Gastrointestinal Stromal Tumor in a Newborn Diagnosed in Prenatal Period: A Case Report and Review of Literature

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Summary: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract. Only 1.5% to 2% of all GISTs are observed in children and adolescents. Most of the pediatric cases are between 10 and 18 years of age, with a median age of 13 years. GIST is extremely rare in the newborn period. We could find only 5 reports on the neonatal cases. Herein, we have reported a case with abdominal tumor that was identified by prenatal ultrasonography and magnetic resonance imaging, and diagnosed as GIST on the seventh day of life. We have also reviewed the neonatal GIST cases reported in the English literature.

Key Words: gastrointestinal stromal tumors, newborn, small intestine tumors

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Gastrointestinal stromal tumor (GIST) is a mesenchymal neoplasm of the gastrointestinal tract, which was first described as a distinct entity by Mazur and Clark in 1983.[1] GIST is distinguished from smooth muscle neoplasms and other sarcomas with its ultrastructural and immunophenotypic features. It arises from the interstitial cell of Cajal of the gastrointestinal stroma. Most of the GISTs occur sporadically. Sporadic GISTs are characterized by somatic activating mutations in KIT tyrosine kinase gene, which is important for the development of interstitial Cajal cells.[2,3] The incidence ranges from 10 to 20 cases per million in the adult population.[2] Of all GISTs, only 1.5% to 2% occur in children and adolescents. According to SEER database, the expected incidence is about 0.08 cases per million under 18 years of age. Most of the pediatric cases are between 10 and 18 years of age, with a median age of 13 years. It is very uncommon under the age of 5 years.[3–5] Herein, we have reported a neonate with GIST, in whom the tumor was detected at prenatal ultrasonography. We have also reviewed neonatal GIST cases reported in the English literature and discussed their clinical features.

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CASE REPORT

A 32-year-old woman (G2, P1) presented for prenatal evaluation at an estimated 36 weeks gestational age by dates. Prenatal ultrasonography revealed a fetal intra-abdominal mass. There was no previous problem in her medical history. Antenatal screening test results were normal. An abdominal magnetic resonance imaging of the mother was performed and a mass filling in the left abdominal space of the fetus was detected (Fig. 1). A 2600 g male baby was delivered by cesarean section at 38 weeks of gestation. He had no congenital abnormalities. An abdominal mass was palpated on the left quadrant on physical examination. Abdominal tomography revealed a presacral mass ($6 \times 7 \times 6$ cm) filling the whole left abdominal space and extending through the left renal hilus (Fig. 2). He was operated upon on his seventh day of life. A mass of 6×6 cm in size, originating from the wall of the ileum, and involving its mesentery was observed. The bowel segment containing the mass was excised and an ileojejunal anastomosis was performed. Microscopic examination of the tumor showed a spindle-cell mesenchymal tumor arising from the submucosal region and the muscularis propia of the intestine (Fig. 3). There were large numbers of lymphocytes and macrophages between the tumor cells. Areas of hemorrhage and necrosis as well as the enlarged vessels were also observed. On immunohistochemical staining, the tumor cells were positive for vimentin, factor 13a, and actin, negative for CD34, SMA-heavy chain, MyoD1, HHF-35, myoglobin, and desmin. C-kit (CD117) was negative. Ki-67 index was lower than 5% and mitosis was rare. The diagnosis of GIST was made on the basis of histopathologic and immunophenotypic features. Chest and abdominopelvic computed tomography were normal at the postoperative first month. After 2 years of follow-up, the patient was alive and well with no evidence of tumor.

