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Case report

Diagnosis and management of high risk gastrointestinal stromal tumor in first trimester pregnancy: A case report and review of the literature

Christina M. Sheedy [a], Anna Weinstein [b], Olivia Chafitz [b], Antonia F. Oladipo [b,*]

[a] Hackensack Meridian School of Medicine, 340 Kingsland St Building 123, Nutley, NJ, 07110, United States
[b] Obstetrics and Gynecology Department, Hackensack University Medical Center, 30 Prospect Avenue, Hackensack, NJ, 07601, United States

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ABSTRACT

Objective: There are less than 20 reported cases of gastrointestinal stromal tumors in pregnancy. Of these reported cases, there are only two that detail GIST in the first trimester. We report our experience with the third known GIST diagnosis in the first trimester of pregnancy. Notably, our case report highlights the earliest known gestational age at time of GIST diagnosis.
Methods: We conducted a literature review of GIST diagnosis in pregnancy via PUBMED, using a combination of the following terms: (pregnancy or gestation) and (GIST). We utilized Epic for chart review of our patient's case report.
Results: A 24 year old G3P1011 presented to the Emergency Department at 4w6d by last menstrual period (LMP) with worsening abdominal cramping, bloating, and associated nausea. Physical exam revealed a large, mobile, nontender mass palpated in the right lower abdomen. Transvagianl ultrasound noted the presence of a large pelvic mass of unknown etiology. Pelvic magnetic resonance imaging (MRI) was obtained for further characterization, revealing a 7.3× 12.4 × 12.2 cm mass with multiple fluid levels, centered in the anterior mesentery. Exploratory laparotomy was performed with en bloc resection of small bowel and pelvic mass, with pathology demonstrating a 12.8 cm spindle cell neoplasm compatible with GIST and notable for a mitotic rate of 40 mitoses/50 high power field (HPF). Next generation sequencing (NGS) was pursued in order to predict tumor responsiveness to Imatinib, which revealed a mutation at KIT exon 11, suggesting a response to tyrosine kinase inhibitor therapy. The patient's multidisciplinary treatment team, consisting of medical oncologists, surgical oncologists, and maternal fetal medicine specialists, made the recommendation for adjuvant Imatinib therapy. The patient was offered termination of pregnancy with immediate initiation of Imatinib, as well as continuation of pregnancy with either immediate or delayed treatment. Interdisciplinary counseling focused on both the maternal and fetal implications of each proposed management plan. She ultimately elected termination of pregnancy, and underwent an uncomplicated dilation and evacuation.
Conclusions: GIST diagnosis in pregnancy is exceedingly rare. Patients with high-grade disease encounter a multitude of decision-making dilemmas, often with competing maternal and fetal interests. As additional cases of GIST in pregnancy are added to the literature, clinicians will be able to implement evidence-based options counseling for their patients. Shared decision-making is contingent upon patient understanding of diagnosis, risk of recurrence, available treatment

* Corresponding author. Prospect Avenue, Suite 601 Hackensack, New Jersey, 07601, United States.
E-mail address: antonia.oladipo@hmhn.org (A.F. Oladipo).

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options, and the treatment-related implications on maternal and fetal outcomes. A multidisciplinary approach is crucial for optimization of patient-centered care.

1. Introduction

Gastrointestinal stromal tumors (GIST) are rare mesenchymal neoplasms, with an average incidence of 10–15 per million per year [1]. Although GISTs only account for 1–2% of primary GI cancers, they are the most common non-epithelial neoplasm that arises in the GI tract. These tumors predominantly arise in those over 60 years old with equal gender distribution. The majority of GISTs are found in the stomach, followed by the small bowel [1]. Symptoms vary depending on the location of the tumor, with the most common clinical manifestations including overt or occult GI bleeding (28–50%), abdominal pain (8–17%), acute abdomen (2–14%), and asymptomatic abdominal mass (5%) [1]. GISTs may also present asymptomatically, with incidental diagnosis occurring in 13–25% of cases [1]. Important prognostic factors for GISTs include tumor size, mitotic rate, and location [2]. Depending on tumor characteristics and location, management strategies may include surveillance, medical therapy, surgery, or a combination thereof [2].

There are less than 20 reported cases of gastrointestinal stromal tumors in pregnancy. Of these reported cases, there are only two that detail GIST in the first trimester. One case was diagnosed at 10 weeks gestation, based on the presence of a pelvic mass [3]. Another case involves a patient who presented at 6 weeks gestation with rectal bleeding [4]. We report our experience with the third known GIST diagnosis in the first trimester of pregnancy.

