Extraosseal Ewing Sarcoma as a Rare Cause of the Blueberry Muffin Baby Syndrome: A Case Report and the Review of the Literature

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Abstract: The blueberry muffin baby syndrome can be caused by a variety of entities, both neoplastic and nonneoplastic. We present a rare case of this syndrome: congenital extraosseal Ewing sarcoma. The patient was a blueberry muffin baby with a retroperitoneal tumor, whose cells were negative for neuronal markers and CD-99 immunohistochemically but were positive for a breakpoint in EWSR1 gene. This tumor could be one of the most primitive/undifferentiated examples in the Ewing/peripheral primitive neuroectodermal tumor family.

Key Words: blueberry muffin baby syndrome, Ewing sarcoma (Am J Dermatopathol 2011;33:733–735)

INTRODUCTION

We report an unusual case of a newborn with a disseminated congenital extraosseal Ewing sarcoma presenting as blueberry muffin baby.

CASE REPORT

A baby girl from the first uncomplicated pregnancy, with no pathology on prenatal ultrasound and uneventful family history was born with multiple blue macules on skin. She had normal birth weight, no signs of stigmatisation, and no problem with postnatal adaptation. On discharge from the maternity hospital, a checkup by dermatologist was recommended. Dermatologist diagnosis was multiple hemangiomas of the skin, and a close follow-up was recommended. After the next checkup with dermatologist at the age of 3 weeks, the clear progression of the skin lesions (Fig. 1) together with failure to thrive led to a prompt admission to the pediatric oncology department. Tumor of the size 5 × 6 × 5 cm infiltrating the mesentrium was found at the left side of the retroperitoneum, and multiple smaller lesions in liver, lungs, mediastinum, bones, brain, and cerebrospinal meninges were observed as well. Biopsy of skin nodule and biopsy of the bone marrow were performed. Bone marrow was infiltrated up to 80% with small round blue cells. The biopsy from the skin nodule showed an infiltrate consisting of groups and sheets of small uniform round cells with high nuclear/cytoplasmic ratio. Nuclei had smooth chromatin and inconspicuous nucleoli (Fig. 2). The cells were mitotically active with proliferation rate of about 95% according to Ki-67. The neoplastic cells initially displayed immunohistochemical positivity for bcl-2 protein and negativity for vimentin, CK1/3, synaptophysin, chromatogranin, neuron-specific enolase, S100, glial fibrillary acidic protein, desmin, actin, MyoD1, CD 99, CD 3, CD 20, CD 117, CD 43, CD 45, CD 45RO, myeloperoxidase, lysozym, CD 68, nespecific esterase, and mast cell tryptase. Laboratory tests were not specific and were abnormal for: Hb 76 g/L, platelets 66 × 10⁹, leu 9 × 10⁹, lactate dehydrogenase of 32, 55 mmol/L, and Ca 2.79 mmol/L.

Whole body scan metaiodobenzylguanidine 105 MBq 123I scan was positive in the area of retroperitoneal tumor and in lungs but not in the bones. Whole body scan of skeleton 340 MBq Tc MDP was negative. Patient’s serum catecholamines were within normal levels repeatedly. The fluorescence in situ hybridization with the specific probe for n-myc gene showed 2 signals. Analysis of messenger RNA levels of tyrosine hydroxylase and neuron-specific protein PGP9.5 genes showed normal and elevated levels for the latter one. High levels of the latter marker, despite usually appearing in neuroblastoma, were described for several tumor types and leukemias. Moreover, whereas tyrosine hydroxylase real-time polymerase chain reaction accuracy was found to be satisfactory, that of PGP9.5 was very low.

Pathologist diagnosis was that of very immature innate neuroblastoma, although the absence of organoid growth of the neoplastic cells and especially negativity of the neuroepithelial markers did not fit the diagnosis. The clinical picture of initial presentation of the disease (the maximum tumor mass in retroperitoneum, the character of the metastases, and blueberry muffin type skin nodules) together with positive scan of metaiodobenzylguanidine rather supported the diagnosis of neuroblastoma.

