Clinical Case Report

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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 Medial 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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Outcomes: After 6 cycles of adjuvant chemotherapy and biological target therapies, metastasis was however detected within a year.

Lessons: In this case, a 13-year-old male patient with advanced colon signet ring cell carcinoma were presented. Unexpectedly, immature ganglion cells could be observed in almost all of the slices of the resected nontumorous area of the specimen. It is critical to raise medical awareness and improve the diagnosis and treatment of the signet ring cell carcinoma. This malignancy and the immature ganglion cells may be associated, possibly caused by some unidentified genetic defects. Genome sequencing, histopathological examination, and long-term follow-up of young patients with related diseases, would help further reveal the potential relationship between tumorigenesis and ganglion cells' immaturity, contributing to understanding the molecular mechanisms.

Abbreviations: AFP = alpha fetal protein, BMI = body mass index, CA-125 = carbohydrate antigen, CA153 = carbohydrate antigen 153, CA199 = carbohydrate antigen, CA72–4 = carbohydrate antigen 72–4, CEA = carcino-embryonic antigen, CT = computed tomography, CYFRA21–1 = cytokeratin 19 fragments, FERR = ferritin, FPSA = free prostate specific antigen, InDel = insertion-deletion, NSE = neuron-specific enolase, PSA = prostate-specific antigen, SCC = squamous cell carcinoma antigen, SNP = single-nucleotide polymorphism.

Keywords: colon signet-ring cell carcinoma, early diagnosis, genetic defects, immature ganglion cells, sporadic adolescent carcinoma

1. Introduction

Gastrointestinal malignancy occurs most commonly in the colorectal region, which represents approximately 12% of all cancers in China.[1] While the incidence is relatively high (over 80%) in the elder 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,[2] accounting for roughly 1% of the surgical patients with CRC.[3,4] Colon signet ring cell carcinoma (CSRCC) in children is an aggressive type of cancer known for its high incidence of metastasis with poor prognosis.[3,5–7] Unfortunately, CSRCC is often diagnosed at the very late stage, likely due to its low morbidity and nonspecific clinical manifestations,[5] which may result in insufficient medical awareness of CSRCC. Usually, the maturity of the enteric ganglion cells in the nontumorous 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 enteric 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 acratia 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 neoplasma 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 (carcino-embryonic antigen: 9.4 μg/L), CA-125 (carbohydrate antigen 125: 72.2 U/mL), NSE (neuron-specific enolase: 17.66 μg/L), and CA72–4 (carbohydrate antigen 72–4: 18.58 U/mL), but lowered FERR (ferritin: 7.3 μg/L). The rest of tumor markers, including PSA (prostate-specific antigen: 0.26 μg/L), FPSA (free prostate specific antigen: 0.13 μg/L), CA153 (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 postcontrast-enhanced computed tomography (CT) of the chest was carried out. The CT scan revealed the significantly thickened transverse colonic 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 neoplasma 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 2.8 cm thickness, 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

