



Transplacental Transmission of Melanotic Tumor in an 8-Month Old Female Infant: A Case Report

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Abstract

Malignant melanoma is rare in children younger than 15 years, accounting for less than 1% of pediatric malignancies. We present an unusual case of an atypical malignant melanoma in an 8-month old female infant. The patient was admitted in our hospital due to swelling and erythema of the left cheek and the mastoid region, followed by otorrhea and fever. Ear fluid cultures revealed the presence of *Pseudomonas Aeruginosa* and she was accordingly treated with IV antibiotics. Despite treatment, no clinical improvement was achieved. The petrous temporal bone CT scan showed a tumor within the mastoid cavity and a biopsy was performed. Pathology reported the presence of a melanocytic tumor of the mastoid process with areas of high grade malignancy. Staging investigations with head and spinal MRI, CT thorax and neck and abdominal US were negative. Genetic testing on the biopsy specimen showed a BRAF-gene exon-15 mutation (p. V600E), also present in her mother. Her mother had been diagnosed with melanoma at the age of twenty, but during this pregnancy, she suffered a disease recurrence with liver and spleen metastases. Sixteen months after tumor excision, our little patient remains completely well without evidence of disease recurrence or progression. Melanoma is one of few malignancies that can be transmitted to the embryo through the placenta, and though extremely unusual it is a diagnosis that needs to be excluded in certain cases.

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Introduction

Malignant melanoma during childhood and puberty is rare. It represents 1%-3% of all cancers affecting patients younger than 20 years and only 0.9% of malignancies diagnosed in children younger than 15 years old [1,2]. Nevertheless, for adolescents between 15 - 19 years, relevant rates are around 7% [3]. In USA, the annual incidence of melanoma during childhood, increased from 2% to 2.9% between 1973 and 2001 [4]. There is a slight predominance of the female gender and especially in puberty with a female / male ratio of 3/2. However, in younger children between 1 to 4 years old, males are affected more often [5,6]. According to disease status, studies have shown a 5-year survival of 100% for in situ disease, 93%-96% for localized disease, 68%-77% for regional metastatic disease and 11%-57% for distant metastatic disease [1].

The diagnosis of cancer during pregnancy is not rare with an incidence of 1 per 1000 pregnancies. The estimated incidence of melanoma among pregnant women is 0.1 to 2.8 per 1000 pregnancies [7,8]. Melanoma is one of several tumors which metastasize to the placenta, including lymphomas, leukemias, breast and lung cancer [9-11]. Placental involvement with maternal cancer has been defined as gross or microscopic evidence of maternal cancer within any section of the placenta. Fetal metastasis has been defined as metastasis of maternal cancer transmitted in the fetus, with no evidence of primary tumor originating in the fetus. Since the first case reported in 1866, only 87 cases of placental or fetal metastasis have been reported. Twenty-seven cases (31%) involved melanoma and six of them (22%) involved transplacental metastases in the infant [12].

We report a case of transplacental transmission of melanotic tumor in an 8-month old female infant.

Case Presentation

An 8-month old female patient was referred to the emergency room of our hospital due to swelling and erythema of the left cheek and the mastoid region, followed by a 4-day otorrhea and fever



Figure 1: Swelling and erythema of the mastoid process.



Figure 2: A petrous temporal bone CT scan: A 2.5 cm x 2 cm x 2 cm mass in the left mastoid cavity with local osteolysis is shown, extending into brain.

up to 38.8°C two days before ago. Upon clinical examination, swelling and erythema of the left mastoid process as well acute infection of the middle ear was noted (Figure 1). There were not any skin lesions. She was initially treated with an empirical IV antibiotic regimen of cefotaxime and clindamycin. The cultures of the ear discharge showed *Pseudomonas Aeruginosa*, so treatment was accordingly modified into ceftazidime and amikacin. Two weeks later, in clinical examination, exacerbation of the periauricular periaural edema and 2-day fever of 38°C was noted. A petrous temporal bone CT scan was decided, that showed a mass sized 2.5 cm x 2 cm x 2 cm in the mastoid cavity (Figure 2).

