Turkish Neurosurgery, 2005, Vol: 15, No: 1, 12-17

Ependymoma With Cartilage Formation: A Case Report

Kıkırdak Formasyonu Olan Ependimoma: Olgu Sunumu

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ABSTRACT

OBJECTIVE: The presence of cartilage and bone in a glial tumor is most unusual. Several mechanisms have been proposed to explain this condition. In some cases, there is a fibrous capsule between tumor tissue and the cartilaginous area together with glial fibrillary acidic protein negativity in cartilage cells; in others, there is no fibrous capsule between cartilage cells and tumor tissue, and the cartilage cells are glial fibrillary acidic protein positive.

CASE REPORT: A 56-year old female with an ependymoma containing a cartilaginous area is reported. The patient had been irradiated 8 years ago. The mechanisms of the occurrence of cartilage in gliomas are reviewed, and the probable effects of irradiation on this condition are discussed.

RESULTS: In our case, there was no fibrous capsule between the ependymoma and the cartilaginous tissue, and the cartilage cells were glial fibrillary acidic protein immunopositive.

CONCLUSION: In this case, it was considered that the cartilage formation resulted from the transformation of neuroepithelial cells to mesenchymal tissue because of the positive response of cartilage cells to glial fibrillary acidic protein and the lack of a fibrous capsule around the cartilaginous area.

KEY WORDS: Ependymoma, glioma, cartilage, metaplasia

ÖZ

AMAÇ: Glial tümörler içinde kıkırdak ve kemik dokusunun bulunması çok nadirdir. Bu durumu açıklamak için değişik görüşler ileri sürülmüştür. Bazı olgularda tümör dokusuyla kıkırdak alan arasında fibröz bir kapsül vardır ve kıkırdak hücrelerinde glial fibriler asidik protein negatiftir; bazılarında ise, kıkırdak hücreleriyle tümör dokusu arasında fibröz kapsül yoktur ve kıkırdak hücreleri glial fibriler asidik protein pozitiftir.

YÖNTEM: Kıkırdak bir alan içeren ependimomalı 56 yaşında bir kadın hasta sunuldu. Hasta 8 yıl önce radyoterapi görmüştü. Gliomalarda kıkırdak doku varlığının mekanizmaları tekrar gözden geçirildi ve bu konuda radyasyonun olası etkileri tartışıldı.

BULGULAR: Ependimoma dokusu ile kıkırdak alan arasında fibröz kapsül yoktu ve kıkırdak hücreleri glial fibriler asidik protein pozitifti.

SONUÇ: Bu olguda kıkırdak hücrelerinin glial fibriler asidik proteine pozitif yanıt vermeleri ve kıkırdak alan çevresinde fibröz kapsül olmaması nedeniyle kıkırdak oluşumunun nöroepitelyal hücrelerin kıkırdak hücrelerine transformasyonuna bağlı olduğu düşünüldü.

ANAHTAR SÖZCÜKLER: Ependimoma, glioma, kıkırdak, metaplazi

Received : 21.04.2004
Accepted : 02.02.2005

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INTRODUCTION

The presence of bony or cartilaginous tissue within a glioma is an exceedingly rare occurrence and has been described in the brain and spinal cord with histological features of ependymomas, papillomas of the choroid plexus, astrocytomas, glioblastomas, and gliosarcomas (2, 12, 14, 15). In 1974, Matthews and Moosy (15) collected 14 cases from the world literature and added 3 of their own. Since then, apart from the 4 cases collected by Kepes et al (12), only sporadic instances have been reported (11, 14, 21).

Several mechanisms have been proposed to explain the presence of bone or cartilage within gliomas such as metaplasia of connective tissue, transformation of neuroepithelial cells to mesenchymal tissue, or tissue of mixed mesenchymal-neuroepithelial nature (12, 14). Unfortunately, there are only a few reported cases and these hypotheses cannot be satisfactorily proven.

A case with ependymoma containing a cartilaginous area, previously treated by radiotherapy 8 years ago, is reported and possible mechanisms of chondroid metaplasia are reviewed.

