Primary pigmented carcinoma of the choroid plexus

A light and electron microscopic study

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Pigmented carcinoma of the choroid plexus was found in a 33-year-old man. Autopsy revealed no primary tumor in the skin or eyes. A slightly cystic pigmented tumor was present in the right lateral ventricle infiltrating the thalamus and striatum. Metastatic implants were found in both temporal lobes and the cerebellum. The spinal cord was covered by black meningeal nodules, and the cauda equina was completely encased by the tumor. Metastases were found in the liver, pancreas, and kidney. Microscopically the mass contained normal choroid plexus with psammoma bodies adjacent to carcinomatous epithelium forming prominent papillae and tubules. Melanin granules were found within the neoplastic cells and in the stroma. Electron microscopy demonstrated melanin granules in various stages of development in the cells, which were joined one to another by desmosome-like structures. This is the second reported case of pigmented carcinoma of the choroid plexus and the first with metastases outside the central nervous system.

KEY WORDS • pigmented carcinoma • choroid plexus • melanoma • electron microscopy • extraneural metastases

ALTHOUGH primary tumors of the choroid plexus have been widely reported in the literature, few cases seem to fulfill the criteria of malignancy as suggested by Russell and Rubinstein and Lewis. Furthermore, to our knowledge, only one example of malignant melanoma of the choroid plexus epithelium has been reported.

We have had the opportunity to study a pigmented neoplasm arising from the choroid plexus epithelium with obvious malignant features and widespread subarachnoid, cerebral, and extraneural metastases. The present report describes the light and electron microscopical features of this tumor and discusses the origin of the melanin pigment in the neoplastic epithelial cells of the choroid plexus.

Case Report

In November, 1973, this 33-year-old man was admitted to a local hospital because of an episode of severe headache associated with sensation of "flashing lights" in the left visual field and weakness and numbness in the left lower extremity. He had had a 3-year history of headaches, sometimes associated with nausea and vomiting. Neurological examina-
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tion revealed left homonymous hemianopsia. Optic
fundii were normal, and other cranial nerve functions were intact. The strength was
decreased in the left lower extremity, which had hypoactive deep tendon reflexes. Plantar
responses were flexor bilaterally. Light touch
and pinprick sensations were impaired in the
left lower extremity, but position and vibra-
tion senses were normal. Skull and chest
x-ray films and routine laboratory tests were
all normal. He was discharged with sup-
portive treatment.

The patient returned in March, 1974, with
progressive loss of strength in both lower ex-
tremities. He complained of severe back pain,
impotence, loss of urinary sphincter control,
and constipation. Neurological examination
disclosed impairment of recent and remote
memory. Fundi and visual field were normal.
There was atrophy and weakness of the
muscles of both hands and legs. Knee and
ankle jerks were absent bilaterally. There was
no plantar response. Touch and pain were im-
paired in both lower extremities, and an
anesthesia area could be delimited in the sad-
dle region. Lumbar puncture revealed an
opening pressure of 285 mm H2O. The
cerebrospinal fluid (CSF) was clear with 340
red blood cells/cu mm. Protein was 600 mg% and glucose 5 mg%. Decompressive lumbar
laminectomy disclosed multiple pigmented
nodular lesions infiltrating the spinal cord.
The diagnosis of melanoma was then
histologically established. The patient was
given steroids, radiation therapy, and
chemotherapy with transient improvement.
Computerized axial tomography (CT)
showed a dense lesion surrounded by an area
of decreased density in the right posterior
parietal area with anterior displacement of
the right trigone (Fig. 1). His condition con-
tinued to deteriorate. He became aphasic and
could barely move his legs. He was
transferred to St. Louis County Hospital on
October 2, 1974, for terminal care and died 2
weeks later.

Postmortem Studies

Preparation of Material

The brain was fixed in 10% buffered for-
malin. For light microscopy, the tissue was
embedded in paraffin, and sections stained
with hematoxylin and eosin, periodic acid
Schiff (PAS), and by the Fontana-Masson

and Prussian blue methods. For electron
microscopy, small fragments of formalin-
fixed tissue from the ventricular mass and
spinal cord were washed with Millonig's
phosphate buffer, postfixed in 2% osmium
tetroxide, dehydrated through graded
alcohols and propylene oxide, and embedded
in epoxy resin. Ultra-thin sections were
stained with uranyl acetate and lead citrate
and examined with a Philips 300 electron
microscope.

Anatomical Examination

General autopsy findings included acute
aspiration bronchopneumonia, bilateral acute
pyelonephritis with abscess formation, acute
erosion of terminal esophagus, cystitis with
multiple calcific concretions, and metastatic
tumor in the liver, left kidney, and pancreas.
There were three well circumscribed
metastatic nodules in the liver (3 X 0.5 X 0.5
cm each), one in the left kidney (5 X 2 X 2
cm), one in the head of the pancreas
(6 X 4 X 3 cm) and one in the body of the
pancreas (7.5 X 2 X 2 cm).