The infant was born at 33 weeks of gestation, weighing 2,130 gm. Due to prematurity premature, she was admitted supported in the Neonatal Intensive Care Unit. Patient's mother had been initially diagnosed with melanoma at the age of twenty. During pregnancy, she suffered a disease recurrence, with metastases in the liver and spleen. A liver biopsy was conducted followed by Real Time PCR HRM analysis. The latter revealed an exon 15-mutation in BRAF gene (pV600E). The mother remained hospitalized for two months and afterwards, underwent a cesarean section. During delivery, the placenta was not investigated. After birth, the mother stayed hospitalized for three more months and finally died at the age of thirty-two due to widespread melanoma disease.

Following a petrous temporal bone CT scan, our little patient underwent a biopsy of the mastoid cavity (Figure 3). Pathology reported the presence of an intermediate to high grade malignant melanocytic tumor of the mastoid process. There were nests of epithelioid melanocytic cells with large nuclei and light-chromatric or full of melanin cytoplasm. In immunohistochemistry, tumour stained positive for HMB-45 (100%), MELAN-A (>80%), S100 protein (>80%) and MITF (>90%). There were no mitoses, atypia or polymorphism and these findings would related with melanotic tumors of uncertain malignant potential. Finally, Real Time PCR HRM analysis identified the exon-15 mutation of the BRAF gene (p.



Figure 3: Multiple friable melanochromic tissue specimens were obtained. There was a corrosion of the posterior wall of the outer ear canal as well as infiltration of the mastoid process, extending to the skull and the underlying meningeal elements.

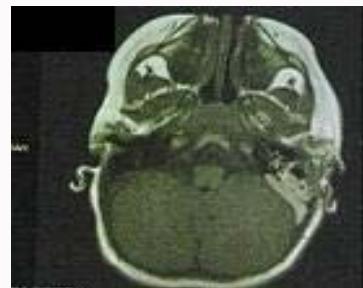


Figure 4: Brain MRI: A space-occupying lesion is identified in the left temporal petrous bone, with pathologic signal intensity, low enhancement and necrotic areas, invading all petrous cavities.

V600E) in the infant, similarly to mother, confirming and that way confirmed the metastatic, transplacental origin of the lesion.

After macroscopically complete surgical excision, our young patient was transferred to the Oncology Department for further support. She underwent a thorough staging workup, including head and spinal MR, CT thorax and neck and abdominal US. Cytology of the cerebrospinal fluid was also negative. The postoperative MRI showed possible residual mass or postoperative findings (Figure 4). There were no signs of metastatic disease.

After consulting the relative European Expert Team in Pediatric Rare Tumors, we decided to adopt a watch-and-wait approach, and reserve further treatment for a possible disease recurrence. A strict, 3-monthly clinical and imaging follow-up protocol was finally proposed. We have been attending to the child in our Department the last sixteen months and she remains well, with no evidence of progressive disease.

Discussion

Melanoma is one of several tumors which metastasize to the placenta including lymphomas, leukemia, breast and lung cancer. A review of literature showed 87 cases of placental/fetal involvement with maternal malignancies, 72 of which these (83%) with isolated placental involvement, 10 (11%) with fetal metastasis without placental examination and 5 (6%) with combined placental and fetal metastasis [12]. Also 27 cases (31%) of either placental or fetal metastasis of melanoma have been described. Microscopic evaluation of the placenta was performed in 24 of 27 patients, and placental involvement was documented in all cases. Eighteen of the above 27 (67%) patients gave birth to healthy infants and 6 (22%) to ill infants with metastatic melanoma; 5 of them died during their first months of

life. The only survivor was a female born at 34 weeks, weighing 2,130 gm [13-15]. Infants born with placental metastasis of melanoma are often born prematurely at a mean gestational age of 34 weeks. These infants have an exceptionally poor prognosis and typically die within 3 months of diagnosis. Our patient was a female infant born at 33 weeks, weighing 2,130 gm. These characteristics are similar with the survivor described above.