CASE REPORT

A 56-year old woman was admitted with complaints of headache of a few months duration. She had been operated on for a right occipital tumor diagnosed as carcinoma metastasis at another center and then irradiated 8 years ago. The primary carcinoma focus could not be found at that time. There was no residual tumor on the early postoperative computerized tomographic (CT) scan. There was a heterogeneous, right temporooccipital cystic tumor, 5 cm in diameter, causing cerebral edema and a midline shift on current CT and magnetic resonance imaging (MRI) scans. The tumor was heterogeneously enhanced after intravenous contrast injection (Figure 1A and B). The patient was operated on and the tumor was totally extirpated.

Histologically, tumor tissue containing perivascular pseudorosettes and widespread necrosis areas were seen on hematoxylin-eosin (HE) preparations (Figure 2A and 2B). There were vessels with hyalinized walls in some areas. Reticulin fibrils were demonstrated by the silver impregnation technique, i.e., Gomori stain. The tumor cells displayed a strong immunopositive response to glial fibrillary acidic protein (GFAP) (Figure 2C), but only

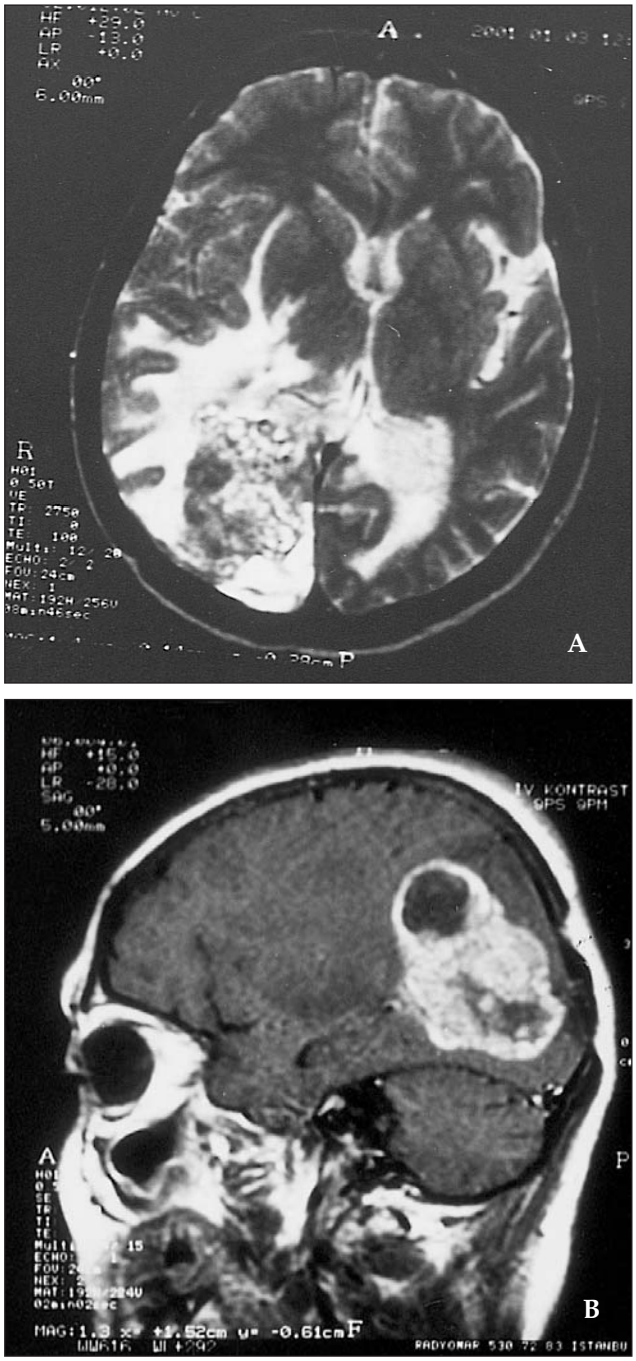

Figure 1: Axial T2-weighted (**A**), and sagittal T1-weighted (**B**) magnetic resonance sections of the patient.

a small number of tumor cells were positive judged by the intracytoplasmic granular pattern to epithelial membrane antigen (EMA), and these showed a negative response to cytokeratin. There was an area displaying chondroid metaplasia, which seemed quite distinct from the tumor tissue but was unencapsulated (Figure 2D). Cells within this area displayed a positive response to GFAP, but negative

