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ORIGINAL ARTICLE

Anticancer Agent Gefitinib and Congenital Anomalies

Madhura Joshi[1] · **P. M. Gopinath**[1] · **K. Kalaichelvi**[2]

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Abstract Congenital abnormalities caused by human teratogenic drugs account for less than 1% of total congenital abnormalities. We report the first case of multiple anomalies associated with antenatal exposure to the anticancer agent Gefitinib. The patient conceived while she was on tablet Gefitinib 250 mg once a day for stage IV adenocarcinoma of lungs. The first scan done at 29 weeks 2 days showed liquor amnii on the upper limit of normal, single umbilical artery, left sided congenital diaphragmatic hernia, ventriculoseptal defect and left radial ray defect. The patient had a preterm delivery after one week and she refused autopsy. It is important to advise patients regarding contraception while undergoing chemotherapy as there is an increased risk of drug induced fetal malformations.

Keywords Congenital abnormalities · Anticancer drugs · Teratogenic drugs · Gefitinib

Congenital anomalies are the major cause of newborn deaths within four weeks of birth and can result in long-term disability with a significant impact on individuals, families, societies and health-care systems. Congenital anomalies can be caused by single gene defects, chromosomal disorders, multifactorial inheritance, environmental teratogens (an agent, which can cause a birth defect) and micronutrient deficiencies [1]. The fact that certain drugs given during pregnancy may prove harmful to the unborn child is one of the classical problems in medical treatment. In the 1960s, pregnant ladies who ingested thalidomide gave birth to children with phocomelia. Numerous other examples of teratogenic effects of drugs are known. It has been documented that congenital abnormalities caused by human teratogenic drugs account for less than 1% of total congenital abnormalities [2].

Case Report

A 36-year-old primigravida, nonconsanguineous couple came for an obstetric ultrasound with a history of 7–8 months of amenorrhea. The couple was married for 9 years with a history of primary infertility. The patient had no history of passive or active tobacco smoking exposure. While taking the treatment of infertility she was diagnosed with stage IV small cell carcinoma of the lungs. She had no other associated medical illness. She had undergone 6 cycles of chemotherapy. She was on tablet Gefitinib 250 mg daily along with Tablet livogen, tablet Liv 52 and Becozyme (-commercial names) for 11 months. She conceived while she was on these medications and pregnancy was diagnosed only after 7–8 months. On general examination, the patient was stable clinically and had the following ultrasound findings.

Ultrasound Findings

The ultrasound findings were as follows:
Single intrauterine gestation corresponding to 29 weeks and 2 days.

✉ Madhura Joshi
madhuravk77@rediffmail.com

P. M. Gopinath
pmgnath@gmail.com

K. Kalaichelvi
kalaikannan6000@gmail.com

[1] Institute of Obstetrics, Gynaecology and IVF, SRM Institutes for Medical Science, Chennai 600026, India

[2] Dr.Rai Memorial Medical Centre and Apollo Speciality Hospital, Chennai, India

Liquor was on upper limits of normal (amniotic fluid index was 21. 6 cm). There was a single umbilical artery (SUA). There was a left sided diaphragmatic hernia. The heart was pushed to the right side. Stomach and small bowel were seen in the thorax. There was an upturned superior mesenteric artery. The lung -head ratio was calculated, which was 36% for the given head circumference. (LHR is fetal lung area to head circumference ratio. It is a commonly used tool for antenatal prediction of postnatal outcomes in cases of congenital diaphragmatic hernia. 36% LHR indicates moderate prognosis at this gestational age.)

Cardiac evaluation was difficult due to dextroposed heart. It showed a perimembranous ventricular septal defect of 6 mm. (Figs. 1, 2, 3 and 4)

On examination of extremities, there was a mesomelic shortening of the left upper limb with absent radius, suggesting a left radial ray defect. The rest of the limbs appeared normal.

