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Case Report

Pediatric Metastatic Gastric Gist, and Imatinib and Pregnancy

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Abstract

Gastrointestinal stromal tumors (GISTS) are rare neoplasms and are currently identified by KIT mutation (CD117) [1]. The discovery of this mutation has allowed the development of a new target therapy drug (Imatinib Mesylate® - NOVARTIS, Basel) that has been revolutionary for the treatment of this disease, promoting a better quality of life and higher survival, even in cases of advanced metastatic disease.

The marked improvement in the quality of life and survival of patients with metastatic GISTs has permitted them to maintain physical activities as well as normal emotional and sexual intercourse.

Keywords: *Gastrointestinal Stromal Tumors (GISTS); CD117; Imatinib*

Introduction

Pediatric gastrointestinal stromal tumors (pGIST) are extremely rare neoplasms, which are current and in most of the cases identified by a mutation in the Kit (CD117) gene 1. Upon discovery of this mutation the development of a Kit-selective tyrosine kinase inhibitor, the specifically targeted drug was developed (Imatinib Mesylate - Novartis, Basel, Swiss), which revolutionized transforming the treatment of the myeloid chronic leukemia (MCL) and GIST.

The author describes the successful management of a patient with pediatric gastric GIST with metastatic implants both in the liver and peritoneal cavity who became pregnant during Imatinib treatment. To the authors' knowledge, there is no documented case of Imatinib use during pregnancy in a patient diagnosed with pediatric GIST at that time.

Case Report

An 18-year-old female was referred to our service because of a metastatic pediatric gastric GIST, to liver and peritoneum. The patient was diagnosed at the age of 15 with the original gastric GIST. She underwent partial gastrectomy and recovered uneventfully. The pathology revealed a high-grade gastric GIST (9 cm in diameter and more than 10 mitoses per 50HPF) and Kit positive. A CT scan was performed (Figure 1) and revealed liver metastases and tumor implants in the left part of the abdomen. Treatment with 400 mg per day of Imatinib Mesylate was initiated and she was advised not to conceive while taking it. Despite the counseling, four months later she became pregnant (sixteen weeks of pregnancy) (Figure 2).