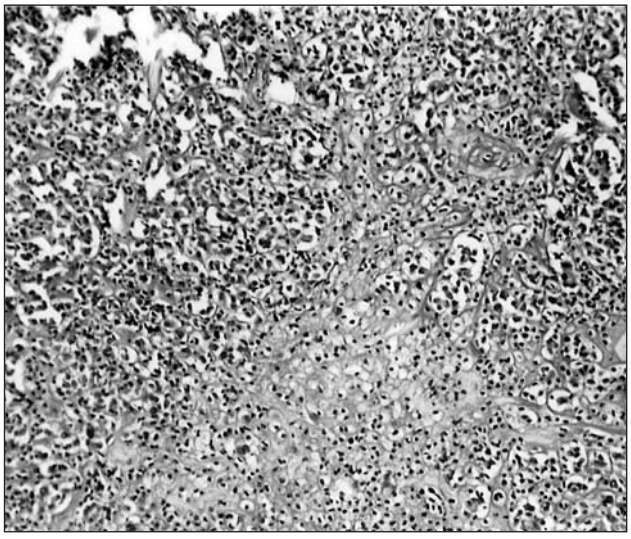

Figure 2 A- Histological section of the tumor representing typical cellular ependymoma features (HE x125).

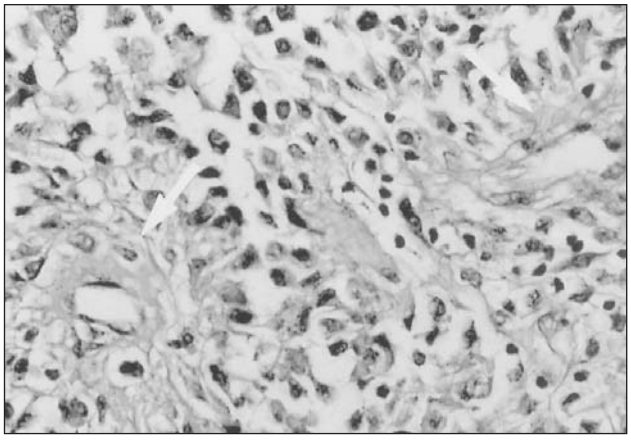

Figure 2 B- Perivascular pseudorosettes (white arrows) (HE x500).

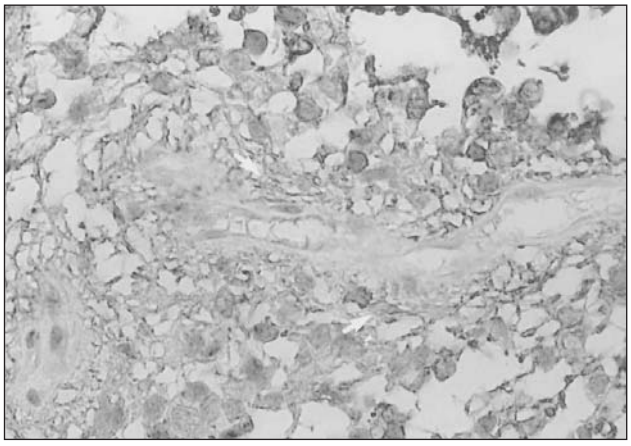

Figure 2 C- Strong immunopositive response (white arrows) on the cell extensions reaching to the vessel wall of the cells on the pseudopapillary structures (GFAP x500).

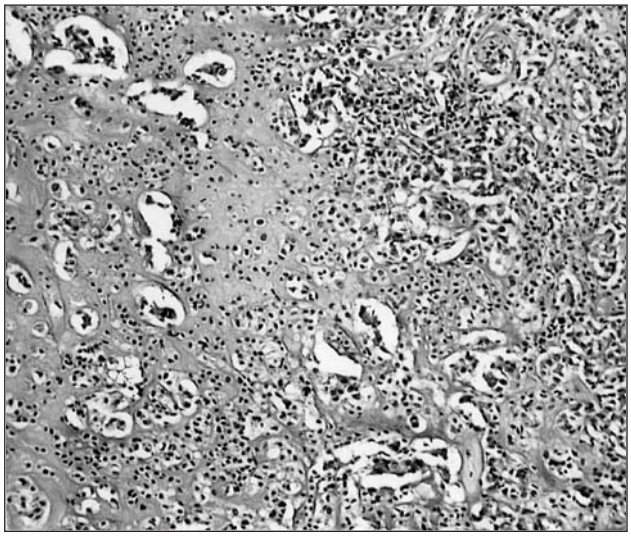

Figure 2 D- Chondroid area (left side of the Figure) in the cellular ependymoma (right side of the figure) (HE x125). Note the lack of a fibrous capsule between the ependymoma and the chondroid area.

