BRIEF REPORT

Vaginal Transmission of Cancer from Mothers with Cervical Cancer to Infants

Ayumu Arakawa, M.D., Hitoshi Ichikawa, Ph.D., Takashi Kubo, Ph.D., Noriko Motoi, M.D., Ph.D., Tadashi Kumamoto, M.D., Ph.D., Miho Nakajima, M.D., Kan Yonemori, M.D., Ph.D., Emi Noguchi, M.D., Ph.D., Kuniko Sunami, M.D., Ph.D., Kouya Shiraishi, Ph.D., Hiroki Kakishima, Hiroshi Yoshida, M.D., Ph.D., Tomoro Hishiki, M.D., Ph.D., Naonori Kawakubo, M.D., Ph.D., Takafumi Kuroda, M.D., Takako Kiyokawa, M.D., Ph.D., Kyosuke Yamada, M.D., Ph.D., Nozomu Yanaihara, M.D., Ph.D., Kazuaki Takahashi, M.D., Ph.D., Aikou Okamoto, M.D., Ph.D., Shinsuke Hirabayashi, M.D., Ph.D., Daisuke Hasegawa, M.D., Ph.D., Atsushi Manabe, M.D., Ph.D., Kentaro Ono, M.D., Masaki Matsuoka, M.D., Yasuhito Arai, Ph.D., Yosuke Togashi, M.D., Ph.D., Tatsuhiro Shibata, M.D., Ph.D., Hiroyoshi Nishikawa, M.D., Ph.D., Kazunori Aoki, M.D., Ph.D., Noboru Yamamoto, M.D., Ph.D., Takashi Kohno, Ph.D., and Chitose Ogawa, M.D.

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 alloimmune 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.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Kohno or Dr. Ogawa at the National Cancer Center, 5-1-1, Tsukiji, Chuo-ku, Tokyo 1040045, Japan, or at tkkohno@ncc.go.jp or chitogaw@ncc.go.jp.

N Engl J Med 2021;384:42-50.
DOI: 10.1056/NEJMoa2030391

Transmission of maternal cancer to offspring is extremely rare and is estimated to occur in approximately 1 infant per every 500,000 mothers with cancer,[1] whereas approximately 1 in 1000 live births involves a mother with cancer.[2] Table 1 provides data on 18 previously reported cases.[3-20] 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[12,16,21] (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.*

Cancer Type and Age at Diagnosis in Child	Primary Site in Mother	Site of Cancer in Child	Presumed Route of Transmission	Method of Examination	Outcome in Mother	Outcome in Child	Reference, Yr
Leukemia or lymphoma							
ALL, 9 mo	—	—	Transplacental	—	Died of disease	Survived	Cramblett et al.,[3] 1958
AML, 20 mo	—	—	Transplacental	Sex-chromosome karyotyping	Survived	Survived	Osada et al.,[4] 1990
NK-cell lymphoma, 4 wk	—	—	Transplacental	Sex-chromosome karyotyping	Died of disease	Died of disease	Catlin et al.,[5] 1999
B-cell lymphoma, 8 mo	—	—	Transplacental	Sex-chromosome FISH	Died of disease	Died of disease	Maruko et al.,[6] 2004
ALL, 11 mo	—	—	Transplacental	Microsatellite marker typing, BCR-ABL breakpoint sequencing	NA	NA	Isoda et al.,[7] 2009
NK T-cell lymphoma, 8 mo	—	—	Transplacental	Microsatellite marker typing	NA	NA	Yagasaki et al.,[8] 2011
Melanoma							
8 mo	Skin	NA	Transplacental	—	Died of disease	Died of disease	Holland,[9] 1949
7 mo	Skin	Left ear	Transplacental	—	Died of disease	Died of disease	Dargeon et al.,[10] 1950
11 days	Skin	Chest wall	Transplacental	—	Died of disease	Died of disease	Brodsky et al.,[11]1965
2 mo	Skin	Left leg	Transplacental	—	Died of disease	Survived (spontaneous regression)	Cavell,[12] 1976
Birth	Skin	NA	Transplacental (placental metastasis histologically confirmed)	—	Died of disease	Died of disease	Ferreira et al.,[13] 1998
7 mo	Skin	Posterior cranial fossa	Transplacental	Sex-chromosome FISH	Died of disease	Died of disease	Trumble et al.,[14] 2005
6 mo	Skin	Left temporal bone	Transplacental	Quantitative PCR	Died of disease	NA	Raso et al.,[15] 2010
3 mo	Skin	Left mastoid process	Transplacental (placental metastasis histologically confirmed)	Sex-chromosome FISH	Died of disease	Survived (spontaneous regression)	Valenzano et al.,[16] 2010
Other solid tumors							
SCLC, 5 mo	Lung	Liver and lung	Transplacental (placental metastasis histologically confirmed)	Sex-chromosome FISH	Died of disease	Survived	Tolar et al.,[17] 2002
Adenocarcinoma, 2 wk	Lung	Multiple lesions on scalp	Transplacental	Sex-chromosome FISH	Died of disease	Survived	Walker et al.,[18] 2002
SCLC, 5 mo	Lung	Cerebellum	Transplacental (placental metastasis histologically confirmed)	—	Died of disease	Died of disease	Teksam et al.,[19] 2004
Neuroendocrine carcinoma, 8 mo	Cervix	Bilateral temporal bone	Transplacental	—	Died of disease	Died of disease	Herskovic et al.,[20] 2014
Neuroendocrine carcinoma, 23 mo	Cervix	Lung	Aspiration into lung	Next-generation sequencing	Died of disease	Survived	Patient 1 in this report
Adenocarcinoma, 6 yr	Cervix	Lung	Aspiration into lung	Next-generation sequencing	Died of disease	Survived	Patient 2 in this report

