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Gliosarcoma: A Case with Unusual Epithelial Feature

Astrocytic tumors, particularly gliosarcoma, may contain epithelial features in the form of trabecular, adenoid, papillary arrangement, and squamous metaplasia. A case of gliosarcoma with unusual epithelial feature is described. The patient was a 60-year-old male with frequent seizures. The mass was 4 cm and in the left frontal lobe. Trabecular or rarely adenoid arrangement of neoplastic astrocytes was present in the mucinous stroma, and there was a distinctive transition between the trabecular area and typical anaplastic astrocytoma. The tumor cells in the trabecular area showed positive immunostain for glial fibrillary acidic protein, but did not react with various kinds of cytokeratin. The sarcomatous area was undifferentiated and was not labeled by factor-VIII, desmin, and anti-smooth muscle actin. Occurrence and histogenesis of epithelial features in gliosarcoma are reviewed. The importance to recognize the existence of epithelial feature in malignant astrocytic tumor is emphasized.

Key Words: *Gliosarcoma; Sarcoma; Brain neoplasms*

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INTRODUCTION

There are several primary intracranial tumors that may occasionally have histological features suggestive of metastatic carcinoma. They are choroid plexus papilloma, papillary ependymoma, pituitary adenoma, papillary meningioma, and medulloblastoma. Tumors of astrocytic origin, however, are usually not included. Only a few astrocytic tumors with epithelial features have been described to date (1). Although most gliomas that had epithelial features were gliosarcoma, glioblastoma and anaplastic astrocytoma could also show epithelial features in the form of trabecular, adenoid and papillary arrangement, and squamous metaplasia. Therefore it is extremely important for pathologists to recognize its existence, particularly in regard to its distinction from metastatic carcinoma. Concerning the pathogenesis in which neoplastic astrocytes may represent epithelial features, Kepes et al. have stressed the role of mesenchymal tissue in gliosarcoma (1), while Mork et al. emphasized the divergent differentiating potential of neoplastic astrocytes (2). Despite several immunohistochemical studies using glial fibrillary acidic protein (GFAP) and various kinds of cytokeratin, the pathogenesis is still uncertain.

Recently, we found a gliosarcoma in a 60-year-old male that showed unusual features resembling epithelial structure. Rarity of this phenomenon and interest in its histogenesis prompted this report. After brain surgery, a detailed study to find the possible primary site of the brain tumor was done. However, no suspicious lesion was found outside the cranial cavity.

CASE PRESENTATION

A 60-year-old man presented frequent seizures. MRI revealed a contrast enhancing mass, 4.0 cm in diameter, in the left frontal lobe. The mass appeared attached to the overlying dura mater (Fig. 1). Preoperative diagnosis was meningioma. The tumor was in the left frontal lobe and was well demarcated from the surrounding brain parenchyma. Total resection of the mass was performed. The mass was round and firm and partly attached to the overlying dura. It appeared greyish white and yellow on cut section and was slightly lobulated. In areas, thick whorl-like trabecular collagenous tissue could be seen after fixation (Fig. 2). Histologically the tumor mass was composed of distinct biphasic pattern. One represented anaplastic astrocytic neoplasm, and the other revealed undifferentiated sarcoma. The anaplastic astrocytoma portion was alternated with reticulin-rich spindle cell sarcomatous portion (Fig. 3, 4). The epithelial feature