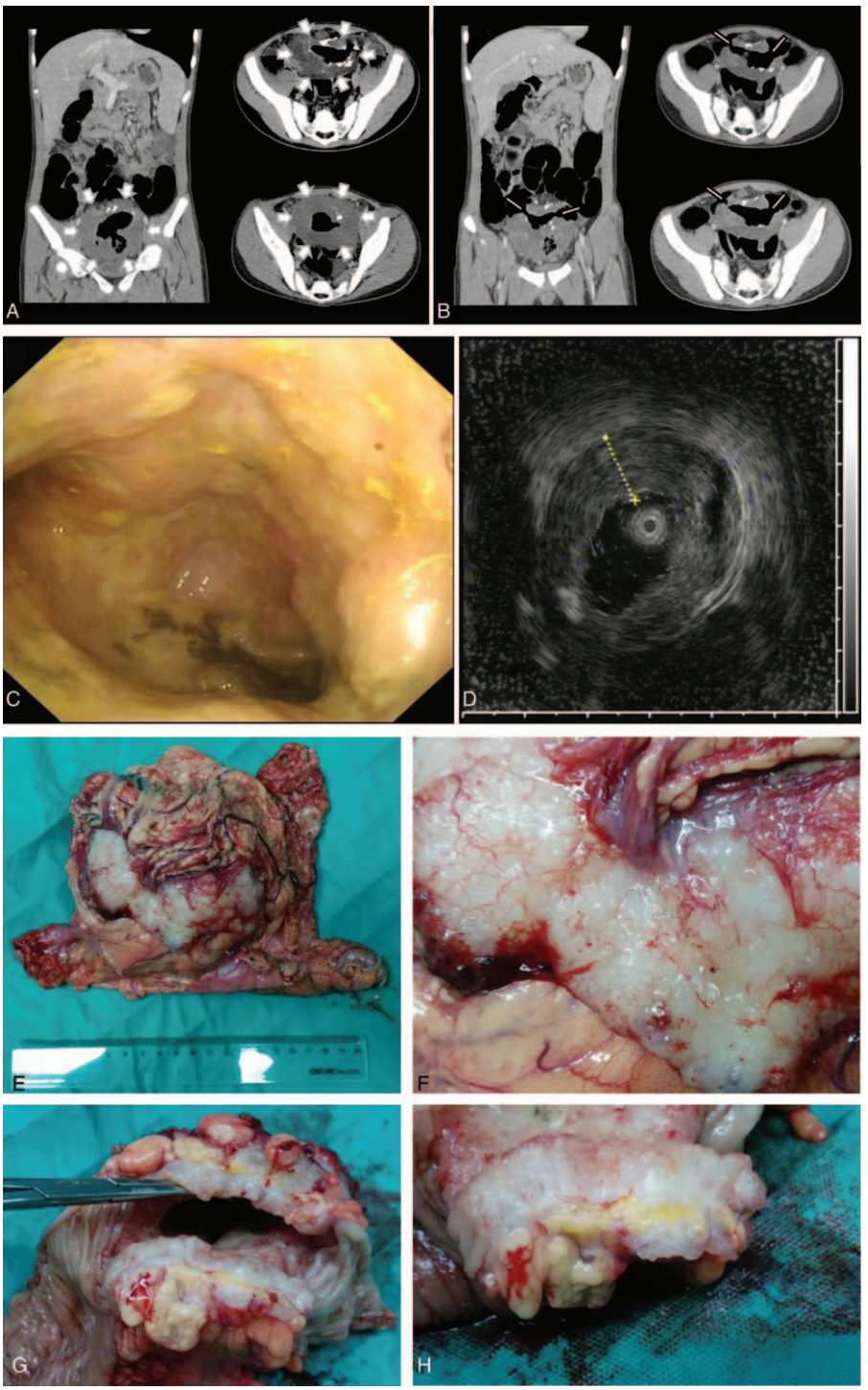

Figure 1. CT scan of the abdomen (A and B). (A) The thickened transverse colonic wall forms a round and hollow mass (arrows marked). (B) The proximal and distal intestinal lumen (arrows) within the mass is interconnected. Endoscopic view (C and D). (C) The circumferential neoplasma is observed with the 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). € 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.

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.

