CASE REPORT

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Gastrointestinal stromal tumor, jejunal atresia and stenosis in a neonate

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Abstract

Gastrointestinal stromal tumors could rise in different areas of the digestive tract, at any age, but very rarely in neonates. We present the case of a 5-day-old male, with intestinal stenosis and atresia (type II) operated for peritonitis. On the resected specimen, the histopathological examination revealed a small gastrointestinal tumor of 8 mm. The immunohistochemical analysis indicated a low malignant potential. He is currently at two years of oncologic follow-up with no evidence of disease.

Keywords: intestinal atresia, intestinal stenosis, gastrointestinal stromal tumor, neonate.

Introduction

Intestinal atresia (IA) is a common small bowel malformation encountered in one out of 1000 live births and could be located at any level of the small intestine [1–3]. Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract. Their overall incidence is between 10–20 per million people; they are usually seen in adulthood and occur very rarely in neonates. Also, GISTs seem to be more frequent in girls [4].

The small bowel is the second most frequent location after stomach; the tumor may be situated on any of its segments [5–9].

As both entities are rarely met in daily practice, we report an even rarer case of association of two concomitant malformations of the small bowel (jejunal atresia and stenosis) and a jejunal GIST discovered in a 5-day-old neonate. To our knowledge, the presence of a GIST on the resected specimen of the small bowel for an obstructive malformation was never reported before in the medical literature.

Patient, Methods and Results

A 5-day-old male neonate was referred to our Department of Pediatric Surgery for altered general status, vomiting, fever, dehydration, lethargy, distended abdomen (Figure 1A). The newborn was vaginally delivered five days before admission, birth weight was 2950 g, APGAR score 8/10 and, apparently, normal stooling was reported in the first two days. After feeding attempts, repeated vomiting episodes occurred, but with clinically normal abdomen. In the last day before presentation to our hospital emergency, severe belly distension, vomiting, increasing volumes of gastric aspirate on the nasogastric tube, and lack of meconium passage, developed progressively. In the medical records of the pregnancy, we have found an urinary tract infection in the second trimester, treated with quinolones and non-steroid anti-inflammatory drugs and the young age of the mother (16 years).

After a short but intense correction of the vascular volume and biological status, the newborn was referred to the surgical team for immediate surgery.

At laparotomy, we found an intestinal obstruction complicated by small bowel diastatic perforations. The source of perforation was an over-distended jejunal loop with necrosis and perforation, between a proximal stenotic bowel and a distal atresic area (Figure 1B).

We performed an enterectomy including all lesions, with an end-to-end primary anastomosis and abundant lavage of the abdominal cavity with warm saline solution and multiple drainage. The postoperative course was complicated by a postoperative peritonitis due to partial necrosis of the proximal bowel end of anastomosis and consecutive leakage. We performed resection of the anastomosis with a new end-to-end enterostomy. After 14

days, the postoperative course progressed to full recovery of the patient and normal gain in weight.

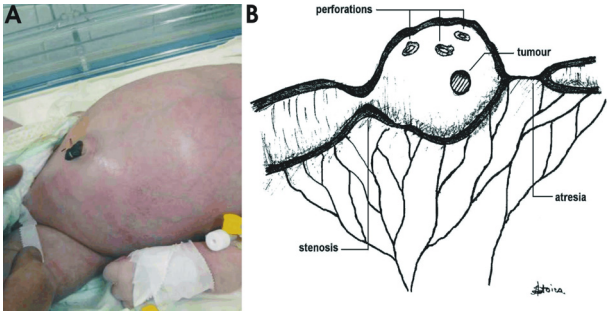

Figure 1 – ***(A) Clinical aspect of the abdomen at presentation. (B) Schematic diagram of the resected specimen.***

Histopathological examination of the resected specimen was performed after fixation in 10% formalin solution for 14 hours. Gross examination revealed, beside the malformations, a small whitish, consistent, not very well delineated, 0.8 cm tumor protruding beneath the mucosa on the opposite to the mesenteric side.

