A Case Report of a Cerebellar Neuroblastoma in a p53 Null Mutation Mouse

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ABSTRACT. We report a case of cerebellar neuroblastoma in a 19-week-old p53 null mutation mouse. A white and soft mass was observed at the cerebellar vermis. Histologically, the tumor consisted of solid growth of round to oval pleomorphic cells with frequent mitotic figures. While there were no typical cellular arrangements of embryonic neurogenic tumors, such as Homer-Wright rosette, perivascular pseudosarote, or streaming of neoplastic neurocytes, small populations of the neoplastic cells were immunohistochemically positive for synaptophysin, microtubule-associated protein 2, S-100 and nestin. Both glial fibrillary acidic protein and vimentin were entirely negative in the neoplastic cells. Based on the biological characteristics of neoplastic cells, this tumor was diagnosed as neuroblastoma of the cerebellar origin.

KEY WORDS: brain tumor, diagnosis, immunohistochemistry, p53 knockout mouse.

This report describes a case of cerebellar neuroblastoma in a p53 null mutation female mouse. The target p53 gene encodes a transcription factor that is important in multicellular organisms, where it plays a role for gate-keeper functions to act as a tumor suppressor that is critical for preventing development of cancer [2]. On week 19 of age, the corresponding animal revealed signs of ataxia, and was subjected to complete necropsy. At necropsy, cerebellar surface was slightly swollen, and after fixation, a white and soft mass was found at the deep area of the cerebellar vermis on the coronal slice. No other particular pathologic abnormalities were observed in this animal. The mass was fixed in 10% neutral buffered formalin for 3 days at room temperature, trimmed, dehydrated, and paraffin embedded, and 4 µm sections were stained with hematoxylin and eosin (HE). As immunohistochemical analysis, avidin-biotin-peroxidase complex (ABC) technique was applied using antibodies against synaptophysin (monoclonal mouse antibody, clone SY38; 1/1,000 dilution; Chemicon International, Temecula, CA, U.S.A.), microtubule-associated protein 2 (MAP2; monoclonal mouse antibody, clone G-A-5; 1/200 dilution; Chemicon International, Temecula, CA, U.S.A.), neuron-specific enolase (NSE: polyclonal rabbit antibody; 1/150 dilution; Lab Vision, Fremont, CA, U.S.A.), S-100 (polyclonal rabbit antibody; 1/1 dilution; Chemicon International, Temecula, CA, U.S.A.), microtubule-associated protein 2, S-100 and nestin. Both glial fibrillary acidic protein and vimentin were entirely negative in the neoplastic cells. Based on the biological characteristics of neoplastic cells, this tumor was diagnosed as neuroblastoma of the cerebellar origin.

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cerebellum. According to the World Health Organization (WHO) International Histological Classification of Tumors of the Nervous System of Domestic Animals [4], candidates for diagnoses of embryonal tumor masses in the cerebellum include medulloblastomas, neuroblastomas and ependymoblastomas. As for the present case, ependymoblastoma could be ruled out based on the histological components that had neither ependymal cells nor ependymal rosettes. On the other hand, small population of neoplastic cells showed positive immunoreactivity for neuronal markers suggestive of the partial neuronal differentiation potential, but the neoplastic cells were entirely negative for glial markers, such as GFAP and vimentin. In the literature on the Pathology of the Mouse, neoplasms of embryonal or undifferentiated cells in the central nervous system are not well classified, and the corresponding tumors are regarded as primitive neuroectodermal tumors, when co-expression of more than one type of intermediate filament is observed in the same neoplasm [7]. Such tumors arising from the cerebellum are named as medulloblastomas. However, classification of