* 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, UMIN000026497). 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.

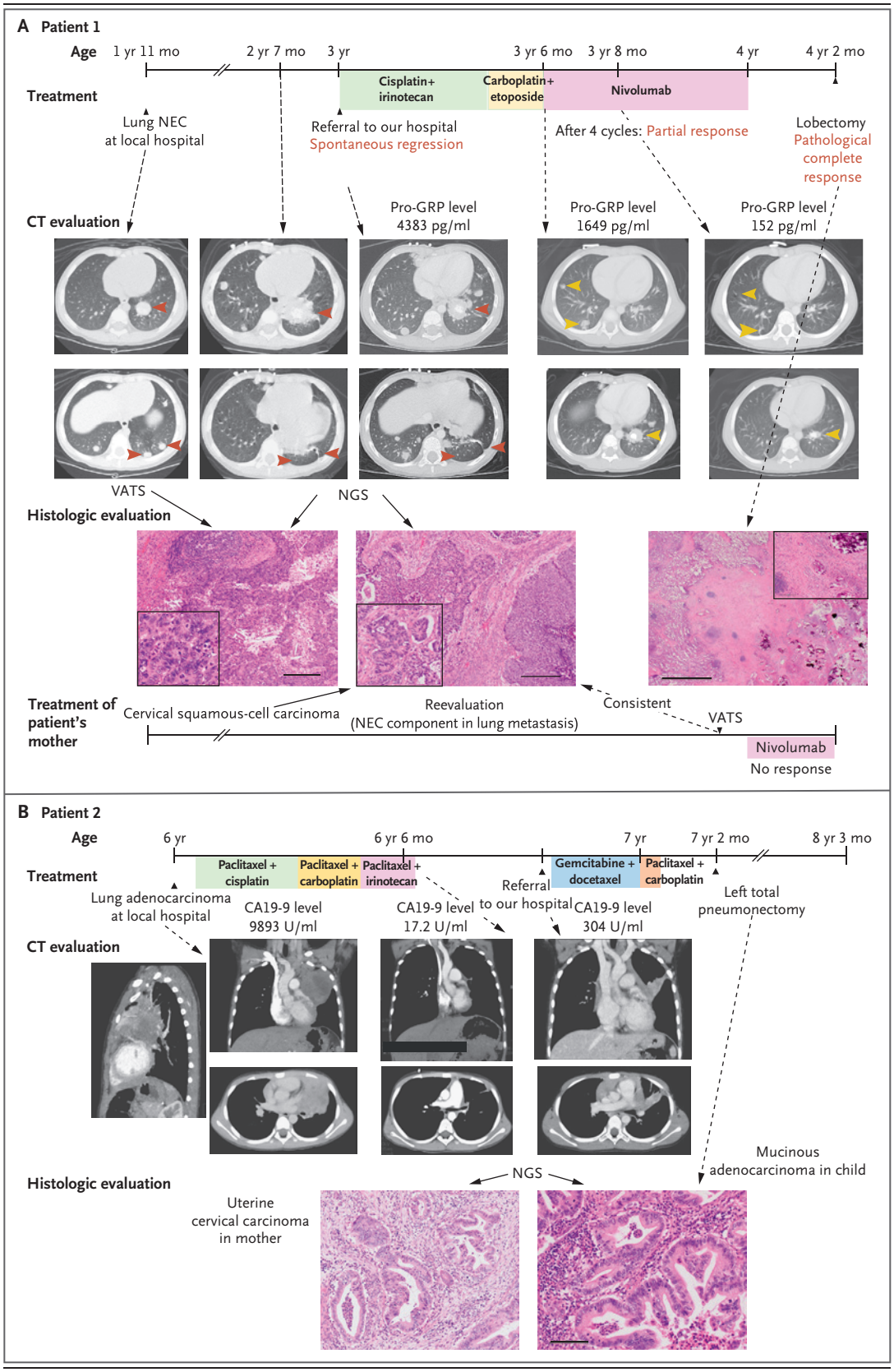
RESULTS

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).

Figure 1 (facing page). Two Cases of Lung Cancer Attributed to Mother-to-Infant Transmission.

Panel A shows the clinical course of Patient 1. A histologic image of the lung tumor (bottom left) resected with video-assisted thoracoscopic surgery (VATS) at a local hospital was indicative of high-grade neuroendocrine carcinoma (NEC) composed of pleomorphic atypical cells, with many mitoses, frequent rosettelike neuroendocrine morphologic features, and necrosis (hematoxylin–eosin staining; the scale bar corresponds to 200 μm, and the inset shows a high-power view). At referral to our hospital after 1 year of follow-up without treatment, spontaneous regression of some tumors was evident on axial computed tomography (CT) (red arrowheads). The patient received 5 cycles of cisplatin and irinotecan, followed by 2 cycles of carboplatin and etoposide chemotherapy. Some tumors had a response, whereas others progressed. Hence, he was enrolled in a clinical trial of anti–programmed cell death protein 1 therapy with nivolumab (3 mg per kilogram of body weight in each 14-day cycle). After 4 cycles of treatment, axial CT showed remarkable shrinkage of all lesions (yellow arrowheads); these decreases were associated with a decrease in the pro–gastrin-releasing peptide (pro-GRP) level. After 14 cycles of treatment, lobectomy was performed and a pathological complete response was confirmed; no viable tumor cells were detected in a fibrous nodule with a tertiary lymphoid structure. On histologic examination, nodular calcification indicated a remnant of tumor degeneration (bottom right, inset [high-power view]; hematoxylin–eosin