2. Methods

We conducted a literature review of GIST diagnosis in pregnancy via PUBMED, using a combination of the following terms: (pregnancy or gestation) and (GIST) and/or (gastrointestinal stromal tumor). Search returned 67 results and after screening, 17 reported cases of GIST diagnosis in pregnancy were identified. We utilized Epic electronic medical record system for chart review of our patient's case report.

3. Results

3.1. Details of case presentation

A 24 year old G3P1011 presented to the Emergency Department at 4w6d by last menstrual period (LMP) with worsening abdominal cramping, bloating, and associated nausea. She had no prior medical, surgical, or family history. Her obstetrical history included one uncomplicated, full term vaginal delivery eight years prior to presentation, and a first trimester loss. Physical exam revealed a large, mobile, nontender mass palpated in the right lower abdomen.

Transvaginal pelvic ultrasound confirmed an intrauterine pregnancy consistent with reported LMP, and noted the presence of a large pelvic mass of unknown etiology (Fig. 1). Pelvic magnetic resonance imaging (MRI) was obtained for further characterization, revealing a 7.3× 12.4 × 12.2 cm mass centered in the anterior mesentery, with multiple fluid-fluid levels indicating a complex mass with fluids of different densities concerning for malignancy (Figs. 2 and 3). Tumor marker CA-125 was elevated at 247. The remaining tumor markers evaluated (CEA, CA 19-9, AFP, Inhibin B) were within normal range.

A multidisciplinary team of gynecologic oncologists and surgical oncologists performed a diagnostic laparoscopy at 5w5d gestation. A large friable mass arising from the small intestine, adherent to the anterior abdominal wall, was identified. Exploratory laparotomy was performed with en bloc resection of small bowel and pelvic mass. There was no evidence of intraoperative tumor spillage. Pelvic organs otherwise appeared normal. Her postoperative course was unremarkable and she was discharged on postoperative day two with outpatient follow-up.

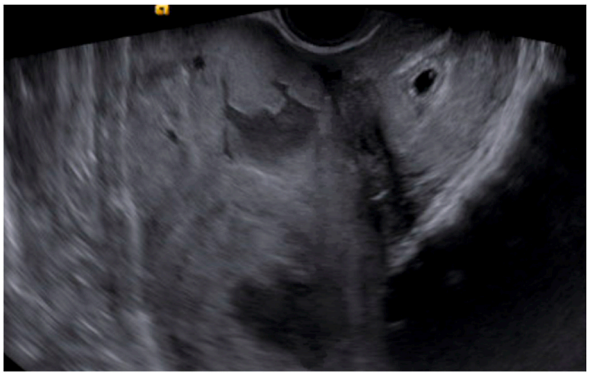

Fig. 1. Transvaginal ultrasound at time of diagnosis.

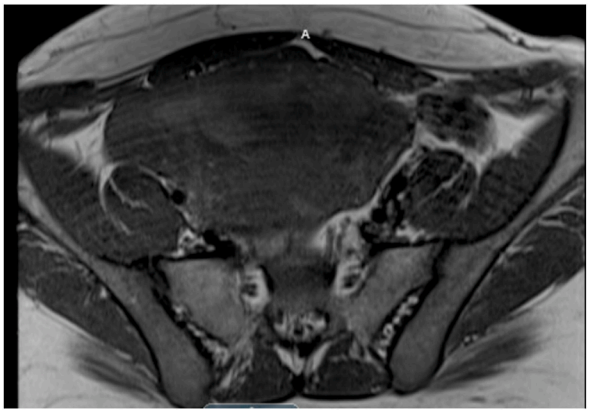

Fig. 2. T1 MRI at time of diagnosis.

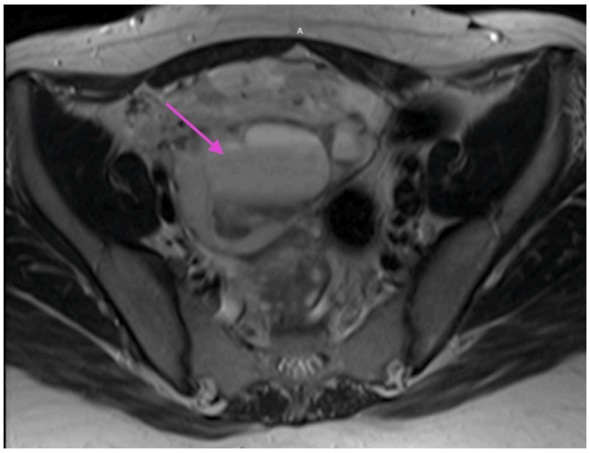

Fig. 3. MRI image at time of diagnosis. Arrow indicating multiple fluid levels present within the mass.

