

Granular Cell Astrocytoma

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• **Granular cell astrocytoma (GCA) is a rare type of malignant brain tumor with distinct morphologic features and aggressive clinical behavior. Almost all GCAs occur in the cerebral hemispheres. It is characterized by a prominent component of bland-looking granular cells. The tumor cells are usually positive for glial fibrillary acidic protein, S100, CD68, and epithelial membrane antigen. The most important differential diagnoses include a number of reactive lesions such as cerebral infarction, multiple sclerosis, and progressive multifocal leukoencephalopathy. Electron microscopic study reveals that the granules of GCA correspond to an increased number of intracytoplasmic lysosomes. The histogenesis of GCA is still unclear, but most people believe it originates from astrocytes. Loss of 9p and 10q were identified in almost all cases of GCA, but they are not specific for this tumor. Surgical excision plus postoperative chemotherapy or radiotherapy is the choice for most patients with GCA.**

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Granular cell astrocytoma (GCA), which has also been called *intracerebral granular cell tumor* or *astrocytoma with granular cell differentiation*, is a rare type of infiltrative malignant brain tumor. It was first described by Markesbery et al¹ in 1973 as *granular cell tumor in the central nervous system*. Later, GCA was found to be a highly aggressive neoplasm, in dramatic contrast to the benign nature of “granular cell tumors” in other parts of the body. Furthermore, most reported GCAs were positive for glial fibrillary acidic protein (GFAP). Therefore, it is considered a rare variant of glial neoplasm with remarkable granular cell changes.² Approximately 50 cases have been reported in the literature. Most of them were presented as case reports. The first large series of GCA was published by Geddes et al³ in 1996 describing 5 cases of astrocytoma composed either entirely or predominantly of granular cells. Later, in 2002 Brat et al² investigated histopathologic features, grading, and outcome of 22 cases and started to use the name *granular cell astrocytoma*.

CLINICAL FEATURES

Based on the literature reports, the ages of the patients range from 25 to 79 years. The mean age is 55 years. The

male-female ratio is 2:1.²⁻⁴ Patients usually present with headache, vomiting, newly onset seizures, aphasia, hemiparesis, blurred vision, and confusion. Almost all GCAs occur in the cerebral hemispheres.²⁻⁴ Only one case was reported in the cerebellum.⁵ Most recently, Baena et al⁶ documented 1 case of GCA in the spinal cord. The most common locations are the frontal, parietal, and temporal lobes. Brat et al² reported that 36% of GCAs were located in the frontal lobe, 27% in the parietal lobe, 27% in the temporal lobes, and 9% in the occipital lobe. Occasionally, GCA can occur in the corpus callosum, basal ganglia, and pineal region.²⁻⁴ Computed tomography scan and magnetic resonance imaging studies usually reveal GCA as a solid or cystic cerebral tumor with pronounced mass effect (Figure 1, A).

HISTOPATHOLOGY

The most distinctive morphologic feature of GCA is its prominent component of granular cells²⁻⁴ (Figure 1, B). These tumor cells are large with distinct cell borders. They are round to oval in shape and characterized by abundant eosinophilic granular cytoplasm. Some tumor cells display a clear central cytoplasmic area and the granules accumulate at the periphery beneath the cell membrane (Figure 1, C). The nuclei of these granular cells are bland, round to oval, varied in size, and often eccentrically located. Occasionally, single small nucleoli can be observed. Lymphocytic infiltration, especially perivascular lymphocytic cuffing, is often noticed (Figure 1, D).²⁻⁴ Tumors can be entirely composed of granular cells, but more often granular cells coexist with conventional infiltrating astrocytoma. Brat et al² reported that among 22 cases of GCA they investigated, 73% (16/22) contained areas of conventional astrocytoma.

