

VAGINAL TRANSMISSION OF CERVICAL CANCER FROM MOTHERS TO THEIR NEWBORNS

TRANSMISSÃO VAGINAL DO CÂNCER DE COLO DO ÚTERO MATERNO PARA O RECÉM-NASCIDO

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Transmission of maternal cancer to their offspring is extremely rare, and its occurrence is estimated to occur in roughly one baby for every 500,000 mothers with cancer, whereas one in every 1,000 live births involves a mother with cancer^(1,2). In these cases, maternal cancers are presumably transmitted via hematogenous (transplacental transmission from mothers to their fetus) and often involve the spread of maternal tumor cells to the child's different organs⁽³⁾. Most cases reported are diagnosed in children under two years of age. In some cases, spontaneous tumor regression in the affected offspring is observed⁽⁴⁾. Transplacental transmission to the fetus is probably rare due to the placental barrier and the fetal alloimmune response⁽⁵⁾.

The vertical transmission of the tumor through the birth canal during vaginal delivery is also theoretically possible. If the mother has cervical cancer, the baby may be exposed to tumor cells in the fluids present in the vaginal canal and can aspirate these cells into the lungs. Therefore, the transmission of the tumor from mothers to their babies may represent a risk in vaginal delivery for women with cervical tumors. However, data on this transmission are lacking.

In January 2021, Arakawa A et al. published two case reports of pediatric lung cancer (in boys aged 23 months and six years old), resulting from maternal transmission of uterine cervical tumors to their children, who were detected incidentally during analysis of next-generation sequencing (NGS) results of routine (which refers to the application of new, faster, lower cost methods and smaller samples for sequencing DNA and RNA structures and have revolutionized genomics and molecular biology) in paired samples of tumor and normal tissue. This analysis was performed to estimate adverse events and the response during cancer treatment. A Gene-Profilng prospective study (measuring gene expression to obtain an overall picture of cell function showing, for example, how cells react to a specific treatment), involving patients with advanced cancer.

At the time of reported cases, there was no suspicion regarding the transmission of the tumor from mothers to their children, because histological characteristics were different.

In both cases, children were male, and the deliveries were vaginal.

The mother of the first case had negative oncotic colpocytology performed during prenatal care and was diagnosed with squamous cell carcinoma of the cervix three months after delivery, and had not received an HPV vaccine. The patient received the proposed treatment (radical surgery and adjuvant chemotherapy) and evolved with lung, liver, and bone metastases developed during the three-year follow-up. The 23-month-old child was diagnosed with neuroendocrine lung carcinoma with focal glandular differentiation and remained in follow-up,

without treatment, at the wish of his parents. At the age of three, surprisingly, some lesions regressed spontaneously when he started chemotherapy cycles with reduction of some tumors and progression of others. The disease progressed in the child despite chemotherapy, having been enrolled in a clinical trial of therapy with nivolumab. After cycles of nivolumab, computed tomography (CT) showed a reduction in all lesions. Then, he underwent lobectomy to resect a remaining nodule. This fibrous nodule with tertiary lymphoid formation and calcification without viable tumor cells indicated a complete pathological response.

Histological examination of the mother's lung tumor revealed poorly differentiated carcinoma with neuroendocrine differentiation. The anatomopathological review of the hysterectomy sample revealed that cervical cancer was predominantly poorly differentiated squamous cell carcinoma with focal neuroendocrine differentiation, associated with a minor adenocarcinoma component; this histological picture was similar to the tumor in his lung, as well as in his son's lung. Histological similarities between the mother's and son's tumor samples led researchers to compare the results of their next-generation sequencing tests. The comparison of gene profiles in the tumor and normal tissue samples confirmed the transmission of the maternal tumor to her child. Both tumors had the same pathogenic KRAS gene (c.G38A: p.G13D) and mutations in the P53 gene (c.G853A: p.E285K). A total of 47 exon alleles of single nucleotide polymorphisms (SNP) carried by the mother, but not inherited in the child's germline and 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).

Fluorescent *in situ* hybridization (FISH) revealed that the boy's tumor lacked the Y chromosome. Sequencing of the complete exome, an efficient way to identify genetic variants in all of an individual's genes, showed an additional number of mutations that were detected in the tumor samples of both the mother and child.

In addition, class I HLA (Human leukocyte antigen), which were not inherited by the child, were lost in the tumor samples of the mother and child.

