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Astrocytes in brain tumours. Differentiation or trapping?

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Summary. Adult astrocytes have been described in several types of gliomas, being accepted as high differentiated cells. Their presence is specially important concerning the concept of undifferentiated neuroectodermal tumours (PNET).

We have studied two series of brain tumors and compared and contrasted them with silver impregnation (89 cases) and GFAP (127 cases). These are our conclusions: these astrocytes show the same morphology not only in neuroectodermal tumours, but also in CNS parenchyma around meningiomas, metastasis and brain lymphomas; many of these astrocytes are mature, normal cells with involutive features, lying among tumoral cells without transitional stages; their presence is directly related to a prominent peritumoral gliosis, a high proliferation rate and an infiltrating growth. On this basis, it is suggested that most of them are astrocytes belonging to the invaded CNS tissue and not true tumoral cells.

Key words: Astrocytes, Brain tumours, Reactive astrocytes, Gliosis, GFAP, Silver impregnation, Neoplasms

Introduction

Mature astrocytes have occasionally been described in gliomas of astrocytic origin and glioblastomas (Ziveri, 1918; Bailey, 1932; Cox, 1933; Costero, 1962) malignant and recurrent astrocytomas (Delpech et al., 1978) as well as oligodendrogliomas (Bailey and Cushing, 1926; Bailey and Bucy, 1929; Kwan and Alpers, 1931; Bailey, 1932; Rio-Hortega, 1932; Cox, 1933; Zülch, 1941, Velasco et al., 1980), ependymomas (Cox, 1933; Zülch, 1956; Velasco et al., 1980) and medulloblastomas (Bailey and Cushing, 1925, 1926; Cox, 1933; Masson, 1956; Zülch, 1956; Delpech et al., 1978; Duffy et al., 1979; Velasco et al., 1980; Coffin et al., 1983; Dickson et al., 1983; Barnard and Pambakiam, 1980; Palmer et al., 1981; Russell and Rubinstein, 1989) and primitive neuroectodermal tumors (Hart and Earle, 1973; Boesel et al., 1978; Markesbery and Challa, 1979; Rorke, 1983). Less frequently, they have been found in the CNS parenchyma around meningiomas, metastasis and brain lymphomas.

Such astrocytes have been considered partly as differentiated tumoral cells and partly as more or less reactive non tumoral astrocytes, coming from the invaded tissue during the tumoral growth. Bailey (1932); Zülch (1940, 1941, 1956) and Velasco et al. (1980) express an eclectic point of view, admitting both possibilities in different tumors.

This controversy affects the evaluation of the capacity of partial and/or multiple differentiation of gliomas, specially the most undifferentiated ones, in which different lines of differentiation have sometimes been described, based on the presence of astrocytes among tumoral cells (see Rorke, 1983). The report of these cells is directly related to the use of special stain methods for the demonstration of astrocytes such as Cajal's gold sublimate (Ziveri, 1918; Bailey and Cushing, 1925, 1926; Bailey, 1932; Zülch, 1941) Rio-Hortega's silver impregnation (Río-Hortega, 1932, 1934; Costero, 1962) and now PAP method for gliofibrillary acidic protein (GFAP). (Delpech et al., 1978; Duffy et al., 1979; Velasco et al., 1980; Barnard and Pambakian, 1980; Mannoji et al., 1981; Palmer et al., 1981; Coffin et al., 1983; Dickson et al., 1983; Roessmann et al., 1983).

Furthermore, most of the papers concerning these cells are based on the study of a unique type of tumor, especially medulloblastomas and PNET systematized studies on different tumoral types lacking.

The aim of this study is the analysis of two parallel series of distinctive brain tumors. The first one has been studied by cold silver carbonate method for astrocytes and the second one has been studied by PAP method for GFAP in order to define the true nature of the astrocytic population found in both series.

Materials and methods

This study is based on the analysis of 216 brain tumors from the files of the Department of Pathology, Hospital General Gregorio Marañón (Madrid) divided

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into two series.

The first group includes 89 cases, as shown in Table 1. These cases have been studied by conventional routine methods and by Rio-Hortega - Polak method for astrocytes with silver carbonate (Polak, 1966) on frozen sections.

The second group includes 127 cases, as detailed in Table 2, They have also been studied with conventional routine methods as well as with immunohistochemical technique (PAP method) for the demonstration of the GFAP, using antihuman GFAP serum and swine antirabbit immunoglobulin (DAKO).