With these findings a detail three generation pedigree was taken. The couple was explained about the findings and need for postnatal surgical interventions and the possibility of hematological abnormalities due to radial ray defects was explained. The prognosis was guarded in view of the constellation of anomalies. Amniocentesis was suggested for karyotyping and DNA storage.

Unfortunately, the patient had preterm stillbirth within a week. A female fetus weighing 824 g was expelled. In spite of counseling the couple was not ready for autopsy nor for any postnatal DNA storage or microarray testing.

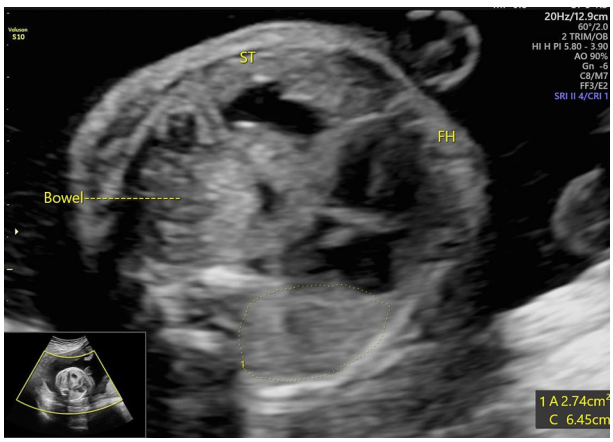

Fig. 1 Ultrasound section at the level of 4 chamber view for the measurement of lung area-showing stomach, bowel in the thorax, heart pushed to the other side