At the age of 3 weeks, chemotherapy according to the Children’s Oncology Group protocol for High-Risk Neuroblastoma, cyclophosphamide–topotecan was started. After initial partial response, she started to progress since the third cycle of neuroblastoma chemotherapy. After 10 weeks of the treatment, there was an obvious disease progression in the skin, bone marrow, and cerebrospinal fluid. The unusually progressive course of the disease questioned the diagnosis of neonatal neuroblastoma. Dr. Hiroyuki Shimada kindly reviewed the case and ruled out the neuroblastoma. The child died at the age of 4 months.

The autopsy documented retroperitoneal tumor with infiltration of brain, leptomeninges, lungs, liver, intestine, abdominal
lymph nodes, bone marrow, subcutaneous soft tissues, and skin. The immediate cause of death was multiorgan failure.

Finally, extended panel of molecular cytogenetic tests including a probe for a breakpoint in \textit{EWSR1} gene [by fluorescence in situ hybridization analysis using Vysis LSI EWSR1 (22q12) dual color, break apart rearrangement probe] (Fig. 3) proved Ewing sarcoma and brought unexpected solution of the case.

\textbf{DISCUSSION}

The term blueberry muffin baby was initially coined by pediatricians to describe cutaneous manifestations observed in newborns infected with rubella during the American epidemic of the 1960s. The differential diagnosis of neonatal blueberry muffin–type skin lesions can be divided into several broad categories. The first category includes malignancies, both hematological and nonhematological (“congenital leukemia cutis”: acute myeloid leukemia, less often acute lymphoblastic/precursor leukemia, Langerhans cells histiocytosis, congenital neuroblastoma, alveolar rhabdomyosarcoma, and disseminated congenital xanthogranuloma), as published so far.

The second group of diseases includes benign neoplasms, that is, multiple lymphangioendotheliomatosis with thrombocytopenia and blue rubber bleb nevus syndrome.

The third group would include nowadays rather sporadic infectious causes: toxoplasmosis, rubella, cytomegalovirus, herpes, blueberry red ringspot virus.

Finally, the fourth group includes extramedullary hematopoiesis in severe fetal and neonatal anemia of any cause in general (hemolytic disease AB0 or Rh incompatibility, twin-to-twin transfusion syndrome, hereditary spherocytosis). Extramedullary hematopoiesis can indeed be a basis for purpuric lesions in patients with bone marrow malignancies, but in our patient, the purpuric lesions were the result of skin infiltration by the neoplastic process.

Acute leukemia was excluded by both negativity of relevant immunohistochemical markers and by extensive search for known chromosomal markers of leukemias.

RNA-binding protein Ewing’s sarcoma is a protein that in humans is encoded by the \textit{EWSR1} gene. This gene encodes a putative RNA-binding protein. Mutations in this gene,
specifically a t(11;22)(q24;q12) translocation, are known to cause Ewing sarcoma and other members of the Ewing family of tumors. The Ewing family of tumors is a group of malignancies that includes Ewing sarcoma of bone, extraosseous Ewing tumors, primitive neuroectodermal tumors (primitive neuroectodermal tumor or peripheral neuroepithelioma), and Askin tumors (primitive neuroectodermal tumor of the chest wall). These tumors all come from the same type of stem cell.

The blueberry muffin type of rash in a neonate is a potentially life-threatening condition with severe sequelae and requires extensive and prompt differential diagnostic work-up. Ewing sarcoma should be included in the differential diagnosis when dealing with a blueberry muffin baby with retroperitoneal tumor.

To our knowledge, the tumor of this case could be one of the most primitive/undifferentiated examples in the Ewing/peripheral primitive neuroectodermal tumor family as the neoplastic cells were negative for neuronal markers and CD99 immunohistochemically, and there are no similar cases reported in the literature.

REFERENCES