**Summary**

Two cases of pediatric lung cancer (in 23-month-old and 6-year-old boys) resulting from mother-to-infant transmission of uterine cervical tumors were incidentally detected during routine next-generation sequencing of paired samples of tumor and normal tissue. Spontaneous regression of some lesions in the first child and slow growth of the tumor mass in the second child suggested the existence of allo-immune responses against the transmitted tumors. Immune checkpoint inhibitor therapy with nivolumab led to a strong regression of all remaining tumors in the first child. (Funded by the Japan Agency for Medical Research and Development and others; TOP-GEAR UMIN Clinical Trials Registry number, UMIN000011141.)

Transcription of maternal cancer to offspring is extremely rare and is estimated to occur in approximately 1 infant per every 500,000 mothers with cancer, whereas approximately 1 in 1000 live births involves a mother with cancer. In these cases, cancer of the blood, skin, lungs, and cervix in the mother was presumably transmitted hematogenously (through transplacental mother-to-fetus transmission) and often involved dissemination of maternal tumor cells to multiple organs (e.g., brain, bone, liver, and soft tissues) in the infant. All the reported cases were diagnosed in children younger than 2 years of age. In some cases, spontaneous tumor regression in the affected offspring was noted (Table 1). Transplacental transmission to the fetus is probably rare because of the placental barrier and the fetal alloimmune response.

Mother-to-infant transmission of tumor in the birth canal during vaginal delivery is also theoretically possible. If the mother has cervical cancer, the infant can be exposed to tumor cells in fluids in the birth canal and could aspirate tumor cells into the lungs. Thus, mother-to-infant transmission of tumor may be a risk of vaginal...
Table 1. Reported Cases of Mother-to-Child Transmission of Cancer.*

<table>
<thead>
<tr>
<th>Cancer Type and Age</th>
<th>Primary Site in Mother</th>
<th>Site of Cancer in Child</th>
<th>Presumed Route of Transmission</th>
<th>Method of Examination</th>
<th>Outcome in Mother</th>
<th>Outcome in Child</th>
<th>Reference, Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia or lymphoma</td>
<td>ALL, 9 mo</td>
<td>Skin</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Survived</td>
<td>Cramblett et al.,3 1958</td>
</tr>
<tr>
<td></td>
<td>AML, 20 mo</td>
<td>Skin</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Survived</td>
<td>Osada et al.,4 1990</td>
</tr>
<tr>
<td></td>
<td>NK-cell lymphoma, 4 wk</td>
<td>Skin</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Died of disease</td>
<td>Catlin et al.,5 1999</td>
</tr>
<tr>
<td></td>
<td>B-cell lymphoma, 8 mo</td>
<td>Skin</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Died of disease</td>
<td>Maruko et al.,6 2004</td>
</tr>
<tr>
<td></td>
<td>ALL, 11 mo</td>
<td>Skin</td>
<td>Transplacental</td>
<td>—</td>
<td>NA</td>
<td>NA</td>
<td>Isoda et al.,7 2009</td>
</tr>
<tr>
<td>NK T-cell lymphoma, 8 mo</td>
<td>Skin</td>
<td>NA</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Died of disease</td>
<td>Yagasaki et al.,8 2011</td>
</tr>
<tr>
<td>Melanoma</td>
<td>8 mo</td>
<td>Skin</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Died of disease</td>
<td>Holland,9 1949</td>
</tr>
<tr>
<td></td>
<td>7 mo</td>
<td>Skin</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Died of disease</td>
<td>Dargeon et al.,10 1950</td>
</tr>
<tr>
<td></td>
<td>11 days</td>
<td>Skin</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Died of disease</td>
<td>Brodsky et al.,11 1965</td>
</tr>
<tr>
<td></td>
<td>2 mo</td>
<td>Skin</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Survived (spontaneous regression)</td>
<td>Cavell,12 1976</td>
</tr>
<tr>
<td></td>
<td>Birth</td>
<td>Skin</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Died of disease</td>
<td>Ferreira et al.,13 1998</td>
</tr>
<tr>
<td>Other solid tumors</td>
<td>SCLC, 5 mo</td>
<td>Lung</td>
<td>Transplacental (placental metastasis histologically confirmed)</td>
<td>Quantitative PCR</td>
<td>Died of disease</td>
<td>NA</td>
<td>Tolar et al.,17 2002</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma, 2 wk</td>
<td>Lung</td>
<td>Multiples lesions on</td>
<td>Next-generation sequencing</td>
<td>Died of disease</td>
<td>Survived</td>
<td>Walker et al.,18 2002</td>
</tr>
<tr>
<td></td>
<td>SCLC, 3 mo</td>
<td>Cervix</td>
<td>Transplacental</td>
<td>—</td>
<td>Died of disease</td>
<td>Died of disease</td>
<td>Teksam et al.,19 2004</td>
</tr>
<tr>
<td></td>
<td>Neuroendocrine carcinoma, 23 mo</td>
<td>Cervix</td>
<td>Lung</td>
<td>Aspiration into lung</td>
<td>Died of disease</td>
<td>Survived</td>
<td>Herskovic et al.,20 2014</td>
</tr>
</tbody>
</table>