Microscopic examination on serial sections through the protrusion in the jejunal wall pointed out an infiltrate in the muscular layer of a neoplastic proliferation with high cellullarity, mainly with fusiform and medium size epiteloid cells. The mitotic index was less than five mitoses/50 HPF (high power field). Adjacent jejunal epithelia presented areas of ulcerations and cystic dilatation of the glands and an acute diffuse moderate inflammatory infiltrate (Figure 2, A and B).

For immunohistochemical analysis were used monoclonal antibodies mouse anti-human for vimentin (V9 clone, Dako), AE1/AE3 (AE1/AE3 clone, Dako), chromogranin A (DAK-A3 clone, Dako), synaptophysin (SY38 clone, Dako), common leukocytary antigen (2B11 clone + PD7/26, Dako), Ki67 (MIB-1, Dako), CD34 (QBEnd 10 clone, Dako), α-SMA (1A4 clone, Dako), desmin (D33 clone, Dako), NSE (BBS/NC/VI-H14 clone, Dako), neurofilaments (2F11 clone, Dako) and polyclonal rabbit anti-human antibodies CD117 (c-Kit, Dako), S100 (Dako).

Reactions were evidentiated by ABC method (Universal LSAB™2 Kit/HRP, Rabbit/Mouse, code K0765, Dako) and revealed with DAB (3.3'-diaminobenzidine, Dako).

The immunohistochemical study of tumoral cells was positive diffusely for CD117 (Figure 3A), vimentin (Figure 3B) and focally for CD34 (Figure 3C). AE1/AE3 was positive in the epithelia and negative in the tumoral cells. S100, neurofilaments and NSE (neuronal specific enolase) were positive in the ganglia and the nervous filaments and negative in the tumoral cells. Alpha-actin and desmin were positive in the smooth muscle cells, negative in the tumoral cells. The myoglobin and the leukocytary common antigen were negative in the tumoral cells. Ki67 proliferation index was 12% (Figure 3D).

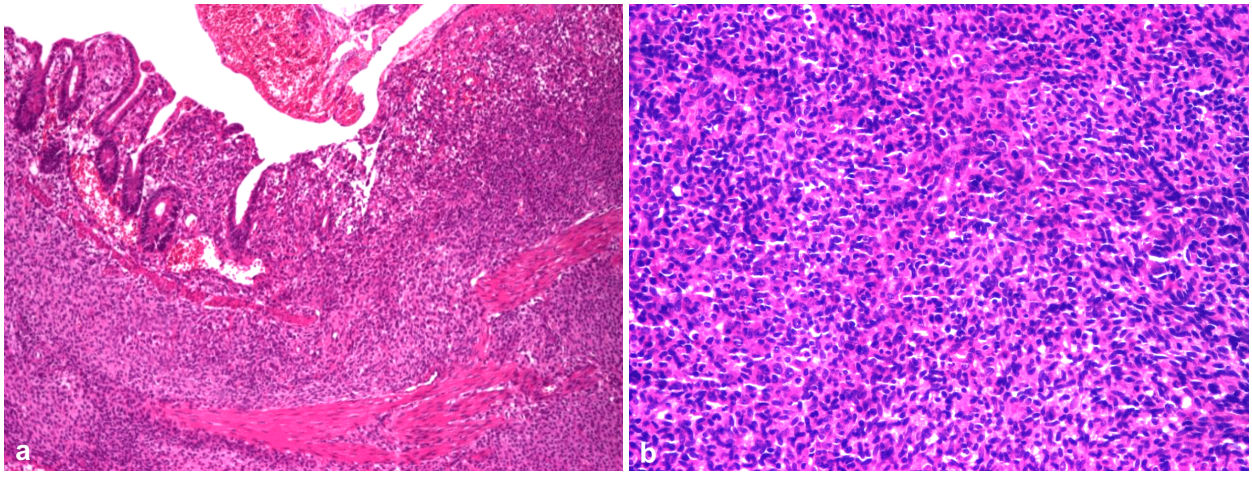

Figure 2 – ***GIST infiltrating muscularis propria and ulceration of jejunal mucosa. HE staining, ×40 (A), ×100 (B).***