Gross examination of the brain disclosed
bilateral mild uncal notchings. The lep-
tomeninges showed darkly pigmented areas
in the basal surface of the temporal lobes and
in the dorsal aspect of the cerebellar

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FIG. 2. Coronal sections of brain show a pigmented intraventricular mass extending to the thalamus, striatum, and temporal lobe.

FIG. 3. Postmortem photograph shows the lumbosacral cord and cauda equina encased in tumor.

hemispheres. Coronal sections of the cerebrum revealed a black, firm intraventricular mass in the right trigone measuring 4 cm in diameter extending anteriorly into the right midthalamic region, posteriorly into the pulvinar, and laterally into the right striatum (Fig. 2). There were two superficial tumor implants, 3 cm in diameter, in the basal portion of both temporal lobes. The cerebral tissue around the lesions was markedly swollen. Sagittal sections of the cerebellum showed multiple small areas of tumor infiltration, mainly in the dorsal and superior aspects of the cerebellar hemispheres. Brain-stem sections were unremarkable.

The spinal cord was edematous, distorted, and compressed by widespread subarachnoid black lesions extending from cervical levels to the cauda equina (Fig. 3). The latter was rather firm, solid, adherent to the dura, and showed no individualization of the roots.

Transverse sections revealed softening of the cord parenchyma in the lumbar levels and complete engulfment of the lumbosacral cord and cauda equina.

Light Microscopy

The intraventricular mass contained proliferated choroid plexus in delicate papillary projections composed of a single layer of cuboidal epithelial cells supported by a stroma of hyalinized connective tissue, as well as calciospherites and even psammoma bodies (Fig. 4 left). In other areas the papillae and tubules showed multiple layers of epithelial cells, some exhibiting nuclear hyperchromatism and moderate pleomorphism (Fig. 4 right). Adjacent to these areas there were irregular and ill-defined papillary structures with marked anaplastic cytological features such as pleomorphism, multinucleation, and giant-cell formation. Striking and
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irregular granules of dark-brown pigment filled many of the neoplastic cells (Fig. 5) and were also seen in the stroma and some phagocytes. With the Fontana-Masson stain this pigment stained black. There was no PAS-positive material in the tumor cells, and the Prussian blue reaction for iron was negative. Papillary fronds of tumor infiltrated the parenchyma adjacent to the primary tumor and the sites of metastatic deposits.

The spinal cord was compressed, distorted, and surrounded by a thick sheath of densely packed cells in the leptomeninges forming small nodules. In some segments the tumor infiltrated the cord parenchyma and the spinal roots. The tumor here lacked any tubular or papillary arrangement and consisted predominantly of sheets of small round or spindle-shaped cells with hyperchromatic nuclei and abundant melanin. Giant cells were also present.

In the extraneural metastases the pattern was more tubular than papillary. Fine and coarse melanin granules were seen scattered in the cytoplasm of the epithelial cells and in the stroma.

Electron Microscopy

Ultrastructurally the tumor consisted of cells showing irregular nuclei with indentations and invaginations of the nuclear envelope, irregularly arranged chromatin material, and one or two large, prominent, markedly electron-dense nucleoli. Numerous spheroid mitochondria with few cristae were distributed throughout the cytoplasm and occasionally almost completely filled the cell body. There were many membrane bound, mature melanosomes, spherical, electron-opaque and fully pigmented, of varying sizes with an average diameter of 400 μm. There were also finely granular premelanosomes,
less electron-dense, in various stages of development (Fig. 6 left). The premelanosomes were occasionally surrounded by a delicate membrane. The pigment granules in the melanosomes were very irregular and dense but occasionally a fine and low density matrix could be seen in immature melanosomes in which the process of melanization was not complete. Some premelanosomes exhibited a fibrillar inner structure displayed in a striated pattern. Sparse, smooth, and rough endoplasmic reticulum and electronlucent vesicles were moderately represented in the cytoplasm. Frequent desmosomes joined adjacent tumor cells (Fig. 6 left) and a basement membrane separated these cells from an interstitium containing fine collagen fibrils (Fig. 6 right). The extracellular space sometimes contained melanosomes and cellular debris.

Discussion

Since von Rokitansky's description in 1844, of a supposed primary carcinoma of the choroid plexus there have been many reports of malignant neoplasms arising from the choroid plexus epithelium. Lewis, however, in reviewing all these reports concluded that most of the published cases were typical benign choroid plexus papillomas, secondary carcinomas, ependymomas (as was von Rokitansky's case), or other varieties of gliomas.

The distinctive characteristics of the primary choroid plexus carcinoma are discussed elsewhere, and include the presence of a transition zone of normal choroid plexus architecture to an undifferentiated pattern, invasion of adjacent nervous tissue, loss of normal papillary architecture at least where invasion occurs, nuclear pleomorphism, and abnormal mitotic figures. Our example meets all these criteria. In addition, the occurrence of metastatic lesions in the liver, kidney, and pancreas confirms the malignant nature of the tumor. In fact, carcinoma of the choroid plexus very seldom spreads to extraneural tissue, and only one lesion with distant metastases has been reported previously. Most of these tumors occur in the lateral ventricles of children, and the left is affected twice as often as the right. In adults they predominantly involve the fourth ventricle; both sexes are equally affected.