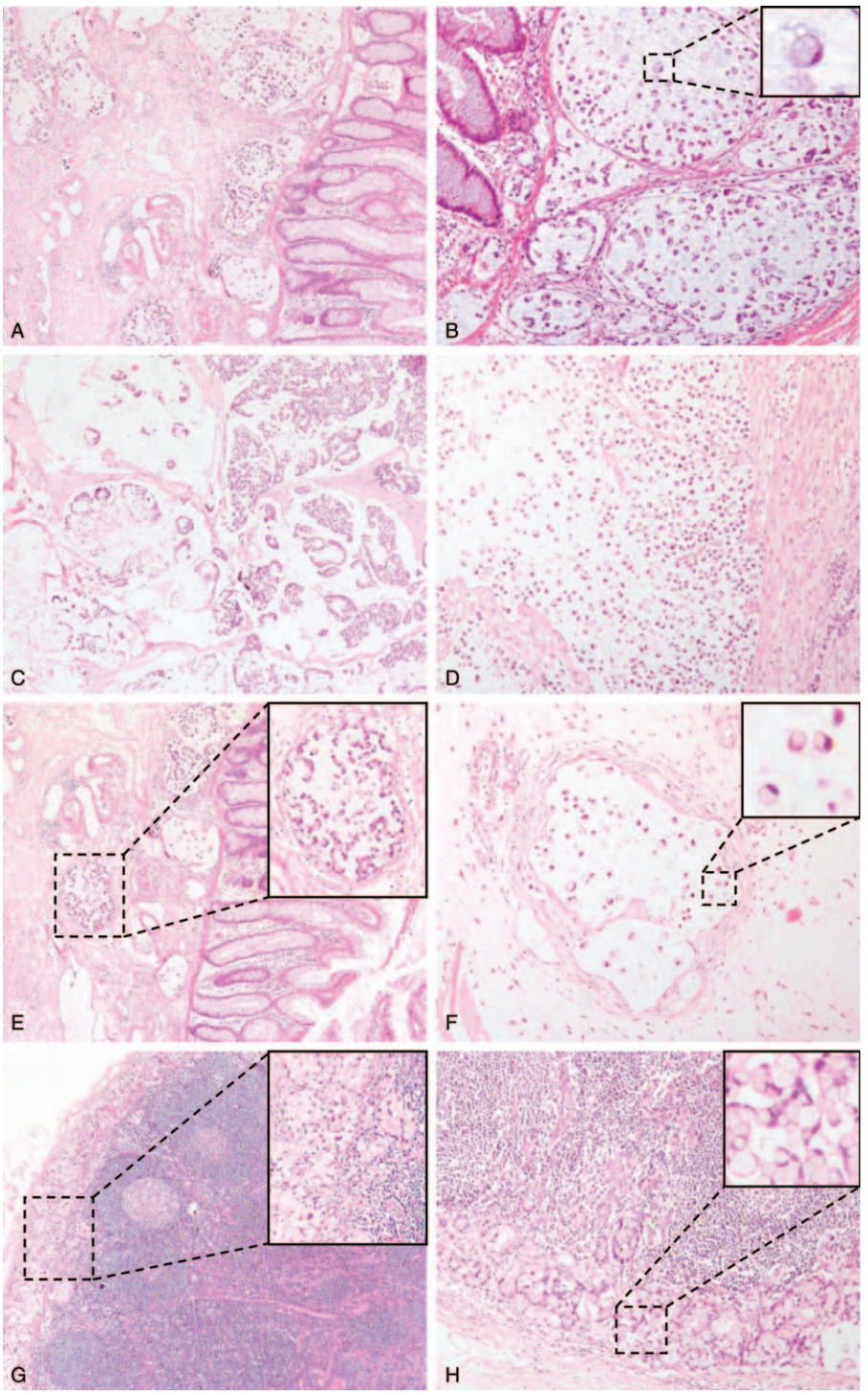

Figure 2. HE staining of the resected tumor specimen. (A, B) Transverse colon mucosa with signet ring cells infiltrating the lamina propria. Representative photographs taken at ×40 magnification (A) and ×100 magnification (B). The inset in B represents a typical signet ring cell. (C) Mucin-secreting 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.