Pathology demonstrated a 12.8 cm spindle cell neoplasm compatible with GIST and notable for a mitotic rate of 40 mitoses/50 high power field (HPF). There was no evidence of vascular invasion or lymph node metastasis, and the proximal and distal margins were uninvolved. Pathologic findings were suggestive of a Stage IIIB small intestinal GIST, based on tumor size greater than 10cm and mitotic rate of >5 mitoses/50 HPF [2].

The patient's probability of two year recurrence-free survival (FRS) was approximated at 1%, based on the Memorial Sloan Kettering Cancer Center (MSKCC) GIST nomogram, which calculates the risk of recurrence for patients who do not receive Imatinib therapy prior to or after surgical resection [5,6]. Next generation sequencing (NGS) was pursued in order to predict tumor responsiveness to Imatinib, which revealed a mutation at KIT exon 11, suggesting a response to tyrosine kinase inhibitor therapy.

The patient's multidisciplinary treatment team, consisting of medical oncologists, surgical oncologists, and maternal fetal medicine specialists, made the recommendation for adjuvant Imatinib therapy. The patient was offered termination of pregnancy with immediate initiation of Imatinib, as well as continuation of pregnancy with either immediate or delayed treatment. Interdisciplinary counseling focused on both the maternal and fetal implications of each proposed management plan. The patient initially elected to continue the pregnancy and to delay adjuvant therapy until the second trimester. She began daily 400mg Imatinib therapy at 14w6d. At 18w1d, the patient expressed desire to terminate the pregnancy, and was subsequently referred to the department of complex family planning at our institution. At 19w2d, she underwent an uncomplicated ultrasound-guided dilation and evacuation. The patient remains on Imatinib adjuvant therapy, undergoing close surveillance by medical oncology.

4. Details of previous case reports

GIST diagnosis in pregnancy is rare, with only eighteen cases previously described in the literature [3,4,7–20]. Details of each case are described in Table 1. A 2015 systematic review of GIST in pregnancy discussed eleven of these cases [21], and our literature search identified six additional published cases of GIST in pregnancy [3,4,7–10]. Of these reported cases, a total of three GIST diagnoses were made in the first trimester, including that of our patient.

In 2009, Scherjon et al. described a 25 year old G1P0 who presented at 10w3d with a large pelvic mass [3,21]. She underwent

Table 1
Characteristics of GIST diagnoses in pregnancy.

Case/ Reference	Age	Gestational Week at Initial Presentation	Presenting Sign/ Symptoms	Location	Stage at Diagnosis	Grade	Treatment	Gestational Week at Delivery	Delivery Method	Fetal Outcome	Maternal Outcome
Scherjon et al. (2009) [3]	25	10	Pelvic mass	Jejunum; Splenic Metastasis	Stage IV	High grade.	Surgery, Adjuvant Imatinib (PP)	41	SVD	Healthy	Recurrent metastatic disease 6 years following initial diagnosis, at which time adjuvant Imatinib initiated
Al Ibrahim (2014) [4]	26	6	Rectal Bleeding	Stomach	T3N0M0	Unknown	Surgery, Imatinib (PP)	40	SVD	Healthy	Unknown
Tanaka et al. (2020) [7]	29	14	Hematemesis	Stomach	Stage IIIA	High Grade	Surgery (PP), Imatinib (PP)	40	SVD	Healthy	NED at 12 months
Charo et al. (2018) [8]	34	8	Abdominal pain/ fullness, Nausea, Vomiting	Jejunum	Stage IIIA	Low grade	Surgery (IP)	40	SVD	Healthy	NED at 20 months
Jove et al. (2017) [9]	28	14	Hematemesis Melena Syncope Abdominal pain	Stomach	Stage II	Low grade	Surgery (IP), Adjuvant imatinib	Unknown	Unknown	Unknown	Unknown
Chennouf et al. (2022) [10]	23	23	Abdominal mass	Stomach and Duodenuml	Stage IV	Low grade	Surgery (PP), Adjuvant Imatinib (PP) Sunitinib (PP), Regorafenib (PP) Ripretinib (PP)	37weeks	SVD	Healthy	Progressive metastatic disease NED at 1 year on alternative regimen
Gozukara et al. (2012) [11]	21	15	Abdominal pain	Omentum	Stage II	Low grade	Surgery (IP)	Unknown	Unknown	Unknown	Unknown
Igras et al. (2012) [12]	42	20	Pelvic Mass Hematochezia (at 36 wk GA)	Duodenum	Stage II	Low grade	Surgery (at time of CD)	36	Emergent CD for hematochezia, severe anemia, preeclampsia	Healthy twins	Unknown
Stubbs et al. (2011) [13]	31	16	Lethargy, dizziness, pelvic mass	Transverse colon	Stage IIIB	High grade	Surgery (at time of CD), Imatinib (PP)	36	CD	Healthy	Unknown
Haloob et al. (2013) [14]	31	18	Lethargy, dizziness, dyspnea on exertion	Jejunum	Stage IIIB	High grade	Surgery (at time of CD), Imatinib (PP)	36	CD	Healthy	NED at 24 months
Lanfazame et al. (2006) [15]	29	22	Abdominal Pain	Unknown	Unknown	Unknown	Surgery	Unknown	Unknown	Unknown	Unknown