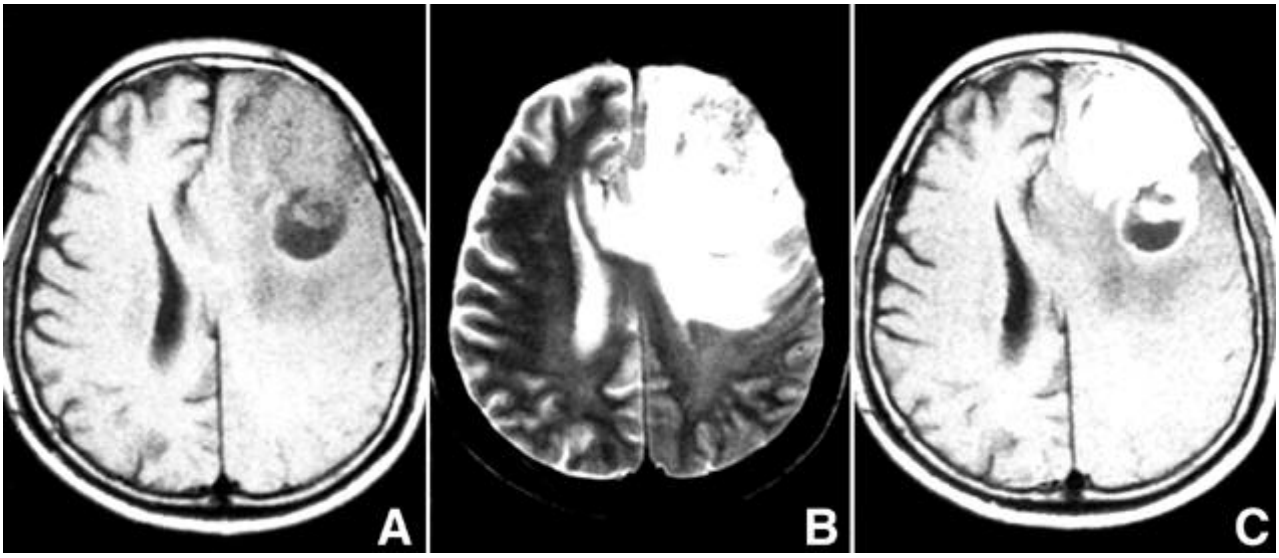

Fig. 1. A: T1WI shows a mixed signal lesion and necrotic component with surrounding edema. B: There is an inhomogeneous signal mass with signal void of some vessels on T2WI. C: Postcontrast T1WI reveals strong enhancement with dural tail sign.

was seen in areas of astrocytic cells in the form of trabecular or rarely adenoid arrangement in the mucinous background (Fig. 5, 6). There was a recognizable transition between the areas of epithelial feature and the areas of anaplastic astrocytoma (Fig. 7). The areas with epithelial feature were immunostained with GFAP (DAKO, U.S.A.) (Fig. 8) and S-100 protein (DAKO). The epithelial feature areas showed no reaction to various kinds of cytokeratin (AE1/AE3 Zymed, U.S.A.; MNF116 DAKO; CK1 DAKO; 34βE12 DAKO; CAM 5.2 Beckton Dikinson, U.S.A.) and epithelial membrane antigen (DAKO). The sarcomatous cells revealed positive immunostain for vimentin (DAKO) and alpha-1-antitrypsin (DAKO). They were negative for factor-VIII (DAKO), desmin (DAKO), anti-smooth muscle actin (DAKO), and lysozyme (Biomeda, U.S.A.).

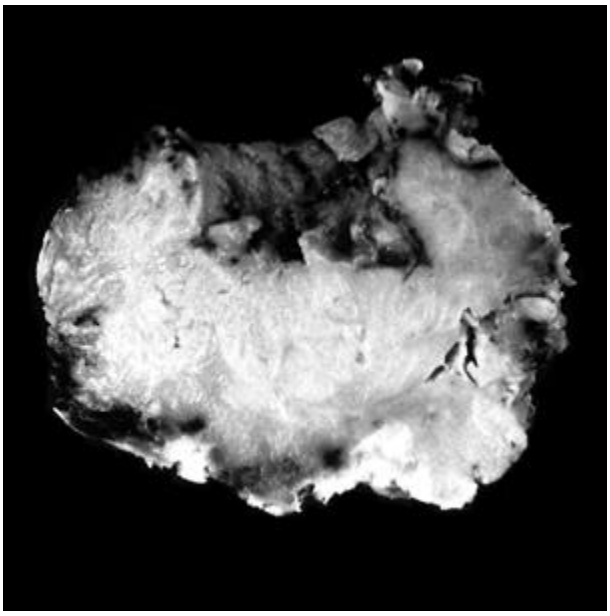

Fig. 2. The frontal lobe mass, measuring 4.0×2.5×2.5 cm in size, appears greyish white and yellow, firm, slightly lobulated and whorled on the cut surface, quite reminiscent of meningioma.

