Congenital malignant melanoma- the unique entity of pediatric melanoma: two case reports and literature review

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Case Report

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Abstract

Background: Pediatric malignant melanoma (MM) is categorized by the age as congenital, childhood and adolescent subtypes. Congenital melanoma is present at birth or in the first year of life. It is an exceedingly rare entity for the low incidence and difficult diagnosis. Here, we present two cases of congenital malignant melanoma. Besides, we describe the special clinicopathologic and molecular features of pediatric MM especially congenital sub-type by reviewing the literature.

Case presentation: We report two cases of congenital malignant melanoma. One is a boy patient who had been born with a mass in the occipital scalp, the other newborn girl presented with a mass at birth on her right shoulder. Two patients all underwent the excision of the nodular lesion. Histological evaluation revealed the boy case is pigmented epithelioid melanocytoma (PEM), a unique low-grade variant of malignant melanoma of the skin. The other is congenital melanoma. After the operation, the boy patient presented with cervical lymph node metastasis on the third postoperative month, but is still alive and is developing well. The girl patient recovered, with no recurrence or metastasis since follow-up.

Conclusions: Congenital melanoma is a rare sub-type of pediatric melanoma. Accurate diagnosis of congenital MM is challenging and requires the combination of clinical presentation, pathologic and molecular findings. The cases we offered will contribute to the understanding of epidemiological features and molecular biology of congenital MM and pediatric MM.

Background

Pediatric melanoma, which ranges between the age of in uterus and 19 years (1), is categorized by the age as congenital, childhood and adolescent subtypes (2). It is different from adult melanoma and there are many differences even among the subtypes of pediatric MM in biological behaviors and molecular pathways (3). Congenital malignant melanoma is a special entity for the low incidence and difficult diagnosis. Accurate diagnosis of congenital MM is challenging and requires the combination of clinical presentation, pathologic and molecular features (4). Here, we present two cases of congenital MM and summarize the important clinical, pathological and genomic aspects of pediatric MM and congenital MM by reviewing the literature.

Case Presentation

Case 1

Written informed consent was obtained from the parents for publication of this case report and accompanying images. In September 2020, a three-month-old male infant was presented to our hospital and his parents complained that the baby had been born with a mass in the occipital scalp. The mass was increased in size without associated seizure, convulsion, high fever, nausea, vomiting or neuropsychiatric disorders. There was no remarkable past history and family history. General physical examination revealed a tenacious, non-tender, and movable scalp mass. The nodular lesion was well

demarcated and its covered skin was smooth with no ulceration and bleeding (Figure. 1). There was no enlarged superficial lymph node during palpation on admission, and no other pigmented skin lesions were observed. A complete neurologic examination revealed no abnormalities. The findings of complete blood cell count, biochemical profile and urine analysis were all normal.

Ultrasound showed a hypo-echoic mass in the subgaleal plane with a clear demarcation from skull. Contrast-enhanced cerebral magnetic resonance imaging (MRI) revealed a 2.5×3.1×4.3cm heterogeneous mass (Figure. 2), which didn't communicate with intracalvarium. According to the ultrasound and MRI findings, haemangioma with hemorrhage was the important consideration.

An excision of the scalp mass was performed. During the operation, a mass with capsule was observed embedding in the subcutaneous space and was jet black in color (Figure. 3). The tumor was removed completely along the periosteum as the boundary was clear.

Histopathologic evaluation revealed the pigmented epithelioid melanocytoma (PEM), a unique low-grade variant of malignant melanoma of the skin (5). PEM occurring in the brain/meninges and eye is considered a benign proliferation of melanocytic cells. However, it is considered a malignant melanoma variant occurring in the skin (5). Under light microscope, we observed that tumor cells extensively involved both the dermis and deep subcutaneous tissues, while no epidermis existed. Epithelioid to spindle to dendritic cells were arranged in an ill-defined fascicular pattern. Most tumor cells contained abundant cytoplasmic melanin pigment. The nuclei were uniform without severe cytologic atypia, with regular nuclear membranes and small nucleoli. Two occasional mitotic figures were observed at a high power field (HPF). At the base, the heavily pigmented cells infiltrated dermal collagen and striated muscle. Cell maturation was generally absent. Vascular invasion of tumor cells can be seen with the lesion. Infiltration of small number of lymphocytes was around the vessel (Figure. 4). Immunohistochemistry (IHC) after melanin bleach study revealed weak positive reaction for S100, HMB45 and MelanA antigen in most tumor cells. The Ki67 index is no more than 10%. Besides, staining for P16, RB and TP53 antigen was positive (Figure. 5).