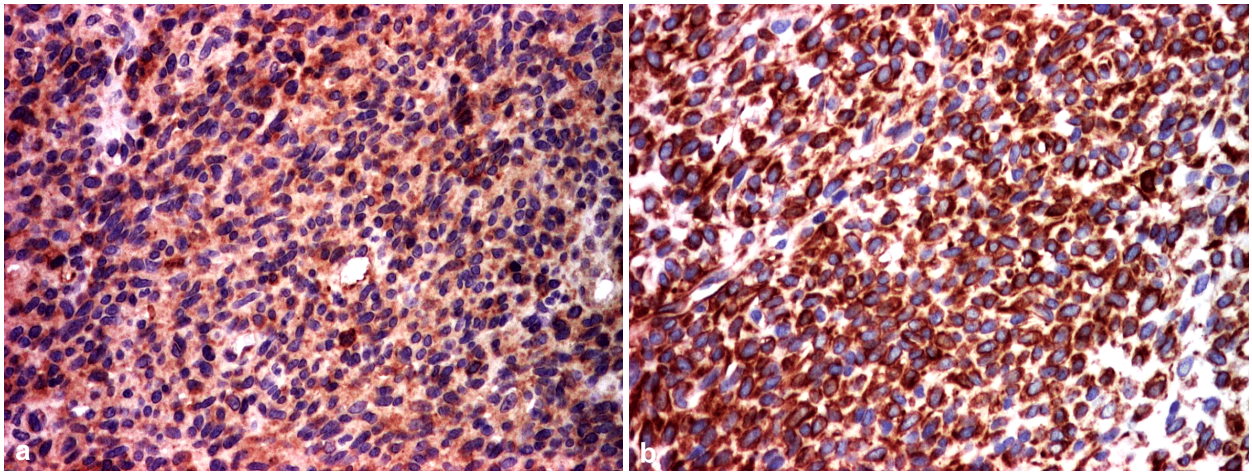

Figure 3 – ***GIST: (A) CD117 immunostaining, ×200; (B) Vimentin immunostaining, ×200.***

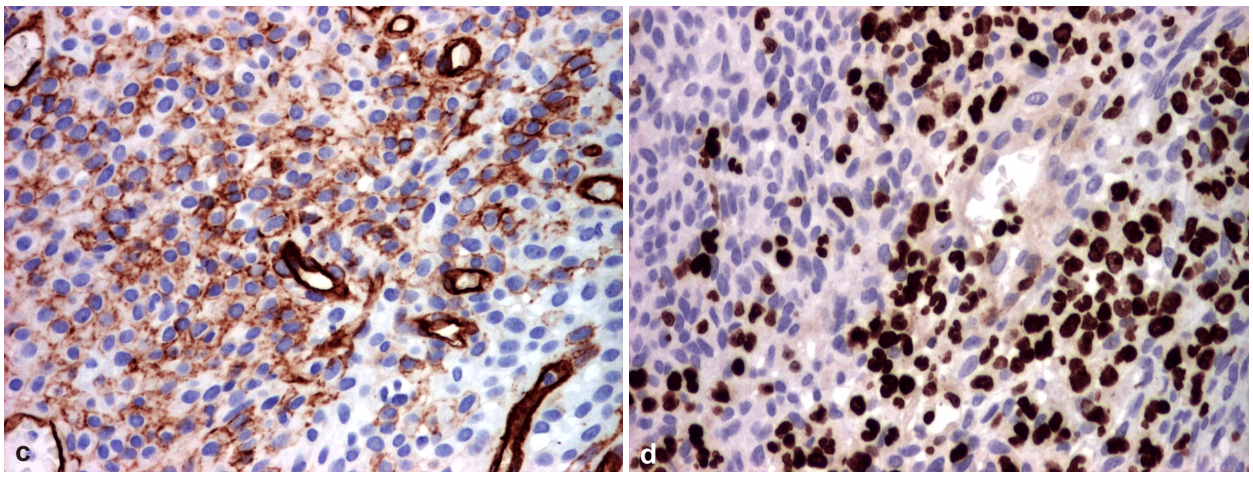

Figure 3 (continued) – ***GIST: (C) CD34 immunostaining, ×200; (D) Ki67 immunostaining, ×200.***

