Primary Reticulum-Cell Sarcoma of the Brain

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Primary brain sarcomas possessing a “reticulum-cell” histologic profile are known to have certain common morphologic features. Among them, the usually cited are the uniformity of cellular characteristics, the presence of argyrophilic reticulin, the fairly characteristic tumor-cell cuffing of the blood vessels within a concentrically laminated frame of perivascular reticulin, the absence or presence of cytoplasmic argyrophilia with Hortega’s silver-carbonate method, the absence of neuroglia, the topographic predilection for the cerebral hemispheres and the high degree of malignancy manifested by the extremely short survival period of patients who harbor them.16,23,28

A variety of histologic types have been described. The important contributions of del Río-Hortega22 shed new light into the histogenesis of these tumors and made differential diagnosis from glial tumors much easier.

In view of the relative rarity of reticulum-cell sarcoma of the brain it seemed worth while to present the clinical and pathologic features of the following case.

Case Report

A 34-year-old, married, white female was admitted to the Jewish Chronic Disease Hospital in September 1961, transferred from another hospital, after a prolonged illness approximately 7 years in duration.

In 1954, the patient had onset of intermittent severe headaches associated with some visual disturbances. Initially these attacks were of daily occurrence, a few seconds in duration and characterized by “objects bobbing up and down with distortion of vision.” During these brief episodes, it was not possible for the patient to walk. In the beginning rest in bed was sufficient to permit her to return to her normal state.

In 1956–1957, the patient was admitted to two different institutions because of a return of symp-
3,500,000 per c.mm. and count of white blood cells was 10,550 per c.mm. Repeated urinalyses were unremarkable. Fasting blood sugar was 72 mg. per 100 ml. and urea nitrogen was 10 mg. per 100 ml. Total serum proteins were 6.5 gm. per 100 ml. with 2.8 gm. of albumin and 3.7 gm. of globulin. The cephalin flocculation test was 3+ in 48 hours and the thymol turbidity 3.9 units. A serum-protein electrophoresis showed an extremely high alpha1 fraction as well as an increase in all globulin fractions and decrease in the albumin fraction. The serum glutamic-oxaloacetic transaminase was 42 units and the glutamic-pyruvic transaminase 50 units. Lumbar puncture a few days after admission yielded clear, transparent fluid with an initial pressure of 340 mm. of water; glucose was 82 mg. per 100 ml., protein was 144 mg. per 100 ml. and count of cells in spinal fluid was 3 cells per c.mm. Roentgenograms of skull and chest showed no abnormal changes. An electroencephalogram indicated a "diffuse dysfunction, possibly greater in the right hemisphere." Electromyography showed changes compatible with a peripheral neuropathy.

Course. The patient was treated with Prednisolone (30 mg. per day), Dilantin and vitamin preparations. Increasing amounts of sedation were required because she was noisy and occasionally belligerent. During the 2nd week of hospitalization the patient became transitorily incontinent. In the 5th week there was one short episode of seizure, unaccompanied by incontinence. Five days prior to death, a sudden rise in temperature (105°F.) developed and the patient became lethargic. Bed sores and purulent vaginitis also were noted at this time. Fever persisted in the succeeding 2 days despite the extensive use of antibiotics. The patient showed a total lack of cooperation and also there were involuntary movements of all limbs. One observer also described nuchal rigidity unaccompanied by Kernig's sign. Tendon reflexes were normal and eyegrounds showed no abnormalities. The emaciation and generalized atrophy of muscles became more and more prominent. Patient's attitude was characterized by greater agitation. One day prior to death another lumbar puncture was performed; the fluid was clear and unremarkable biochemically. Following this procedure, she became more unresponsive and exhibited shallow respirations. The temperature exceeded 107°F. on the following day and was accompanied by basilar pneumonitis. The blood pressure became labile and she expired on Nov. 11, 1961.

Autopsy. The principal findings were limited to the brain and lungs. The brain weighed 1310 gm. The cerebral hemispheres were asymmetric grossly, the right one appreciably larger than the left and distorted by a large mass located in the temporal and occipital lobes and protruding through, up to the plane of the basilar leptomeninges (Fig. 1). After fixation in 10 per cent neutral formalin, coronal sections disclosed a single, well circumscribed mass located principally in the parietal, temporal and part of the occipital white matter of the right cerebrum. The line of demarcation between the neoplasm and surrounding tissues was established sharply and in places a clear cleavage was possible. The growth was extremely dense, granular and colored a dark brownish-green.

Histologic Study. Sections of formalin-fixed tissue were stained with hematoxylin and eosin, phosphotungstic-acid hematoxylin, Masson trichrome and Gomori's stain for reticulin. Frozen sections of wet formalin tissue were stained by del Rio-Hortega's method for microglia.