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

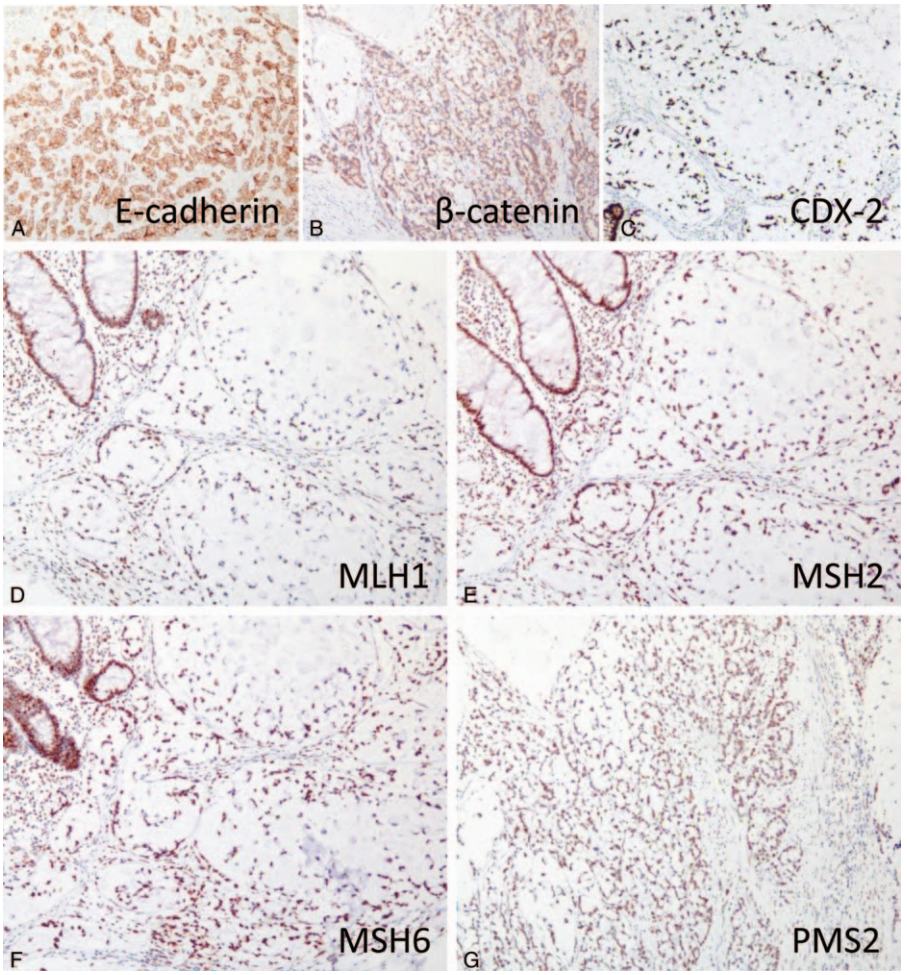

Figure 3. Immunohistochemical staining. (A) E-cadherin with cytoplasmic positivity in tumor cells; (B) β-catenin with cytoplasmic positivity in tumor cells; (C) CDX-2 with nuclear positivity in tumor cells. (D–G) A 4-antibody panel for the evaluation of the mismatch repair genes complex shows the normally preserved expression of MLH1 (D), MSH2 (E), MSH6 (F), and PMS2 (G) proteins. Representative photographs taken at ×100 magnification.

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, $T_{4b}N_{2b}M_0$, 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 regiments 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.[2,4–6] Our case was also diagnosed at the late stage ($T_{4b}N_{2b}M_0$, 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