Results

Astrocytomas

In the cases studied by silver impregnation, no non-tumoral astrocytes were found in hemispheric low grade astrocytomas, nor in cerebellar astrocytomas. On the other hand, malignant astrocytomas showed some adult astrocytes, sometimes well preserved and sometimes swollen, specially in the peripehral areas and surrounding the blood vessels (Fig. 1A). Recurrences of astrocytomas showed many multipolar astrocytes mixed with the tumoral cells (Fig. 1E). With this method, the immature neoplastic cells remained weakly stained, in contrast with the high definition of adult astrocytes.

The low grade astrocytomas either from the cerebral hemispheres or from the cerebellum, studied by PAP method for GFAP, showed inconspicuous pictures similar to those of the silver impregnation. The tumoral cells were highly positive so that adult astrocytes, if present, could not be differentiated from the tumoral ones. Malignant astrocytomas showed very complex images, with many positive neoplastic cells mixed with some adult astrocytes (Fig. 1B). As both types of cells were simultaneously stained, their differentiation, if not impossible, is very difficult.

Glioblastomas

The group of glioblastomas stained by silver impregnation showed a weak stain of tumoral cells. On the other hand, a high number of adult astrocytes was found, specially around the blood vessels and taking part in the peritumoral reactive gliosis. These cells lying among the neoplastic ones, frequently showed involutive stigmata, such as clasmatodendrosis, and a high argentophilia or cytoplasmic swelling. Because of this contrast between the non stained tumoral cells and adult astrocytes, the differentiation of both types of cells was very clear (Fig. 1C).

The PAP method revealed a similar stain of adult astrocytes showing similar pictures as those of silver impregnation. These cells were frequently perivascular and showed the same involutive images. However, as in the case of malignant astrocytomas, this method also stained the most differentiated tumoral cells, so that the distinction between the two cell populations was difficult (Fig. 1D). In our experience, the positive stain of macrophages loaded with GFAP detritus, which has been reported as a cause of mistake, has not been a problem for the interpretation of microscopic images.

Oligodendrogliomas

All the cases studied with silver impregnation showed very demonstrative images. A high number of astrocytes were found among the unstained tumoral cells, specially around the blood vessels. These astrocytes were well preserved and they were strongly related to the peritumoral gliosis. The method showed a sharp difference between the high positivity to silver reagent and the negativity of tumoral cells, thus avoiding an eventual mistake (Fig. 2A).

The results of GFAP study were similar to those of silver impregnation, with positive astrocytes lying among negative oligodendrocytes and surrounding the blood vessels (Fig. 2B). Conventional oligodendrogliomas were GFAP negative, but gliofibrillar and eosinophilic oligodendrocytes were positive to GFAP as well as to silver method.

Medulloblastomas and PNET

Silver impregnation showed a high number of

Table 1. Cases studied with silver impregnation

TYPE	NUMBER
Astrocytomas of the brain hemispheres	
Low grade	5
Malignant	3
Recurrences	2
Cerebellar astrocytomas	4
Glioblastomas	20
Oligodendrogliomas	5
Ependymomas	5
Medulloblastomas	6
Meningiomas	16
Metastasis	19
Brain lymphomas	2
TOTAL	89

Table 2. Cases studied with PAP method

TYPE	NUMBER
Astrocytomas of the brain hemispheres	
Low grade	13
Malignant	19
Cerebellar astrocytomas	8
Glioblastomas	22
Oligodendrogliomas	6
Ependymomas	2
Medulloblastomas	5
Central neurocytomas	2
Cerebellar mixed tumor	1
Meningiomas	22
Metastasis	24
Brain lymphomas	3
TOTAL	127

Fig. 1. Adult astrocytes, frequently in relation to blood vessels demonstrated by silver impregnation in: **A.** Malignant astrocytoma; x 100. **C.** Glioblastoma; x 200. **E.** Recurrent astrocytoma; x 600. Similar astrocytes demonstrated by GFAP in: **B.** Malignant astrocytoma; x 200. **D.** Glioblastoma; x 400

astrocytes in all medulloblastomas while tumoral cells remained unstained. The astrocytes showed a very definite, adult, well-preserved morphology without intermediate cells between them and medulloblasts. They were located surrounding the blood vessels and under the pia (Fig. 2C).