The primary nature of the tumor is suggested by its gross and its microscopic appearance, and by the fact that remnants of the choroid plexus stroma, including calciosferites and psammoma bodies could be identified in the large intraventricular mass. A detailed and rigorous postmortem examination, including the orbital contents, ruled out the possibility of other primary sites. Further observations of the ultrastructure of the tumor yielded some evidence of its origin. It is known that choroidal epithelial cells have infolded plasma membrane, pinocytotic vesicles, high concentration of mitochondria per unit area of cytoplasm, chromatin aggregates between the pores of the nuclear membrane, and occasionally two nucleoli, and that desmosomes join one epithelial cell to another. The tumor cells in our case exhibited most of these characteristics, including the presence of
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FIG. 6. Electron micrograph of tumor cells. **Left:** Melanosomes and premelanosomes in various stages of development. Focal membrane thickenings resembling desmosomes (arrows) are found at cell junction. × 15,000. **Right:** Tumor cells along papillary projection lined by a distinct basement membrane (arrow). × 15,000.

desmosomes. In addition, a basement membrane separated the cells from a collagenous interstitium. Finely granular premelanosomes and coarser membrane-bound melanosomes were abundant in the cytoplasm, suggesting melanogenesis in the tumor cells of the choroidal epithelium. Extracellular melanosomes, seen in some instances, probably were derived from degenerating tumor cells.

Electron microscopic studies of primary malignant melanomas of the nervous system are scarce in the literature, but the most striking finding in the available observations is the presence of melanocytes with spheroidal membrane-bound premelanosomes at various stages of development and fully pigmented mature melanosomes. No particular ultrastructural feature of these neoplasms has been found useful in differentiating them from cutaneous melanomas. However, differences in the submicroscopic structure of premelanosomes, melanosomes, and mitochondria have permitted the distinction of two groups of melanomas. Type A melanomas contain cigar-shaped melanosomes, helical premelanosomes, and longish mitochondria with numerous cristae, whereas Type B melanomas display more spherical melanosomes, granular premelanosomes, and spherical mitochondria with few cristae. The ultrastructural features of our case correspond to those of Type B melanomas.

There is only one previous report of a pigmented tumor arising from the choroidal epithelium. Although microscopic evidence of the origin of the tumor is presented, the eyes were not examined. There were metastases in the cerebrum and spinal cord but none outside the nervous system.
Primary melanomas of the nervous system have their origin in melanocytes which normally occur in the human leptomeninges and they have been widely reported since Virchow's description of diffuse melanosis of the central nervous system. Most of these tumors involve only the leptomeninges, although some invade the brain and cord and others are confined to the brain parenchyma. The criteria for diagnosis should include histological evidence that melanocytosis preceded melanomatous transformation and an adequate autopsy with examination of all possible sites of tumor origin, including the eyes. Brain metastases have been found in 39% of all patients who die of malignant melanoma. On the other hand, although some authors were doubtful whether central nervous system melanomas could metastasize outside the cerebrospinal axis, a few well documented cases have been reported by others. Recent evidence has ascribed the high incidence of bleeding in the melanomas to the presence of fenestrae and other changes in the endothelial cells of the tumor capillaries.

The origin of melanin in the epithelium of the choroid plexus is a matter of speculation. In amphibians, melanin-pigmented cells have been found in the interstitial spaces of the choroid plexus; in man, however, melanin has not been identified, although various inclusions and pigments have been reported. Even the possibility of an occasional presence of pial melanocytes in the stroma of the choroid plexus would not explain the melanogenesis within the epithelial cells. The nature and the pathways of formation of melanin in the central nervous system are still largely unknown. The melanin found in neurons of substantia nigra, locus caeruleus, and in some other nuclei of the brain stem (neuromelanin) has histochemical properties different from those of other melanins. Neuromelanin and other melanins have many similarities but the latter do not contain lipid globules. The melanin granules are composed of two other distinct components: a finely granular, medium dense matrix, which may be grossly similar to lipofuscin, and a very electron-dense coarsely granular material with reducing properties. Although tyrosine is considered to be the parent substance of the melanins, there are different possible routes in melanogenesis. Some authors have suggested that neuromelanin, like other melanins, is synthesized by the oxidation of catecholamines, whereas others have proposed that it derives from oxidation of dopa. Infrared studies have favored the first hypothesis by showing that neuromelanin has a spectrum very similar to that of other catecholamine melanins.

Although our present study provides evidence of melanogenesis in neoplastic epithelial cells of the choroid plexus, the nature and significance of the melanin in this unusual location remain to be explained.

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