CYTOCHEMISTRY AND IMMUNOHISTOCHEMISTRY

The cytoplasmic granules of this tumor are periodic acid-Schiff positive and diastase resistant.²⁻⁴ Immunohistochemical studies show that most GCAs are positive for GFAP.²⁻⁵ The cytoplasmic GFAP staining can be presented in a uniform pattern or with a targetoid appearance (central clearing).^{2,3} However, Brat et al² found that GFAP immunostaining in GCA was generally low (<30%), and in some cases it was focal and patchy. Negative GFAP immunostaining was reported in a few articles.^{7,8}

Granular cell astrocytoma is positive for CD68, epithelial membrane antigen (EMA), and S100 (Figure 2, A through C).²⁻⁴ CD68 is a 110-kd lysosomal glycoprotein highly expressed by monocytes and macrophages.⁹ Although it is used as a characteristic marker for histiocytic differentiation, the expression of CD68 has been identified

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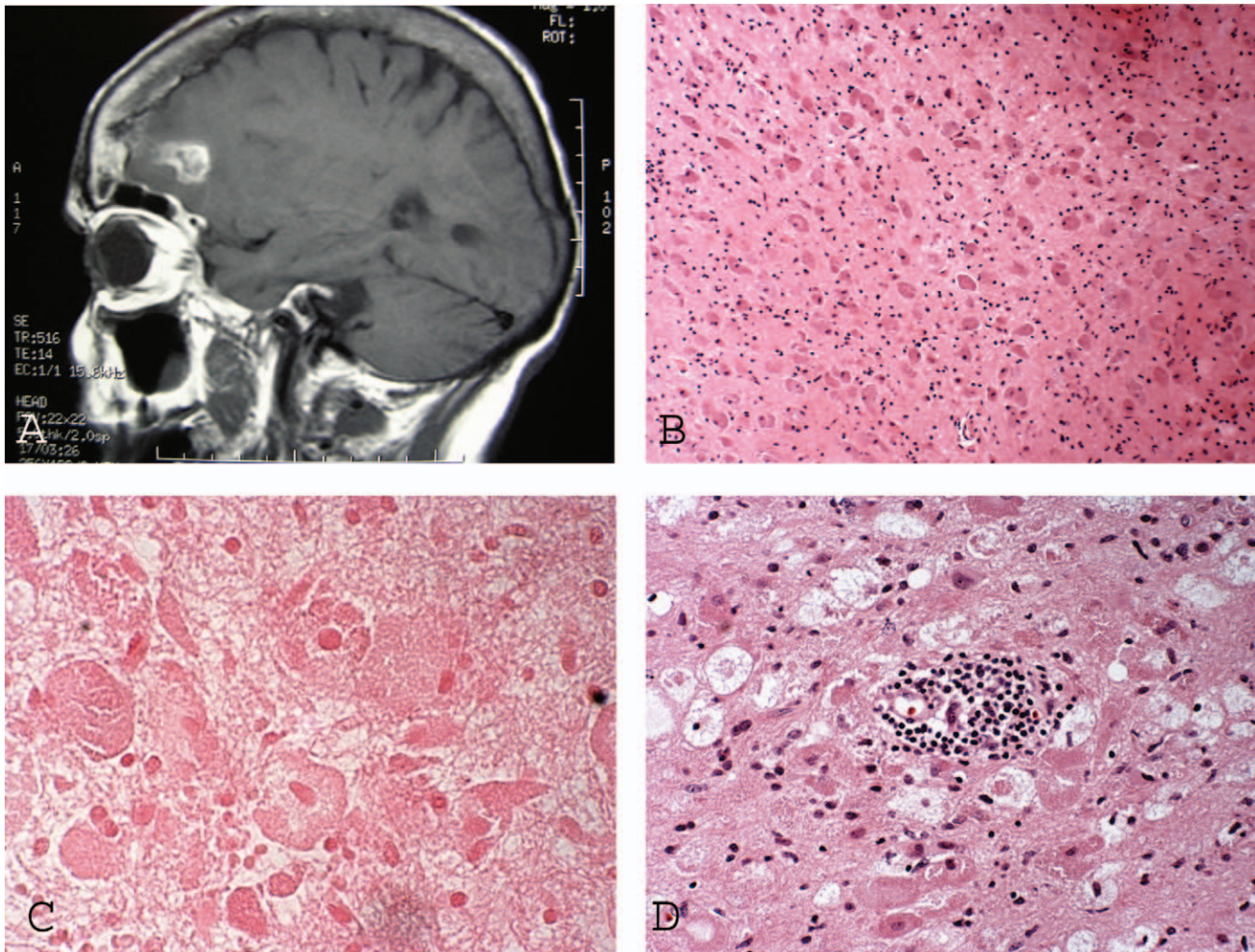