* ALL denotes acute lymphoblastic leukemia, AML acute myeloid leukemia, BCR-ABL breakpoint cluster region-Abelson, FISH fluorescence in situ hybridization, NA not available, NK natural killer, PCR polymerase chain reaction, and SCLC small-cell lung carcinoma.
delivery among women with cervical tumors. However, data on such mother-to-infant transmission are lacking.

Here, we report two cases of pediatric lung cancers that probably developed through mother-to-infant transmission of cervical carcinoma. These two cases were identified incidentally during an analysis of the results of routine next-generation sequencing testing of paired samples of tumor and normal tissue. This analysis was undertaken in TOP-GEAR (Trial of Onco-Panel for Gene-profiling to Estimate both Adverse Events and Response during Cancer Treatment), a prospective gene-profiling trial involving patients with advanced cancer.22

**METHODS**

We performed next-generation sequencing of paired samples of tumor and normal tissue to detect mutations in 114 cancer-related genes as a part of a prospective clinical trial.22 We used a next-generation sequencing–based solid-tumor test in which germline DNA was used as a control. This National Cancer Center Oncopanel test is a hybridization capture–based next-generation sequencing assay.

Nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks) was administered to Patient 1 in a phase 1 trial of nivolumab involving Japanese children with relapsed or refractory solid tumors (UMIN Clinical Trials Registry number, UMIN0000026497). Detailed information on the materials and methods for this trial is provided in the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org. The research protocol was approved by relevant institutional review boards or ethics committees. The parents of the children provided written informed consent.

**RESULTS**

**PATIENT 1**

A 23-month-old boy (Patient 1) presented to a local hospital with a 2-week history of a productive cough. Computed tomography (CT) revealed multiple masses scattered along the bronchi in both lungs, and a lung biopsy performed by means of video-assisted thoracoscopic surgery (VATS) revealed neuroendocrine carcinoma of the lung with focal glandular differentiation (Fig. 1A).

...
A cervical cytologic test performed in the mother 7 months before the birth was negative, and the infant was delivered transvaginally at 39 weeks of gestation. The 35-year-old mother, who had not received vaccination against human papillomavirus (HPV), received a diagnosis of squamous-cell carcinoma of the cervix 3 months after the infant’s birth. After the diagnosis, she underwent radical hysterectomy with pelvic lymphadenectomy, followed by four cycles of adjuvant chemotherapy. At that time, transmission of the tumor to her son was not suspected because the histologic characteristics were thought to be different from those of her son.

In accordance with his parents’ wishes, Patient 1 received frequent follow-up but did not receive treatment. One year after the diagnosis of neuroendocrine carcinoma, the lesions progressed. He was referred to our hospital for further treatment at 3 years of age (Fig. S1A in the Supplementary Appendix). Surprisingly, some of the lesions had spontaneously regressed by that time (Fig. 1A). However, round opacities on radiographic images indicated that multiple foci of the tumor were still present in both lungs. CT imaging confirmed that tumor masses were spread along the bronchi (Fig. 1A). The patient received five cycles of chemotherapy with cisplatin (at a dose of 60 mg per square meter of body-surface area on day 1) and irinotecan (60 mg per square meter on days 1, 8, and 15 of each 28-day cycle), followed by two cycles of carboplatin (400 mg per square meter on day 1 and 2) and etoposide (100 mg per square meter on days 1 to 5 of each 28-day cycle). Some of the tumors shrank, but others subsequently progressed (Fig. S1B).

Lung, liver, and bone metastases developed in the mother during 3 years of follow-up after her last treatment. Histologic examination of the mother’s left lung tumor obtained by VATS revealed poorly differentiated carcinoma with neuroendocrine differentiation. Pathological reexamination of the hysterectomy specimen revealed that the cervical cancer was predominantly poorly differentiated squamous-cell carcinoma with focal neuroendocrine differentiation admixed with a minor component of adenocarcinoma; this histologic picture was similar to the tumor in her lung as well as that in her son’s lung (Fig. 1A).