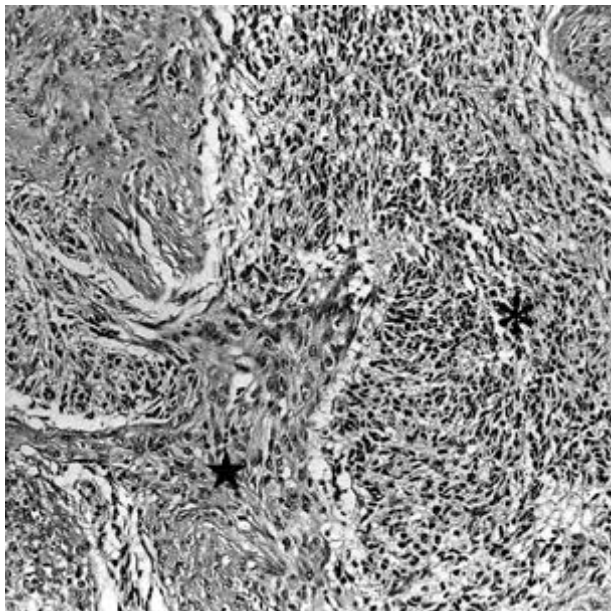

Fig. 3. Distinct biphasic pattern with areas of closely packed cells (asterisk) alternating with cellular strands and streams of fibroblast-like cells (star) (H&E, ×100).

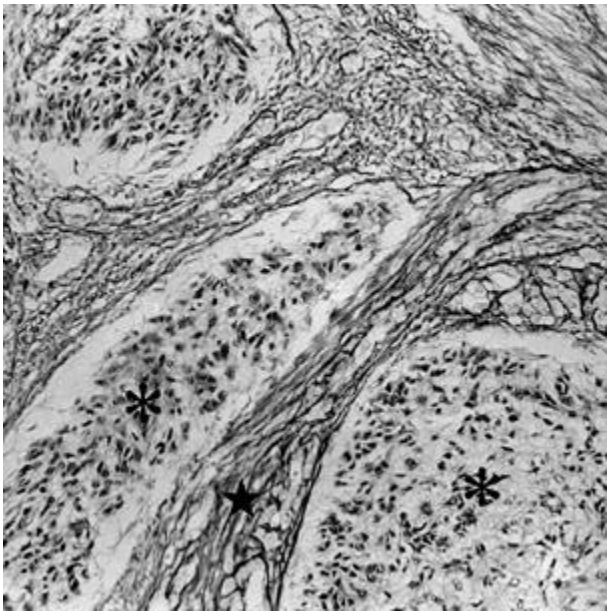

Fig. 4. Reticulin stain accentuates the difference between positively stained sarcomatous areas (star) and negatively stained glial components (asterisk) (Gordon and Sweets' reticulin stain, ×100).

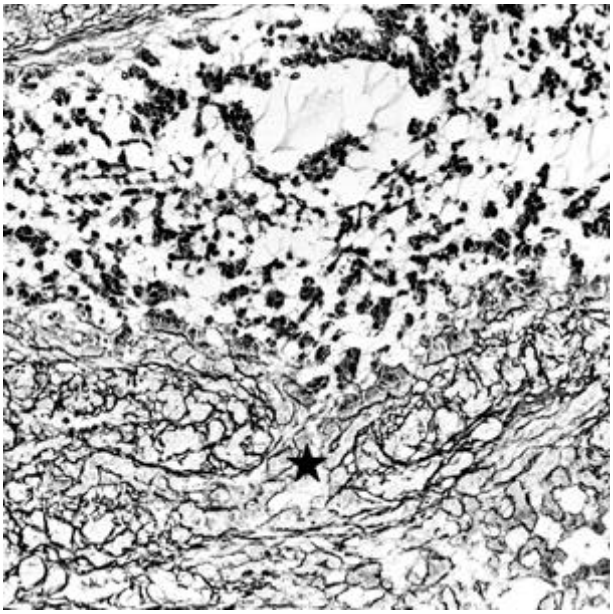

Fig. 5. At the top of this figure the neoplastic astrocytes are freely floating in the pool of mucin. At the bottom of this figure sarcomatous portion has rich reticulin (Gordon and Sweets' reticulin stain, ×100).