The histopathological diagnosis was of a gastrointestinal stromal tumor with low malignant potential according to the risk assessment criteria (size of the tumor, low mitotic index and location on the jejunum) used by the *Armed Force Institute of Pathology* (*Miettinen's Criteria*) [6] and endorsed by *European Society of Medical Oncology* [10].

The patient was under a two years pediatric oncology follow-up. During this period, he had a normal development and actually has no evidence of the recurrence of the tumor, without any specific treatment.

Discussion

The incidence of jejunoileal atresia was variably reported in literature, ranging from 1:7500 newborns in Latin countries to one in every 3000/3500 newborns in the USA [11–15]. The prevalence is estimated between 1.3 and 2.25 cases per 10 000 live births. It generally represents one third of all causes of intestinal obstruction in newborns [2].

Intestinal atresia can occur at different levels on the small bowel and it is classified into four types according to the anatomic malformations [3]. Our case corresponds to a type II atresia in which the two ends of the bowel are separated by a chord. Proximally to the atretic area, there was an intestinal stenosis, so in fact there was an association of malformations. Bowel distension is more important in distal localization of the malformation. In our case, distension occurred due to severe peritonitis after five days of evolution. We consider that in our case the evolution to peritonitis was specifically due to the presence of a stenosis proximally to the atretic zone, the stenotic area reacting like a "valve", trapping fluid and air between the two-malformed areas, followed by bowel distension, ischemia, necrosis and perforations.

GISTs are most frequently present in patients over 40-year-old (range 55–60-year-old) and only exceptionally in children. Their location on the gastrointestinal tract could be anywhere between the lower esophagus to the anus. The small intestine is the second most involved in 25–35% of cases, after the stomach in 60–70% [7]. In our case, the small tumor (0.8 cm) was detected by the anatomopathologist in the intestinal wall between the two malformations on the resected specimen.

Hayashi *et al.*, in a review of published cases of GISTs in children found two peaks of incidence less than 1-year-old and between 10- and 15-year-old and that the female sex is more affected. The overall location pattern was similar to that in adults [8]. Literature reports are controversial regarding the number of cases. Geramizadeh *et al.* reported three cases until 2005 [9] and a study of Cypriano *et al.* identified seven cases in 40 years [16]. Until 2004, there were 16 cases of GIST reported in the literature with an age range between 8- and 18-year-old [16, 17].

According to a review by Shimomura *et al.*, in 2010, there were only three previously reported cases of small bowel GIST, diagnosed accordingly to current criteria, in neonates and 12 in pediatric population (less than 18-year-old). The age of the patients was between 0 and 14 days, gender ratio 2:1 for female, tumor size median 37.5 mm (range 15–35 mm), location jejunum (2) and ileum (1), risk classification low (2), medium (1). All of them were revealed by intestinal obstruction and in all cases, a complete excision by surgery was achieved. All three cases were without evidence of disease at one-year follow-up and none of them received postoperative therapy with Imatinib [18].

Recently, Kurucu *et al.*, found five cases of GIST in newborn, published in the literature, and is presenting a case of a prenatally diagnosed abdominal tumor, diagnosed as a GIST in the seventh day of life [19].

Diagnosis of GIST was grounded on the immuno-marking staining that was positive for CD117, CD34 and Ki67 and vimentin. GIST exhibits the overexpression of KIT tyrosine, diffuse immunostaining in tumor orienting the diagnosis [7, 16–18, 20].