The immunohistochemical images were the same as the preceding ones in medulloblastomas with high GFAP-positive astrocytes lying among the negative tumoral cells (Fig. 2D). Only occasionally some histiocytes with intracytoplasmic GFAP-positive material were found in the perivascular spaces and in the vicinity of necrotic areas. In a case of mixed cerebellar tumor, some astrocytes lay on the borderline between the neuroblastic fields and the tracts (Fig. 2G). In the 2 central neurocytomas, astrocytes lay in the periphery of all clusters, and in the tracts of neuropil they were among them (Fig. 2E). Also in the central neuroblastoma some astrocytes were demonstrated without any intermediate stages between them and the undifferentiated tumoral cells (Fig. 2F).

Ependymomas

The results of silver impregnation in these tumors were the poorest in our series of neuroectodermal CNS tumors. Only a few isolated adult astrocytes were present, showing involutive images, clasmatodendrosis, swelling, etc (Fig. 3A).

Some GFAP-positive adult astrocytes were also present in the immunohistochemical study. However, these images were more confusing than those of silver impregnation, as many tumoral cells were also GFAP-positive, especially those lying around the blood vessels in pseudorossettes (Fig. 3B).

Meningiomas

In many cases of meningiomas adult astrocytes could be found by both methods. They constantly lay in the surrounding subyacent, compressed brain tissue or in tracts of brain tissue among the peripheral nodules of the tumor. They were never found among the tumoral cells (Fig. 3C).

Metastasis

Surrounding the carcinomatous metastasis, a very active peritumoral gliosis could be demonstrated by both silver impregnation and immunohistochemistry. These astrocytes frequently showed progressive or involutive images, with argentophilia and/or swelling. When the tumor grew with multiple confluent nodules, tracts of reactive brain tissue could remain among them, showing hypertrophic astrocytes within the residual neuropil (Fig. 3D).

As in case of meningiomas, the astrocytes found in the metastasis did not belong to the tumoral tissue itself, but to the invaded CNS tissue.

Lymphomas

In our series of lymphomas, silver impregnation demonstrated some astrocytes, sometimes with special features -argentophilia, swelling- or showing involutive vacuoles and clasmatodendrosis, among the tumoral cells and among the numerous microglia cells (Fig. 3E).

GFAP also demonstrated astrocytes showing a higher contrast between them and the lymphoma cells and microglia, since this method specifically stained the former, the latter remaining negative (Fig. 3E).

Discussion

Specific methods like Cajal's gold sublimate, Rio-Hortega's silver impregnation and the immunohistochemical method for GFAP allows one to find a high number of astrocytes in gliomas, with the morphology of differentiated cells.

Frequently, their presence has been considered dependent on tumoral cells of higher degree of differentiation, as in the case of malignant astrocytomas and glioblastomas, on astrocytic differentiation of undifferentiated multipotential cells, as in medulloblastomas and PNET, or on simultaneous proliferation of two cell lines, as in mixed gliomas. The possibility of persistence of astrocytes belonging to the invaded tissue and included in the tumoral mass during the neoplastic growth has only occasionally been considered.

However, the consideration of these cells as a part of the tumoral cell population involves some difficulties. Focal astrocytic differentiation in astrocytomas and glioblastomas or initial differentiation in neuroectodermal undifferentiated neoplasms can be seen, but such phenomenon seems to be doubtful in oligodendrogliomas, ependymomas and in non neuroectodermal tumors, such as meningiomas, metastasis and lymphomas. Furthermore, the interpretation of these cells is made difficult because in most reports they are referred to as a single type of tumor using a single method. On the other hand, the use of two different stains for astrocytes (silver impregnation and GFAP) and specially, the study of many different groups of tumors reveals that the cytological characteristics and the topographic distribution of intratumoral astrocytes is always the same in all cases.

1. Technical aspects

The method of gold sublimate requires formol-bromure-fixed material. Its excellence in normal tissue decreases in pathological or tumoral material. This is the reason why it has been rejected.

Silver carbonate impregnation is an empiric technique, in which silver precipitates on argentophilic cell surface. The cold variant for oligodendroglia and microglia (Rio-Hortega, 1920), modified by Polak (1966), impregnates the hypertrophic astrocytes, while neoplastic cells remain unstained.