staining; the scale bar corresponds to 2 mm). Histologic examination of the uterine cervical cancer (bottom center; hematoxylin–eosin staining; the scale bar corresponds to 200 μm) in the patient's mother showed similar morphologic features, including poorly differentiated squamous-cell carcinoma (right) with neuroendocrine and glandular differentiations (left). A high-power view of the neuroendocrine component (inset) showed rosette formation. The tumor samples from the mother and child showed immunoreactivity for neuroendocrine markers, including synaptophysin and chromogranin A (data not shown). Next-generation sequencing (NGS) comparing the tumor samples and the normal tissues from the mother and child indicated mother-to-infant transmission. Panel B shows the clinical course of Patient 2. CT of the chest at first presentation (at 6 years of age) showed a mass that was 6 cm in diameter at the hilar region of the left lung. The tumor had a response to 10 cycles of combination chemotherapy in total, with a radiologic response and a decrease in the level of CA19-9. At referral to our hospital, CT of the chest at relapse (when the child was 7 years of age) showed a tumor mass between the upper and lower lobes of the left lung. After treatment with 3 cycles of the gemcitabine and docetaxel and 1 cycle of paclitaxel and carboplatin chemotherapy, a left total pneumonectomy was performed. Histologic examination showed mucinous adenocarcinoma (bottom right; hematoxylin–eosin staining; the scale bar corresponds to 100 μm). The tumor had unusual morphologic features of a primary lung cancer and was similar to the uterine cervical adenocarcinoma in the patient's mother (bottom left, hematoxylin–eosin staining). Both tumors had abundant lymphocyte and neutrophil infiltration. Comparative NGS analysis indicated mother-to-infant transmission.