Next-generation sequencing testing of paired samples of tumor and normal tissue was independently performed in the analysis of DNA from the lung tumor in the child and from the cervical tumor in his mother. Histologic similarities between the tumor samples from the mother and child prompted us to compare the results of their next-generation sequencing tests. The comparison of the gene profiles in the samples of tumor and normal tissue confirmed that transmission of maternal tumor to the child had occurred (Fig. 2A and Table S1); both tumors had the same pathogenic KRAS (c.G38A:p.G13D) and TP53 (c.G853A:p.E285K) mutations. A total of 47 exonic single-nucleotide polymorphism (SNP) alleles, which were carried by mother but not inherited in the child’s germline, were detected as apparent somatic mutations in the tumor in the child. Each data point in the scatter plot represents a variant observed in the tumor in the patient, the mother’s blood cells, or both. PD-1 denotes programmed cell death protein 1. As shown in Panel B, the tumors in Patient 2 and his mother had the same KRAS (c.G35A:p.G12D) and STK11 (c.464+1G→A) mutations. A total of 38 exonic SNP alleles, which were carried by mother but not inherited in the child’s germline, were detected as apparent somatic mutations in the tumor in the child. Each data point in the scatter plot represents a variant observed in the tumor in the patient, the mother’s blood cells, or both. As shown in Panel C (left side), fluorescence in situ hybridization analysis of lung tumor specimens obtained from Patient 1, his mother, and Patient 2 indicated that the tumor cells in the specimens from the children showed only X chromosome signals (pink), whereas the stromal cells had signals of both X and Y chromosomes (green). Specimens stained with hematoxylin and eosin are shown on the right.
A Patient 1

Cervical Tumor

Mother

KRAS: G13D
TP53: E285K

Child

Lung Tumor

KRAS: G13D
TP53: E285K

→

Mother's
47 SNP alleles
(not inherited
by child)

No response to PD-1 therapy

Spontaneous regression
Response to PD-1 therapy

B Patient 2

Cervical Tumor

Mother

KRAS: G12D
STK11: splice site

Child

Lung Tumor

KRAS: G12D
STK11: splice site

→

Mother's
38 SNP alleles
(not inherited
by child)

Slow growth of tumor

C Histologic Analysis of Tumor Specimens

Tumor from Patient 1

Tumor from the Mother of Patient 1

Tumor from Patient 2
carcinoma was diagnosed (Fig. 1B). A cervical hilar region of the left lung; mucinous adenocarcinoma, which is an unusual morphologic finding for a primary lung tumor, was revealed at a university hospital for radical hysterectomy and bilateral salpingo-oophorectomy 3 months after delivery. She died of the disease 2 years after the surgery. We did not suspect maternal transmission of the cancer when the child received a diagnosis at 6 years of age.

The tumor in the boy was considered to be inoperable. He received five cycles of paclitaxel (210 mg per square meter on day 1 of each 14-day cycle) and cisplatin (90 mg per square meter on day 1 of each 14-day cycle) followed by three cycles of paclitaxel (210 mg per square meter on day 1 of each 14-day cycle) and carboplatin (400 mg per square meter on day 1 of each 14-day cycle) and two cycles of paclitaxel (210 mg per square meter on day 1 of each 21-day cycle) and irinotecan chemotherapy (125 mg per square meter on day 1 of each 21-day cycle). He had a partial response, with a reduction in levels of the tumor marker CA19-9 to normal levels. The treatment was discontinued. Three months later, the disease recurred in the left lung (Fig. 1B). After five cycles of chemotherapy (gemcitabine at a dose of 675 mg per square meter on days 1 and 8 and docetaxel at a dose of 75 mg per square meter on day 8 of each 21-day cycle) plus one cycle of paclitaxel and carboplatin chemotherapy, he underwent total left pneumonectomy. Pathological examination of the lung showed mucinous adenocarcinoma, which is an unusual morphologic finding for a primary lung tumor, but it was similar to the uterine cervical tumor in the mother. He was followed for 15 months after pneumonectomy and was free from disease.

Samples of the cervical tumor from the mother and from the lung tumor of the child were submitted for next-generation sequencing tests. Although the normal samples from the mother and child differed (as expected), the similarity of the gene profiles of the tumor samples from the mother and child indicated mother-to-infant transmission (Fig. 2B and Ta-
ble S1). Both tumors had the same KRAS (c.464+1G→A) mutation and 38 exonic SNP alleles that were carried by the mother but not inherited in the child’s germline were detected in the tumor sample from the child. FISH analysis revealed that tumors lacked the Y chromosome (Fig. 2C). Whole-exome sequencing detected an additional 14 somatic mutations that were present in tumors from both the mother and the child (Table S2). Loss of HLA class I alleles was not detected in tumor samples from either the mother or the child. Tumors from both the mother and the child were positive for HPV type 16 (Fig. S3).