DISCUSSION

GISTs are rarely seen in children. They represent $< 2.5\%$ of all nonrhabdomyosarcoma soft tissue tumors, which account for 3.5% of all childhood malignancies.[6] The clinical and pathologic features of pediatric GIST are different from the GIST that occurs in older patients. Nearly 75% of the pediatric cases are female and the median age is 13 years.[3–5] Pediatric cases generally present with symptoms due to abdominal mass, intestinal obstruction, or gastrointestinal bleeding. The tumor involves the stomach in 85% of the pediatric cases, although only 50% of all adult GISTs are located in the stomach.[2–8] Multifocality is another important feature of pediatric GIST that was reported in 23% of the patients.[3–5] The greatest dimension of the tumor ranges from 1.5 to 35 cm. The histopathologic features show epithelioid or mixed epithelioid/spindle-cell types in the majority of pediatric tumors (44% and 28%, respectively), although 70% of adult GISTs have spindle-cell morphology. Mitotic rates varied widely from 0 to 250 per 50 high-power fields in pediatric GIST. In contrast with the adult cases, mitotic rates and tumor size are not related to the clinical behavior.[2–8] Most of the pediatric GIST follows a quite indolent course. Pappo and Janeway[3]

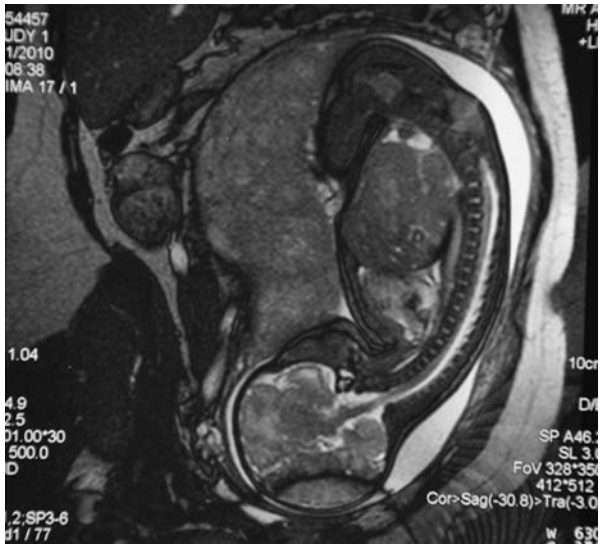

FIGURE 1. Magnetic resonance imaging showing a large mass filling the left abdominal space of the fetus.

reviewed 121 pediatric cases with GIST surviving for a median of 16 years from the time of diagnosis; only 6 of those patients died of the disease.

Like clinicopathologic features, the molecular biology of pediatric GIST is different from that of adult ones. Mutations in *KIT* or *PDGFRA* tyrosine kinase genes are present nearly in 90% of the adult cases, whereas only 7% to 15% of the pediatric cases have these mutations.[2–4,8–10] Despite the lack of mutation, consistent activation of KIT and downstream targets, including Ras-MAPK and P13K-AKT-MTOR, were reported. Therefore, it was suggested

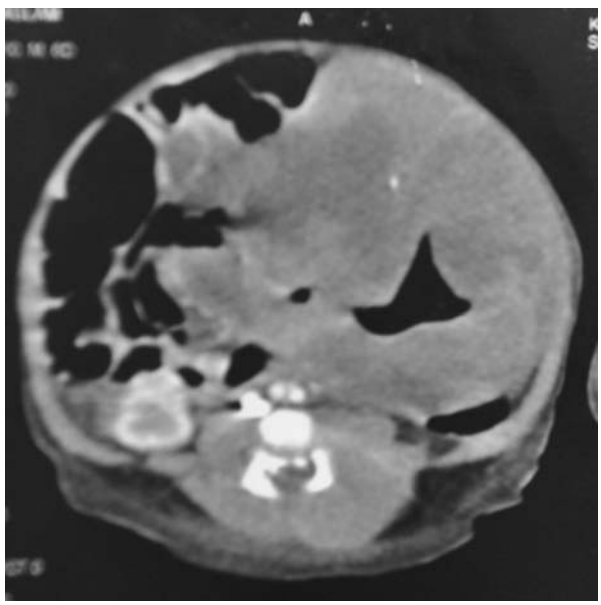

FIGURE 2. Abdominal tomography demonstrating a presacral mass $6 \times 7 \times 6$ cm in diameter filling the whole left abdominal space and extending through the left renal hilus.

