survived 1–3 y after diagnosis |
| Am J Surg. 1977                   | 14     | F      | TC       | A                | In over 5 and a half years of follow-up, the patient has remained free of any signs of metastatic disease. |
| Am J Surg. 1974                   | 12, 18 | 1M: 1F | 1TC: 1SC | 2A | One died 6 wks after surgery, the other survived 16 y with no evidence of recurrence |
| Ann Surg. 1965                    | 12–20  | 5M: 6F | 3AC: 2TC: 1DC: 5SC | 2MA: 5MA/SR: 4A | 2 living and well for 30 and 44 mo, respectively, 9 died 2 d to 3 mo after surgery |

\(A=\text{adenocarcinoma}, \ AC=\text{ascending colon}, \ CA=\text{caecum}, \ CC=\text{cecum}, \ DC=\text{descending colon}, \ F=\text{female}, \ M=\text{male}, \ MA=\text{mucinous adenocarcinoma}, \ MA/SR=\text{mucus-secreting adenocarcinoma with “signet ring” pattern}, \ MT=\text{multiple}, \ RC=\text{rectum}, \ SC=\text{sigmoid colon}, \ SR=\text{signet ring cell carcinoma}, \ TC=\text{transverse colon}.\)
Literature review of the cases with immature enteric ganglion cells.

| Literature | Disease | Symptom | Outcome |
|------------|---------|---------|---------|
| J Med Assoc Thai. 2014 | Hirschsprung disease | Delay or failure to pass meconium, constipation, abdominal distension and bilious vomiting | Neonatal functional intestinal obstruction |
| Pediatr Surg Int. 2011 | Hirschsprung disease | Delayed passage of meconium, constipation, abdominal distension and bilious vomiting | Neonatal functional intestinal obstruction |
| Clin Auton Res. 1994 | Hirschsprung disease | Meconium disease | Immature ganglion cells were all mature 2–16 wks after ileostomy, and closed the ileostomy |
| Clin Auton Res. 1981 | Hirschsprung disease | Meconium disease | Immature ganglion cells are present in the transitional zone of HSCR. |
| Pediatr Surg Int. 1997 | Hirschsprung disease | Meconium disease | Immature ganglion cells are present in the transitional zone of HSCR. |