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.

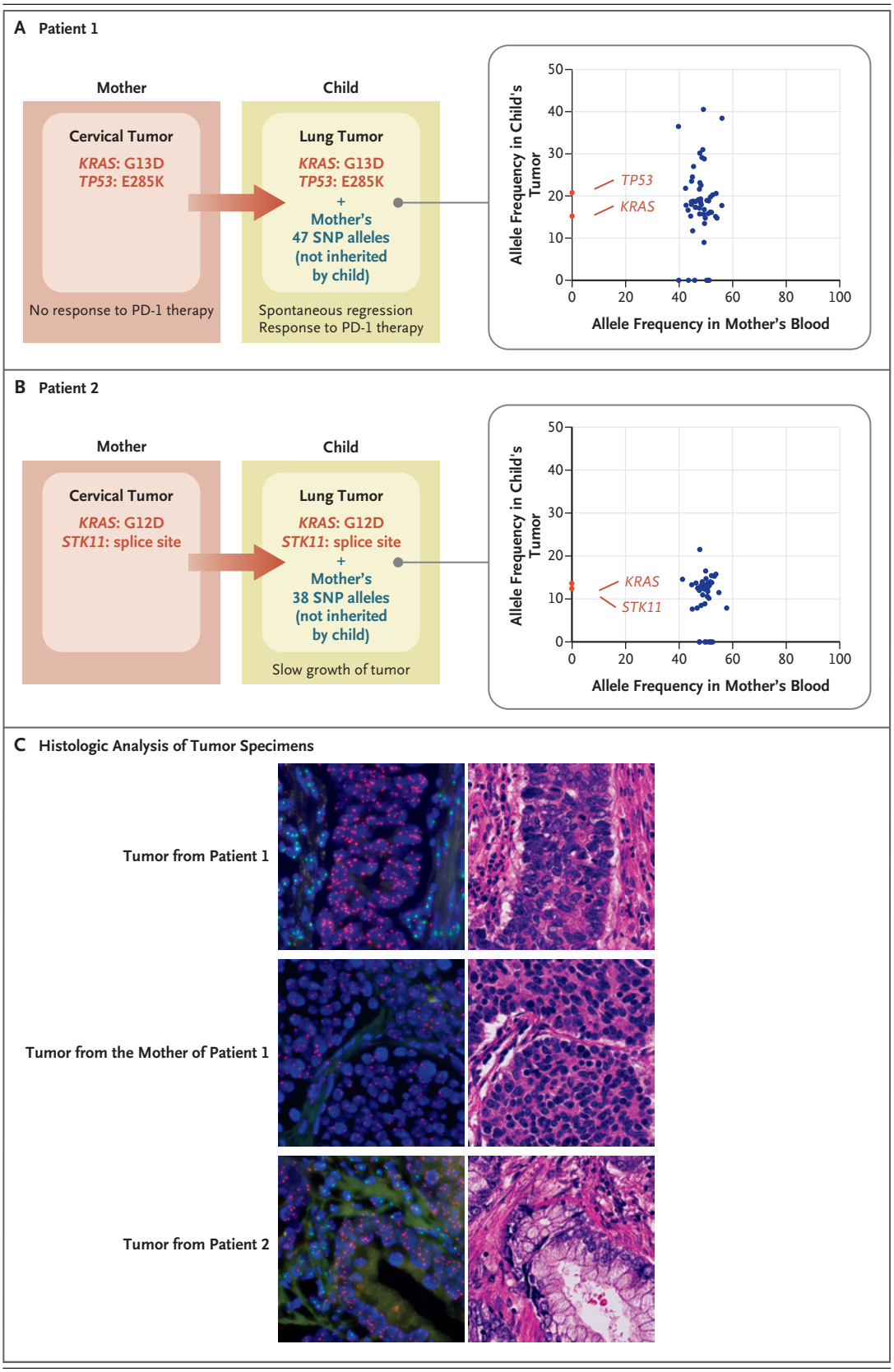
In accordance with his parents' wishes, Patient 1 received frequent follow-up but did not receive treatment. One year after the diagnosis of neuroendocrine carcinoma, the lesions progressed. He was referred to our hospital for further treatment at 3 years of age (Fig. S1A in the Supplementary Appendix). 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, and 47 exonic single-nucleotide polymorphism (SNP) alleles carried by the mother but not inherited in the child's germline were detected in the child's tumor (i.e., the child's tumor was related to the mother's tumor and contained genes that were not in the child's germline genome). Fluorescence in situ hybridization (FISH) analysis revealed that the tumor in the boy lacked the Y chromosome (Fig. 2C). Whole-exome sequencing showed an additional 20 somatic mutations that were detected in tumor samples from both the mother and child (Table S2), and HLA class I alleles that were not inher-