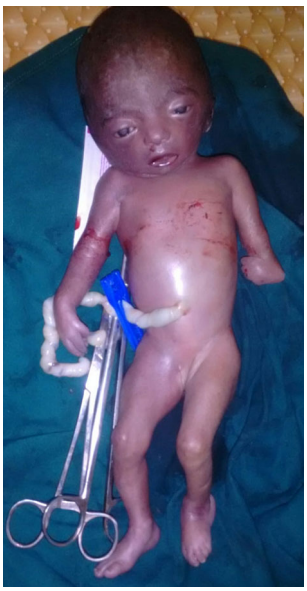

Fig. 2 Preterm stillbirth of 824 grams, left radial ray defect visible

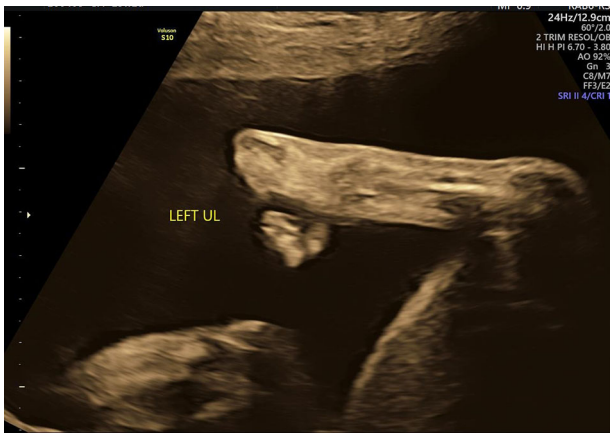

Fig. 3 3 D image of left upper limb showing radial ray defect

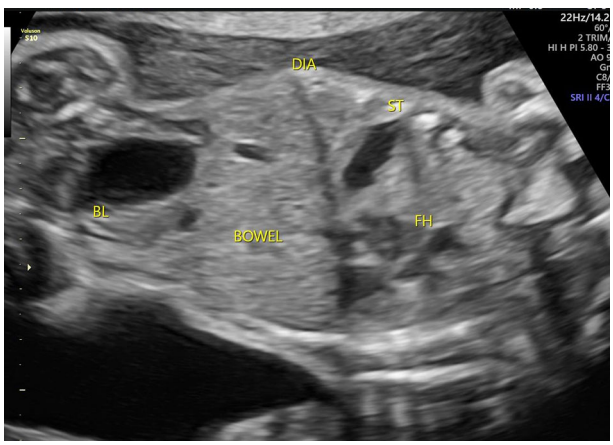

Fig. 4 Coronal view of abdomen and thorax showing stomach in the thorax

Discussion

Pregnancy is a special physiological condition where drug treatment presents a special concern because the physiology of pregnancy affects the pharmacokinetics of medications used and certain medications can reach the fetus and cause harm. How a drug affects the fetus depends on the stage of development and the strength and dose of the drug [3]. Limited information exists regarding the effects of drugs in the period of conception and implantation. It is suggested that women who are at the risk of conceiving or who wish to become pregnant should withdraw all unnecessary medications 3–6 months before conception [4]. Certain drugs taken early in pregnancy (15–21 days after fertilization) during the period of blastogenesis may act in an all or nothing fashion; killing the embryo or not affecting it at all. During this early stage, the embryo is highly resistant to birth defects. The embryo is highly vulnerable to birth defects between the 3rd week and 8th week after fertilization; which is the period of organogenesis. All major organs start developing during this period. Drugs reaching the embryo during this stage may cause a miscarriage, an obvious birth defect, or a permanent but subtle defect, that is noticed later in life. At the 9^{th} week the embryo is referred to as a fetus. Development during this time is primarily maturation and growth. Exposure to drugs during this period is not associated with major congenital malformations but they may alter the growth and function of normally formed organs and tissues [3]

Drugs that a pregnant woman takes can affect the embryo in several ways. They can act directly on the embryo causing damage or abnormal development leading to birth defects or death. They can also alter the function of the placenta usually by constricting blood vessels and reducing the blood supply of oxygen and nutrients to the embryo from the mother and thus resulting in a baby that is underweight and underdeveloped. Moreover, they can cause muscles of the uterus to contract forcefully; indirectly injuring the fetus by reducing the blood supply or triggering pre-term labor and delivery [3].

In the present case, the most probable cause of the findings in the fetus was the intake of the anti-cancer agent Gefitinib. Gefitinib is a selective tyrosine kinase receptor inhibitor (TKI), used in the therapy of small cell lung cancer. Gefitinib is an anilino quinazoline with antineoplastic activity. It inhibits the catalytic activity of numerous tyrosine kinases including the epidermal growth factor receptor (EGFR), which may result in inhibition of tyrosine kinase-dependent tumor growth. Specifically, this agent competes with the binding of ATP to the tyrosine kinase domain of EGFR, thereby inhibiting receptor autophosphorylation and resulting in inhibition of signal transduction. Gefitinib may also induce cell cycle arrest and inhibit angiogenesis. Gefitinib crosses the placenta and reaches the fetus. The reports evaluating its pharmacodynamics indicate that approximately 20% of maternal plasma concentration of Gefitinib was observed in cord blood [5].

Since cord blood or amniotic fluid concentration of gefitinib could not be obtained in the present case, a direct correlation between the use of gefitinib and the birth defects found could not be established.

Secondly, the couple refused for an autopsy so the confirmation of the ultrasound findings and associated occult findings could not be obtained.

In 1979, the US Food and Drug Administration (FDA) developed a system that determines the teratogenic risk of drugs by considering the quality of data from animal and human studies. FDA classifies various drugs used in pregnancy into five categories, categories A, B, C, D and X.[6]. According to the FDA, this system was overly simplistic, led to misinformation, did not adequately address the available information. The clinicians and patients were often confused by the meaning of the pregnancy risk categories and the system did not take into consideration the risks in breast milk. In 2015, the FDA replaced the former pregnancy risk letter categories on prescription and biological drug labeling with new information to make them more meaningful and the Pregnancy and Lactation Labeling Final Rule (PLLR) went into effect on June 30, 2015. The A, B, C, D and X risk categories, in use since 1979, are now replaced with narrative sections and subsections to include [7]

1. Pregnancy (includes Labor and Delivery): (Pregnancy Exposure Registry, Risk Summary, Clinical Considerations, Data)
2. Lactation (includes Nursing Mothers) (Risk Summary, Clinical Considerations, Data,)
3. Females and Males of Reproductive Potential, (Pregnancy Testing, Contraception, Infertility, References)

Even though the new system is better than the old it still does not provide a definitive “yes” or “no” answer in most cases and clinical interpretation is still required on a case-by-case basis [7–10].

