ORIGINAL ARTICLE

Clinicopathologic Features of NSCLC Diagnosed During Pregnancy or the Peripartum Period in the Era of Molecular Genotyping

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ABSTRACT

Introduction: Cancer will be diagnosed in one in 1000 women during pregnancy. The outcomes of NSCLC diagnosed during pregnancy are dismal, with most patients dying within 1 year. Actionable mutations are more likely to be found among younger patients with NSCLC. However, most previous reports of NSCLC diagnosed during pregnancy did not include molecular genotyping.

Methods: We performed a retrospective analysis of patients seen at our institution between 2009 and 2015 to identify women in whom NSCLC was diagnosed during pregnancy or the peripartum period and determined clinicopathologic features, including molecular genotype.

Results: We identified 2422 women with NSCLC, including 160 women of reproductive age. Among the women of reproductive age, eight cases of NSCLC diagnosed during pregnancy or the peripartum period were identified; all were diagnosed in minimal or never-smokers with metastatic adenocarcinoma. Six of these patients were found to have anaplastic lymphoma kinase gene (*ALK*) rearrangements, whereas the remaining two were *EGFR* mutation positive. We observed a borderline significant association between a diagnosis of NSCLC during pregnancy or the peripartum period and *ALK* positivity ($p = 0.053$). All eight women in whom NSCLC was diagnosed during pregnancy or the peripartum period received treatment with genotype-directed therapies after delivery. The median overall survival has not been reached at a median follow-up of 30 months.

Conclusions: Although a diagnosis of NSCLC during pregnancy or the peripartum period is rare, diagnostic evaluation should not be delayed in pregnant women presenting with symptoms worrisome for lung cancer. Evaluation should include testing for targetable molecular alterations.

Keywords: Pregnancy; ALK; EGFR; Lung cancer

Introduction

With an estimated incidence of 1 in 1000, a diagnosis of cancer during pregnancy is a rare occurrence.[1] Pregnant patients tend to present at an advanced stage, largely owing to diagnostic delays fueled by attribution of symptoms to other diseases and efforts to ensure fetal well-being.[2] Even when a diagnosis is made early, management strategies must account for the potential increased risk for complications during the period of fetal organogenesis.[3] As cultural shifts have fostered a trend toward childbearing closer to the end of

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reproductive age, an increase in the incidence of cancer diagnosed during pregnancy is anticipated. To date, there have been more than 50 published cases of lung cancer during pregnancy. The patients, most of whom were smokers,[4,5] presented at a median age of 36 years and median gestation of 29 weeks.[4] The median survival for patients in whom lung cancer was diagnosed during pregnancy in these reports was quite dismal, with most patients dying within 1 year.[4,5]

In the past decade, it has become increasingly apparent that NSCLC comprises distinct molecular subgroups with characteristic clinicopathologic features. However, most published cases describing lung cancer in pregnancy predate the adoption of routine molecular profiling.[2,6] Given that younger age is associated with increased likelihood of harboring actionable molecular alterations and that treatment with targeted therapies is associated with superior outcomes than with standard chemotherapy, it is possible that the previously reported poor outcomes may not be applicable in the modern era.[7–9] To investigate the frequency of lung cancer diagnoses during pregnancy or the peripartum period among genetically defined subsets of NSCLC, we performed a retrospective analysis of consecutive patients seen at our institution between 2009 and 2015. We present a series of eight women in whom NSCLC was diagnosed during pregnancy or the peripartum period.

Methods

We performed a retrospective review of records of consecutive patients with NSCLC seen at Massachusetts General Hospital from 2009 to 2015 to identify patients in whom NSCLC was diagnosed during pregnancy or the peripartum period. The peripartum period was defined as the time from the last month of pregnancy until 12 weeks after delivery. Clinical information was obtained from several databases that contained information for 2422 women with NSCLC and confirmed by review of the electronic medical record. The study was approved by the institutional review board at Massachusetts General Hospital. Descriptive statistics were used to compare baseline characteristics. Fisher's exact test was used for two sample comparisons. Statistical significance was defined as a p value less than 0.05.