Figure 2 (facing page). Gene Profiles of the Tumors in the Mothers and Children.

As shown in Panel A, the tumors in Patient 1 and his mother 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 the 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.



ited by the child were lost in tumor samples from both the mother and child (Fig. S2). Polymerase-chain-reaction analysis performed with a set of pan-HPV primers,[23] followed by Sanger sequencing, revealed that both tumors were positive for HPV type 18 (Fig. S3).

The disease in the child progressed despite two chemotherapy regimens, so he was enrolled in a clinical trial of nivolumab therapy (see the overview of the trial in the Supplementary Appendix). After four cycles of nivolumab (at a dose of 3 mg per kilogram every 2 weeks), CT showed shrinkage of all the lesions (Fig. 1A), and the pro–gastrin-releasing peptide level decreased from 1649 to 152 pg per milliliter. He received a total of 14 cycles of nivolumab. The response continued for 7 months without the appearance of new lesions. We then performed lobectomy to resect the remaining nodule. This fibrous nodule with tertiary lymphoid formation and calcification without viable tumor cells indicated a pathological complete response (Fig. 1A). Flow cytometric analysis of the resected tumor showed a considerably higher fraction of immune cells (88%) than that in nontumorous lung tissue (33%) (Fig. S1C). A higher fraction of B cells (44%) as well as CD4+ and CD8+ T cells were also noted in the tumor sample; these findings were consistent with a response of the tumor to anti–programmed cell death protein 1 (PD-1) therapy.[24-26] The patient had no evidence of disease recurrence at 12 months after lobectomy.

His mother was enrolled in a phase 2 trial of anti–PD-1 therapy (Japan Medical Association Center for Clinical Trials number, I JMA-IIA00345) in which nivolumab was administered at a dose of 240 mg every 2 weeks. However, the tumor progressed despite four cycles of nivolumab, and she died 5 months after disease progression. Immunohistochemical staining revealed that the tumors in the child and mother were negative both for PD-1 and for programmed cell death ligand 1 (PD-L1) (Fig. S4).

PATIENT 2

A 6-year-old boy (Patient 2) presented to a local hospital with chest pain on the left side. CT revealed a mass measuring 6 cm in diameter at the hilar region of the left lung; mucinous adenocarcinoma was diagnosed (Fig. 1B). A cervical polypoid tumor had been detected in the patient's mother during pregnancy; however, since cervical cytologic analysis was negative and the tumor was stable without any intervention, she delivered the boy vaginally at 38 weeks of gestation. Biopsy of the cervical lesion after the delivery revealed adenocarcinoma, and she was referred to 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.G35A:p.G12D) and *STK11* (c.464+1G→A) mutations, 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 that tumor 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.[28,29] 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 (JP19lk1403003, JP18kk0205004, 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 (JP18K07036) 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 the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Narumi Takamatsu and Aoi Miyata for assistance with pathological assessment, Sachiyo 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., C.O.), 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. Shiraishi, T. Kohno), Cancer Genomics (Y.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), Jikei 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