(*continued on next page*)

Table 1 (*continued*)

Case/ Reference	Age	Gestational Week at Initial Presentation	Presenting Sign/ Symptoms	Location	Stage at Diagnosis	Grade	Treatment	Gestational Week at Delivery	Delivery Method	Fetal Outcome	Maternal Outcome
Valente et al. (1996) [16]	32	Unknown	Unknown	Unknown	Unknown	Unknown	Surgery	Unknown	Unknown	Intubated at birth, healthy at 9 month follow up	NED at 9 months
Varras et al. (2010) [17]	28	Postpartum Day 10	Acute abdomen, hemoperitoneum	Small Intestine	Stage IIIB	High grade	Surgery (PP), adjuvant Imatinib (PP)	Full term	SVD	Healthy	NED at 3 years
Mahdaui et al. (2012) [18]	38	Unknown	Unknown	Epiploica	T4L_N_	Unknown mitotic rate	Surgery, Adjuvant Imatinib	TOP	Not applicable	Not applicable	Unknown
Charrif et al. (2014) [19]	42	5th month?	Biliary colic, vomiting	Liver	T4L_M_	Unknown mitotic rate	Surgery (PP), neoadjuvant Imatinib; re-operation (PP)	35 weeks	CD	Healthy	partial radiologic/ clinical response documented; Unknown long term follow up
Coveney et al. (2011) [20]	42	23	Pelvic mass; Hematochezia on POD#1 s/p CD	Retroperitoneum	Stage IIIA	Low grade	Failed Embolization Attempt; Surgery (pp)	37weeks- CD for preeclampsia with monochorionic diamniotic twin gestation	CD	Healthy twins	Unknown
This case (2022)	24	4	Abdominal pain/ bloating, nausea Pelvic Mass	Small Intestine	Stage IIIB	High Grade	Surgery (IP), Adjuvant Imatinib (IP)	TOP	Not applicable	Not applicable	NED at 6 months

CD: Cesarean Delivery.
SVD: Spontaneous Vaginal Delivery.
TOP:Termination of pregnancy.
PP: Postpartum.
IP: Intrapartum.

diagnostic laparoscopy at 15w1d of a 20 cm tumor involving the jejunum, appendix, epiploic appendices, and rectouterine pouch. Laparotomy and en bloc tumor resection including the jejunum and appendix was performed. Pathology confirmed GIST diagnosis with positive splenic metastasis. Her postoperative course was complicated by an obstructive ileus, prompting re-exploration with duodenal biopsy. Pathology confirmed duodenal GIST, requiring partial duodenectomy and gastroenterostomy. Patient did not receive Imatinib, as she was not enrolled in the ongoing phase III clinical trial for adjuvant Imatinib in GIST. She had a spontaneous vaginal delivery at 41w6d of a healthy neonate.

Three years later she had a second pregnancy with an uncomplicated course and delivery. The patient was followed with close surveillance and remained with no evidence of disease (NED) for five years. She was diagnosed with duodenal, ovarian, and peritoneal metastatic recurrence six years after initial diagnosis, requiring resection. Two months postoperatively, another recurrence was suspected on surveillance imaging and she was initiated on adjuvant Imatinib therapy. Patient remained NED at two year follow-up.

In 2014, Al Ibrahim et al. described a 26yo G1P0 who presented at six weeks gestation with significant rectal bleeding and underwent laparoscopic resection of a T3 mass [4]. Pathology confirmed GIST diagnosis. She had a spontaneous vaginal delivery at 40 weeks gestation and received adjuvant Imatinib postpartum. Long term patient and neonatal outcomes are unavailable for review.