Results

Patients

From the 2422 women with NSCLC, we identified 160 women of reproductive age, defined as 18 to 45 years old. In eight (5%) of these 160 women, NSCLC was diagnosed during pregnancy or the peripartum period (Fig. 1). All eight patients presented with metastatic lung adenocarcinoma and had either minimal or no prior tobacco exposure (Table 1). The median age at diagnosis was 35 years (range 29–43 years). The lung cancer diagnoses were made in all trimesters. The predominant symptoms at presentation during pregnancy or the peripartum period (see Table 1) were similar to those routinely observed in patients with lung cancer and included cough and dyspnea (cases 1, 5, and 7), fatigue (case 5), weight loss (case 6), and pain at sites of metastatic involvement (cases 6 and 8). Two women whose cancer was diagnosed in their first trimester presented with symptoms attributable to brain metastasis, including extremity weakness (case 3) and seizure (case 4).

Correlation between Molecular Features and NSCLC Diagnosis during Pregnancy or the Peripartum Period

Of the women of childbearing age, NSCLC harboring *EGFR*, anaplastic lymphoma kinase gene (*ALK*), *KRAS*, or *ROS1* alterations was diagnosed in 126 (79%) women (see Fig. 1). Among these 126 women, 48 (38%) had *EGFR*-mutant NSCLC and 48 (38%) had *ALK*-positive NSCLC. *ROS1*-positive or *KRAS*-mutant NSCLC was diagnosed in 11 (9%) and 19 (15%) women of childbearing age, respectively. Consistent with previous reports, a greater proportion of all women with *ALK*-positive (31%) and *ROS1*-positive (38%) NSCLC were of childbearing age than in the *EGFR*-mutant (9%) and *KRAS*-mutant (6%) groups (Table 2).[10,11]

NSCLC was diagnosed during pregnancy or peripartum in 12.5% (six of 48) of the *ALK*-positive patients, 4% (two of 48) of the *EGFR*-mutant patients, 0% (none of 11) of the *ROS1*-positive patients, and 0% (none of 19) of the *KRAS*-mutant patients of childbearing age with a diagnosis of NSCLC. In all cases of *ALK*-positive NSCLC, the diagnosis was made using the U.S. Food and Drug Agency–approved Vysis Break-Apart Dual-Color Fluorescence In Situ Hybridization Probe Kit (Abbott Molecular, Des Plaines, IL). For cases 7 and 8, the diagnosis of NSCLC harboring an *EGFR* exon 19 deletion was made by next-generation sequencing. Testing for additional oncogenic drivers was performed for all eight cases, and no concurrent oncogenic mutations were detected. The small number of women of reproductive age limited drawing statistical conclusions about predisposition toward presentation during pregnancy or the peripartum period by mutation status. However, when women of reproductive age with *ALK*-positive NSCLC were compared with women of reproductive age with *ALK*-negative NSCLC, there was an association between NSCLC diagnosis during pregnancy or the peripartum period and *ALK* positivity of borderline statistical significance ($p = 0.0533$).