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**References**

[1] Chen W. Cancer statistics: updated cancer burden in china. Chin J Cancer Res 2015;27:1.
[2] Afroza A, Hasan S, Akramuzzaman M, et al. Carcinoma-rectum in an 11 years old boy. Mymensingh Med J 2007;16:570–2.
[3] Anthony T, George R, Rodriguez-Bigas M, et al. Primary signet-ring cell carcinoma of the colon and rectum. Ann Surg Oncol 1996;3:344–8.
[4] Anith S, Elmeshal O, Amarti Rifi A. Primary signet ring cell carcinoma of the colon and rectum. Bull Cancer 2015;102:880–8.
[5] Bells S, Aytac HO, Karagulle E, et al. Outcomes of surgical treatment of primary signet ring cell carcinoma of the colon and rectum: 22 cases reviewed with literature. Int Surg 2014;99:691–8.
[6] Makino T, Tsujinaka T, Mishima H, et al. Primary signet-ring cell carcinoma of the colon and rectum: report of eight cases and review of 154 japanese cases. Hepatogastroenterology 2006;53:845–9.
[7] Messerini L, Palomba A, Zampi G. Primary signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum 1995;38:1189–92.
[8] Bughaghs AG, Emergy JL. Functional obstruction of the intestine due to neurological immaturity. Prog Pediatr Surg 1971;3:37–52.
[9] Smith B. Pre- and postnatal development of the ganglion cells of the rectum and its surgical implications. J Pediatr Surg 1968;3:386–91.
[10] Burki T, Kho L, Scheinberg I, et al. Neonatal functional intestinal obstruction and the presence of severely immature ganglion cells on rectal biopsy: 6 year experience. Pediatr Surg Int 2011;27:487–90.
[11] Niramis R, Tongsin A, Lettsaitt A, et al. How to manage low gut obstruction in neonates with immature ganglion cells in the colonic wall? J Med Assoc Thailand 2014;97(Suppl 6):366–73.
[12] Galliani CA, Sanchez IC, D’Errico MM, et al. Selected case from the arkadi m. Rywin international pathology slide club: carcinoma of the transverse colon in a young girl. Adv Anat Pathol 2015;22:217–24.
[13] Pamukcu O, Selcukbiricik F, Bilici A, et al. Signet cell carcinoma of colon and rectum: a report of six cases and review of the literature. Eur J Pediatr Surg 2003;13:66–8.
[14] Karnak I, Ciftci AO, Senocak ME, et al. Colorectal carcinoma in children. J Pediatr Surg 1999;34:1499–504.
[15] Sebbag G, Lantsberg L, Arish A, et al. Colonic carcinoma in the adolescent. Pediatr Surg Int 1997;12:446–8.
[16] Hwang EH, Chung WH. Adenocarcinoma of the transverse colon in a child with survival: a case report. Yonsei Med J 1993;34:287–92.
[17] Redkar RG, Kulkarni BK, Naik A, et al. Colloid carcinoma of rectum in a 11 year old child. J Postgrad Med 1993;39:218–9.
[18] Brown RA, Rode H, Millar AJ, et al. Colorectal carcinoma in children. J Pediatr Surg 1992;27:919–21.
[19] Anderson A, Bergdahl L. Carcinoma of the colon in children: a report of six new cases and a review of the literature. J Pediatr Surg 1976;11:967–71.
[20] Rao BN, Pratt CB, Fleming ID, et al. Colon carcinoma in children and adolescents. A review of 30 cases. Cancer 1983;53:1322–6.
[21] Goldthorn JF, Powars D, Hays DM. Adenocarcinoma of the colon and rectum in the adolescent. Surgery 1983;94:409–14.
[22] Enker WE, Palovon E, Kirner JB. Carcinoma of the colon in the adolescent: a report of survival and an analysis of the literature. Am J Surg 1977;133:737–41.
[23] Wolloch Y, Dintiman M. Carcinoma of the large intestine in children. Am J Surg 1974;127:693–5.
[24] Sessions RT, Riddell DH, Kaplan HJ, et al. Carcinoma of the colon in the first two decades of life. Ann Surg 1965;162:279–84.
[25] Yang S, Liu G, Zheng S, et al. Signet-ring cell carcinoma of the colon: a case report of a 9-year-old boy. Oncol Lett 2015;10:1632–4.
[29] Pandey A, Gangopadhyay A, Sharma S, et al. Pediatric carcinoma of rectum: Varanasi experience. Indian J Cancer 2008;45:119–22.
[30] Ladd AP, Grosfeld JL. Gastrointestinal tumors in children and adolescents. Semin Pediatr Surg 2006;15:37–47.
[31] Kawai H, Satomi K, Morishita Y, et al. Developmental markers of ganglion cells in the enteric nervous system and their application for evaluation of hirschsprung disease. Pathol Int 2014;64:432–42.
[32] Tatekawa Y, Kanchiro H, Kanokogi H, et al. The evaluation of meconium disease by distribution of cathepsin d in intestinal ganglion cells. Pediatr Surg Int 2000;16:53–5.
[33] Toyosaka A, Tomimoto Y, Nose K, et al. Immaturity of the myenteric plexus is the aetiology of meconium ileus without mucoviscidosis: a histopathologic study. Clin Auton Res 1994;4:175–84.
[34] Venugopal S, Mancer K, Shandling B. The validity of rectal biopsy in relation to morphology and distribution of ganglion cells. J Pediatr Surg 1981;16:433–7.
[35] Huebner RJ, Todaro GJ. Oncogenes of rna tumor viruses as determinants of cancer. Proc Natl Acad Sci U S A 1969;64:1087–94.
[36] Ferraro A. Altered primary chromatin structures and their implications in cancer development. Cell Oncol 2016;39:195–210.
[37] Willis RE. Human gene control by vital oncogenes: revisiting a theoretical model and its implications for targeted cancer therapy. Int J Mol Sci 2012;13:316–33.
[38] Spranger S, Gajewski TF. Tumor-intrinsic oncogene pathways mediating immune avoidance. Oncoimmunology 2016;5:e1086862.
[39] Symonds DA, Vickery AL. Mucinous carcinoma of the colon and rectum. Cancer 1976;37:1891–900.
[40] Fukui Y. Mechanisms behind signet ring cell carcinoma formation. Biochem Biophys Res Commun 2014;450:1231–3.
[41] Pernot S, Voron T, Perkins G, et al. Signet-ring cell carcinoma of the stomach: impact on prognosis and specific therapeutic challenge. World J Gastroenterol 2015;21:11428–38.