Fluorescence in situ hybridization (FISH) analysis in 6p25 (RREB1), 6q23(MYB), 11q13 (CCND1) and centromere 6 (Cep6) with determined criteria showed abnormalities (Figure. 6). There were increased c-MYC gene copy numbers in FISH analysis. Homozygous deletion of CDKN2A gene was not found. Previous studies have shown that a 4-probe FISH assay targeting 6p25 (RREB1), 6q23 (MYB), 11q13 (CCND1) and centromere 6 (Cep6) on 2 chromosomes could help in the distinction of cutaneous benign nevi and melanoma which the latter exhibits chromosomal aberrations, with the sensitivity of 87% and specificity of 95% (6, 7). 8q24 (MYC) and 9p21(CDKN2A) have also been identified as chromosomal copy number changes in melanoma using both comparative genomic hybridization (CGH) and FISH (8). MYC gain or homozygous deletion of CDKN2A is positively correlated with ulceration and it is a factor which is associated with poor prognosis, therefore, an increase in MYC number or deletion of CDKN2A may be associated with a more aggressive clinical course(9–17).

Besides, mutations in BRAF V600E and C-KIT were not detected through polymerase chain reaction (PCR) assay. The patient presented with cervical lymph node metastasis on the third postoperative month, but is still alive now over the one-year follow-up period.

Case 2

A one-day newborn girl was referred to Yunnan Children's Hospital with a mass presented at birth on her right shoulder. She was delivered safely by Caesarean section after 44 weeks pregnancy. The first fetal ultrasonography (23 weeks) revealed a hypo-echoic mass measuring 2.6×1.9 cm (Figure. 7) on the upper outside of the right scapula and increased gradually to 5×10 cm at birth. During the whole prenatal examination, the mass was suspected as benign teratoma. Her past history and family history were unremarkable. Physical examination showed a blueish and soft mass on the right shoulder, with ulceration and minimal bleeding of the superficial skin (Figure. 8). Apart from benign nevi on her left leg, abdomen and vulva, there was no other pigmented lesion. The neck and axillary lymph nodes weren't palpable. Preoperative images including abdominal, head and chest computed tomography (CT) showed no evidence of metastasis.

CT scan demonstrated the mass closed to ribs, and enclosed right scapula which showed moth eaten and expansionary destruction. MRI revealed a heterogeneous high density mass on T2WI involving triceps muscle and subscapular muscles.

After 20 days at admission, the patient underwent the excision of shoulder's mass. At the skin opening, a blackish, soft, solid-cystic tumor was observed. The tumor appeared to present as invasive growth. Although the mass was adherent to right scapula and clavicle, most of it was totally removed.

The hematoxylin and eosin (HE) sections were sent to our department for consultation. At scanning magnification, the resection specimens showed atypical tumor cells arranging in nests and sheets and infiltrating both the epidermis and throughout the dermis, with the formation of erosion and ulcers in the epidermis. Tumor cells arranged in sheets were spindle with cytoplasmic melanin pigment, showing the characteristics of melanocytic cells. Lesion with ill-defined nested architecture was composed of large epithelioid cells, with large nucleoli and moderate to severe atypia. Abnormal mitotic figures were readily observed. Mature melanocytic cells were not observed (Figure. 9A-C). IHC for both SOX10 and HMB45 antigen was strongly positive in lesional cells and Ki67 index is about 25% (Figure. 9D-F). According to these observations, a diagnosis of congenital melanoma was made and was confirmed by three experienced dermatopathologists.

BRAF (V600E) mutation was not detected by PCR, and so were TERT and C-KIT (Sanger sequencing) mutations.

There is no metastasis or recurrence of the patient during a follow-up period of 14 months. The patient is now 14-month-old and growing and developing well.

Discussion And Conclusions

Epidemiology

Malignant melanoma is the most common potentially fatal neoplasm of the skin (5). It appears to more frequently affect adults, especially among women 25 to 29 years old. Cases in children are quite rare but have been increasing (18).