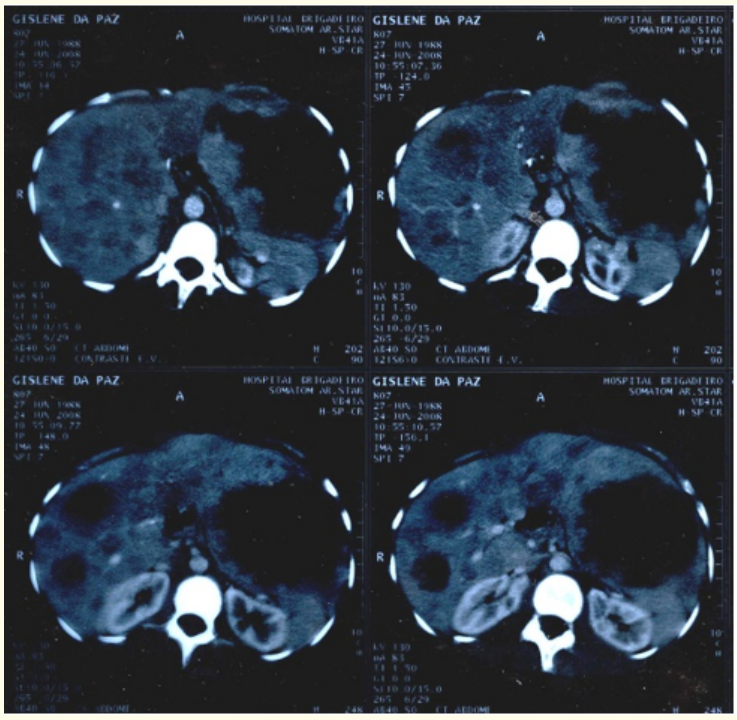


Figure 1: *CT scan with liver metastases before the pregnancy.*

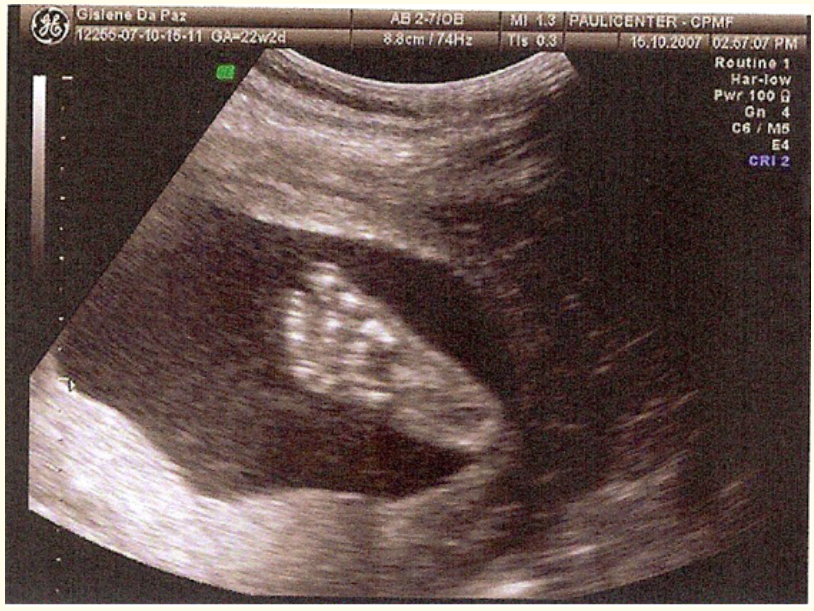


Figure 2: *Ultrasound confirms the 16 weeks of pregnancy.*

The pregnancy of a patient with a neoplastic disease requiring cytotoxic treatment always poses a therapeutic dilemma. The patient decided to continue medication and pregnancy. Prenatal care surveillance was made every 15 days, with monthly ultrasound studies. Pregnancy underwent uneventfully and a cesarean was carried on with no further complications. A female infant was born with Apgar scores of 9 and 10, 3210g weight and 49 cm in length (Figures 3 and 4).

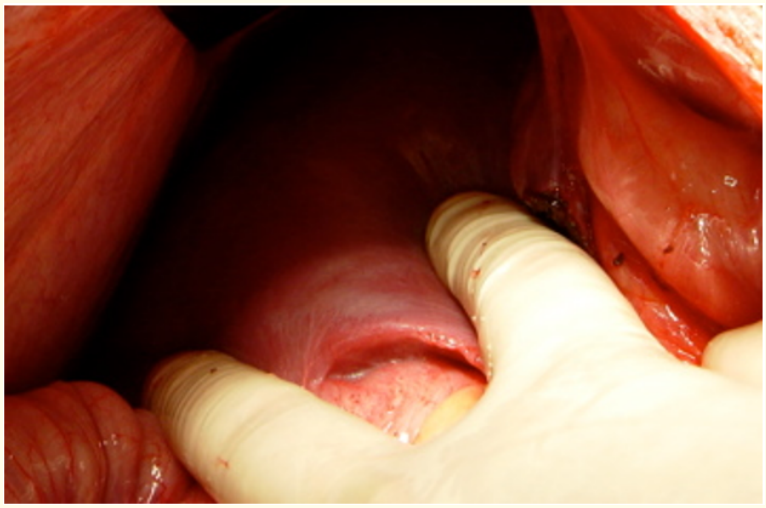


Figure 3: *Liver Metastasis during the Cesarean surgery.*

Figure 4: *Apgar scores of 9 and 10, 3210 g weight and 49 cm in length.*

There were no perinatal complications. Samples were collected for quantification of Imatinib Mesylate and its metabolic product CGP74588.

