CASE REPORT

Large cell/anaplastic medulloblastoma with myogenic, melanotic and neuronal differentiation: A case report of a rare tumor

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Abstract

Medulloblastoma is an embryonal neuroepithelial tumor of the cerebellum and is the most common malignant central nervous system tumor in children. Different histological variants and patterns have been described. The classic variant represents the majority of cases. This report describes a rare case of large cell/anaplastic medulloblastoma with myogenic, melanotic and neuronal differentiation arising in the cerebellum of a 3-year-old boy who presented with headache and vomiting. Magnetic resonance imaging demonstrated a heterogeneously enhanced lesion in the fourth ventricle. Surgical resection of the tumor was accomplished, but a residual tumor was left behind because of the involvement of the brainstem. Postoperatively, the patient received chemotherapy and radiotherapy. Currently, 20 months after treatment, the patient has survived without further progression. Pathological examination revealed a high grade primitive neuroepithelial tumor with foci of myogenic features, melanin containing epithelial elements and ganglion-like cells, which were confirmed by immunohistochemistry.

INTRODUCTION

Embryonal tumors of the central nervous system (CNS) are the most common malignant brain neoplasms in children and include different distinct types. Of these, medulloblastomas are the most common and account for 12-25% of all CNS tumors and 40% of all malignant brain tumors in this age group. They are tumors of the cerebellum, with 75% arising in the vermis. A male predilection of 1.5:1-2:1 has been noted. [1] The World Health Organization (WHO) currently distinguishes five variants of medulloblastoma: Classic medulloblastoma, desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, anaplastic medulloblastoma, and large cell medulloblastoma. Medulloblastoma with myogenic and/or melanotic differentiation is very rare, with only eight cases reported so far. [3],[4],[5],[6],[7] Anaplasia or areas of large cell components have only been described in one of these reports. [5] We present this case due to its extreme rarity.

CASE REPORT

A 3-year-old boy presented with severe headache, vomiting, and excessive sleepiness for 2 weeks. He sought medical advice in Jizan where he was initially shunted and referred to King Fahad Medical City for further investigation and management. On physical examination, he was lethargic and had an unsteady gait. Magnetic resonance imaging (MRI) studies of the brain revealed a heterogeneously enhanced posterior fossa tumor arising from the fourth ventricle with no spinal seeding (Figure 1). The patient underwent tumor resection under neuronavigation intraoperative MRI guidance and received postoperative chemotherapy and radiotherapy. The patient is currently alive, 20 months after treatment, with no progression of the residual tumor (Figure 1).

Histologically, the specimen showed small fragments of tan gray and white tissue, and measured approximately 3 cm in total. Histological examination of the formalin-fixed, paraffin-embedded and hematoxylin, and eosin-stained tissue sections revealed a dense cellular neoplasm consisting mainly of sheets of cells with a high nuclear to cytoplasmic ratio, nuclear molding and a fine chromatin pattern (Figure 2a). Areas of large cells with large vesicular nuclei and prominent nucleoli were also observed. In addition, there were areas of large cells, with abundant cytoplasm and Nissl substance scattered in an abundant neuropil background, which are representative of neuronal differentiation (Figure 2b). Immunohistochemical staining showed that these cells were positive for neuronal markers such as synaptophysin and CD56. There were also foci of tumor showing strap cells with eosinophilic cytoplasm and Nissl substance scattered in an abundant neuropil background, which are representative of neuronal differentiation (Figure 2b). Other areas displayed cords, tubules and single cells with intra-cyttoplasmic pigment similar to melanin (Figure 2c). The strap cells were immunohistochemically positive for desmin which is consistent with myogenic differentiation (Figure 3). These structures were immunopositive for cytokeratin AE1/AE3 and HMB45 which are indicative of melanotic differentiation. Increased mitotic activity and apoptosis were seen in addition to brisk Ki67 proliferation index (50-60%). INI1 immunohistochemical stain was negative. Based on these findings, the diagnosis of large cell/anaplastic medulloblastoma with myogenic and melanotic differentiation was made (Figure 3).

DISCUSSION

C-myc amplification on cytogenetic studies was negative.

DISCUSSION

http://www.ijpmonline.org/printarticle.asp?issn=0377-4929;year=2014;volume=57;issue=2;spage=294;epage=297;aulast=Fathaddin;atitle=Large%20cell/anaplastic%20medulloblastoma%20with%20myogenic%2C%20melanotic%20and%20neuronal%20differentiation%3A%20A%20case%20report%20of%20a%20rare%20tumor
Large cell medulloblastoma was described in 1992 by Giangaspero et al. It is characterized by enlarged neoplastic cells with large, round vesicular nuclei and prominent nucleoli. Large areas of necrosis along with high mitotic and apoptotic rate are common findings. [8] In a large series from a pediatric oncology group, 70% of large cell tumor cases had tumors with marked nuclear atypia and lacking prominent nucleoli (anaplasia) were observed either alone or in association with the morphological characteristics of typical large cell medulloblastoma. Because this morphological finding was associated with similarly aggressive biological behavior, the researchers advocated using the term "large cell/anaplastic medulloblastoma" for this variant. [8] This variant, which accounts for 20-25% of all medulloblastoma cases has a high rate of c-myc amplification and a significant association with poor clinical outcome. [8] In a study performed on seven cases of large cell/anaplastic medulloblastoma, six of the cases had cerebrospinal fluid dissemination on initial presentation. In two of the cases, the large cell/anaplastic features only appeared late in the course of the disease, after tumor recurrence and/or systemic metastasis. Isochromosome 17q, the most common genetic abnormality occurring in cases of classic medulloblastoma, was found in five of six cases, suggesting that this may be a common early event for both classic medulloblastoma and the large cell/anaplastic variant. Amplification of c-myc was found in three of six cases tested. [8]

