Primary Sarcoma of the Reticuloendothelial System of the Brain

Report of a Case

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This report describes the morphological features of a primary intracerebral neoplasm which warrants classification as a reticulum cell sarcoma. Evidence is presented to demonstrate that this tumor arose from the adventitial histiocytes and provides an exceptionally clear example of the distinctive origin of this type of neoplasm. Criteria useful for recognizing this type of tumor and necessary for its diagnosis are presented.

Case Report

The patient was a 70-year-old white woman who was transferred to Mercy Hospital on March 10, 1964, in coma. There was a past history of gradual mental deterioration, slurring of speech, headaches, and vomiting for several months before her lapse into coma, which occurred 9 weeks before admission.

Examination. The neurological examination showed a comatose elderly woman who responded only to painful stimulation by weakly moving all 4 extremities. There were no lateralizing signs and no papilledema. The Babinski extensor response was present bilaterally. A lumbar puncture done 4 days later, revealed slightly xanthoehromic spinal fluid with an opening pressure of 200 mm. of water. The fluid contained 216 mg. of protein per 100 ml. and 3 lymphocytes. Her level of consciousness varied from day to day, but was never normal. Ventriculography revealed a moderate enlargement of the lateral ventricles without displacement. Air was present in the subarachnoid space over the cerebrum and cerebellum but not within the cerebral aqueduct or 4th ventricle. Pneumoencephalography did not visualize the ventricular system.

Course. Coma increased and she developed lateral and vertical nystagmus and quadripareisis more marked on the left side. She died on May 24, 1964, 21 months after admission.

Post Mortem Examination. The cerebral hemispheres appeared roughly symmetrical and edematous. On coronal sections the brain showed marked symmetrical dilatation of both lateral ventricles, and slight dilatation of the 3rd ventricle. In the region of the basal ganglia and hypothalamus there were two independent slightly hemorrhagic tumor nodules 1.5X2.5 cm. on each side. These extended from the anterior cerebral commissure back to the hypothalamus for a distance of 3.5 cm. The cerebellum contained a large, fairly well circumscribed tumor in the left hemisphere. It measured 3X4X3.2 cm. and had almost completely obliterated the 4th ventricle. The tumor appeared to be the result of the union of two smaller tumor nodules. The cerebral aqueduct was patent.

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FIG. 1. Phagocytic tumor cells in the hypothalamus. Note abundance of mitotic figures and prolongation of the cytoplasm in some of these cells. (H. & E. X375.)

Microscopic examination of the various tumor nodules disclosed a similar cytologic pattern. The tumor cells were moderately pleomorphic. Most had an elongated indented nucleus with a prominent and dispersed chromatin network, indistinct nuclei, and a moderate amount of eosinophilic, sometimes vacuolated, cytoplasm. Frequently irregular, pseudopod-like projections of the cytoplasm were noted which were suggestive of a phagocytic type of activity (Fig. 1), and ingested particulate material was present in an occasional cell. Interposed between the tumor cells there were numerous rod cells and smaller cells with round hyperchromatic nuclei and small amounts of eosinophilic cytoplasm quite similar to reactive microglial cells present at the periphery of the tumor. There were numerous small areas of necrosis and large numbers of abnormal mitotic figures. In some areas of tumor, the overlying leptomeninges appeared infiltrated by tumor but there was no evidence of diffuse meningeal involvement. Microscopic examination of other areas of the brain showed the tumor to be multifocal, with numerous large and small foci of tumor present in the corpus callosum, medulla, and cerebrum. None of these areas showed abnormalities on gross examination. The different, independent foci of tumor were all similar in cellularity and degree of malignancy. Frequently the tumor cells were seen arising from the adventitial layer of small and medium size blood vessels (Figs. 2 and 3) as well as from capillaries (Fig. 4).
Tumor cells stained by Penfield's modified silver carbonate method for microglia and oligodendroglia, revealed no cytoplasmic metallophilia, although the nuclei were strongly argyrophilic. No glial fibrils were observed after staining with Mallory's phosphotungstic acid hematoxylin. However, strands of coarse and fine reticulin fibrils generally unrelated to blood vessels were observed in different areas by Gomori's reticulin stain (Fig. 5). There were no foci of tumor elsewhere in the body, and there was no evidence of a primary tumor in other organs which could have given rise to cerebral metastases. Thus, the cerebral origin of the neoplasm was established beyond reasonable doubt. Pathological findings in other organs included bilateral pneumonitis with mild emphysema, fibrous pleural adhesions, pulmonary edema, and arterionephrosclerosis.