5. Discussion

GISTs may present with a variety of symptoms, including abdominal pain, abdominal mass, bloating, constipation, nausea, vomiting, weight loss, GI bleeding, and anemia [22]. Many of these symptoms can be attributable to normal pregnancy, making diagnosis particularly challenging in this patient population. We present the third known case of GIST diagnosed in the first trimester of pregnancy. Notably, our case report highlights the earliest known gestational age at time of GIST diagnosis.

Our case report describes the only GIST diagnosis in the first trimester that was managed with adjuvant Imatinib therapy in pregnancy. While termination of pregnancy precludes the ability to determine long term neonatal outcomes, the effects of Imatinib therapy in pregnancy have previously been described [23]. The teratogenic potential of Imatinib complicates the management of high grade GIST in early pregnancy.

Research regarding Imatinib use in pregnancy is limited. Animal models have demonstrated teratogenic effects of Imatinib in pregnant rats, resulting in neural tube and cranial bone defects [24]. Existing clinical data suggests that exposure to Imatinib in pregnancy may result in an increased risk of spontaneous abortion and fetal anomalies [23]. In a study of 125 patients who took Imatinib during pregnancy, 35 elected for termination, 18 had spontaneous abortions, and 72 elected for continuation of pregnancy. Of the expectantly managed pregnancies, there were 63 non-anomalous live births. The remaining nine pregnancies resulted in neonates with varying congenital anomalies, one of which was a stillbirth [23].

Many of the aforementioned cases of GIST in pregnancy were diagnosed prior to the widespread use of Imatinib as adjuvant therapy. Imatinib first received Federal Drug Administration (FDA) approval for treatment of Chronic Myelocytic Leukemia (CML) in 2001 [25]. In 2002, it was approved for treatment of advanced or metastatic GIST [25]. Adjuvant Imatinib therapy in patients with resectable disease received accelerated approval in 2008, based on the early findings of a phase III, double-blind, placebo-controlled, multicenter trial [26]. In 2012, the FDA granted Imatinib full approval for adjuvant treatment of GIST [25]. The optimal duration of adjuvant Imatinib therapy is unknown, however NCCN guidelines recommend treatment for at least three years based on data that demonstrated improved recurrence-free survival (RFS) using a 36-month regimen [2,27].

The previously described cases featured use of Imatinib therapy in the postpartum period or prior to conception (Table 1) [3,4,7–20]. There were no case reports highlighting initiation of Imatinib in the first trimester, when teratogenic drugs are known to have the most deleterious effect on fetal organogenesis. The timing of our patient's diagnosis contributed to the complexity of its management: the benefit of Imatinib in a patient with a high risk for tumor recurrence had to be weighed against the risk of Imatinib initiation in the first trimester of a desired pregnancy.

When a diagnosis of cancer is made in early pregnancy, patients may elect to terminate the pregnancy and initiate immediate treatment [28]. They may also elect to continue the pregnancy and initiate immediate treatment at time of diagnosis, with the understanding of potential teratogenic treatment effects. Extent of teratogenicity may differ based on the gestational age at which treatment is initiated, with the most significant fetopathy seen in cases of treatment during the first trimester [28]. Counseling also includes the option to delay treatment until the second or third trimester, which mitigates teratogenic potential for the fetus but impacts patient outcome. Delaying treatment until the postpartum period avoids any teratogenic effect, but certainly increases risks surrounding a delay in care [28].

The reported incidence of GIST in pregnancy is low, and data regarding the course, management, and maternal/fetal outcomes is limited. We summarize eighteen cases of GIST diagnosed during pregnancy, with emphasis on the three cases that were diagnosed in the first trimester. Given the paucity of available literature, reporting such cases furthers our understanding of a rare oncologic condition, and advances our capability to effectively manage it in the pregnant population.

6. Conclusion

GIST diagnosis in pregnancy is exceedingly rare. Patients with high-grade disease encounter a multitude of decision-making dilemmas, often with competing maternal and fetal interests. As additional cases of GIST in pregnancy are added to the literature, clinicians will be able to implement evidence-based options counseling for their patients. Shared decision-making is contingent upon patient understanding of diagnosis, risk of recurrence, available treatment options, and the treatment-related implications on maternal and fetal outcomes. A multidisciplinary approach is crucial for optimization of patient-centered care.

Consent

Written informed consent was obtained from the patient for publication of this case report and associated images. A copy is available for review upon request.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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