Fig. 1. A. Low-power view of the cerebellar tumor developed in a p53 null mutation mouse. Tumor is located at the cerebellar vermis with growth primarily expansive, but invasion to the pons through infiltration to the cerebellar peduncle is evident. HE. ×12.5. B. High-power view of neoplastic cells consisting of uniformly darkly stained pleomorphic round to oval cells with small to scant cytoplasm showing ill-defined cell borders and single hyperchromatic nuclei containing one or two distinct nucleoli. Apoptotic as well as mitotic figures are evident. HE. ×400. C. Small fraction of cells shows positive intercellular immunoreactivity for synaptophysin. ×600. D. Scattered positive cells (arrows) for MAP2 in the cytoplasm. ×600. E. A few populations of neoplastic cells show positive immunoreactivity for nestin in the cytoplasm. ×600. F. Neoplastic cells are entirely negative for GFAP as shown in the present figure with the micrographic view identical to the Plate E. Note positive immunoreactivity of cellular processes of reactive astrocytes. Inset shows the strong immunoreactivity in the reactive astrocytes with prominent cellular processes at the periphery of the tumor. ×600 (Relative magnification of the inset: ×250).
embryonal tumors with single differentiation potential as in the present case is lacking in this textbook. According to the WHO classification criteria above mentioned [4], medulloblastomas are defined as embryonal neoplasms with both neuronal and glial differentiation potentials, whereas neuroblastomas are those with limited neuronal differentiation. Therefore, we consider that the present case could be diagnosed as a cerebellar neuroblastoma according to the WHO classification criteria [4].

Developing radial or Bergmann glia have shown to express nestin intermediate filament protein in addition to neuronal stem cells [11]. In addition, recent studies have shown that cultured nestin-positive cells from postnatal mouse small bowel have a potential to differentiate into neurons, glia, and smooth muscle cells suggesting that nestin expression in glial cells originate from neuronal stem cells [9]. However, nestin-positive cells in the present study lacked expression of GFAP and vimentin, and therefore, these cells lacked evidence for differentiation into glial cells.

A highly frequent induction of the medulloblastomas was reported in Rb conditional knockout mice in addition to p53 null mutation [6]. In addition, p53 null mutations dramatically accelerate medulloblastoma formation in Drosophila gene Patched (ptc1) heterozygous or poly (ADP-ribose) polymerase (PARP-1) null animals [10]. In the latter report, biological characteristics of the lesion development were well examined, and lesions typically started on the outer surface of the cerebellum from remnant granule cell precursors of the developmental external germinal layer [10]. In the present case, on the other hand, the tumor was generated from the deep area of cerebellar vermis, forming an extensively infiltrative tumor cell mass lateral to the 4th ventricular surface. Despite extensive examination of the tumor mass with existing cortical layers of the cerebellar vermis using immunostained tissue specimens for neuronal markers, anatomical relationship between the tumor mass and existing cerebellar lobule could not be observed in the present case. This observation may suggest that the cell origin of neoplastic transformation in the present case could be neuronal stem cells locating at the ventricular zone in the roof of the 4th ventricle, different from the remnant granule cell precursors in the medulloblastomas generated in PARP-1/p53 double null mice [10].

In addition to predominant neuronal differentiation characteristics, scattered GFAP-positive cells were observed in a few medulloblastomas of PARP-1/p53 double null mice [10]. On the other hand, mice lacking p53 without manipulation of other genes rarely develop brain tumors [3]. Therefore, due to rare frequency of the induction, it would be difficult to investigate variations in differentiation potentials in tumors which developed in the cerebellum of mice targeting p53 gene alone. It should be noted that cases diagnosed as astrocytomas or gliomas containing astrocytic components in rats or mice of both spontaneous and chemically-induced cases usually lack GFAP expression, suggesting alterations in phenotype change by neoplastic transformation [5, 8]. According to the WHO Classification of Tumors of the Central Nervous System [1], primary embryonal tumors developed in the cerebellum are classified into the entity of medulloblastomas, irrespective of the direction of differentiation potentials. This is because the medulloblastomas are much more common than supratentorial embryonal tumors in the childhood brain tumors [1], and therefore, have long been well-established as a clinico-pathological entity. Thus, cerebellar neuroblastomas classified on the basis of the domestic animal classification scheme can be classified into “medulloblastomas” in humans.

REFERENCES