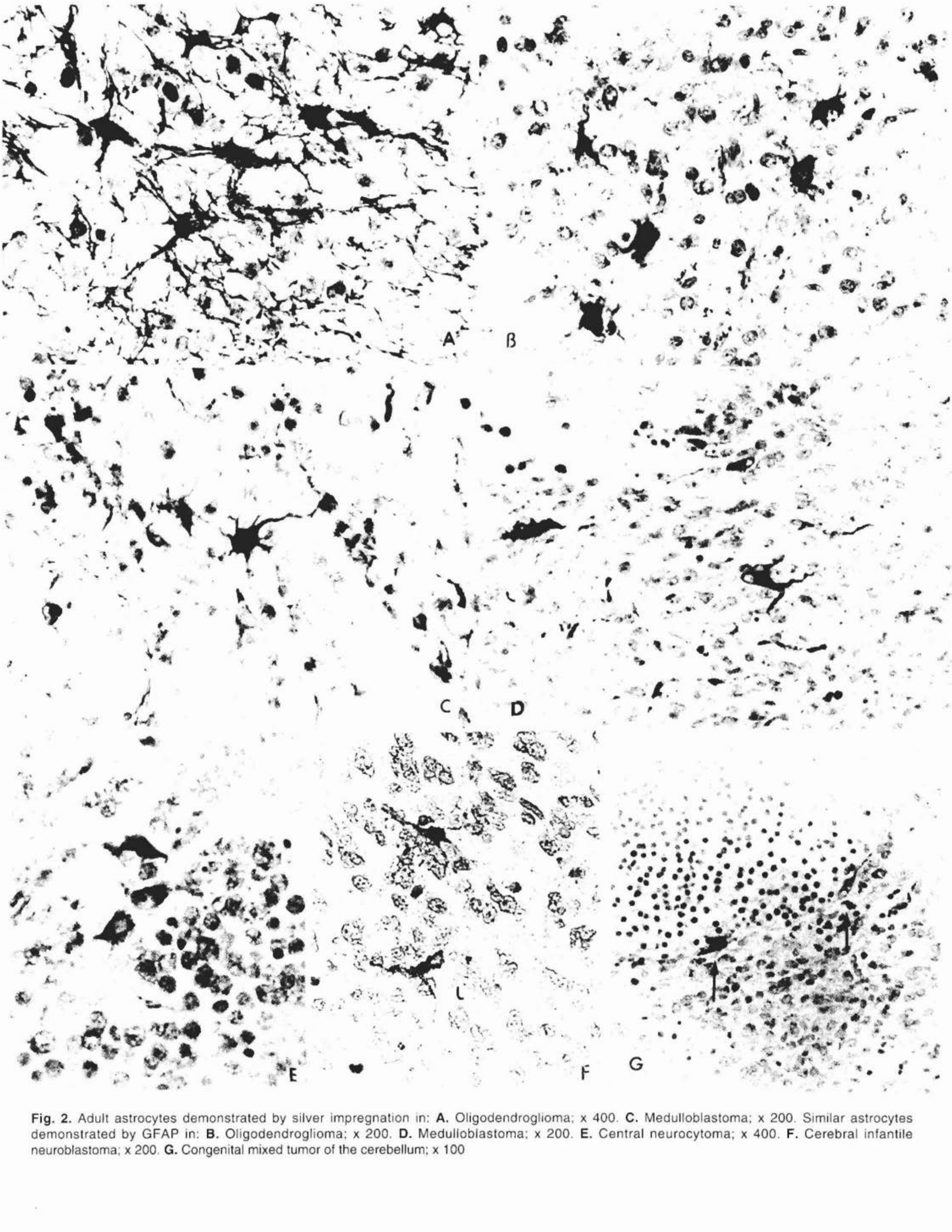

Fig. 2. Adult astrocytes demonstrated by silver impregnation in: **A.** Oligodendroglioma; x 400. **C.** Medulloblastoma; x 200. Similar astrocytes demonstrated by GFAP in: **B.** Oligodendroglioma; x 200. **D.** Medulloblastoma; x 200. **E.** Central neurocytoma; x 400. **F.** Cerebral infantile neuroblastoma; x 200. **G.** Congenital mixed tumor of the cerebellum; x 100