response to EMA. The tumor was diagnosed as an ependymoma with cartilage formation. The former histological preparations diagnosed as carcinoma metastasis 8 years ago were reevaluated. Microscopic examination revealed a tumor containing perivascular pseudoresettes and wide necrosis areas (Figure 3A). The tumor cells displayed an immunonegative response to GFAP, but strong intracytoplasmic granular positivity to EMA on their apical surfaces (Figure 3B). Cartilaginous areas were not present. It was thought that the tumor might have been misdiagnosed as carcinoma. Conclusively, no evidence of a primary focus was present in either occasion. Moreover, an eight-year survival is incompatible with such a histologic diagnosis.

There were no complications after surgery. New history revealed that the patient had admitted to the center where the first operation had been performed for headache 10 months later. She had been operated on again for tumor relapse, and the tumor had been diagnosed as ependymoma but without cartilaginous transformation. There were no complaints 15 months after the operation.

DISCUSSION

The presence of bone or cartilage in a glioma is most unusual. Matthews and Moosy (15) collected 14 cases from the world literature and added 3 of their own. Since then, apart from the 4 cases collected by Kepes et al (12), only sporadic instances have been reported. Several mechanisms have been proposed

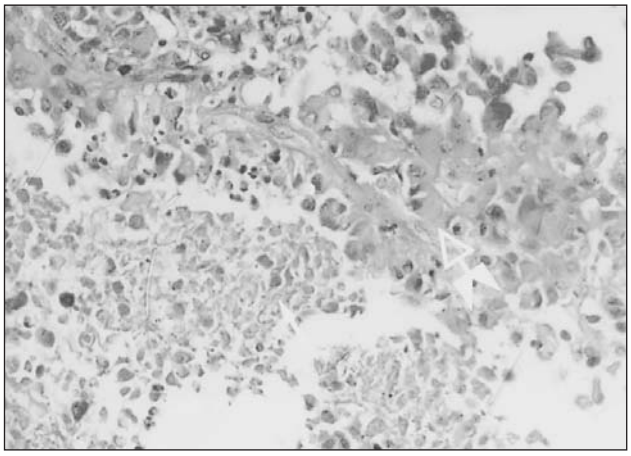

Figure 3 A- The tumor tissue containing necrotic area (filled white arrow) and pseudopapillary structures (empty arrow) (HE x310).

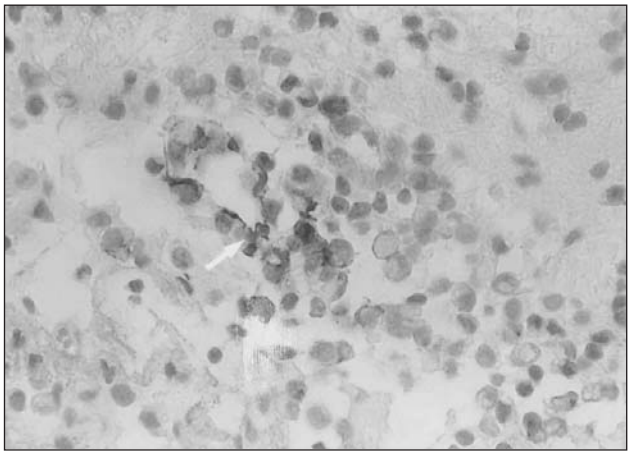

Figure 3 B- Intracytoplasmic granular EMA positivity (red lines pointed with white arrow) on apical surfaces of tumor cells (EMA x500).

to explain this condition such as chondroid metaplasia of connective tissue within the tumor (14, 15, 20, 21, 22, 23), transformation of neuroepithelial cells to mesenchymal tissue (12, 13, 18, 19, 24), mixed mesenchymal-neuroepithelial nature such as gliosarcomas (2, 14), teratomatous nature of the cartilaginous tissue (12, 14), heteroplasia (12), and ossification as an end stage of mucoid degeneration (11, 12, 14). However, given the rarity of these findings, no single explanation of the presence of cartilaginous or bony tissue within a glial tumor has yet gained acceptance.