Discussion

The reticulum cell sarcoma is a malignant tumor which stems from the reticulum cell or primitive histiocyte. In the central nervous system there are three representatives of this cell series. These are the microglial cells, the cells present in the adventitial sheaths of blood vessels,
and the cells lining the perivascular spaces. This perivascular connective tissue layer within the central nervous system surrounds arteries, arterioles, veins and venules but not capillaries. It is considered to be an invagination of the subarachnoid space along the walls of vessels as they leave this space to enter the brain substance.

The relation of microglia to cells of the reticuloendothelial system of other tissues became evident when Russell, using aseptic puncture wounds in the cerebrum of experimental animals as a stimulus to phagocytosis, demonstrated the ability of these cells to store trypan blue. During the same experiment, granules of dye were also conspicuous in ameboid and spindle-shaped cells lying in the adventitia of the blood vessels and leptomeninges near the wound.

According to Dunning and Furth, microglia and histiocytes are morphologically and functionally identical and constitute a single cell type. In their resting state, the microglia, adventitial histocytes, and leptomeningeal histiocytes are located in different regions of the brain. The microglia are found free in the gray matter and to a lesser extent in the white matter. The adventitial and leptomeningeal histiocytes are closely associated with the blood vessels. Each may give rise to the tumor cells that characterize neoplasms of the reticuloendothelial system. The cytological characteristics of these tumors seldom justify identification of the specific cell type involved unless one is able to establish unequivocably the specific area within the brain from which the tumor cells originated.

The histological diagnosis was established by the morphologic pattern of the tumor cells which showed phagocytic-like activity, elongated, indented nuclei with indistinct nucleoli, multifocal vascular origin, and the presence of reticulin fibers. Support is added to the theory of reticuloendothelial origin of the tumor cells, since reticulum cells are capable of forming these fibers. Although microglial phagocytes were widely disseminated throughout the tumor, the majority of the tumor cells were not microglial phagocytes and were not stained by Hortega’s silver carbonate method. According to Marshall, this is a basic stain in differentiating reticulum cell sarcoma from microglioma. Penfield demonstrated similar microglial cells in gliomas although in lesser number and established that their function is restricted to dendrophagocytosis. Unlike astrocytes and oligodendroglial cells, these microglial phagocytes multiply by mitosis and it is not uncommon to see mitotic figures in these cells. They are therefore liable to be confused with neoplastic cells. The frequency of cells in mitosis scarcely seems enough to account for their great number in foci of tissue damage. It is probable that they are augmented by the influx of histiocytes from the perivascular tissue.

Neoplasms of the reticuloendothelial system of the brain have been described in the literature under a variety of titles, some of which are perivascular sarcoma, perithelial sarcoma, reticulum cell sarcoma, and microgliomatosis. Zülch states that such tumors should remain unclassified for the time being. Most of the confusion as to the proper nomenclature of this group of tumors, stems from the various definitions of a reticulum cell. This cell has been defined as either a primitive undifferentiated stem cell or the histiocyte that derives from it. The primitive reticulum or stem cell is neither phagocytic nor metallophilic and is not a part of the reticuloendothelial system. It is a primitive multipotent cell that can give rise to the fixed tissue histiocyte or macrophage. Microglial histiocytes are phagocytic; they become impregnated with silver carbonate stains to varying degrees, and they belong to the reticuloendothelial system by virtue of their phagocytic ability. Thus, the arguments concerning classification of these tumors are largely semantic. The various terms used for these tumors of single cell origin and somewhat variable characteristics are greatly dependent on the state of differentiation of the cells comprising any one tumor and in the interpretation of the term “reticulum cell” given by pathologists.

