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CASE REPORTS

First Case Report of Pregnancy on Alectinib in a Woman With Metastatic ALK-Rearranged Lung Cancer: A Case Report

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ABSTRACT

This is the first case report of a patient with *ALK*-rearranged metastatic lung adenocarcinoma who became pregnant during treatment with alectinib. A multidisciplinary team of gynecologists, neonatologists, oncologists, psychologists, and pharmacologists was set up to handle the case. According to patient's preference, the study drug was continued throughout pregnancy and the woman delivered a healthy baby girl at 35 weeks and 5 days of gestation. Fetal parameters remained normal during pregnancy. At birth, alectinib levels were 14 times higher in maternal plasma than in the fetus (259 versus 18 ng/mL). The average concentration of alectinib in the placenta was 562 ng/g. The baby was followed during her first 20 months, and no developmental anomalies were observed. After 32 months from diagnosis, the mother is well and in partial remission.

Keywords: Case report; ALK rearrangement; Lung cancer; Alectinib; Pregnancy

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Drs. Scarfone and Fumagalli contributed equally to this work.

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Introduction

Lung cancer (LC) in pregnancy is rare. Nonetheless, advanced maternal age has increased the incidence of cancer during pregnancy.[1] Often an activating mutation is found in pregnant patients with LC, reflecting the age-selected population.[2]

Studies in mice have revealed a possible role for *ALK* in the development of the fetal nervous system. *ALK*-knockout mice develop behavioral alterations without any apparent developmental or anatomical anomalies.[3]

No safety data are available regarding *ALK* inhibitors during pregnancy or their effect on the fetus.

Here, we describe the first case of a patient with metastatic *ALK*-rearranged LC who became pregnant during alectinib treatment that was continued throughout the pregnancy.

Case Report

In April 2018, a 31-year-old woman was diagnosed with having metastatic *ALK*-rearranged LC. After ruling out a pregnancy, she was started on alectinib 600 mg twice daily. Alectinib is a potent second-generation *ALK* inhibitor with high intracranial activity. In patients with untreated *ALK*-rearranged disease, alectinib had greater activity and efficacy with lower toxicity than crizotinib, with a 5-year overall survival rate of 62.5% versus 45.5%, respectively, and a hazard ratio of 0.67 (95% confidence interval: 0.46–0.98).[4]

Patients achieved a very good partial response according to investigator assessment at the first radiologic re-evaluation performed after 10 weeks of treatment.

After two months, the patient discovered that she was seven weeks pregnant, with spontaneous conception on week 12 after alectinib start.

The case was discussed within a multidisciplinary team, and the following three different options were offered:

1. Termination of pregnancy and continuation of alectinib, on the basis of the clinical need to continue alectinib and the scanty data on its administration during pregnancy.
2. Discontinuation of alectinib and continuation of pregnancy, discouraged because of the risk of disease progression.
3. Continuation of pregnancy and alectinib, cautiously recommended if the patient did not want termination of pregnancy.

Thoroughly informed on the scarcity of data and the risk of maternofetal harm, she decided to continue the pregnancy with a close follow-up (Supplementary Data). No abnormal findings were detected and fetal growth was always adequate (Fig. 1).

Throughout the pregnancy, the patient continued full-dose treatment, without toxicity and with persistent response. An elective cesarean section was done at 35 weeks and 5 days of gestation, and a healthy baby girl was born (Supplementary Data). Postnatal course was complicated by respiratory distress syndrome requiring surfactant and noninvasive ventilatory support for three days. All assessments during the neonatal period were normal. The baby was discharged 12 days after birth, with good clinical conditions.

Placental Findings

Placental samples were treated as discussed in the Supplementary Data.

No significant morphologic alterations were found compared with a gestational age-matched placenta from a normal control. The percentage of immature intermediate villi was slightly higher, indicating active placental growth (Fig. 2). No malignant cells were found.

Alectinib in Plasma, Amniotic Fluid, and Placental Tissue

Alectinib levels were determined as described in the Supplementary Data. Results are summarized in Table 1.

Placental weight was 405 g. The patient stopped alectinib on the day before cesarean section, but owing to the long half-life, the drug reached steady-state concentrations as already reported.

The placental barrier reduced fetus exposure to alectinib by 14 times compared with the maternal one, with the concomitant concentrations of 259.0 ng/mL and 18.0 ng/mL in the maternal plasma and in the cord blood-derived fetal plasma. Because a similar concentration (23.1 ng/mL) was found in the amniotic fluid, fetal exposure was modest. Alectinib penetrates the different sections of the placenta at an average concentration of 562 ng/g, which is 30 to 40 times that in the cord blood-derived fetal plasma. The drug distribution in tissues was homogeneous, and despite the conspicuous concentration, the low passage in the cord blood-derived fetal plasma indicates how separation and filtering by the placental barrier were considerable.