The capsule described grossly was composed of collagenous tissue (Fig. 2) with intervening collections of hemosiderin. A considerable proportion of the neoplasm had undergone cystic degeneration and hemorrhage. However, at the inferior margin of the cystic encapsulation was a considerable mass of tumor composed of fairly uniform cells, characteristically averaging 13 to 20 microns in diameter, spherical and ovoid in external contour with a centrally located nucleus. No significant processes could be seen emerging from the tumor cells. In many areas, the cytoplasm was sharply defined and amphiphilic in staining characteristics (Fig. 3). In other areas, it was difficult to outline its borders. The phosphotungstic-acid hematoxylin stain showed no fibrils arising from the tumor cells. A characteristic feature was given by the presence of thick-walled blood vessels. A Masson trichrome stain showed the wall to be composed of rather thick bands of collagen. The lumen of these blood vessels was considerably small in comparison to the diameter of the entire cross section of the vessels. Sections stained for reticulin by Gomori's method revealed delicate fibers arranged concentrically and streaming radially from the above mentioned vessels, commonly separating or enclosing groups of tumor cells (Fig. 2).
Section 4. Sections stained by microglial techniques failed to show argyrophilic material within the cytoplasm of the neoplastic cells.

Grossly, the tumor did not appear to extend beyond the limits of the capsule, but sections from the edges of the tumor disclosed that the growth had invaded the brain tissue by perivascular extension. In fact, there was a peculiar hyperplasia of the surrounding vessels with cuffing by neoplastic cells in the Robin-Virchow spaces. These areas demonstrated a well defined reticulin enclosing two or more blood-filled vascular spaces (Fig. 5) suggesting a hyperplasia of the blood vessels with secondary arrangement of the perivascular reticulin. In close contact with the fibers of reticulin were sheets of tumor cells (Fig. 6). The intervening brain tissue showed a considerable number of reactive astrocytes with some hemosiderin and the products of cellular degeneration.

No neoplasm was found anywhere else. The right and left lungs appeared similar grossly. They were dark red-blue and subcrepitant. Microscopic

Fig. 2. Low-power view of portion of tumor (lower half) separated from the cerebral tissue by a fibrous capsule (arrow). Hematoxylin and eosin, ×50.

Fig. 3. High-power view of the tumor. The cells are spherical or ovoid in shape and contain a fairly large, vesicular nucleus. Hematoxylin and eosin, ×380.
sections showed bronchopneumonia and moderate congestion.

Comments

The concept of primary brain sarcoma was not well established until 1929, when Bailey5 defined its histological characteristics and outlined its possible histogenetic basis. He classified the sarcomata of the brain into four categories: (1) perithelioma, (2) perithelial sarcoma, (3) fibroblastoma and (4) alveolar sarcoma. Although the peculiar perivascular cuffing of neoplastic cells had been observed previously, he recognized the importance of the presence of reticulin in the definition of this tumor as one of mesodermic origin. Abbott and Kernohan1 reported on 12 cases of primary sarcoma of the brain and proposed a classification of such tumor into three histologic types, namely: (1) fibrosarcoma, (2) perivascular sarcoma ("perithelial" or "adventitial" sarcoma), and (3) sarcoma of unknown type. They pointed out the extreme malignancy of the perivascular sarcoma, a fact which was borne out by the short survival period of those patients who sustained it and established the importance of the tumor-cell cuffing, the concomitant formation of rings of reticulin around the vascular spaces and the relatively uniform morphology of the neoplastic cells as diagnostic criteria for this type of tumor. Kinney and Adams17 discussed the histogenetic basis of mesoblastic brain neoplasms. According to them, two types of cells of mesenchymal tissue could be responsible for the development of the reticulum-cell sarcoma: (a) the histiocyte and (b) the microglia. The histiocytes are present in the leptomeninges and in the perithelium of the cerebral vessels. The microglial cells are present as such throughout the cerebral tissue. A tumor from the first type of cells would be a reticulum-cell sarcoma while a malignant growth of the second type of cells should be called a microglioma. Russell and Rubinstein24 stated that a histological differentiation is possible using the Hortega silver-carbonate method which demonstrates the characteristic mettallophilic properties of the microglia. The ameboid cellular morphology and a pronounced peritumoral increase of fibrillary astrocytes would be other diagnostic features of such tumors. Geréb,11 in reporting a primary reticuloendotheliosis of the brain in a 27-year-old man, characterized by multiple tumor foci located in the diencephalon and

Fig. 4. Fibers of reticulin are arranged concentrically around thick-walled blood vessels. Others are converging towards the blood vessels, separating the tumor cells. Gomori's silver stain, ×375.
vicinity of the fourth ventricle, emphasized the similarity in the distribution of the tumor in his case with the ontogenetic patterns of microglial migration.