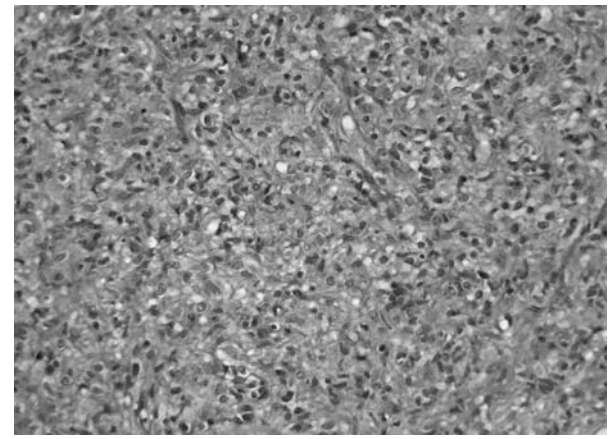

FIGURE 3. Monotonous neoplastic cells with bland-looking oval to spindle-cell nuclei are seen to be admixed with capillary-sized vessels. No matrix formation is noted. (hematoxylin and eosin, $\times 400$).

that *KIT* may play some role in the oncogenesis of wild-type GIST.[3,9,10]

Although most of the GISTs occur sporadically, few cases with familial GIST have been reported. In addition to germline *KIT* mutation, germline mutation in the succinate dehydrogenase (*SDH*) gene has been identified in familial GIST. Patients with Carney triad (GIST and extra-adrenal paraganglioma and pulmonary chondroma) and Carney-Stratakis syndrome (GIST and paraganglioma) have germline mutation or deletion in subunits of *SDH* gene. This gene acts as a typical tumor-suppressor gene. It was recently determined that 10% to 15% young patients with wild-type GIST have somatic *SDH* mutation in the absence of a personal or family history of the syndrome and germline mutation. Moreover, all pediatric wild-type GIST and many adult wild-type GIST cases lack normal SDH protein expression and enzymatic activity, even in the absence of mutation *SDH*.[2–4,8–10] Adult wild-type GIST cases have an activating mutation of *BRAF-V600E*, which is a member of the RAF serine threonine proteinkinase family and a component of the Ras-RAF-ERK signaling pathway. However, it is not clear that this mutation is responsible for driving tumorigenesis. Moreover, the presence of *BRAF* mutation has not yet been demonstrated in pediatric GIST patients.[9,10] Insulin-like growth factor-1 receptor (IGFR-1) pathway is upregulated in the majority of GIST cases. However, the levels of expression are much higher in wild-type GISTs. Moreover, it is 5 times higher in pediatric wild-type cases than adult ones. IGF-1 and its receptor IGFR-1 are central mediators of cellular growth and proliferation.[3,4,8–10] In addition to *IGFR-1* and *SDH*, some other key genes including cytokine receptor-like factor-1, pleomorphic adenoma gene , fibroblast growth factor 3 and 4, brain and acute leukemia cytoplasmic, and NEL-like 1 are overexpressed, specifically in pediatric wild-type GIST cases.[3,4,9,10] In contrast, typical chromosomal changes include 1p, 14q, 22q, and 9p regions, which contribute to the clinical progression of adult GIST, are not identified in pediatric GIST.[3,4,8–10]

Twenty-one cases of GIST under 20 years of age were registered to SEER from 1967 to 2007. Sixty percent of them were between 15 and 19 years of age and 35% were

TABLE 1. Neonatal Patients With Gastrointestinal Stromal Tumor Reported in the Literature