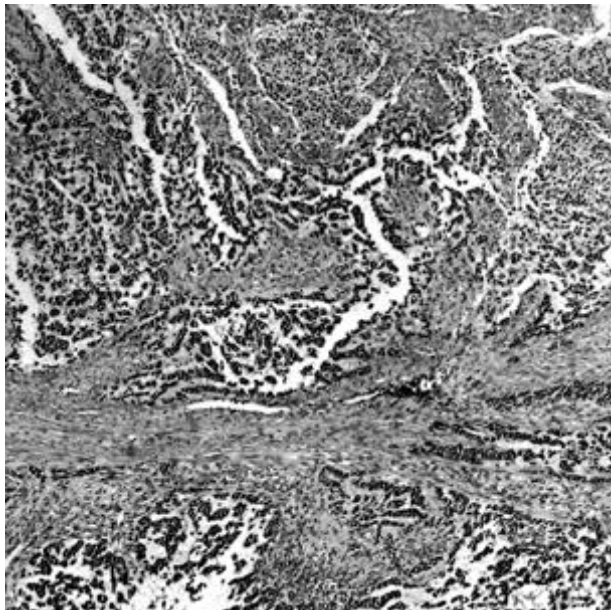

Fig. 6. The neoplastic astrocytes are frequently arranged in trabecular structure (H&E, ×40).

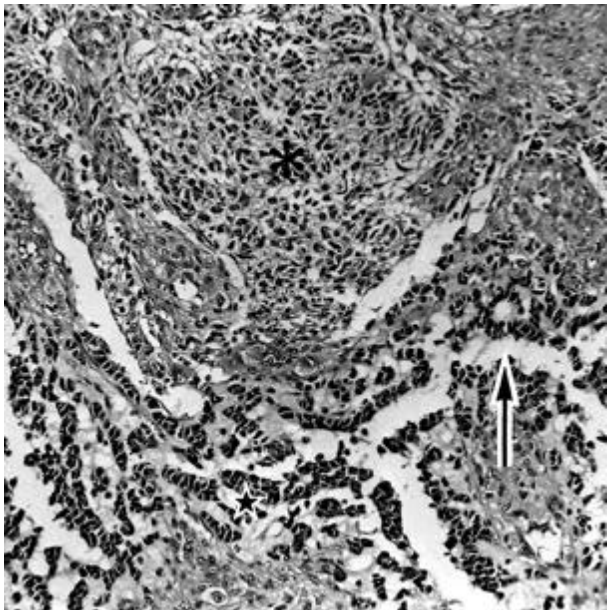

Fig. 7. High magnification of the upper portion of the Fig. 6. There is distinct transition between much more typical astrocytic area (asterisk) and the area showing epithelial feature (star). The neoplastic astrocytes are rarely arranged in adenoid feature (arrow) (H&E, ×100).

DISCUSSION

The term "gliosarcoma" has been used since Stroebe recognized sarcomatous change from the glioblastoma multiforme, and the clinicopathologic characteristics of gliosarcoma have been described in detail (3). Gliosarcoma accounts for 1.8-8% of all glioblastoma multiforme (4-6). Gliosarcoma is a neoplasm mixed with anaplastic glioma and sarcoma. The anaplastic glioma is mainly composed of astrocytes and rarely oligodendrocytes (7, 8)