Molecular pathogenesis of melanoma involved mutations in the BRAF gene that result in substitutions at the V600 residue of the protein (BRAFV600 mutations). Large single center studies and meta-analyses have reported BRAFV600 mutation rates of 40%-45% in clinical specimens [16-18]. The most common BRAFV600 mutation results in the substitution of valine with glutamic acid (BRAFV600E), representing 70% of detected BRAF mutations [17,19]. Mutations that result in substitution with lysine (BRAFV600K) are the second most common (20%), while other rare substitutions include BRAFV600D and BRAFV600R. Three targeted therapies have been approved currently for the treatment of patients with stage IV or unresectable melanoma with BRAFV600 mutations. Vemurafenib, Trametinib and Dabrafenib are potent and selective small molecule inhibitors of BRAFV600 mutant proteins [20-23].

The tendency of melanoma to metastasize to the fetus is poorly understood compared to other relevant tumor types. Two hypotheses can be invoked to explain the rare occurrence of tumor metastasis to the fetus: the placental barrier and the ability of the fetus to reject foreign maternal cells [24].

Although the risk of metastasis is low, it is recommended that pathologists should carefully examine the placentas of women with known or suspected metastatic melanoma, grossly and histologically. Immunohistochemical staining for melanoma antigens should be performed on histological sections, using S-100, HMB-45, or other appropriate markers. The examination of cord blood buffy coat for the presence of tumor cells using immunohistochemical staining or reverse transcriptase polymerase chain reaction may be useful [25-27]. Also research evaluation to establish the maternal origin of the tumor (including karyotyping, cytogenetics, and HLA typing of the mother, infant, and tumors) may be of value. Advances in cytogenetic tumor analysis using cellular DNA markers that permit discrimination between maternal and fetal cells now make possible the confirmation of the maternal origin of the tumor more conclusively.

The management of melanoma during pregnancy requires several difficult decisions as the disease involves both the mother and the fetus. Physicians should be encouraged to thoroughly examine the placenta generally in mothers with metastatic melanoma as there is a high risk of transmission to the fetus. Of particular concern are the pregnancy outcome, the gestational age, the risk of metastasis to the placenta or fetus and the treatment options for metastatic melanoma during pregnancy. The pregnancy must be postponed for about two or three years after treatment completion [28].

Infants with clinical evidence of maternally derived metastases have an exceptionally poor prognosis [12]. Thus, neonates delivered with concomitant placental involvement but without clinical evidence of disease should be considered a high-risk population and close observation and follow-up is recommended. If the neonate does not present with metastases at birth, recommendation is periodic evaluation for development of melanoma for at least 24 months. Recommendations for follow-up include skin inspection [10,29],

abdominal ultrasound [10,30] and screening for methanogens in the child's urine [10,29]. In addition, evaluation should include a baseline chest x-ray and liver enzymes, including lactate dehydrogenase, which may be repeated every 6 months.

Reports of primary malignant melanoma of the middle ear mucosa support the hypothesis that melanocytes are present in the middle ear [31-35]. Melanocytes are distributed throughout the mucous membrane of head and neck. The middle ear mucosa, like the nasopharyngeal and oral, is derived embryologically from pharyngeal pouches. Very few cases of primary middle ear malignant melanomas have been reported in bibliography and relevant articles and have been observed in adults. However melanin may induce or be a response to inflammation. The significance of extracellular melanin in the setting of chronic ear disease is unclear. *In vitro* studies, IFN- γ treated melanocytes can efficiently process and present antigen through MHC class II molecules to Th1-like T cells, effectively describing an integral role within the immune system. In the described case our patient was an infant and according to the literature the primary tumor has been described in adults as a case report [36].

We have identified some limitations in this case report. Unfortunately, the placenta at the time of delivery was not examined by a pathologist. The BRAFV600 could be due to germline mutation, however, we did not send out samples of normal tissue as we had the mother's medical history and the child was phenotypically normal.

Conclusion

There is definitely a risk of transplacental transmission of melanoma from mother to fetus, but fortunately this risk is low. Women diagnosed with metastatic melanoma during pregnancy do not need to abort their fetus. However physicians should be encouraged to thoroughly examine the placenta in all mothers with metastatic disease.

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