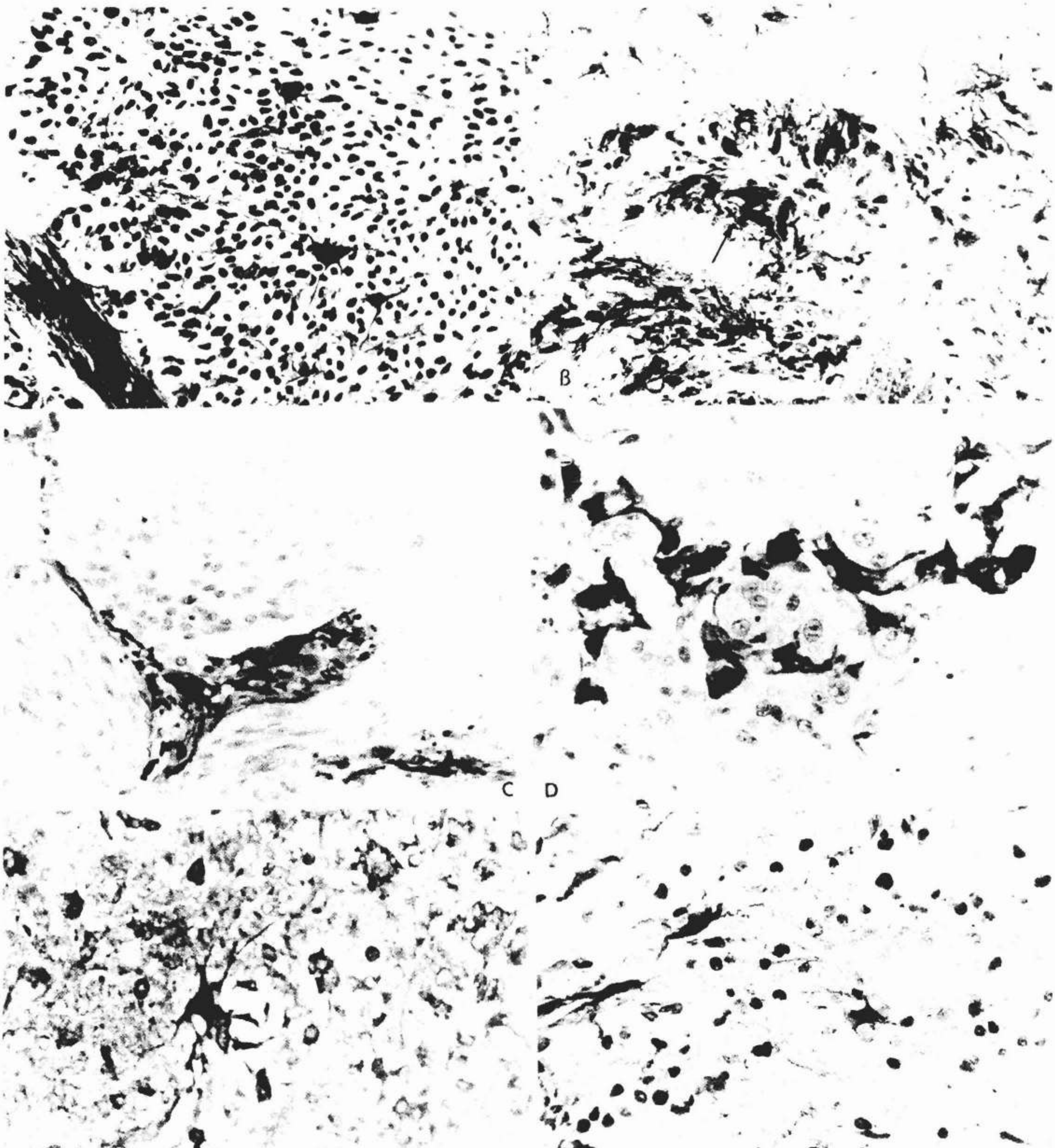

Fig. 3. Adult astrocytes demonstrated by silver impregnation in: **A.** Ependymoma; x 200. **E.** Brain lymphoma; x 400. Similar astrocytes demonstrated by GFAP in: **B.** Ependymoma; x 100. **C.** Meningioma; x 200. **D.** Carcinomatous brain metastasis; x 400. Brain lymphoma; x 200

GFAP technique offers the highest reliability and reveals the specific protein in astrocyte cytoplasm. Its realization is quite simple and its positivity offers histochemical value (Rubinstein, 1982).

However, there are a few conditions which modify the application of both techniques. Rio-Hortega-Polak's method defines all the non tumoral astrocytes, leaving neoplastic cells only as shadows and is a good aid for the identification of such astrocytes. PAP stain demonstrates every cell containing this protein, but because of this, it shows not only normal astrocytes but, also the most differentiated astrocytic tumoral cells, some cells of ependymomas and oligodendrogliomas as well as macrophages fagocyting GFAP.

2. Cytological aspects

The gliomas of the astrocytoma-glioblastoma group and the ependymomas offer the greatest difficulties, as in nearly every case some relatively mature cells can be found. In these cases silver impregnation offers better results, as it is capable of staining adult astrocytes while tumoral cells remain unstained. PAP method stains not only adult astrocytes but also intermediate differentiated cells. However, their morphology and their perivascular location is the same as those of the astrocytes found in the other groups of this study.