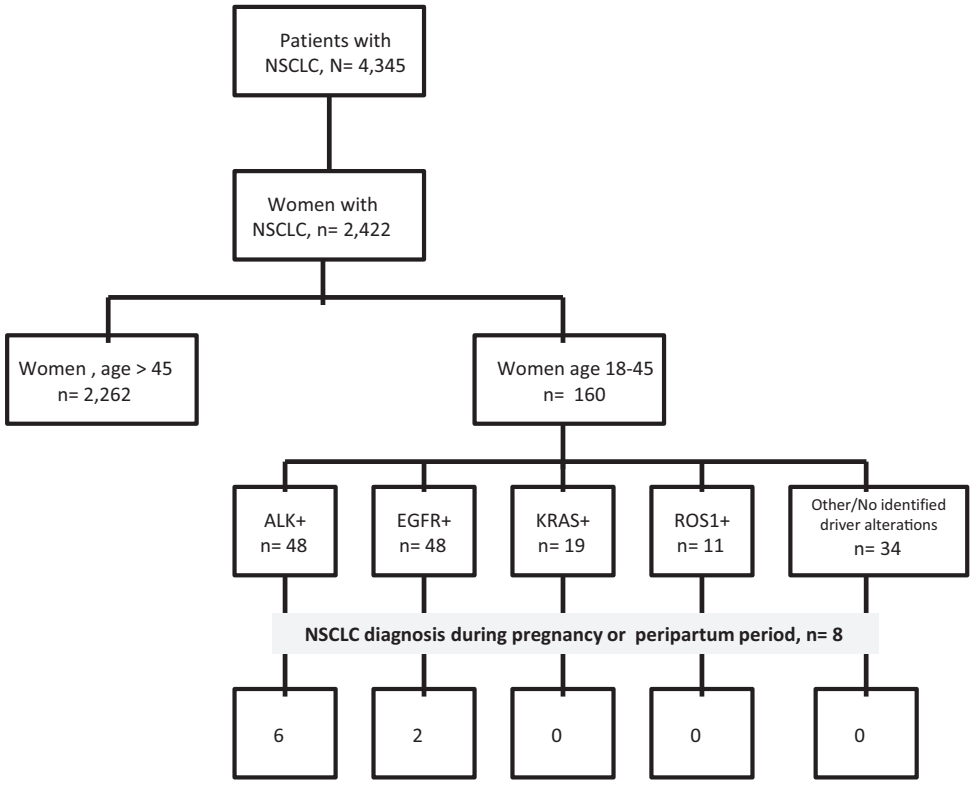

Figure 1. Incidence of pregnancy/peripartum NSCLC at a single institution between 2009 and 2015. ALK, anaplastic lymphoma receptor tyrosine kinase.

Pregnancy Outcomes

Two patients, both of whom had their cancer diagnosed early in gestation, elected for pregnancy termination. The remaining six continued their pregnancy after the diagnosis of NSCLC or had their disease diagnosed after delivery. In the two of these six patients, complications developed during pregnancy. Patient 8 had a preexisting history of cervical insufficiency diagnosed during prior pregnancies. She underwent urgent cesarean section at 25 weeks in the setting of cervical incompetence. Her child died 3 weeks after delivery. Placental abruption prompting an emergency cesarean section at 29 weeks developed in patient 6. Although her child suffered from intrauterine growth restriction, the baby is currently doing well. The remaining patients delivered healthy babies.

Treatment Outcomes

None of the women were treated with targeted therapies during pregnancy. However, patient 4 received carboplatin and paclitaxel during her second and third trimesters. Patient 4 was also treated with a gamma knife for symptomatic brain metastases during her second trimester. Overall, the median time to initiation of

Table 1. Characteristics of Eight Patients with Diagnosis of NSCLC during Pregnancy or the Peripartum Period

Case	Age at Diagnosis (y)	Race	Smoking History	Gestational Age at Diagnosis	Tumor Histologic Type	Stage at Diagnosis (TNM, Seventh Edition)	Molecular Driver
1	36	White	Never	30 wk	Adenocarcinoma	IVa	*ALK*
2	36	White	Former, 4 pack-years	12 wk postpartum	Adenocarcinoma	IVb	*ALK*
3	33	White	Never	5 wk	Adenocarcinoma	IVb	*ALK*
4	29	White	Never	9 wk	Adenocarcinoma	IVb	*ALK*
5	35	White	Never	15 wk	Adenocarcinoma	IVb	*ALK*
6	31	White	Former, 14 pack-years	38 wk	Adenocarcinoma	IVb	*ALK*
7	43	Asian	Never	2 wk postpartum	Adenocarcinoma	IVa	*EGFR* exon 19 deletion
8	35	Asian	Never	8 wk postpartum	Adenocarcinoma	IVb	*EGFR* exon 19 deletion

TNM, tumor, node, and metastasis classification; *ALK*, anaplastic lymphoma kinase gene.

Table 2. Correlation between Driver Mutation Status and Diagnosis of NSCLC during Pregnancy or the Peripartum Period

Oncogenic Driver	Total No. Women (n = 2422)	No. Women of Childbearing Age (Age 18-45 y) (n = 160)	Total No. Pregnant Patients (% Relative to Total No. Women of Childbearing Age by Driver) (n = 8)
ALK	156	48	6 (12.5%)
EGFR	547	48	2 (4%)
KRAS	311	19	0
ROS1	29	11	0
Unknown/other	1379	34	0

ALK, anaplastic lymphoma kinase gene.

systemic therapy after diagnosis was 4 weeks (range 1–8 weeks). All of the women received treatment with genotype-directed therapies after delivery, with most receiving targeted agents in the first-line setting.