The most commonly accepted hypothesis is chondroid metaplasia of connective tissue within the tumor (14, 15, 20, 21, 22, 23). Patches of ossification of cartilaginous metaplasia have been described in hematomas and in parasitic infections (8, 16, 25). In these conditions, it is the granulation tissue around the necrotic-hemorrhagic lesion that undergoes metaplasia (14). In a glioma, the cells of mesenchymal origin are the main fibroblasts and endothelial cells of blood vessels which, in response to stimuli as yet unidentified but perhaps attributable to growth factors produced by the glioma, might undergo chondroid metaplasia. Maleci et al (14) concluded that some findings in their case support this hypothesis in a few histological sections in which blood vessels with thickened walls were the site of mucopolysaccharide accumulation.

Another interesting hypothesis is transformation of neuroepithelial cells to mesenchymal tissue. In the description of their four cases, Kepes et al (12) drew attention to the presence of transitional elements between glial and cartilaginous cells and to the presence of GFAP-positive chondrocyte-like cells. They concluded that the cartilage arose from chondroid metaplasia of the glioma cells. Transition from astrocytic to cartilaginous elements, characterized by increasing deposition of chondroid ground substance between the astrocytes and gradual morphologic transformation of glial cells to more rounded forms with a vacuolated cytoplasm, indistinguishable from chondrocytes of mesenchymal origin, was observed in all four tumors. Many of these cells had retained positive staining for GFAP by the immunoperoxidase method, attesting to their astrocytic nature. The process appears to be analogous to changes seen in pleomorphic adenomas of the salivary glands where cells of epithelial lineage become surrounded by basophilic matrix material making the epithelial cells appear as chondrocytes. Such cartilage is histologically indistinguishable from the more conventional cartilage of mesenchymal origin (12). According to Kepes et al (12), the production of cartilage by neoplastic astrocytes may be related to their ability to secrete, under certain circumstances and occasionally in large amounts, basement membrane material and other forms of mucopolysaccharides, which may become condensed to form a chondroid ground substance.

There are some clinical and laboratory findings supporting this hypothesis. Soeur et al (24) reported a case of intramedullary ependymoma producing collagen. Kishikawa et al (13) confirmed by

immunohistochemical studies that glial cells may produce myxoid material related to chondroitin sulphate A and C. Norling et al (18) reported the presence of a chondroitin sulphate proteoglycan capable of forming large aggregates with hyaluronic acid in cultures of human glial and glioma cells. The major difference between the product of these glial/glioma cells and cartilage chondroitin sulphate proteoglycans relates to the glycan rather than to the protein moiety of the molecule. Perides et al (19) isolated a glial hyaluronate binding protein (GHAP) from human brain white matter and also from a surgically removed glioma showing a striking similarity to cartilage proteins. Other hyaluronic acid binding proteins like the one isolated by Perides et al have been isolated from human brain6, from Ranvier nodes of central and peripheral nerve fibers as well as connective tissues and particularly the stroma of tumors (7), and from human brain and spinal cord white matter where it had colocalized with GFAP (3).