1. Maternal and fetal blood (umbilical cord);
2. Maternal and fetal urine;
3. Amniotic fluid;
4. First meconium;
5. Placenta and umbilical cord for pathological examination.

After the obstetric procedure, a careful evaluation of the abdominal cavity was performed and confirmed the presence of numerous liver metastases and tumor implants in the left part of the peritoneum (Figure 2). Biopsies of the liver metastasis were collected for histological and genetic studies (Exon). The patient stopped taking Imatinib 48hs before de delivery. After the delivery Imatinib was reintroduced (400 mg/day) and breastfeeding was not permitted.

The child has been closely followed since birth, at the pediatric outpatient clinic of our institute (Federal University of São Paulo, São Paulo). Her growth and development have been normal (Figure 5).

Figure 5: *Health girl in 2019.*

The patient died on July 2014 due to the progression of the disease.

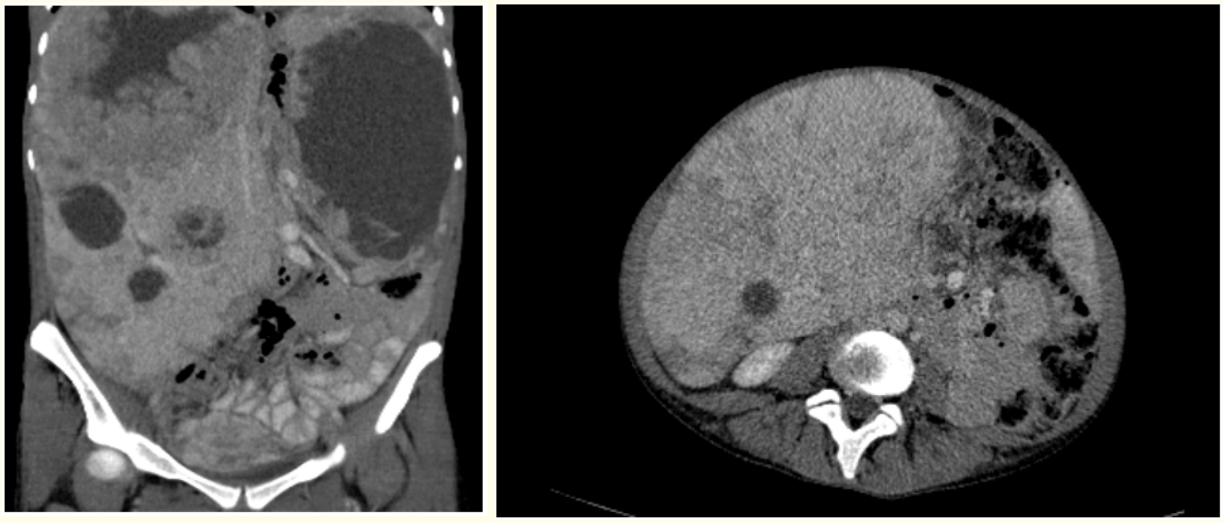
The samples were collected according to the Department of Pharmacology, University of Pittsburgh guidelines where all exams were conducted.

Pathology

The lesion of the liver confirmed metastatic GIST. There was no evidence of GIST free cells or metastasis in the amniotic liquid and placenta. Exon in the liver metastasis was 17.

Evolution

The patient remained clinically asymptomatic under Imatinib 400 mg/daily with no reported side effects until 2010. She started complaining from abdominal distension and an abdominal computed tomography revealed disease progression in the liver and the right upper part of the abdomen (Figure 6a and 6b).



a ***b***

Figure 6a and 6b: *CT Scan before the pregnancy under Imatinib Mesylate.*

The disease has progressed and 800 mg was attempted but discontinued after a few days due to side effects (abdominal pain, diarrhea, and weakness). She started on 600 mg and a partial response was observed. In 2013 was decided to shift to Sunitib 35 mg per day with significant improvement of clinical conditions and grade I side effects. After 8 months under Sunitinib, the disease progress and no other medication were viable and the multidisciplinary team decided to return to Imatinib with partial response. After 60 days the patient at age of 25 passed away.