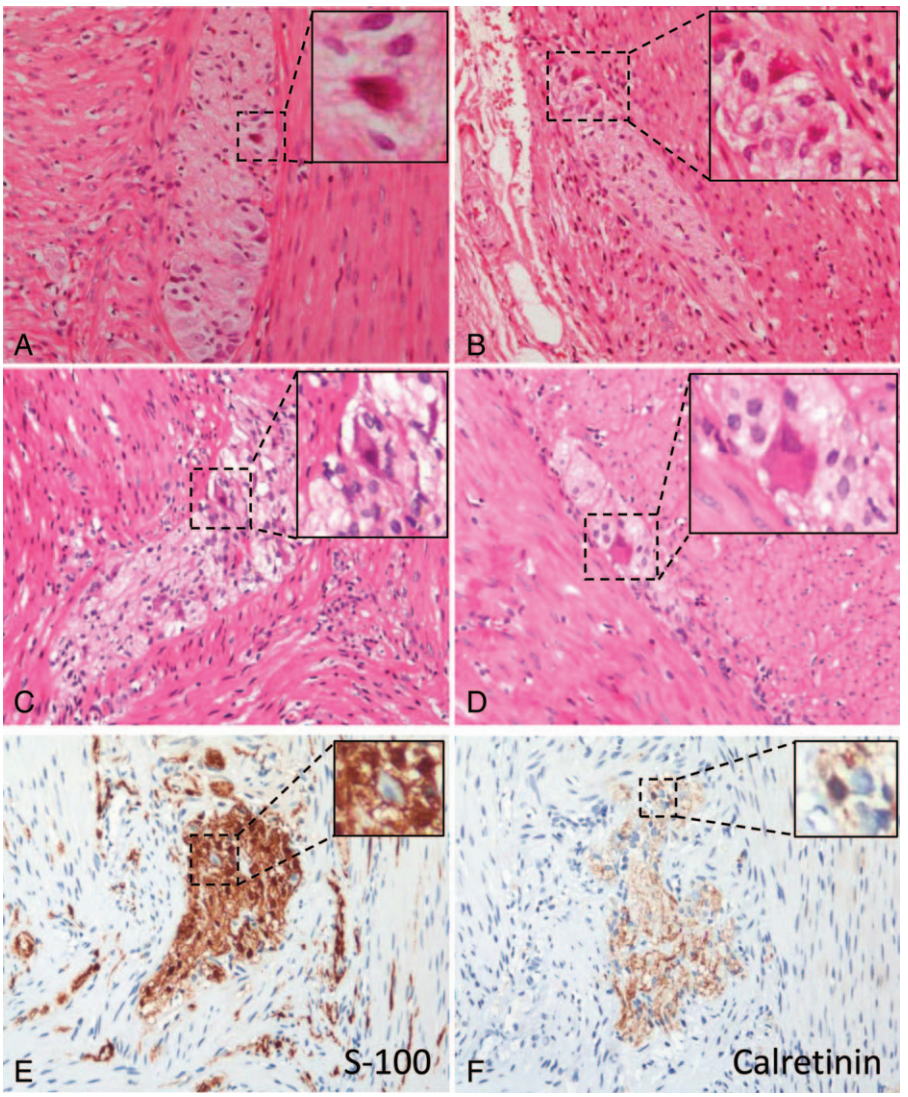

Figure 4. HE staining showing the immature ganglion cells. (A–D) The enteric ganglion contains immature ganglion cells. Representative photographs taken at ×200 magnification. The enlarged images show the details of the immature enteric ganglion cells. (E, F) IHC staining of S-100 (positive in nerve fibers and negative in ganglion cells) and Calretinin (positive in both nerve fibers and ganglion cells). The enlarged images show the details of the immature enteric ganglion cells.

usually shows tubular differentiation, pediatric or adolescent colorectal adenocarcinoma often tend to be mucinous or signet-ring-cell-rich.[17,29,30] 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.[9–11,31–34] The immature enteric ganglion cells were reportedly observed in either term or pre-term neonates with neonatal functional intestinal obstruction and Hirschsprung disease.[10,11,31] These ganglion cells would mature over time and disappear in normal children in the age of 2 to 5 years.[8,9] Venugopal et al[34] 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.[10] 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,[35–38] 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.

Table 1

Literature review of the CRC under 20 years of age in the last 5 decades.

Literature	Age, y	Gender	Location	Pathological type	Outcome
Oncol Lett. 2015	9	M	TC	SR	Chemotherapy 7 times for 1 year following surgery, mesenteric lymph node metastasis was identified in the stoma close surgery, died 2 wks after discharge
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: 5DC: 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 = adenocarcinoma, AC = ascending colon, CA = colloid adenocarcinoma, CC = cecum, DC = descending colon, F = female, M = male, MA = mucinous adenocarcinoma, MA/SR = mucus-secreting adenocarcinoma with "signet ring" pattern, MT = multiple, RC = rectum, SC = sigmoid colon, SR = signet ring cell carcinoma, TC = transverse colon.

The abundance of signet ring cells with CRC was reported to be an independent prognostic factor associated with an unfavorable outcome.[4] Its aggressiveness is mainly due to its unique epidemiology, oncogenesis, and intrinsic tumor biology that cause immune evasion and chemoresistance.[39–41] 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.[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.[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,[29] 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

Table 2

Literature review of the cases with immature enteric ganglion cells.

Literature	Cases	Symptom	Disease	Outcome
Pathol Int. 2014	21 HSCR (2–12 y) and 18 normal (0–84 y)	NA	Hirschsprung disease	Immature ganglion cells are present in the transitional zone of HSCR.
J Med Assoc Thai. 2014	1 term and 5 pre-term neonates	Delay or failure to pass meconium, progressive abdominal distension and bilious vomiting	Low gut obstruction in neonates	Showed mature ganglion cells at the age of 3 mo
Pediatr Surg Int. 2011	8 term neonates	Delayed passage of meconium, constipation, abdominal distension and bilious vomiting	Neonatal functional intestinal obstruction	Showed mature ganglion cells 2–9 mo
Pediatr Surg Int. 2000	3 neonates	Intestinal obstruction and tenacious meconium	Meconium disease	Immature ganglion cells were all mature 2–16 wks after ileostomy, and closed the ileostomy
Clin Auton Res. 1994	9 neonates	Delay or failure to pass meconium, solid feces	Meconium ileus	The intramural ganglia were mature at the age of 1–2 mo.
J Pediatr Surg. 1981	51 (<1 mo): 35 (1–12 mo): 14 (>12 mo)	Punch biopsies from 100 infants and children undergoing autopsy	Died of causes unrelated to bowel motility	<1 mo: 100% have immature ganglion cells; 1–12 mo: 97% have immature ganglion cells; >12 mo: 71% have immature ganglion cells
J Pediatr Surg. 1968	30 fetus, infants, and children	Patient with an anomaly of the nervous system or a history suggestive of achalasia cardia, pyloric stenosis, or Hirschsprung disease, was excluded	Autopsy	At birth, the ganglion cells have not yet reached full morphologic maturity, full maturation takes place gradually. In children from 2 to 5 y, fully mature ganglion cells were plentiful, earlier stages of maturation were seldom seen.

HSCR = Hirschsprung disease, NA = not applicable.

regarding this disease to teenagers would help increase the awareness and improve the management of this disease.

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