The problem is still unsettled as some authorities\(^1\) believe that the microglial cells do not undergo neoplastic transformation. Others\(^6,28\) used the terms “reticulum-cell sarcoma” and “microglioma” interchangeably after the neoplastic cells in their cases proved to be positive by the silver-carbonate method. Still others have demonstrated the reactive response of mesodermal elements to the presence of glial tumors in such a fashion and proportion that a careful histological study is necessary before deciding upon the pathological category of a given tumor. Wilke,\(^27\) in a report of 6 cases of space-occupying granulomatous processes of the brain, made reference to an “inflammatory reticuloendotheliosis or granulomatous encephalitis,” which would establish the morphological basis for the transition from inflammatory to overt neoplastic processes of mesodermal nature in the central nervous system. Cases of associated glioma and sarcoma have been reported\(^4,10,29\) and the participation of phagocytic microglial cells in gliomatous tumors first was noted by Penfield in 1925.\(^21\) Feigin et al.\(^4\) studied 433 brain tumors from this point of view and reported a considerable angioplastic response accompanied by an endothelial hyperplasia which paralleled the degree of malignancy of the neoplasm. They agreed with Gough\(^29\) in that this seems to be a tissue response peculiar to the central nervous system but cast doubt as to the possible sarcomatogenous role of the microglia in view of its incapacity to form connective-tissue fibers. However, metallophilic tumor cells have been described which meet all the morphological characteristics of a sarcomatous growth containing fibers of reticulin.

The labeling of this tumor as either a reticulum-cell sarcoma,\(^1\) primary mesenchymal tumor of the brain,\(^29\) perithelial sarcoma,\(^14\) microglioma,\(^6\) or stem-cell sarcoma indicates, as Losli\(^18\) pointed out, a lack of “unanimity of thought to taxonomy.” The matter is complicated further by the various attempts of classification made by those who have studied these tumors.\(^1,3,15,17,19,24,28\) In a recent comprehensive study, Kernohan and Uihlein\(^16\) reviewed a series of 40 patients with neoplasms that had similar histologic characteristics and which they categorized as sarcomas of the reticuloendothelial system.

**Fig. 5.** A group of blood vessels in the peritumoral area which is surrounded by fibers of reticulin arranged concentrically. Gomori's silver stain, ×375.
The relative scarcity of mesenchymal representatives in the central nervous system, the peculiar tissue architecture of the brain, the infrequency of this tumor in relation to other neural growths and the fact that the very physiomorphological concept of "reticulum cell" is not yet fully established, are all factors that militate against a solid pathological definition and classification.

One of the salient features of this type of neoplasm is the high degree of malignancy as indicated by the extremely short survival period observed from the time the diagnosis is made. The average duration of symptoms in the series of cases of Abbott and Kernohan was 9 weeks in the group of perivascular sarcomas. Fisher et al. reported on 2 patients, 1 of which died 3 weeks and the other 9 weeks after the onset of symptoms. Of the 5 patients reported by Troland et al. only 1 survived 1½ years after the clinical diagnosis was made.

In the case reported herein it is actually difficult to ascertain the duration of the disease, because the diagnosis was not made up to the time of her last hospitalization. However, the patient had symptoms for many years which might have been caused by the neoplasm. Histologically part of the tumor was surrounded by a capsule composed of bands of collagen. A review of the literature discloses that only one report described a similar tumor with a well defined capsule. In areas of the tumor provided with a vascular supply, such vessels were thick-walled, the wall being composed of fairly thick bands of collagen. Comparison of this unique feature of intratumoral areas with the remarkable overproduction of reticulin around the peritumoral blood vessels would suggest that a continuous angiosclerotic process with subsequent stenosis of the lumen of such vessels probably was one of the features of this neoplasm. To assume a morphogenetic affinity between reticulin and collagen seems to be justified in view of electron microscopic studies made in recent years.

As stated previously, repeated attempts with Hortega's stain failed to demonstrate any cytoplasmic argyrophilia on the part of the tumor cells. According to current concepts, this fact justifies the designation of our case as a reticulum-cell sarcoma. However, Russell and associates conceived the existence of an anaplastic form of the mature, metallophilic microglial cell. They suggested that such cells may be the reticulum cell.

Summary

A case of primary reticulum-cell sarcoma
of the brain is described, occurring in a 34-
year-old female with neurological symptoms of long duration that possibly could be attributed to the neoplasm. Necropsy revealed a large neoplasm confined to the brain, occupying the parietal, temporal and a portion of the occipital lobes of the right cerebrum. Microscopically, it proved to have a morphological similarity to the reticulum-cell group of sarcomata. The neoplasm contained argyrophilic fibers of reticulin and a net of vascular spaces surrounded by a fairly thick layer of collagenous fibers. In peritumoral areas there was hyperplasia of blood vessels which showed perivascular cuffing by tumor cells encased in concentric rings of reticulin. The possible atherosclerotic role of such increased reticulin is discussed.

Attention is directed to the protracted clinical course shown by our patient in spite of the high degree of malignancy attributed to this category of neoplasms. The histological features of the tumor could explain, at least in part, such apparent incongruence.

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