Pediatric malignant melanoma can be defined as the malignant neoplasm of melanocytes between the age of in uterus and 19 years (1). It accounts for 0.3–0.4% of all cutaneous melanomas (19) and 1.3–3% of children malignancies (20). Pediatric MM possesses unique clinical behaviors and has a better prognosis compared with adult melanoma (21). Further, the prepubertal and postpubertal MM differ considerably in biological natures (3). For these reasons, pediatric melanoma is classified based upon patient's age into congenital, childhood and adolescent subtypes (2). Among them, adolescent melanoma is the most common type.

Childhood and adolescent melanoma have many differences in clinicopathologic characteristics, with the latter sharing many similarities with adults. The risk factor of younger children is genetic predisposition, while sunlight exposure plays a more important role in elder children. Histologically, prepubertal melanoma often presents as Spitzoid, nodular and unclassified subtypes. Postpubertal melanoma usually shows the same morphology including acral, superficial spreading subtypes with traditional adult melanoma (22).

For pediatric melanoma, the most common site was the trunk (23) and the major clinical complaints are lesion enlargement and bleeding. Tumor is almost greater than 1mm, which can be explained by its delayed diagnosis, and is more prone to have regional lymph node metastasis compared with adults partly due to thicker depth, which has no statistical correlation with poorer prognosis (24). Visceral metastasis which indicates poor clinical outcomes, is less seen in pediatrics (25). Unlike adult melanoma, Breslow thickness and lymph node metastasis of pediatrics may not be the categories of clinical stage.

Pathogenesis and genetic mechanisms

Melanoma tumorigenesis likely represents a multistep process including oncogene activation and tumor suppressor gene inactivation (26). The molecular pathways of pediatric melanoma are dysregulated stepwise in the following sequence: (1) activation of the BRAF/NRAS, (2) telomerase reactivation, (3) abrogation of the P16-retinoblastoma (P16-RB) pathway, (4) dysregulation of the phosphatidylinositol 3-kinase and the AKT (PI3K-AKT) pathways (27). In NRAS mutated melanomas, this pathway is directly activated through NRAS, which further activates the mitogen-activated protein (MAP) kinase and the PI3K-AKT pathways. In BRAF-mutant melanomas, it is completed through alterations of PTEN (negative regulator of PI3K-AKT) (28).

No molecular pathways have been found to be specific to pediatric MM, and the bio-markers often overlap with that of adult counterparts. In pediatric melanomas, BRAF is the main oncogenic driver of

traditional adult sub-type while NRAS is unique to melanomas arising CMN (4). Those two oncogenetic aberrations result in further activation of MAP kinase pathway, then lead to melanocytic cell lineage proliferation.

Oncogene-induced senescence also restricts tumor progression. P16/INK4a, which can be encoded by CDKN2A gene located on the short arm chromosome 9, inhibits cell cycle through blocking the phosphorylation of Rb proteins to induce senescence. Tumor cells may overcome senescence through the aberrant expression of P16/Rb pathway, by loss, inactivating mutation or epigenetic alteration of CDKN2A or other genes (29). Biallelic loss of CDKN2A characterizes the low-risk/borderline-risk spitzoid or nevoid pediatric melanomas.

Pediatric melanomas have a favorable biological behavior and prognosis (30), even it usually presents with severe symptoms, and it maybe relate to the absence of telomerase reverse transcriptase (TERT) dysregulation and exhibit chromosomal instability. TERT expression can be deregulated through promoter mutations, methylation and structural rearrangements. Promoter mutations are seen in about 70% of adult melanomas and occur at 124 and 146 base pairs upstream of the start condon. TERT oncogene is commonly expressed in malignant adult melanomas and biologically aggressive adolescent melanomas (31–33). Therefore, TERT expression and other clinicopathologic parameters are considered as prognostic marker for pediatric melanoma.

Currently, whole genome sequencing revealed mutations such as C-kit, HRAS, GNAQ and NF1 are associated with pediatric melanomas. To establish the genetic alterations specific to pediatric MM, molecular biology needs to be further researched.