Through PCR, it was revealed that both tumors, of the mother and the child, were positive for HPV type 18.

The mother of the second case was diagnosed with cervical polyp during pregnancy, after negative oncotic colpocytological analysis. Cervical lesion biopsy after delivery revealed adenocarcinoma. She underwent radical surgery and died of the disease two years after treatment. Her six-year-old son was diagnosed with an inoperable lung tumor, whose histopathological diagnosis was mucinous adenocarcinoma.

At the time, there was no suspicion of maternal cancer transmission.

He received cycles of chemotherapy with partial response and reduced levels of the tumor marker CA19-9 to normal levels. The treatment was interrupted. Three months later, the disease relapsed in

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the lung. After new cycles of chemotherapy, the patient underwent left total pneumectomy. The histopathological examination of the lung showed mucinous adenocarcinoma, which is an unusual morphological finding for primary lung tumor but was similar to the tumor of the uterine cervix of the mother. He was followed for 15 months after pneumectomy and was free of the disease.

Samples of the mother's cervical tumor and the child's lung tumor were submitted for next-generation sequencing. Although the normal samples of both the mother and child differed (as expected), the similarity of gene profiles of their tumor samples indicated transmission between mother and child, which had the same mutations in the KRAS genes (c.G35A: p.G12D) and STK11 (c.464 + 1G → A), in addition to a total of 38 exonic SNP alleles, which were carried by the mother, but not inherited in the child's germline, and detected as apparent somatic mutations in the child's tumor. In addition, there was loss of HLA class I alleles that were not detected in tumor samples from both mother and child.

FISH analysis revealed that this tumor did not have the Y chromosome. And the tumors of both mother and child were positive for HPV type 16.

Some discoveries and similarities in the present article, between the tumors of mothers and children in the cases reported above, make us reflect on the possible vertical transmission of the tumor through the birth canal during vaginal delivery⁽⁵⁾, namely, the absence of the Y chromosome in tumors of male children; sharing many somatic mutations, which although were not inherited in the children's germline, were found in the tumors of both mothers and their children; and the presence of HPV DNA. In addition, the peribronchial pattern of tumor growth in both children suggests that the tumors were transmitted from mothers to their children through the vaginal canal, by aspirating contaminated vaginal fluids with malignant cells during delivery.

Cells of the maternal tumor are likely to have been present in the amniotic fluid, secretions or blood of the cervix, being aspirated by the newborns during vaginal delivery.

In cases of placental transmission, tumors would manifest by multiple metastases disseminated in the brain, bones, liver, lungs, and soft tissues, not being restricted only to the lungs, more specifically along the bronchi, as in the cases described^(1,3,5).

In addition, class I HLA (Human leukocyte antigen) alleles, which were not inherited by the child, were lost in the tumor samples of both the mother and child. Since HLA proteins are known to provide the main antigenic targets for allograft recognition and rejection, the loss of HLA alleles may have contributed to the survival of maternal tumor cells in children.

Patient 1 had spontaneous regression of various lesions within a year after the tumor was detected, during the follow-up period when he was not yet receiving treatment; this regression rarely occurs in metastatic neuroendocrine carcinomas⁽⁵⁾. In the child of case 2, the tumor grew very slowly, and the clinical manifestations did not occur before the age of six. Slow growth is very rare for metastatic cervical adenocarcinoma; therefore, it seems likely that an alloimmune response in the child affected the rate of tumor growth.

Some important points of these cases to ponder are the importance of the HPV vaccine in the primary prevention of HPV infection; the quality and repetition of screening tests (conventional

oncologic cytology, in liquid and DNA-HPV test) in the woman's gynecological routine in order to provide adequate secondary prevention of cervical cancer, with an impact on reducing its incidence in the female population. Further research still needs to be developed to ensure the protection of newborns delivered through C-sections, avoiding the transmissibility of the cervical tumor to children. Moreover, considering the precursor lesions of cervical cancer, future studies should verify if the cesarean delivery in women with these conditions protects their offspring, especially in those not vaccinated. Close monitoring these babies can warn us about the change in conducts. Next-generation sequencing in tumor samples and normal tissue can be a useful tool to diagnose the origin of cancer, detect those transmitted from mothers to babies, and understand the prevalence and mechanisms of this transmission.

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Conflict of interests

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