In the literature is mentioned the focal positivity of intestinal GISTs for CD34 in 30–40% of cases, for S100 in all cases, and rarely for alpha actin and nestin [7, 21–23].

Growing patterns most frequently described for GIST are fusiform, epitelioid and mixed [7]. In the literature, there are also mentioned neural differentiation or angiogenic hemangioma like differentiation, but without any influence on prognosis [7, 9].

As far as we know, it is the third jejunal GIST immunohistochemically confirmed in a newborn less than 1-year-old, presenting a fusiform histological growth pattern. Most frequently reported histological growth patterns for GISTs are with fusiform, epithelioid or

mixed cells [5, 6]. There are also reports of angiogenic hemangioma-like or neural differentiation with no role in the prognosis [5, 6, 9].

The surgical excision with microscopic negative margins is the mainstay of treatment as the only curative modality. In our case, complete resection was achieved because of a large enterectomy required to excise the two congenitally malformed areas and because of re-resection. Lymph node metastases are rare, and routine removal of lymph nodes is typically not necessary.

The histopathological criteria for assessment of the malignancy potential of GIST tumor are based on statistical studies and take into account the anatomic location on the digestive tract, size and number of mitoses on high power fields. Most authors refer to the scale that is that used by the *Armed Force Institute of Pathology* (*Miettinen's Criteria*) [6] and also endorsed by *European Society of Medical Oncology* [10]. In our case, the small size, jejunal localization and small number of mitoses, situates the tumor in the category of low risk of malignancy, on the aforementioned scale.

However, those criteria are not applicable to every GIST, because in pediatrics pathology, the risk of metastasis is considered 10 folds higher than in adults, as metastasis were reported even in tumors classified as low risk [17, 24].

Overall, in pediatric GISTs, adequate surgical excision of primary tumors and metastases combined with adjuvant therapy, when indicated, leads to a survival rate of more than 90% at five years follow-up [16–18, 24].

Gold *et al.* published a nomogram for assessing the probability of survival without recurrence of the disease at two years and five years postoperatively. This nomogram consists in a scale of points in which a certain number of points are assigned to the corresponding size of the tumor, the mitotic index and the location on the gastro-intestinal tract. In our case, using the tumor's features we obtained a more than 90% probability for disease free survival [25].

Imatinib mesylate (imatinib) is an orally administered competitive inhibitor of the tyrosine kinases associated with the KIT protein (stem cell factor receptor), ABL protein and platelet-derived growth factor receptors. The KIT tyrosine kinase is abnormally expressed in gastro-intestinal stromal tumor, for which there has been no effective systemic therapy [26]. Although Imatinib is now considered the elective and effective adjuvant treatment for GIST. In our case, the oncologist decided not to give any treatment to the patient, because of classification of low risk for malignancy.

To our knowledge, this is the first case published in the literature with an association of small bowel malformation and a GIST. It would be interesting to know if there are genetic similarities between those two entities.

Actually, no specific genes or genetic mutations were associated with intestinal atresia. Anyway, some genes seem to be involved: ITGA2 (integrin alpha 2, MIM: 92974) and NPPA (natriuretic peptide precursor A, MIM: 108780) [27]. Jejuno-ileal atresia or stenosis are believed to be caused by an intrauterine mesenteric vascular accident [27].

In GIST, there are mutations of at the gene that encodes the tyrosine kinase receptor for a growth hormone, found on the surface of tumor cells. The most frequent mutations of the genes are encountered in the 11^{th} exon in 50–71% of cases, and in the 9^{th} and 13^{th} in the rest of cases [28]. Apparently, there are no common genetic pathways for pathogenesis of those entities.

Conclusions

The peculiarity of our case was the association of three events in a newborn: intestinal stenosis followed by an intestinal atresia distally, therefore leading not only to intestinal obstruction but to peritonitis as well, and the occurrence of a small gastrointestinal stromal tumor with low malignant potential on the resected specimen of enterectomy.

Author contribution

All authors made equal contribution to the paper, equal to that of the first author.

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