Diagnosis and treatment

The pathologic diagnosis of melanoma is increasingly dependent on the combination of clinical features and molecular biology (4). The traditional ABCD characteristics, which include asymmetry, border irregularity, color variegation, diameter ≥ 6 mm, are may not adequate for children. Pediatric melanoma also presents as amelanosis, bleeding, color uniformity, diameters variability and evolution (any morphologic or symptomatic change in the lesion), the additional modified ABCDE standards have been proposed for suspicious lesions in children (22). Differential diagnosis for melanoma is atypical melanocytic neoplasms such as melanocytic tumors of uncertain malignant potential (MELTUMP), borderline tumors, and atypical Spitz tumor. However, the atypical presentation and rarity often lead to the difficulty in making certain diagnosis of malignancy even for the expert dermatopathologists using currently histopathologic criteria. Recently, molecular techniques including CGH and FISH to identify chromosomal abnormalities have emerged as a promising diagnostic aid to traditional microscopy. CGH can offer greater sensitivity and specificity than FISH in identifying spitzoid lesions of uncertain malignant potential from melanoma (34).

The treatment of children is often based upon adult studies due to the rarity. Surgical excision has been the mainstay of therapy for localized cutaneous melanoma, and narrower margins for lesions are enough

to prevent local recurrence. The sentinel lymph node biopsy in pediatric patients with melanomas ≥ 1 mm in thickness is recommended, whereas the operation is very selectively for children under 14 with melanomas < 1 mm. The purpose of sentinel lymph node biopsy is for surgical staging and further treatment guidance.

Subtypes of congenital MM

Congenital malignant melanoma is present at birth or in the first year of life and is exceedingly rare, with only 29 cutaneous cases (Table. 1) reported in the English language medical literature since 1925 (24, 35). It is a unique entity and the epidemiological features is difficult to determine due to the limited cases. We can only recapitulate some aspects through case reports. Baby boys account for about 74% and the male predisposition may develop in the embryonic period mainly because of biologic basis for disease except for acquired factors (36). The common sites are neck and head especially scalp (37). Congenital MM is associated with a poorer outcome. However, the spontaneous regression of congenital MM has also been reported.

Congenital MM may arise in the following three ways. The first is vertical transmission through placental metastases from a maternal melanoma. This type is particularly rare, and one possible reason is that fetus rejects maternal cancer cells as immunoreaction (38, 39) which is obtained in the latter half of the third trimester (40, 41). Newborns often initially present with skin lesions and abdominal swelling. The prognosis is extremely poor as it accompanies extensive visceral metastases and patient usually dies during the first year of life. Liver is the most common involved for the reason of placental blood firstly enters the vascular plexus of the liver then travels to all parts of the body in the placental-fetal circulation (36). Placenta needs to be examined grossly once melanocytic cells are found. However, melanocytic deposits in the placenta require an exclusion of congenital melanocytic nevi with placental infiltration by melanocytes, which is a benign pigmented lesion (42). Of note, metastasis to the placenta is indicative of stage IV and guide appropriate treatment of the mother (43). The transmission from fetus to mother through metastatic placenta has yet been reported.

The second is developing from giant congenital melanocytic nevi (GCMN) and is the commonest type. The size definition of GCMN is greater than 40cm in diameter at least (44). Congenital melanocytic naevi (CMN) represents pigment cells malformations that have formed during ontogenesis and are visible at or shortly after birth (45). GCMN is a predisposing condition and its risk of developing into melanoma increases with size. The occurrence of GCMN is about 1 in 20000 neonates and carries a 2%-4.5% lifetime risk of malignant transformation (46, 47). The prognosis of GCMN-associated melanoma is poor, with the disease-free survival of one hour to five years.

The visual diagnosis of malignant transformation is difficult as epidermal changes are not apparent, so it has been in advanced stage once diagnosed. Due to the close relationship with MM, the complete excision of GCMN is recommended to decrease the risk of evolution. As the difficult accomplishment in giant lesions and cosmetic influence in lower lesions, positive management remains controversial. Another treatment is follow-up closely by professional doctors whether the lesions are removed or not

(36). When some children are associated with neurological abnormalities such as headache, vomiting, epilepsy, CMN with neurocutaneous melanocytosis should be considered and MRI examination should be performed for diagnosis.

The third type is de novo melanoma, which may not be associated with a congenital melanocytic nevus. The two cases we described above are both de novo. We define de novo as melanoma arising from a non-lesional skin (48) and scalp is the common site. The prognosis in de novo melanoma is better than the other two. Patients often have lymph node or distant metastasis after treatment during the first year, which doesn't reveal poorer diagnosis. Early diagnosis and treatment is important. Our two cases both underwent surgical removal of the mass and are still alive after the follow-up, although the former presented with lymph node metastasis.