References	Age at Diagnosis	Sex	Antenatal USG	Location Size	Histology	Immunohistochemistry	Treatment	Survival
Wu[14]	1 d	M	Normal (26 wk) dilated bowel loop (39 wk)	Jejunum 3.5 cm	Mostly spindle + epithelioid areas	C-kit (+), vimentin (+), CD34 (+), actin (–), SMA (–), desmin (–), keratin (–)	Surgery	Awod 1 y
Shenoy et al[15]	1 d	M	NM	Terminal ileum 2.5 cm	Spindle cell	C-kit (NM), vimentin (+), CD34 (+), actin (+), SMA (NM), desmin (NM), keratin (NM)	Surgery	Awod 1 y
Bates et al[16]	14 d	F	NM	Jejunum 1.5 cm	Mostly spindle + epithelioid areas	C-kit (–), vimentin (+), CD34 (–), actin (NM), SMA (+), desmin (–), keratin (NM)	Surgery	NM
Geramizadeh et al[17]	6 d	F	NM	Cecum 3 cm	Spindle	C-kit (+), vimentin (+), CD34 (–), actin (–), SM actin (NM), desmin (–), keratin (–)	Surgery	Awod 1 y
Tanyeri et al[18]	1 d	F	NM	Terminal ileum 6 cm	Spindle	C-kit (–), vimentin (NM), CD34 (+), actin (NM), SM actin (+), desmin (+), keratin (NM)	Surgery	Died at 2 mo
This study	Prenatal 36 wk	M	Abdominal mass (36 wk)	Ileum 6 cm	Spindle	C-kit (–), vimentin (+), CD34 (–), actin (NM), SM actin (–), desmin (–), keratin (NM)	Surgery	Awod 2 y

Awod indicates alive without disease; NM, not mentioned; USG, ultrasonography.

between 10 and14 years of age. There was only 1 case below 1 year of age.[4] Benesch et al[5] reviewed 113 pediatric cases reported in the literature. The median age was 13 years with a range of 1 day to 21 years. In 2009, Pappo and Janeway[3] reviewed 121 cases below 18 years of age; 3 of them were newborn.

Only 0.5% to 2% of childhood malignancies occur during the newborn period. The reported incidence of neonatal tumors varies from 17 to 121 per million live births.[11] Most of the neonatal tumors are benign in nature. Malignant neoplasms are uncommon, and their clinical and biological behaviors differ from comparable tumors that occur in older children. Some, such as congenital fibrosarcoma, follow a benign course, although they are malignant according to histologic criteria. Others, such as neuroblastoma, may regress in the course of time. Histologically, teratoma (23.5%) and neuroblastoma (22.5%) are the 2 most common tumors in the newborn followed by soft tissue sarcomas (8%), renal tumors (7.1%), brain tumors (5.9%), and leukemia (5.9%). The majority of the malignant neonatal tumors are embryonic in origin.[11,12] Most common mesenchymal neonatal tumors are hemangioma, hamartoma, rhabdomyosarcoma, and fibroblastic tumors. GIST is extremely rare in the newborn.[3,13]

In the English literature, we could find only 5 cases (2 male, 3 female) who were diagnosed with GIST in the newborn period (Table 1).[14–18] We believe that our case is the first neonate that the abdominal mass was diagnosed in the prenatal period by ultrasonography and magnetic resonance imaging. The other 5 cases presented with symptoms of intestinal obstruction in the postnatal period. Neonatal abdominal masses comprise a very broad spectrum of lesions ranging from congenital malformative lesions (eg, hydronephrosis, intestinal lymphangiomas, and intestinal duplication) to benign and malignant tumors. They may present as an asymptomatic mass; however, they may cause intestinal obstruction, volvulus, and gastrointestinal bleeding. Owing to the widespread use of antenatal ultrasonography, it is not infrequent to discover abdominal masses during the prenatal period.[19] However, the 5 reported cases to date were all diagnosed in the postnatal period as a consequence of symptoms and signs of intestinal obstruction such as vomiting, delayed passage of meconium, abdominal distension, and tenderness. Rectal bleeding was reported in only 1 patient.[14–18] There is no female preponderance in the newborn period, unlike that in the older children. In neonates, the tumor arises from the wall of the intestine in all the cases (the ileum in 3 cases, jejunum in 2 cases, and cecum in 1 case), although GIST was more frequent in the stomach in older children. The maximum size of the tumor among the 6 cases was 6 cm. Similar to the pediatric cases, C-kit was usually found to be negative (4 of the 6 cases). All the neonatal GIST cases were treated with surgery only. All the patients were alive without any disease at 1 year, except 1 who died at 2 months because of infection.[14–18]

In summary, although it is very rare, GIST must be kept in mind in differential diagnosis of neonatal intra-abdominal tumors. Although the 6 cases are not sufficient to make conclusive statements, it can still be suggested that the neonatal GIST shows some differences from the tumors seen in the older children.

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