According to the new system, based on its mechanism of action and data from animal reproduction studies, Gefitinib has shown fetal harm when administered to a pregnant woman. In animal reproductive studies, oral administration of Gefitinib from organogenesis through weaning resulted in fetotoxicity and neonatal death at doses below the recommended human dose. Animal data indicate that a single dose of Gefitinib in rats crosses the placenta after an oral dose of 5 mg/kg (30 mg/m^2, about 0.2 times

the recommended human dose on a mg/m^2 basis). When pregnant rats were treated with 5 mg/kg from the beginning of organogenesis to the end of weaning there was a reduction in the number of offspring born alive. This effect was more severe at 20 mg/kg (approximate the human clinical dose on a mg/m^2 basis) and was accompanied by high neonatal mortality soon after parturition. In rabbits, a dose of 20 mg/kg/day (240 mg/m^2, about twice the recommended dose in humans on a mg/m^2 basis) caused reduced fetal weight [11].

It is not known whether Gefitinib is excreted in human milk. Animal studies indicate the Gefitinib and its metabolites are present in rat milk at a concentration higher than those in maternal plasma. Because of the potential for serious adverse reactions in nursing infants from this drug, women are advised to discontinue breast-feeding during treatment with Gefitinib [11].

Australian categorization system for prescribing medicines in pregnancy have classified drugs into A, B1, B2, B3, C, D. According to Australian government therapeutic goods administration (TGA), Gefitinib has been classified as a Category C drug. (Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.[11]. There are no data from the use of Gefitinib in pregnant women. When Gefitinib was administered during organogenesis, an increase in the incidence of incomplete ossifications was observed in rats and reduced fetal weights were observed in rabbits at maternally toxic doses. Malformations were not observed in rats; they were observed in rabbits only at a severely maternally toxic dose. Women of childbearing potential must be advised to avoid becoming pregnant while receiving therapy.

To date, there have been only approximately 60 reported cases of lung cancer diagnoses during pregnancy [12]. Among these, there are five reports in which EGFR-TKIs were used; in all cases, delivery occurred without evidence of congenital malformations [5, 13–16]. However, two cases of fetal growth restriction were observed and a reversible increase in hepatic enzymes was observed in one case (twin pregnancy) [13, 16].

When patients receive chemotherapy, contraception should be actively encouraged throughout the treatment period [17]. Additionally, contraception for the first 3–6 months following the final administration of chemotherapy is recommended [17]. If the patient is pregnant while receiving chemotherapy, termination of pregnancy is an option as there is an increased risk of drug-induced fetal malformations. In practice, patients and their families must make the extremely difficult decision of whether to continue or terminate the pregnancy in a limited period of time. The clinician should explain that termination is not the turning point that necessarily results in clinical improvement of cancer. Treatment options must be suggested in the context of the limited evidence that is available. Indeed, this process is associated with increased psychological stress for all parties and requires a multidisciplinary approach [18].

The pharmacokinetics and pharmacodynamics of each anti-cancer are essentially different from other drugs used for the long term, so adverse effects cannot be predicted and defined in the same manner. Even fetal anomalies may be of a diverse type and nature to be potentially lethal for survival.

Conclusion

This case is presented here because this is the first observed association between the anticancer drug Gefitinib (EGFR-TKI) with SUA, diaphragmatic hernia, radial aplasia and cardiac anomaly in a human fetus [18].

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Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no conflict of interest.

Consent to Participate Not applicable.

Consent for Publication Taken.

Data Availability and Materials Not applicable.

Ethical Approval Not applicable.

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