Figure 1. A, Axial magnetic resonance imaging shows a solid/cystic mass of granular cell astrocytoma in the frontal lobe. B, Neoplastic cells of granular cell astrocytoma are characterized by abundant eosinophilic granular cytoplasm and eccentrically located nuclei (hematoxylin-eosin, original magnification $\times 100$). C, Neoplastic cells of granular cell astrocytoma display a targetoid appearance with a clear central area (hematoxylin-eosin, original magnification $\times 400$). D, Perivascular lymphocytic cuffing is often noticed (hematoxylin-eosin, original magnification $\times 400$).

in a number of tumors including melanoma, leiomyosarcoma, and pleomorphic xanthoastrocytoma.⁹⁻¹¹ Conventional astrocytomas were rarely reported to express CD68. Leenstra et al¹² found 6 well-characterized astrocytoma cell lines expressing a panel of macrophage markers including CD68. The significance of this finding is not clear. They proposed that the expression of macrophage phenotype may promote tumor growth through elevated production of growth factors and angiogenic factors.¹² In EMA-positive cells, immunoreactivity is either uniform throughout the cytoplasm or accumulated at the cell periphery, which is consistent with the distribution of the cytoplasmic granules observed on hematoxylin-eosin-stained slides. No true membrane staining is present. Ki-67 usually is negative or very low in GCA (Figure 2, D). The MIB-1 index was reported to range from 1.1% to 2.9% in 1 study¹³ and 0.5% to 15% in another.¹⁴ The low MIB-1 index suggests that the granular cells of GCA are senescent cells and the granules may represent degenerative changes of astrocytes.¹³ Bcl-2 was found to be negative in GCA.¹³ However, only 3 cases have been investigated. Granular cell astrocytoma is also reported to be

positive for the protein degradation marker ubiquitin, lysosomal membrane glycoproteins LAMP-1 and LAMP-2.^{2,3}

ELECTRON MICROSCOPY

Ultrastructural studies demonstrate that GCA contains large numbers of autophagic lysosomes in the form of dense bodies, multivesicular bodies, and vacuoles. The lysosomes are distributed at the periphery of the cytoplasm corresponding to the distribution of the granules observed on hematoxylin-eosin-stained slides.²⁻⁴ It is believed that the granules of GCA correspond to an increased number of intracytoplasmic lysosomes, which also provide the structural basis for positive CD68 expression observed in GCA. Various amounts of intermediate filaments can also be observed in GCA tumor cells. They are often located at the periphery of the cells.²⁻⁴ By contrast, conventional astrocytoma contains only scattered lysosomes but innumerable intermediate filaments.¹⁵

DIFFERENTIAL DIAGNOSIS

Histologically, the granular tumor cells can be confused with macrophages. Therefore, it is important to differen-