**DISCUSSION**

Here, we report two cases of lung cancer in children that was caused by transmission of cervical tumors from the children’s mothers. The transmission was demonstrated by the fact that the tumors in both male children lacked the Y chromosome and shared multiple somatic mutations, an HPV genome, and SNP alleles (which were not inherited in the children’s germline) with tumors from the mothers. The peribronchial pattern of tumor growth in both children suggested that the tumors arose from mother-to-infant vaginal transmission through aspiration of tumor-contaminated vaginal fluids during birth. In other cases of rare mother-to-fetus transmission of cancer, the offspring present with multiple disseminated metastases in the brain, bones, liver, lungs, and soft tissues; these metastases are consistent with presumed hematogenous spread from the placenta (Table 1). However, in our two patients, tumors were observed only in the lungs and were localized along the bronchi. It is likely that maternal tumor cells were present in the amniotic fluid, secretions, or blood from the cervix and were aspirated by the infants during vaginal delivery. These cases indicate that mother-to-infant transmission of uterine cervical cancer is possible during vaginal delivery; therefore, cesarean section should be recommended for mothers with uterine cervical cancer.

HLA class I alleles, which were not inherited by Patient 1, were lost in the tumors in this child and his mother. This phenomenon has been reported in a case of mother-to-fetus transmission of leukemia cells.7 Since HLA proteins are known to provide major antigenic targets for allograft recognition and rejection,27 the loss of HLA alleles might have contributed to the survival of the maternal tumor cells in the child. Patient 1 had spontaneous regression of several lesions within 1 year after detection of the tumor, during the follow-up period when he was not receiving treatment; this regression occurs extremely rarely in metastatic neuroendocrine carcinomas. In addition, the remaining tumors evidently had a response to anti–PD-1 immune checkpoint inhibitor therapy, although neither PD-1 nor PD-L1 was expressed in this patient, and immune checkpoint therapy is known to be ineffective in most solid tumors in children.26,29 In contrast, this patient’s mother did not have a response to the same anti–PD-1 therapy. In Patient 2, the tumor grew very slowly, and clinical manifestations did not occur until he was 6 years of age. This slow growth is very rare for metastatic cervical adenocarcinoma; therefore, it appears likely that an alloimmune response in the child affected the rate of tumor growth.

We report two cases of transmission of uterine cervical tumors in mothers to the lungs of infants. Next-generation sequencing of paired samples of tumor and normal tissue may be a useful tool to diagnose cancer that is transmitted from mothers to infants and to understand the prevalence of this transmission.

Supported by grants-in-aid (JP19kk0205004, and JP20kk0205012) from the Japan Agency for Medical Research and Development, grants-in-aid (31-A-12, 30-A-6, and National Cancer Center Biobank) from the National Cancer Center Research and Development Fund, grants-in-aid for scientific research (JP18kk0205036) from the Ministry of Education, Culture, Sports, Science and Technology, and funding for the Phase 1 Trial of Nivolumab for Japanese Pediatric Patients with Relapsed or Refractory Solid Tumors from Ono Pharmaceutical.

Disclosure forms provided by the authors are available with full text of this article at NEJM.org.

We thank Narumi Takamatsu and Aoi Miyata for assistance with pathological assessment, Sachio Mitani of the Fundamental Innovative Oncology Core of the National Cancer Center Research Institute for performing the next-generation sequencing tests, and Maiko Matsuda and Yoko Shimada for performing the human papillomavirus test.
APPENDIX

The authors’ affiliations are as follows: the Departments of Pediatric Oncology (A.A., T. Kumamoto, M.N., A.M.), Laboratory Medicine (T. Kubo, K. Sunami, H.K.), Diagnostic Pathology (N.M., H.Y.), Breast and Medical Oncology (K. Yonemori, E.N.), Pediatric Surgical Oncology (T.H., N.K.), and Experimental Therapeutics (N. Yamamoto), National Cancer Center Hospital, the Departments of Clinical Genomics (H.I., T. Kubo) and Immune Medicine (K.A.), and the Divisions of Genome Biology (K. Shiraiishi, T. Kohno), Cancer Genomics (V.A., T.S.), and Cancer Immunology (Y.T., H.N.), National Cancer Center Research Institute, the Division of Translational Genomics, Exploratory Oncology Research and Clinical Trial Center (H.I., T. Kubo, T. Kohno), the Children’s Cancer Center, National Center for Child Health and Development (T.H.), the Departments of Obstetrics and Gynecology (T. Kuroda, K. Yamada, N. Yanaihara, K. Takahashi, A.O.) and Pathology (T. Kiyokawa), Iikei University School of Medicine, the Departments of Pediatrics (S.H., D.H., A.M.) and Integrated Women’s Health (K.O.), St. Luke’s International Hospital, and the Department of Pediatrics, Toho University School of Medicine (M.M.), Tokyo, and the Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo (S.H., A.M.) — both in Japan.

REFERENCES


Copyright © 2021 Massachusetts Medical Society.