The slow growth of the low grade astrocytomas results in a scarce reactive gliosis and in the death of astrocytes before their engulfing among the tumoral cells. Probably this, and not the insufficiency of both methods, is the cause of their absence.

In oligodendrogliomas, the distinction between tumoral cells and astrocytes is obvious. Only the eosinophilic cells of some oligodendrogliomas (Takei et al., 1976; Escalona Zapata, 1981) and the gliofibrillary oligodendrocytes (Herpers and Budka, 1984) are GFAP-positive. But the morphology of such GFAP-rich oligodendrocytes is quite different from true astrocytes which are always larger, multipolar and located in perivascular areas.

This is also the case of undifferentiated neuroectodermal tumors, not only medulloblastomas, but also central neurocytoma (Hassoun et al., 1986), mixed cerebellar tumours (Gullotta, 1966) and PNET (Rorke, 1983). In these tumors, some little GFAP- and silver-positive cells can be found as a sign of focal astrocytic differentiation, but the majority of the positive cells are large, adult, multipolar astrocytes with a tendency to locate around the vessels, near the arachnoid and on the border between the tumor and the invaded brain tissue.

The differences between astrocytes and tumoral cells are highest in ependymomas. In these tumors, the scarce astrocytes are quite different from the ependymocytes, even from those GFAP-positive cells taking part in the gliovascular rosettes (Cruz-Sánchez et al., 1988). The astrocytes lie in the perivascular areas and show quite normal features.

Finally, the demonstration of some astrocytes around meningiomas, lymphomas and metastasis supports the concept that in both types of growth -aggressive in metastasis, slow in meningiomas- areas of invaded CNS tissue can be included in the tumor. In these cases the perivascular distribution of the astrocytes is most obvious. These findings invalidate an eventual tumoral origin of such astrocytes, supporting their preexistent nature.

Thus, in our series, the astrocytes included in brain tumors showed common cytological characteristics in all groups studied. They had the morphology of adult astrocytes with a variable amount of cytoplasm and many radial processes. Sometimes, as in medulloblastomas and oligodendrogliomas, their morphology was slightly different from the normal astrocytes, while, in glioblastomas and malignant astrocytomas, involutive images appeared with cytoplasmic vacuoles, thickened processes and eventually clasmatodendrosis. It is also significant that in our series no intermediate cells were found between the undifferentiated tumoral cells and these astrocytes.

3. Topographic aspects

The distribution of the adult astrocytes is irregular but they tend to accumulate in the periphery of the tumors or around the blood vessels. The closer they are to the vascular tree, the better preserved they are, while involutive images appear when astrocytes lie further away from the vessels. This fact contrasts with the behaviour of the tumoral tissue, in which the most undifferentiated cells lie near the vasculature, while the highest differentiated ones are far away.

They have never been found in arachnoidal metastasis of malignant gliomas which have shown astrocytes in the intracerebral location (Cox, 1933; Zülch, 1940; Coffin, 1983).

Also, some biological characteristics of gliomas play a role in their presence. A strongly reactive peritumoral gliosis facilitates the inclusion of astrocytes among the tumoral cells, as happens in glioblastomas, malignant astrocytomas and metastasis as well in the recurrences of gliomas. Also, the aggressive growth, quickly invading the adjacent tissue, as in glioblastomas and malignant astrocytomas, is an important factor. The slow but infiltrating growth with dissection of the brain tissue, characteristic of oligodendrogliomas (intra and interfascicular growth of Scherer, 1938) has the same consequence. In medulloblastomas and lymphomas, both mechanisms -infiltrating and dissecting growth- coexists. On the other hand, the lack of astrocytes in the true tumoral tissue in meningiomas and metastasis, where they are located in the peripheral areas or in the tracts of brain tissue lying among the neoplastic foci, is due to the expansive behaviour of both types of growth.

The inclusion of host structures in malignant tumors is not exclusive to gliomas. The enclosure of lung alveoli inside lung carcinomas and the presence of normal follicles inside thyroidal anaplastic carcinomas have been reported (Alvarez Fernandez, 1982; Rosai et al., 1985).

It is concluded that mature astrocytes found inside gliomas cannot always be considered as dependant on the differentiation of neoplastic cells, but that most of them are cells belonging to the invaded tissue.

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