Child Development and Maternal Follow-Up

At term equivalent age, the newborn underwent brain magnetic resonance imaging that revealed a normally developed and myelinated brain. A few isolated noncystic white matter lesions were observed. At 3 months of age, a small laterocervical fistula became obvious and was treated conservatively. No other congenital abnormalities were observed. Throughout the first year, infant growth was normal and her general health was good. At 19 months of corrected age,

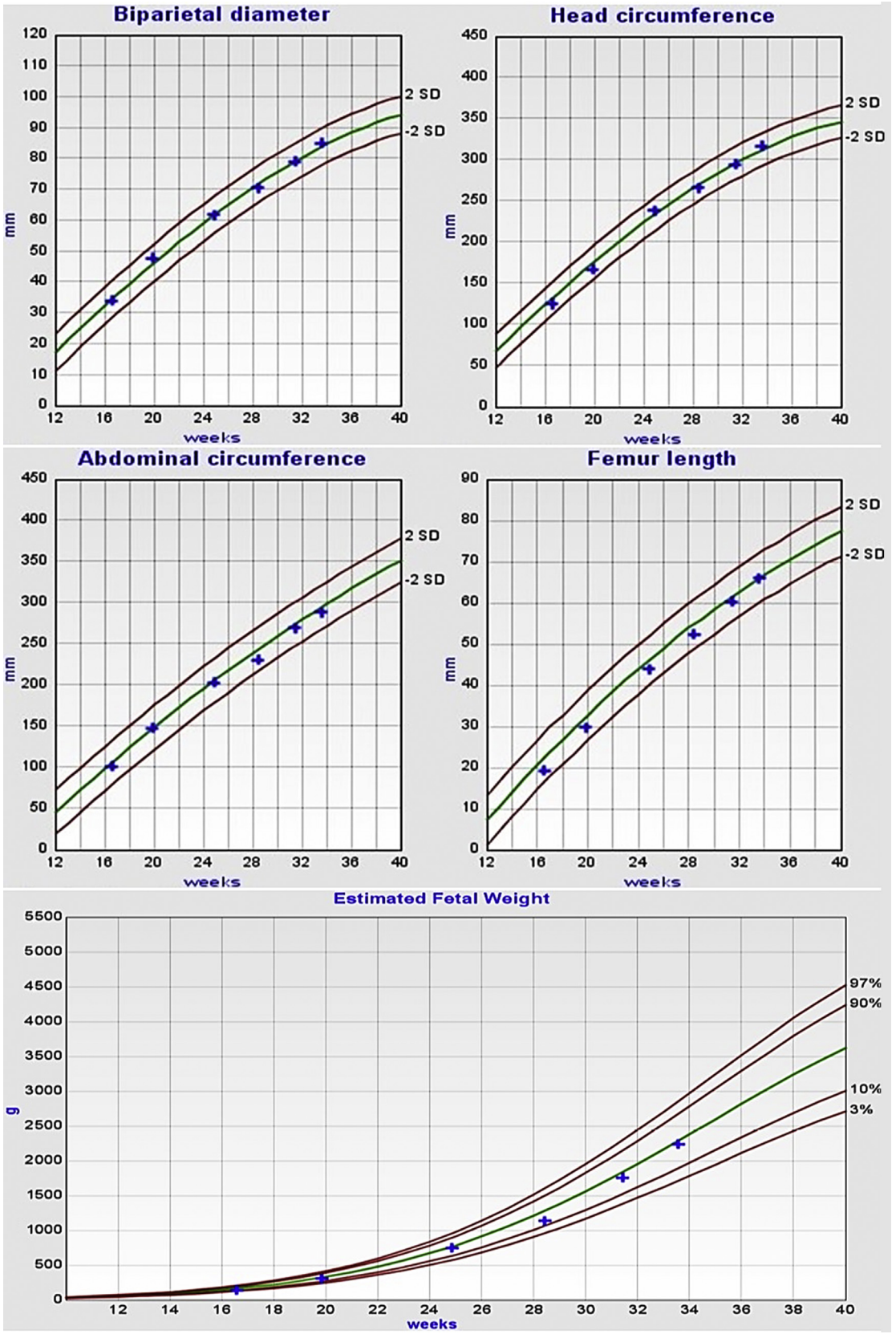

Figure 1. Fetal growth charts illustrating serial measurement of the main biometric parameters and the estimated fetal weight throughout pregnancy. The crosses indicate a normal fetal growth for all the measurements.