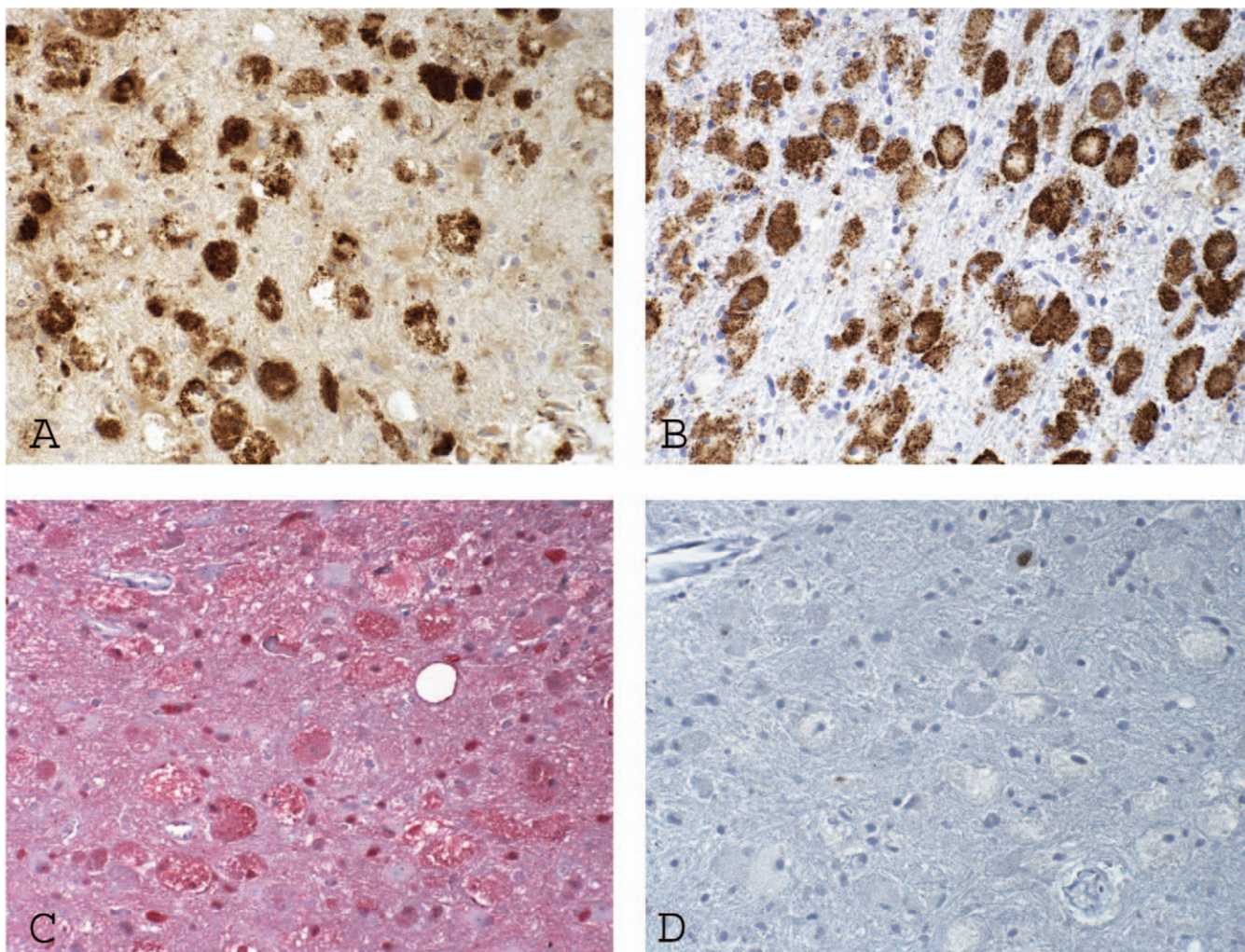


Figure 2. A, CD68 cytoplasmic positivity in granular cell astrocytoma (original magnification $\times 200$). B, Epithelial membrane antigen cytoplasmic positivity in granular cell astrocytoma (original magnification $\times 200$). C, Positive S100 stain in granular cell astrocytoma (original magnification $\times 200$). D, MIB-1 expression is low in granular cell astrocytoma. Note: positive staining observed in a reactive astrocyte (original magnification $\times 200$).