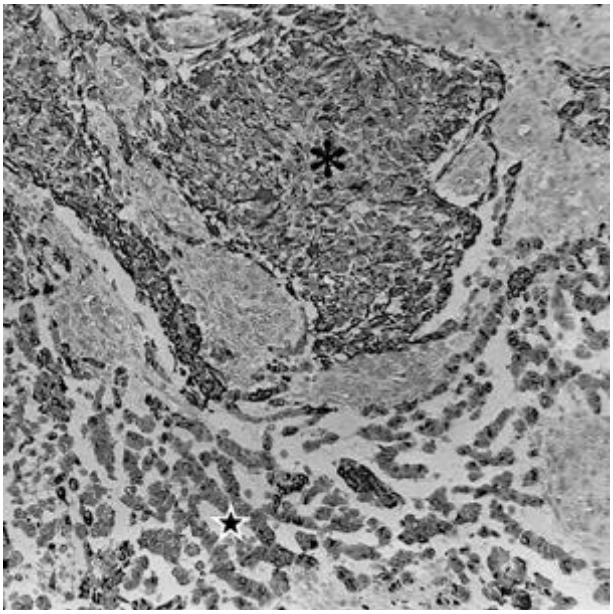

Fig. 8. The same area seen in Fig. 7. Both cellular (asterisk) and epithelial areas (star) are positive for glial fibrillary acidic protein immunostaining (ABC method, ×100).

or ependymal cells (9). The lesion is commonly mistaken clinically for a meningioma due to its frequent dural attachment and firmness, as in our case. The sarcomatous portion of the gliosarcoma presents mostly fibrosarcoma (4) or malignant fibrous histiocytoma (5, 10), but may show differentiation towards smooth muscle (11), skeletal muscle (12), bone (13), and cartilage (14). The sarcomatous portion is considered to have possibly arisen from neoplastic transformation of vascular endothelial cells (1, 3-5, 15-17), perivascular adventitial fibroblast (6, 18-20) or adventitial histiocytes (21). McComb et al. (18) and Schiffer (20) favored fibroblasts over vascular endothelial cells, because the tumor cells were negative for factor-VIII, although they did not exclude the possibility that the tumor cells had lost the antigenicity for factor-VIII during neoplastic transformation of endothelial cells.

This case is quite similar to the case of Banerjee et al. (14) in that the sarcomatous portion is undifferentiated and does not belong to any specific type of sarcomas. In typical cases of gliosarcoma, the sarcomatous portion is present at the central portion and the anaplastic glioma portion is located at the peripheral portion of the tumor, and therefore the sarcoma portion is considered to be a secondary malignant change in the preexisting anaplastic glioma (6). In gliosarcoma, the mesenchymal portion should be anaplastic, and it should be distinguished from exuberant endothelial cell proliferation frequently found within glioblastoma multiforme or from extensive desmoplasia secondary to meningeal invasion of anaplastic astrocytes.

Histologically, the anaplastic astrocytoma portion of the gliosarcoma can be easily distinguished from the sarcomatous portion, although the anaplastic astrocytes may be intimately admixed with sarcomatous cells so that GFAP immunostaining is required to define the anaplastic astrocytes. In extremely rare cases, these neoplastic astrocytes can be arranged in trabecular, adenoid, and papillary structure which might be confused with metastatic carcinoma, and they may show squamous metaplasia.

In 1956, Rubinstein described a gliosarcoma with arrangement of trabecular pattern (1). Kepes et al. reported a total of 8 cases of gliosarcoma with adenoid feature in 1982 and 1985 (1, 22). In 1988, Mork et al. reported 2 cases with papillary arrangement and 6 cases with squamous metaplasia (6, 23) (Table 1). The previously reported malignant gliomas with epithelial features correspond mostly to gliosarcoma and partly to glioblastoma multiforme (23) or anaplastic astrocytoma (24). Rubinstein described that the pathogenesis by which the neoplastic astrocytes can represent epithelial features may be due to mechanical pressure to neoplastic astrocytes by compartmentalization of the sarcomatous portion. Kepes et al. described that Rubinstein's interpretation was unsatisfactory, because the adenoid feature could be seen in the case of glioblastoma multiforme or anaplastic astrocytoma (1). The adenoid arrangement of neoplastic astrocytes might be due to connective tissue formed by fibroblastic activity of astrocytes (1) or due to divergent differentiating potential of neoplastic astrocytes (23). Mandybur et al., in his experimental study, found rich connective tissue in the area of adenoid feature within human glioblastoma multiforme that was transplanted to nude mice, and he suspected that the connective tissue induced adenoid feature of neoplastic astrocytes (25).

In review of papers, we found that the astrocytic tumors, showing epithelial feature, tended to have a greater degree of anaplasia than usual anaplastic astrocytoma. Therefore, we suspected that the degree of anaplasia of neoplastic astrocytes was related to epithelial features by uncertain mechanisms. However, further studies should be done about the relationship between epithelial features of anaplastic astrocytes and connective tissue or the degree of anaplasia of neoplastic astrocytes.