Although the classification of these tumors is relatively clear, the exact cell of origin is still controversial. In many of the cases reported, no attempt was made to determine the exact site of origin of the tumor. It has often been stated that the tumor arose from the adventitial cells of the perivascular spaces. Bailey in 1929 described a primary sarcoma of the brain under the name perithelial sarcoma. He felt that the tumor originated from the leptomeninges over the surface of the brain or from the perivascular extension of the leptomeninges surrounding the penetrating blood vessels which he termed perithelium. Yuile in 1938 described a primary brain tumor that he called a reticulum cell sarcoma. He suggested its origin from the undifferentiated mesenchymal cells, the derivatives of which are the various tissue phagocytes of the body. Hsi in 1940 concluded that primary sarcomas of the brain, which reproduced the structure of sarcomas elsewhere in the body, must arise from the leptomeningeal tissue either over the surface of the brain or around the blood vessels. Abbott and Kernohan in 1943 described 12 cases of primary sarcomas of the brain which they classified as fibrosarcoma (3 cases), perithelial sarcoma (7 cases), and sarcomas of unknown type (2 cases). They concluded that perivascular sarcomas of the brain probably originate from any connective tissue situated within the brain or from the pia mater deep in the sulci. Kinney and Adams reported 2 cases of primary intracranial sarcoma which they classified as reticulum cell sarcoma. They favored...
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Feigin et al. have described hyperplastic vascular changes in the presence of primary cerebral tumors, generally malignant, and most marked with the glioblastoma multiforme. The cellular hyperplasia may assume neoplastic properties forming a sarcomatous tissue intermingled with the pre-existing glioblastomatous tissue. In our case, the affected blood vessels were seen frequently in areas of normal brain tissue; furthermore, no tumor emboli were present in the perivascular spaces or lumina of any blood vessels. If one assumes that the involvement of the blood vessels is an expression of tumor spread through the perivascular connective tissue, the theory that this type of intracranial sarcoma was derived from primitive reticulum cells, the progenitor of the meningeal histiocyte or microglial cell. Russell et al. in 1948 reported 7 cases of focal tumor-like proliferation in the brain which they designated by the term microgliomatosis. In 4 of their cases the lesions were confined to the brain, while in the remaining 3 cases there were similar proliferations in other organs of the body, particularly in those that were the main sites of the reticuloendothelial system. They considered the tumor cells to be microglia that had undergone neoplastic growth rather than a proliferation of the reticulum cells. With specific silver impregnation techniques they recognized 3 types of lesions. They based their classification on the studies of Marshall who showed that the microglial cell will become impregnated with Del Rio-Hortega silver carbonate stain, while the primitive reticulum cell will not. They concluded that proliferation of microglial cells can take a tumor-like form. Since microglial cells evolve from the primitive reticulum cells present in the brain as well as elsewhere, it is not surprising that variable numbers of the latter are demonstrated in most forms of microgliomatosis. The exact origin of the microglia cell is not definitely known. Del Rio-Hortega in his studies, concluded that the microglia cells arise late in the embryonic life from mesenchymal cells in the pia mater and also from the adventitial histiocytes around blood vessels.

Demonstration, in our case, of the precise origin of the tumor cells from the adventitia of the blood vessels gives added support to the theory that the tumor originates in the vascular histiocyte. Burstein et al. in a review of neoplasms of the reticuloendothelial system of the brain in 1963, classified them arbitrarily into reticulum cell type, microglial type, Hodgkin's type, and mixed type. They demonstrated that these various subgroups differed only in the abundance of one or another cell type, but were similar in histological appearance and clinico-pathological behavior. They concluded that the tumor originated in the perivascular connective tissue. The assumption that these tumors originated in the adventitial coat of the blood vessels has been mentioned by different authors in a vague and inconclusive form. The reports show only a few isolated blood vessels affected in this way. In our case, numerous affected blood vessels were present and in a section through the medulla almost all blood vessels including the capillaries were involved (Figs. 6 and 7). The tumor cells may be seen arising distinctly from the adventitial layer of the wall of the vessel without invasion of the media or intima (Fig. 8).

The fact that the capillaries do not have a Vichow-Robin space precludes the origin of the tumor from this perivascular connective tissue.

Fig. 6. Small capillaries in the medulla, showing distinctly the tumor cells arising from their adventitial wall. (H. & E. ×575.)

Fig. 7. Small artery in the medulla, with tumor cells arising from the wall. (H. & E. ×575.)
lar spaces, one would expect to find diffuse invasion of the entire vessel wall, rather than a sharp localization to its adventitia, as in our case.

These tumors may have other sites of origin, but we wish to emphasize that they do originate from the adventitia of the cerebral blood vessels, and that this fact may explain the multifocal origin of the tumors as in our case. The extremely short clinical history may be attributable to the rapid growth of the tumor from multifocal sites of origin.

Summary

A primary multifocal neoplasm of the brain, diagnosed as a reticulum cell sarcoma, is presented. Diagnosis is based on the phagocytic activity of the tumor cells, the presence of transitional mature microglial cells and of reticulin fibers, and the absence of cytoplasmic metallocphilia. Morphological evidence is presented to emphasize that this type of tumor can originate from histiocytes in the adventitia of the wall of blood vessels.

References