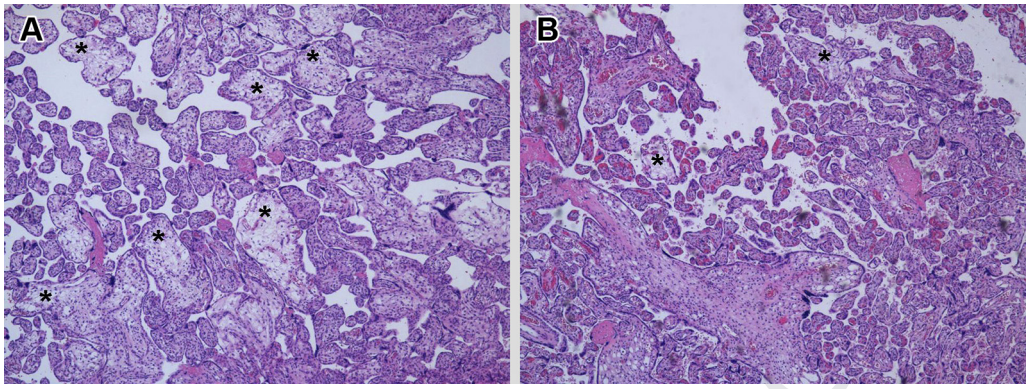

Figure 2. Comparison between patient's and control placenta (35 + 5 gestational age) EE 5×. (*A*) Patient's placenta: Immature intermediate villi (*) are evenly dispersed within the specimen, representing approximately 40% of the total villous volume. (*B*) Control placenta: Immature intermediate villi (*) tend to concentrate as small groups in the centers of the villous trees, with typical reticular stroma. Most villi are stem villi, mature intermediate villi, and terminal villi (75% of the total villous volume). EE, XXX.

pediatric, ophthalmic, and neurodevelopmental assessments revealed normal development. After 32 months from diagnosis, the patient is still in partial remission according to investigator assessment and can take full care of her baby (Supplementary Data).

Discussion

Although pregnancy in patients with LC is a rare event, young *ALK*-positive patients enjoy prolonged survival with good quality of life with specific treatments. Information on teratogenicity of *ALK* inhibitors in humans is lacking with only two reports of pregnant women treated with crizotinib for short periods of time and at late stage of pregnancy.[5,6]

We approached this unique situation by setting up a team of gynecologists, neonatologists, oncologists, psychologists, and pharmacologists, discussing all aspects with the patient and her husband. Cancer during pregnancy poses a medical and ethical dilemma for both clinicians and patients, because the decision involves two lives at risk.[7] In this complex process, adopting a participatory stance and respecting the patient's preferences is essential.

Table 1. XXX

Biological Sample	Alectinib Concentration (ng/mL or ng/g)
Maternal plasma	259.0
Cord blood fetal plasma	18.0
Amniotic fluid	23.1
Central cotyledon	
Fetal side	639[a]
Medial side	569[a]
Maternal side	635[a]
Peripheral cotyledon	
Fetal side	613[a]
Medial side	550[a]
Maternal side	447[a]
Intermediate cotyledon	
Fetal side	559[a]
Medial side	606[a]
Maternal side	441[a]

[a]Two separate samples from adjacent parts of the placenta were used.
Note: Alectinib concentration in maternal and cord blood fetal plasma, amniotic fluid, and different placental sections. The patient stopped alectinib on the day before cesarean section, but owing to the long half-life, the drug reached steady-state concentrations.

Obstetric and Neonatologic Considerations

Alectinib was continued during pregnancy, including the first trimester, in view of the stage of the disease at diagnosis and the clinical response, although there is increased risk of toxicity with chemotherapy in the first trimester.

No obstetrical complications were observed, but given the potential harmful effects of alectinib and according to patient's preference on the delivery method, a cesarean section was scheduled at a gestational age of more than 34 weeks, to favor lung maturation and reduce the risk of severe postnatal morbidities. The postnatal course was mildly complicated by morbidities consistent with the late preterm birth. Brain magnetic resonance imaging findings were consistent with mild prematurity-related abnormalities associated with a clinical favorable outcome although still debated.

Pharmacologic Considerations

Alectinib did not seem to influence the embryofetal development, probably because of the low penetration of the drug through the placenta.

However, we cannot exclude some undetectable or delayed toxic effects, particularly considering the continuous long-time exposure. For this reason, we plan to continue monitoring the child for the next years to rule out cognitive and behavioral problems as any deficit in academic performance.

Conclusions

This case reveals that alectinib treatment during the entire pregnancy is not necessarily associated with detectable changes in the embryofetal development.

Although the low transplacental passage of alectinib offers an explanation for the lack of teratogenic effects, caution is still needed to draw firm conclusions on the basis of only one case, and longer follow-up is essential to exclude any late effects on the child.

For the time being, fertile patients on oncologic treatments must be informed and the use of contraceptives should be recommended.

The patient-shared decision-making and the multidisciplinary approach is crucial to deal with these cases, respecting women's decision to continue or terminate pregnancies.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.02.005.

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