For the six *ALK*-positive patients who received crizotinib, progression-free survival (PFS) ranged from 5 weeks to 60 weeks, with a median of 16 weeks. Of the four women with PFS less than or equal to 16 weeks while receiving crizotinib, one progressed in the lungs only (patient 5) and the others had both extracranial and intracranial progression (patients 3, 4, 6). For the two patients with *EGFR*-mutant NSCLC, PFS was 28 weeks and 18 weeks. Seven of the eight patients went on to receive additional tyrosine kinase inhibitors (TKIs) after development of acquired resistance to their first targeted agent. The median overall survival in the eight cases has not been reached at a median follow-up of 30 months after diagnosis. All of the women are alive with the exception of patient 2 who died of leptomeningeal spread of her NSCLC. Notably, all the patients survived beyond 4.5 months after diagnosis, which is the median overall survival previously reported in the literature for women diagnosed with NSCLC during pregnancy (Table 3).[5]

Discussion

Worldwide, lung cancer is the most common and most lethal malignancy.[12] Although a diagnosis of lung cancer during pregnancy is a rare occurrence,[1] the incidence is thought to be increasing—a finding largely attributed to the prevalence of smoking among young women and the increasing incidence of pregnancy at later reproductive age.[5] In this report, we describe a single-institution, retrospective analysis in which we identified eight patients in whom NSCLC was diagnosed during pregnancy or the peripartum period, all of whom had limited or no prior tobacco exposure. Our observations, and similar findings in previous reports, suggest that never-smokers may comprise a relatively high proportion of those in whom NSCLC is diagnosed during pregnancy or the peripartum period.[13] These findings suggest that risk factors beyond tobacco exposure might predispose to the development of NSCLC during pregnancy and the peripartum period.

Oncogenic driver mutations were present in all eight identified cases of NSCLC in pregnancy or the peripartum period. Most published cases of NSCLC diagnosed during pregnancy in never- or light smokers with molecular testing available harbored *EGFR* mutations.[14–17] In our series, however, among the different molecular subgroups, *ALK*-positive NSCLC predominated. This discrepancy may be explained by the rarity of diagnosis of NSCLC during pregnancy or the peripartum period, the relatively recent identification of *ALK* as an oncogenic driver, younger age of patients with *ALK*-positive NSCLC relative to other genotypes, variation in frequency of testing for *ALK* rearrangements across institutions, referral bias, and reporting bias. Establishing a correlation between molecular genotype and development of NSCLC during pregnancy or the peripartum period is challenging because of the low incidence of NSCLC diagnosed among pregnant women. In our series, however, a comparison of *ALK*-negative NSCLC with *ALK*-positive NSCLC in women of childbearing age was suggestive of a trend toward an association between *ALK* rearrangement and a higher likelihood of diagnosis of NSCLC during pregnancy or the peripartum period.

Most previously published reports of NSCLC during pregnancy predated routine molecular genotyping and, as such, relied on chemotherapy for systemic treatment. Treatment with TKIs may account for the improved outcomes seen in our series and recently published case reports.[14–19] Indeed, most of the patients reported in our series are alive more than 2 years after their lung cancer diagnosis (see Table 3). Little, however, is known about the safety of targeted agents during pregnancy. Several reports of successful use of EGFR TKIs during pregnancy have recently been published.[14-17,20] These reports demonstrate that despite transplacental transfer of erlotinib and gefitinib, there is limited accumulation of the TKIs.[16,17,21] Moreover, one study suggests that

Table 3. Clinical Summaries of the Cases of Eight Patients with a Diagnosis of NSCLC during Pregnancy or the Peripartum Period