tiate GCA from a number of reactive lesions such as cerebral infarction, multiple sclerosis, and progressive multifocal leukoencephalopathy. Helpful features for the differential diagnosis include the following: (1) GCA tumor cells display at least some cellular polymorphism and atypia. The tumor cells vary in size and shape with occasional small nucleoli. In addition, granular tumor cells ranging in size from 60 to 100 μm in diameter are often significantly larger than macrophages.² Unlike macrophages, granular cells of GCA display a central clear cytoplasmic area with the granules accumulating at the periphery of the cell, under the cell membrane. (2) GCA tumor cells are positive for GFAP, which is usually negative in macrophages. However, because GFAP immunostaining in GCA can be focal and weak or even negative,² GFAP staining is not always helpful in establishing the diagnosis. Positive GFAP can confirm the diagnosis of GCA, but negative staining should not exclude the diagnosis of GCA, especially when the sample size is small. (3) GCA may be associated with the conventional type of astrocytoma.²⁻⁴ Brat et al² reported that among 22 cases of GCA they studied, 16 (73%) cases were mixed with conventional astrocytoma. Geddes et al³ found that 15 of 27 cases of

GCA reported in the literature were associated with anaplastic astrocytes. However, conventional infiltrating astrocytoma may not always be present, especially in small biopsies. (4) Macrophages, the mimicker of GCA, can be observed in cerebral infarct, but it is usually accompanied by eosinophilia of neurons ("red neuron") and neutrophil infiltration. Red neurons are not reported in GCA. (5) Multiple sclerosis is an autoimmune-mediated demyelinating disorder located in white matter. Even though it can present with abundant macrophages and perivascular lymphocytic cuffs, the lesions are characterized by multiple well-demarcated demyelinated plaques different from the diffuse infiltrative growth pattern of GCA. (6) Progressive multiple leukoencephalopathy is a viral encephalitis involving the white matter. It usually affects immunocompromised patients and is caused by JC polyomavirus. The lesions are characterized by irregular, ill-defined patches of demyelination, lipid-laden macrophages, and reduced numbers of axons. The most important diagnostic feature of progressive multifocal leukoencephalopathy is the presence of greatly enlarged oligodendrocytes with glassy amphophilic intranuclear viral inclusions. (7) Clinical history can be helpful in the differential diagnosis because clinical

presentations are different among these diseases. Cerebral infarct tends to happen abruptly within hours. Granular cell astrocytoma may take several weeks or months to develop. Multiple sclerosis and progressive multifocal leukoencephalopathy usually manifest as chronic diseases with long clinical courses.

It is also important to differentiate GCA from granular cell tumor of the neurohypophysis or infundibulum, which is a benign primary tumor located intrasellarly and/or suprasellarly.¹¹ This tumor is histologically very similar to GCA and characterized by nests of large polygonal cells with abundant granular cytoplasm and sometimes spindle cells. Variable expression of GFAP protein has been described in a subset of granular cell tumors of the neurohypophysis.¹⁰ The tumor cells are positive for periodic acid–Schiff stain, neuron-specific enolase, α_1 -antitrypsin, and α_1 -chymotrypsin.¹¹ More importantly, granular cell tumor of the neurohypophysis is a benign, slowly progressive tumor without invasive growth pattern.

Pituicytoma used to be regarded as a synonym of granular cell tumor of the neurohypophysis,¹¹ but this is a misnomer. In 2000, Brat et al¹⁶ studied a series of 9 cases of pituicytoma and clarified the definition of this tumor. Pituicytoma is a rare low-grade glioma of the sellar and suprasellar region, which is thought to originate from pituicytes, a specialized glial cell, of the stalk and posterior lobe of the pituitary gland. The tumor is histologically different from GCA and characterized by elongated, bipolar spindle cells arranged in interlacing fascicles and/or storiform growth pattern. The tumor cells contain oval to elongated nuclei, small inconspicuous nucleoli, and eosinophilic, slightly fibrillary cytoplasm, without granularity or vacuolization. Periodic acid–Schiff stain is rarely positive in pituicytoma.^{16,17} Imaging study usually reveals a well-circumscribed solid mass located in the sellar or suprasellar region. Therefore, morphologically and clinically, pituicytoma is distinct from GCA and granular cell tumor of the neurohypophysis and should be regarded as a different disease entity.