1. Greaves M, Hughes W. Cancer cell transmission via the placenta. Evol Med Public Health 2018;2018:106-15.
2. Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California Cancer Registry. Am J Obstet Gynecol 2003;189:1128-35.
3. Cramblett HG, Friedman JL, Najjar S. Leukemia in an infant born of a mother with leukemia. N Engl J Med 1958;259:727-9.
4. Osada S, Horibe K, Oiwa K, et al. A case of infantile acute monocytic leukemia caused by vertical transmission of the mother's leukemic cells. Cancer 1990;65:1146-9.
5. Catlin EA, Roberts JD, Erana R, et al. Transplacental transmission of natural-killer-cell lymphoma. N Engl J Med 1999;341:85-91.
6. Maruko K, Maeda T, Kamitomo M, Hatae M, Sueyoshi K. Transplacental transmission of maternal B-cell lymphoma. Am J Obstet Gynecol 2004;191:380-1.
7. Isoda T, Ford AM, Tomizawa D, et al. Immunologically silent cancer clone transmission from mother to offspring. Proc Natl Acad Sci U S A 2009;106:17882-5.
8. Yagasaki H, Ohashi H, Ito M, et al. A novel mechanism of transplacental cancer transmission: natural killer/T-cell lymphoma in the paratesticular region is of maternal origin. Blood 2011;117:6046-7.
9. Holland E. A case of transplacental metastasis of malignant melanoma from mother to foetus. J Obstet Gynaecol Br Emp 1949;56:529-36.
10. Dargeon HW, Eversole JW, Duca VD. Malignant melanoma in an infant. Cancer 1950;3:299-306.
11. Brodsky I, Baren M, Kahn SB, Lewis G, Tellem M. Metastatic malignant melanoma from mother to fetus. Cancer 1965;18:1048-54.
12. Cavell B. Letter: transplacental melanoma — one-year survival. Pediatrics 1976;57:978-9.
13. Ferreira CM, Maceira JM, Coelho JM. Melanoma and pregnancy with placental metastases: report of a case. Am J Dermatopathol 1998;20:403-7.
14. Trumble ER, Smith RM, Pearl G, Wall J. Transplacental transmission of metastatic melanoma to the posterior fossa. Case report. J Neurosurg 2005;103:191-3.
15. Raso A, Mascelli S, Nozza P, et al. Detection of transplacental melanoma metastasis using quantitative PCR. Diagn Mol Pathol 2010;19:78-82.
16. Valenzano Menada M, Moioli M, Garaventa A, et al. Spontaneous regression of transplacental metastases from maternal melanoma in a newborn: case report and review of the literature. Melanoma Res 2010;20:443-9.
17. Tolar JP, Coad JE, Neglia S. Transplacental transfer of small-cell carcinoma of the lung. N Engl J Med 2002;346:1501-2.
18. Walker JWT, Reinisch JF, Monforte HL. Maternal pulmonary adenocarcinoma metastatic to the fetus: first recorded case report and literature review. Pediatr Pathol Mol Med 2002;21:57-69.
19. Teksam M, McKinney A, Short J, Casey SO, Truwit CL. Intracranial metastasis via transplacental (vertical) transmission of maternal small cell lung cancer to fetus: CT and MRI findings. Acta Radiol 2004;45:577-9.
20. Herskovic E, Ryan M, Weinstein J, Wadhwani NR. Maternal to fetal transmission of cervical carcinoma. Pediatr Radiol 2014;44:1035-8.
21. Tolar J, Neglia JP. Transplacental and other routes of cancer transmission between individuals. J Pediatr Hematol Oncol 2003;25:430-4.
22. Sunami K, Ichikawa H, Kubo T, et al. Feasibility and utility of a panel testing for 114 cancer-associated genes in a clinical setting: a hospital-based study. Cancer Sci 2019;110:1480-90.
23. van den Brule AJ, Meijer CJ, Bakels V, Kenemans P, Walboomers JM. Rapid detection of human papillomavirus in cervical scrapes by combined general primer-mediated and type-specific polymerase chain reaction. J Clin Microbiol 1990;28:2739-43.
24. Ribas A, Sanghoon Shin D, Zaretsky J, et al. PD-1 blockade expands intratumoral memory T cells. Cancer Immunol Res 2016;4:194-203.
25. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 2018;378:1976-86.
26. Griss J, Bauer W, Wagner C, et al. B cells sustain inflammation and predict response to immune checkpoint blockade in human melanoma. Nat Commun 2019;10:4186.
27. Vago L, Perna SK, Zanussi M, et al. Loss of mismatched HLA in leukemia after stem-cell transplantation. N Engl J Med 2009;361:478-88.
28. Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020;21:121-33.
29. Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020;21:541-50.