Case	1	2	3	4	5	6	7	8
Pregnancy outcomes								
Gestational age at diagnosis	30 wk	12 wk postpartum	5 wk	9 wk	15 wk	28 wk	2 wk postpartum	8 wk postpartum
Timing of delivery	32 wk	N/A	Pregnancy termination	34 wk	Pregnancy termination	29 wk	N/A	N/A
Pregnancy complications	None	None	___	None	___	Placental abruption	None	Premature delivery at 25 wk due to cervical incompetence
Treatment outcomes								
Interval from diagnosis to first systemic therapy	4 wk	4 wk	4 wk	8 wk	1 wk	2 wk	4 wk	6 wk
First TKI (line of therapy)	Crizotinib (3)	Crizotinib (2)	Crizotinib (1)	Crizotinib (2)	Crizotinib (1)	Crizotinib (1)	Gefitinib (1)	Erlotinib (1)
Investigator-assessed PFS while patient was receiving first TKI	60 wk	28 wk	16 wk	8 wk	16 wk	5 wk	28 wk	18 wk
No. additional TKIs	1	0	2	1	1	1	5	1
Additional TKIs (investigator-assessed PFS)	Ceritinib (unknown)	N/A	Ceritinib (12 wk) Alectinib (ongoing response at 28 wk)	Ceritinib (ongoing response at 80 wk)	Alectinib (24 wk)	Alectinib (6 wk)	Erlotinib (16 wk) Afatinib (4 wk) Icotinib (6 wk) Afatinib + cetuximab (28 wk) Osimertinib (52 wk)	Osimertinib (12 wk)
Survival outcome								
Clinical status	Alive 5 y after diagnosis	Died 2 y after diagnosis	Alive 2.5 y after diagnosis	Alive 3 y after diagnosis	Alive 2.5 y after diagnosis	Alive 6 mo after diagnosis	Alive $\geq$5 y after diagnosis	Alive 11 mo after diagnosis

PFS, progression-free survival; N/A, not applicable.

gefitinib may be preferable to erlotinib for use in pregnant patients with *EGFR*-mutant NSCLC as erlotinib may cross the placenta at a higher rate than gefitinib does.[21] To our knowledge, there are no published reports of treatment with ALK inhibitors during pregnancy. There are, however, two published cases of *ALK*-positive NSCLC diagnosed in patients during pregnancy or the peripartum period who were treated with crizotinib after delivery, in both cases after disease progression while they were receiving chemotherapy.[18,19] Reassuringly, review of the eight cases in our series suggests that for women whose NSCLC is diagnosed late in gestation, it may be possible to delay TKI treatment for a brief period until after delivery.

Interestingly, five of the eight patients had only brief responses to TKI treatment. In contrast, the clinical outcomes of pregnant patients with *EGFR*–mutant and *ALK*-positive NSCLC previously reported in the literature were comparable to those reported for nonpregnant patients.[14,16,18,19] It is possible that the shorter PFS in this series may be confounded by additional factors, including diagnostic delays in two cases (cases 6 and 8). Alternatively, a diagnosis of NSCLC during pregnancy or the peripartum period may predispose to a particularly aggressive clinical course. Notably, three of the four patients with short PFS while receiving crizotinib experienced central nervous system (CNS) progression. The CNS has previously been identified as a sanctuary site in patients with *ALK*-rearranged NSCLC on account of the pharmacokinetics of crizotinib.[22] Patient 3 went on to have a durable response on the CNS-penetrant ALK-inhibitor alectinib. Patient 4 underwent stereotactic radiosurgery and continues to respond to ceritinib at 20 months. Despite the reduced PFS of patients while receiving targeted agents, the patients in this series had improved overall survival compared with those in case reports of patients treated with chemotherapy. This may be a reflection of the clinical development of active next-generation TKIs in patients who have progressed while receiving initial TKIs. Indeed, seven of the eight patients were treated with additional TKIs.

Although this analysis represents observations based on patients seen at a single institution and is limited by the small number of cases identified, the findings reinforce current guidelines, which recommend that molecular genotyping be performed for all patients with metastatic nonsquamous lung cancer. On the basis of our experience and review of recent case reports, molecular studies for patients whose lung cancer is diagnosed during pregnancy or the peripartum period should at a minimum include testing for *EGFR* mutations and *ALK* and *ROS1* rearrangements. Outcomes after a diagnosis of NSCLC during pregnancy or the peripartum period may be improved in women treated with genotype-specific agents compared with previously observed outcomes with chemotherapy in an unselected population.

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