HISTOGENESIS

The histogenesis of GCA is still unclear, but most people favor its astrocyte origin because of the positive GFAP immunostaining and its coexistence with conventional astrocytoma in a substantial portion of reported cases.^{2–4} Melaragno et al⁴ demonstrated that the soft tissue form of granular cell tumor is negative for GFAP and EMA immunostaining. This result indicates that GCA and granular cell tumor have different cell origins, which may be the reason for their different biologic behaviors. It is unclear if GCA is truly an entity in its own right or simply prominent degenerative change with lysosomal accumulation in varying proportions of tumor cells. Kornfeld¹⁸ proposed that granular cells were transformed neoplastic astrocytes that developed from the cells containing abundant cytoplasmic intermediate filaments and a few granules to the ones containing less or no cytoplasmic intermediate filaments and abundant granules. This hypothesis provides an explanation for the “transitional areas” observed in some cases in which GCA is admixed with conventional astrocytoma.

Interestingly, most GCA cases reported in the literature displayed strong cytoplasmic immunostaining for EMA (Figure 2, B). Epithelial membrane antigen is a monoclonal antibody prepared initially against breast epithelial

cell membranes. It is considered to be an epithelial marker, but the staining can be seen in many other cells and tumors such as plasma cells, monocytes, meningioma, synovial sarcoma, and anaplastic large cell lymphoma. Although Geddes et al considered this type of EMA staining to be nonspecific because it was cytoplasmic instead of membranous staining, there were different opinions concerning a potential epithelial differentiation derived from astrocytoma.¹⁹ Further studies are needed to determine the histogenesis of GCA and the significance of EMA staining.

Grading

In 2 studies, GCA was diagnosed when the tumor had at least more than 30% granular cells.^{2,20} Granular cell astrocytoma was graded based on the criteria for astrocytoma of the 2000 World Health Organization. Grade 2 was defined as tumors with occasional nuclear atypia and absence of mitosis. However, finding a rare mitosis does not upgrade the tumor to anaplastic astrocytoma. Grade 3 was defined as tumors with hypercellularity, distinct nuclear atypia, and marked mitotic activity. Grade 4 was defined as tumors with pseudopalisading necrosis and/or endothelial hyperplasia.^{2,21,22}

Genetic Alterations

No genetic alterations were found to be specific for GCA. Castellano-Sanchez et al²⁰ found that GCA displayed higher frequencies of loss of heterozygosity at 1p, 9p, 10q, 17p, and 19q than conventional infiltrating astrocytomas of similar grades. Loss of 9p and 10q were identified in almost all cases, including low-grade lesions. *TP53* mutations, p14 and p16 combined deletions were observed in some high-grade GCA tumors. Epidermal growth factor receptor amplification is a common event in high-grade astrocytoma, but it was not identified in a small series of GCA.²⁰ Further studies are needed to investigate the genetic alterations of GCA.

Treatment and Prognosis

Surgical removal plus postoperative chemotherapy or radiotherapy is the choice for most patients with GCA. However, because of its aggressive clinical behavior, most patients with GCA die within 1 year.² Compared with conventional astrocytoma, the prognosis of GCA is much worse. According to Brat et al,² the average survival of patients with grade 3 and 4 conventional astrocytoma was 3 years and 11 months, respectively. In contrast, the average survival of patients with grades 3 and 4 GCA was 8.4 and 7.3 months, respectively. It is unclear why GCA behaves in such an aggressive manner despite its low mitotic rate and MIB-1 index. Castellano-Sanchez et al²⁰ found that GCA displayed a higher frequency of loss of heterozygosity at 9p and 10q than the conventional astrocytoma of similar grade, which may contribute to its aggressive clinical behavior.

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