Medulloblastoma was first described in 1939 by Marieso and Goldstein and up to now fifty cases have been reported in the literature. They tend to have similar clinical behavior to classical medulloblastoma when treated with the same therapeutic strategy. Histologically, medulloblastomas exhibit loci of rhabdomyoblastic differentiation, as evidenced by abundant eosinophilic cytoplasm and occasionally, visible cross-striations corresponding to strap cells. Rhabdomyoblastic differentiation can be confirmed by immunohistochemical staining for myogenin, desmin, and actin. [8][9] It has been proposed that medulloblastomas may originate from undifferentiated neural crest cells, ectomesenchyme or variations of malignant teratoma. [5]

Melanotic medulloblastoma is a very rare tumor with only 11 reported cases since its first description by Fowler and Simpson in 1962 as a "malignant melanin-forming tumor of the cerebellum." Histologically, neuroepithelial cells are seen in tubulopapillary formations with cytoplasmic melanin pigment. [5] The histogenesis of these tumors is controversial. Some authors consider these tumors as variants of melanotic neuroectodermal tumors of infancy; however, the latter behave usually in a benign fashion. [7] Others have suggested that melanotic medulloblastoma is a hybrid tumor, in which the pigmented cells are of neural crest origin and the nonpigmented cells are of neuroectodermal origin. [7][8]

While seven reports have described myogenic and melanotic differentiation in medulloblastoma, there has only been one report of myogenic and melanotic differentiation in a large cell/anaplastic variant. Polydorides et al. have reported a large/anaplastic medulloblastoma with myogenic and melanotic differentiation arising in a 2-year-old boy who presented with vomiting and gait ataxia and underwent an aggressive clinical course. Molecular genetic analysis of the tumor showed amplification of the c-myc gene in the tumor cells along with the gain of 17q. The patient received postoperative chemotherapy; however, 10 months later, he had recurrent/refractory disease with diffuse leptomeningeal involvement and the family declined further treatment. To the best of our knowledge, this was the first case to have this combination in a large cell/anaplastic variant. [5] The prognosis of medulloblastoma depends on several parameters in addition to the pathologic variant which includes: Status of resection, extent of spread, age and molecular type. In our case, amplification of the c-myc gene was not detected and the patient has been stable for 20 months following surgery with no progression or recurrence of the disease.

The first case of myogenic and melanotic differentiation in medulloblastoma was reported in 1973 by Banerjee et al. [7] The second case was reported by Dunwicker et al. in 1981, they reported a case of a 3-year-old boy with a tumor containing elements of medulloblastomatous, rhabdomyosarcomatous and melanotic tissues. [7] In 1987, Kalimo et al. have reported a case of a 5-year-old girl with a primitive neuroectodermal tumor demonstrating neuronal, myogenic and melanotic differentiation. The tumor recurred following surgery and radiation and the child died within 6 months. [7] In 2006, Mehta et al. described a pigmented medulloblastoma in a 3-year-old girl who presented with dysarthria, urinary incontinence and difficulty in walking. [6] A case of a 23-month-old male with cerebellar medulloblastoma with melanotic tubular structure reported in 2008 by Nozza et al. The patient was treated with surgery and postoperative chemotherapy and radiotherapy and at 24 months after diagnosis, the child achieved complete remission. [4] In the same year, Sakata et al. have reported a case of a 6-year-old boy who presented with severe morning headaches, which were due to a medulloblastoma that demonstrated classic, myoblastic, neuronal, glial, and melanotic differentiation. [6] The patient did not show any signs of recurrence during the follow-up period following surgery, radiation, and chemotherapy.

The final example of a medulloblastoma with myogenic and melanotic differentiation was reported by Borcek et al. in 2010. This case occurred in a 4-year-old boy who presented with headache and vomiting. [7]

Histological differential diagnoses include atypical/rhabdoid teratoid (AT/RT) tumor, rhabdomyosarcoma and medullopithelioma.

The presence of epithelial elements and cells with rhabdoid features in our case warranted the consideration of AT/RT. These tumors harbor mutations in the hSNF5/INI1 gene and do not show immunohistochemical staining for this gene product. However, nuclear immunostaining for INI1 was present in our case. Epithelial structures with melanin pigments are not features of rhabdomyosarcoma. Medullopithelioma typically arises in the cerebrum. Their defining feature is the formation of tubules, ribbons, or less frequently, papillae resembling the epithelial structuring of the primitive neural tube.

CONCLUSION

Large cell/anaplastic medulloblastoma is a rare variant with the best prognosis among medulloblastoma variants. This diagnosis strafes the patient to a high risk group requiring maximal therapy. We described a case of large cell/anaplastic medulloblastoma combining myogenic, melanotic and neuronal differentiation, which is extremely rare. This supports the theory that medulloblastoma arises from stem cells and is in agreement with the current WHO classification, which considers myogenic and melanotic differentiation as patterns that can occur in any variant.

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References


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