In view of the terminology described in the cases with epithelial features, we thought that the term "differentiation" could be usable in the case reported by Mork et al. (23), because in his report the neoplastic cells with squamous feature revealed positivity not only for cytokeratins but also for GFAP, and these immunohistochemical findings suggested epithelial differentiation of neoplastic astrocytes. In cases with adenoid or papillary features, however, cytokeratin immunoreactivity or ultra-

Table 1. Clinicopathologic features of patients with malignant gliomas showing epithelial feature appearing in literatures

		Site	Type	Epithelial feature	GFAP	Cytokeratin	Initial diagnosis
Kepes (1)	64/M	P	GS	A, M	+	?	GS with unusual imitation of glandular tissue in the glial component
	58/F	F	GS	A	+	?	GS with focal epithelioid and adenoid arrangement of glial cells
	66/F	T	GS	A, M	+	?	?
	57/F	P	GS	A, M	+	?	GS
	60/F	P	GS	A	+	?	?
Kepes (22)	78/?	?	GS	A	?	?	?
	57/?	?	GS	A	?	?	?
	2/?	?	AA	A	?	?	?
Galloway (24)	49/F	F	AA	A	+	?	Undifferentiated malignant neoplasm, most likely MC
Mørk (2)	21/M	F	GM	A, P	-	?	Medulloepithelioma with areas of GM
	62/M	T	GS	A, P	+	?	Medulloblastoma with sarcoma and GM
Mørk (29)	72/F	F	GS	A, M, S	+	+	MC in glioma
	42/F	P	GS	A, S	+	−	Possibly carcinoma
	51/F	F	GM	S	+	+	MC in glioma
	59/M	F	GS	S	+	+	MC in astrocytoma
	43/M	F	GM	A, S	+	+	MC in malignant glioma
	60/F	T	GS	S	+	+	Malignant teratoma

?, not mentioned; A, adenoid; AA, anaplastic astrocytoma; F, frontal lobe; GM, glioblastoma multiforme; GS, gliosarcoma; M, mucin; MC, metastatic carcinoma; P, papillary; P, parietal lobe; S, squamous; T, temporal lobe

structural findings suggestive of epithelial differentiation was not mentioned, suggesting that the term "epithelial feature" is more appropriate than "epithelial differentiation". Therefore, the epithelial features except for squamous metaplasia in gliosarcoma should be dealt with in another pathogenesis. Cytokeratin positivity of neoplastic astrocytes may be due to the fact that they express non-glial intermediate filaments during their neoplastic transformation (10, 26) or cross reactivity (27). Neoplastic astrocytes may exhibit positive reaction to cytokeratin which is widely used to recognize epithelial differentiation. Therefore, cytokeratin positivity in intracranial tumors does not always mean a metastatic origin (6, 10, 26, 28). In this case, the possibility of metastatic mucinous carcinoma to preexisting anaplastic astrocytoma should be excluded, because the tumor cells with epithelial feature have abundant mucinous background. However, there was a definitive transition between the areas showing epithelial feature and the area of anaplastic astrocytoma. Besides these areas reacted strongly with GFAP and did not react with cytokeratins. Therefore, it was concluded that the tumor cells with epithelial features was astrocytic in origin. The presence of transition between epithelial features and anaplastic astrocytoma portion is extremely important to distinguish this tumor from metastatic carcinoma. In cases of carcinomas metastasized to preexisting glioma, there was no evidence of transition between them (29). Attention should be paid to the diagnosis of papillary arrangement among epithelial features, because several primary intracranial tumors, i.e., choroid plexus papilloma, papillary ependymoma, and medulloblastoma could have papillary structures and show positive reaction to GFAP, that could be misdiagnosed as medulloblastoma or medulloepithelioma (2, 30) (Table 1).

In conclusion, we concur with the study of Kepes et al. who described that the recognition of adenoid formation of neoplastic astrocytes could be very important in avoiding unnecessary clinical work-up for primary tumor.

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