Discussion

Pregnancy in patients with malignancies who require cytotoxic treatments remains a dilemma. Most of the information in the literature derived from animal studies so there is almost no information in human beings. Furthermore, data are limited to isolated case reports.

The cytotoxic effect of antineoplastic drugs in the embryo or fetus can be evaluated in two ways: Immediate effects that can be instantly recognized by miscarriage or teratogenicity effects and, on the second hand, a few late effects that will appear and are listed as gonadal endocrinology errors, lack of normal growth and development milestones. These events would require years to be detected or diagnosed. There are also future problems that would affect and only manifest in future generations.

Imatinib Mesylate (ST1571 Gleevec®, Novartis, Basel, Switzerland) is the standard therapy in cases of unresectable or metastatic GIST and Chronic Myeloid Leukemia (CML). Imatinib is well tolerated and adverse events reported in more than 50% of patients are generally mild and easily managed with medication. Grade 3 and 4 adverse effects are rare.

Imatinib Mesylate was a new drug at that time and the Food and Drug Administration classified it in category D. Pharmacological activity anti-tirozinoquinase also affects normal cells in gametogenesis, hematopoiesis and melanogenesis phases. It also affects apoptosis and cell adhesion processes. These are important functions in embryo cells and fetus development. There is evidence confirming the teratogenicity [5] of this drug, however, the benefits of its use during pregnancy may be acceptable despite the risks, when the disease (CML and GIST) is life-threatening and no other drug or treatment can be indicated. Mesylate Imatinib has shown small medication transfer through the placental barrier [1]. Animal studies showed an evident risk of teratogenicity in rats but not in rabbits [2] and several published case reports showed a good outcome of these cases confirming its efficacy and safety regarding this concern. At a dose equivalent to 800 mg administered to rats during organogenesis cases of encephalocele and anencephaly were described [3].

It is noteworthy that there was not yet enough clinical experience to confirm unequivocally the safety in pregnancy. Therefore, the drug is not recommended for use during pregnancy [5]. Pye., *et al.* (2008) published a collection of 180 cases of women exposed to Imatinib during pregnancy [6]. Of those, complete information was obtained from 125 patients. There were 12 children born with abnormalities and three with complex malformations in 2003, Hensley and Ford in a smaller series reported sixteen cases of spontaneous or therapeutic abortion (Three of them progressed to term with two normal and one with hypospadias).

Breastfeeding should be evaluated. Studies in rats have shown Imatinib and its metabolism products are excreted in the animal milk. There is clinical evidence that Imatinib and CGP74588 (drug metabolism product) are excreted in human milk 1, but there is no consensus regarding the risk posed for newborns. Studies have shown that 1.5% of the dose appears in breast milk exposes the infant to a dose of approximately 30% of the administered dose in the mother. It is not advised to breastfeed while the mother is using Imatinib Mesylate [4].

The genetic study of GIST has gained much importance because it is directly related to response to Imatinib use. It is known that the best response and consequently, better survival outcomes are observed in cases of GIST with Exon 11 and worse in cases where there is no mutation. In our case, although gastric origin was confirmed there were mutations detected in exon 9 and 11. Seventeen exon Kit and gene 12, 14 and 18 of gastric PDGRF came positive in the sample. Liver metastasis resection during the cesarean section was Exon-17 positive. This exon is directly related to acquire resistance to Imatinib.

The findings were presented in conjunction with several other cases reported in the literature do not mean Imatinib Mesylate might be safely administered during pregnancy.

Conclusion

Data from the literature of pregnant women of partners using imatinib showed no problems. Case reports of women using imatinib during their pregnancy showed a few induced abortions and spontaneous miscarriage cases as well. However, there are also cases of gestation and delivery of normal newborns. This does not mean that the use of imatinib mesylate is recommended during pregnancy. The patient died in April 2015 due to disease progression. She had received compassion way new and experimental drugs with no response.

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