The main supporting point of the hypothesis suggesting transformation of neuroepithelial cells to mesenchymal tissue is the positive response of the cells to GFAP in the cartilaginous area of the glial tumor as in the cases presented by Kepes et al (12). However, no such transition was seen in another example of cartilage formation in a fourth ventricle glioma (23). An ependymoma, which was surrounded by a fibrous capsule, and in which cartilage had developed in the adventitia of blood vessels, also failed to show evidence of GFAP staining in any of the tissue elements in the report of Kepes et al (12). Normal, developing and neoplastic glial cells may be capable of differentiation to cartilage under certain specific and exceptional circumstances (2); and a positive response to GFAP may be lost during advanced differentiation. Jacobsen and Papadimitriou(10) reported mesodermal differentiation with evident cartilage formation of cell lines obtained from human gliomas inoculated into nude mice. They did not observe positive staining for GFAP or S-100 protein in these cells. Ducatman and Scheithauer (9) reviewed a series of malignant peripheral nerve tumors showing focal cartilaginous differentiation and commented that a concept that unifies the diverse elements sometimes present in peripheral and central nervous system tumors is that of ectomesenchyme, that is, migratory cells of neural crest origin that show both mesenchymal and neuroectodermal features. The presence of glial hyaluronate binding (GHAP) positive cells in the periventricular germinal layer of a 22-week human fetus and a polar spongioblastoma case containing GHA-positive and also GFAP positive cells support this idea4.

In the gliosarcoma case presented by Banerjee et al (2), the cartilage islands were closely related to proliferating cells around the blood vessels, several layers of proliferating perivascular cells appeared to commonly separate cartilage cells from the vascular lumen, and the cells in the cartilaginous areas were GFAP-negative. Fibrous capsules around islands of cartilage have been reported in four cases of gliomas (15). However, in one case, the cartilage area was not enclosed in a fibrous capsule (14). In this last case, GFAP-positive cells were embedded within the cartilaginous area. In our case, the cartilaginous area was also not enclosed in a fibrous capsule, and GFAP-positive cells were embedded within this area.

There may be various sources of cartilaginous areas in glial tumors. In some cases, such as tumors with fibrous capsules and GFAP-negativity, cartilaginous tissue may arise from connective tissue within the tumor such as perivascular mesenchymal tissue; and in other cases, such as tumors with GFAP-positive cartilaginous cells and without a fibrous capsule around the cartilage areas as in our case, it may have developed from neoplastic glial cells.

Another acceptable hypothesis for cartilaginous areas in glial tumors is a mixed mesenchymal-neuroepithelial nature as in gliosarcomas (14). Banerjee et al (2) have reported a gliosarcoma case with cartilage formation. On the other hand, the cartilaginous cells are not neoplastic in most glioma cases containing cartilaginous areas (12, 14). Other possibilities, such as teratomatous nature of the cartilaginous tissue (12, 14), heteroplasia (12), and ossification as an end stage of mucoid degeneration (11, 12, 14) are not widely accepted.

In the patient presented here, the tumor recurred 8 years after radiotherapy. The initial diagnosis was carcinoma metastasis but a review of the previous pathology preparations were consistent with ependymoma at that time. It can be speculated that the misdiagnosis could be due to false negativity of GFAP immunoreactivity, the strong positivity of EMA immunoreactivity on apical surfaces of cells (Figure 3B) and the fact that tumor was reported to

be extraaxial. In addition, surface spreading and pseudopapillary characteristics of tumor cells (Figure 3A) and the presence of desmoplasia due to meningeal involvement on conventional histochemical reactions were also basic factors influencing the first diagnosis. During the second operation, it was clearly seen that the tumor was inraaxial and even extended to the ventricle. In the samples removed at the second operation, the cells on perivascular pseudorosettes were immunopositive to GFAP (Figure 2C), and only a very small number cells were immunopositive to EMA in intracytoplasmic granular pattern. These findings were interpreted as consistent with ependymoma. Meningioma was not included in the differential diagnosis because of GFAP positivity.

The role of radiotherapy in the occurrence of mesenchymal metaplasia is debatable in a neuroepithelial tumor. Squamous metaplasia after radiotherapy is well known in some tissues and tumors such as pituitary gland and pituitary adenomas (17), or prostate gland (5). However, mesenchymal metaplasia is an unusual manifestation in epithelial tumors after radiotherapy. Alper et al (1) have reported a case with colon metastasis with diffuse bone metaplasia previously operated on for stomach carcinoma who was treated with radiotherapy postoperatively. Radiotherapy might have played a possible role in occurrence of cartilaginous metaplasia in our case.

ACKNOWLEDGEMENTS:

The authors wish to thank Zeki Aksu for his technical aid regarding the photographs.

This case was presented as a poster presentation at the Sixteenth Scientific Congress of the Turkish Neurosurgical Society (Istanbul, Turkey, 2002).

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