In conclusion, congenital malignant melanoma is a rare entity and should be distinguished from other benign melanocytic lesions. Accurate diagnosis requires the combination of clinical presentation, pathologic and molecular findings. The surgical treatment and follow-up are essential once diagnosed. It is hard to summarize the epidemiological features and molecular biology because the data on patient are limited, in this case, a large volume of cases for this kind of disease is very much needed for early diagnosis and treatment.

Abbreviations

MM: Malignant melanoma; PEM: Pigmented epithelioid melanocytoma; FISH: Fluorescence in situ hybridization; CGH: Comparative genomic hybridization; HE: Hematoxylin and eosin; MAP: mitogen-activated protein; TERT: telomerase reverse transcriptase; MELTUMP: Melanocytic tumors of uncertain malignant potential; CMN: Congenital melanocytic naevi

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the parents for publication of case reports and accompanying images.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Authors' contribution

Kailun Xu and Zhaoyun Sun analyzed and interpreted the patient data regarding congenital malignant melanoma. Wenbin Guan, Lifeng Wang and Can Li performed the histological examination of melanoma, and Kailun Xu is a major contributor in writing the manuscript. All authors read and approved the final manuscript."

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Tables

Table 1 Characteristics of the 3 subtypes of congenital malignant melanoma

Variable (n=29)	Placental (n=4)	GCMN (n=12)	De novo (n=13)
Age at diagnosis, y			
Range	1.6-8	birth-7	birth-12
Mean	0.7	0.7	3.36
Median	5	birth	3.25
Gender			
Male	3	8	9
Femle	1	4	4
Race			
Caucasian	2	6	9
Non-causian	2	6	4
Primary leion site			
Scalp/neck	1	5	3
Viscera metastasis	3	0	0
Maternal melanoma history			
	4	0	0
Follow-up, m			
	8.4	1.2	98.3

Figures

Figure 1

The mass was in the occipital scalp and there were no ulceration and bleeding of the skin overlying the mass.

Figure 2

The images showed the mass was hyperintense on T1WI, both hypointense and hyperintense on T2WI, slightly hyperintense on DWI.

Figure 3

The tumor was dark purple in color and was well demarcated.

Figure 4

Histological findings. A. Excisional mass showed epithelioid to spindle cells were arranged in an ill-defined fascicular pattern (HE, ×100). B. Immature melanocytes infiltrated adipose and fibrotic tissue (HE, ×100). C. Vascular invasion of tumor cells can be seen (HE, ×200). D. Cells contained abundant cytoplasmic melanin pigment (HE, ×200). E. The nuclei were uniform without severe cytologic atypia (HE, ×200). F. 2 mitotic figures at a high power field (HE, ×400).

Figure 5

Immunohistochemical staining after melanin bleach. Tumor was weakly positive for (A) HMB45 antigen (HE, ×400), (B) S100 antigen (HE, ×400), (C) MelanA antigen (HE, ×400), (D) A Ki67 showed a focally elevated proliferation rate, although not more than 10% (HE, ×400) and was positive for (E) P16 antigen (HE, ×400), (F) RB antigen (HE, ×400) and (G) P53 antigen (HE, ×400).

Figure 6

FISH showing amplifications in all 4 FISH probes (A) the centromeric portion of chromosome 6 (Cep6), aqua signals, (B) 6q23 (MYB), gold signals, (C) 6p25 (RREB1), red signals, (D) 11q13 (CCND1), green signals.

Figure 7

Ultrasound showed a well-defined mass with both solid and cystic echos at the right shoulder.

Figure 8

The mass was blueish in color and there were ulceration and minimal bleeding of the overlying skin.

Figure 9

Morphology and immunohistochemical stains.

A/B. The lesion presented as melanocytes arranged in nests and sheets, with erosion and ulcer of the overlying epidermis. Lesional cells were large spindle to epithelioid cells with cytoplasmic melanin pigment (HE, ×40 (A), ×100(B)).

C. Moderate to severe cytologic atypia was present in the form of nuclear enlargement and irregularity, and nucleoli. Frequent abnormal mitotic figures were present (HE, ×400).

D. The lesion was strongly HMB45 protein positive (HE, ×200).

E. S100 protein strongly and diffusely stained the lesional cells (HE, ×200).

F. Ki67 index was 25% (HE, ×200).