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Two Primary Melanomas of the Human Brain

(primary cerebral melanoma/malignant change)

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A malignant melanoma and a melanin-pigmented tumor, both showing spontaneous intracerebral hemorrhage, were reported. A definite diagnosis of melanoma was made almost exclusively by histological examination of tumor tissue obtained at operation or autopsy. A search for primary tumor foci was performed in both cases before and after death. No extracerebral melanomas were found. Thus, these cases can safely be regarded as primary cerebral tumors.

In the present paper two assumptions were made. One assumption concerning spontaneous intracerebral hemorrhage from melanomas is that tumor cells release a chemical factor which causes the formation of fenestrate and subsequent hemorrhage. Another assumption concerning malignant changes of melanoma cells is that malignant change is influenced by genetic factors.

Primary melanoma of the central nervous system has been described as a rare entity and, in most cases reported, malignant (1, 2).

We are reporting two cases of melanoma without other involvement. One case was a malignant melanoma arising at the temporal lobe of the left hemisphere ; the other was a melanin-pigmented tumor of the third ventricle. These cases both contained intracerebral hemorrhage. A definite diagnosis of melanoma was attained almost exclusively by histological examination of tumor tissue obtained at operation or autopsy.

The purpose of this report is to discuss the probable mechanism of intracerebral hemorrhage from melanoma and the cause of malignant changes of melanoma cells.

CASE 1

A 7-year-old boy was in excellent health until he suddenly complained of headache. Again after 7 months, he complained of headache and entered a somnolent state. He was admitted to the Emergency Center for Brain Disease, Kagoshima City Hospital, and was diagnosed as spontaneous intracerebral hematoma by cerebral angiography (Fig. 1). At operation the hematoma was

large, over 4 cm in diameter. He was discharged after one month in hospital because of improvement in his clinical condition. But after another month, he complained of the same symptoms of headache and vomiting. The patient was again admitted to our center in a somnolent state. Physical examination revealed bilateral pupils reacting promptly to light, paralysis of the left abducens, stiffness in the neck, and positive Kernig's sign. The pathological reflexes were bilaterally positive. Peripheral blood and numerous blood chemistry were within normal limits except for an elevated white blood cell count. The initial lumbar puncture had an elevated opening pressure ; the cerebrospinal fluid was bloody. Carotid angiography and RI scintigram showed a mass lesion of the left temporal lobe. The patient was reoperated on with a preoperative diagnosis of spontaneous intracerebral hematoma, and the hematoma and tumor-like substance in the temporal lobe were removed. The biopsy specimen was diagnosed as a malignant melanoma. Treatment for malignant melanoma was then started. The patient was given 5000 rads radiation to the temporal region and an anticarcinogen. The patient became lethargic 5 months after admission, then developed bulbar paralysis and paralysis of all the extremities. His condition deterioreated gradually and he died 16 months after onset.

Pathological Findings

No evidence of melanoma outside of the central nervous system was found. The melanoma included patchy black pigmentation on the subarachnoid space over the entire cerebral hemisphere and spinal cord. After fixation, his brain was examined by coronal sections, revealing heavilly pigmented tumor mass filling the lateral ventricle.

Histologically the meninges were diffusely involved by the tumor which contained abundant melanin pigment. The cells were densely arranged and infiltrated the blood vessel walls. Unusually rich vascularity and diffuse meningeal invasion were noted. Spindle-shaped cells were seen in the space of Robin-Virchow as the tumor grew from the leptomeninges into the cerebral cortex. The tumor was comprised of large pleomorphic cells with large nuclei and prominent nucleoli. Mitoses were also noted. Under high magnification, fine brown granules were seen scattered throughout the cytoplasm. The appearance of the tumor is consistent with a menigeal malignant melanoma. This tumor involved the leptomeninges as well as the parenchyma of the brain, which suggests a leptomeningeal origin of melanoma tumors.

For electron microscopy, the tissue obtained at operation was fixed in 10% buffered formalin at pH 7.35 for 2 days. After overnight washing in 0.1 M phosphate buffer containing 8 % sucrose at pH 7.35, the tissue was postfixed in 1 % osmium tetroxide in Caufield's buffer, dehydrated in graded concentration of ethanol, and embedded in epon. Thick sections were stained with toluidine blue for selection of fields. Thin sections made by an LKB ultrotome were poststained with uranyl and lead citrate and examined under a JEM 7 or a Hitachi 500 microscope.

Cytologically the tumor cells had roughly two cellular components : melanocytes containing melanosomes in varying stages of melanization ; and melanophages containing large, irregular melanosome complexes in varying states of degradation. The former contained numerous mature melanin granules called melanosome stage IV, and some premelanosomes, which were spread throughout the cytoplasm (Figs. 6 and 7). Each of these organelles were limited by a unit membrane. The rough endoplasmic reticulum was not extensive, but the mitochondria were abundant in some areas (Fig. 8). The nucleus was usually oval with a shallow indentation. The nucleoli were enlarged and showed a branching anastomosing coarse thread-like structure (the reticular nucleolonema) (Figs. 10—12). Occasionally, myelin-like structures were detectable (Fig. 13). The latter contained many heavily pigmented organelles termed "melanosome complexes", which were surrounded by a single membrane. Such melanosome complexes contained recognizable melanosomes and also much granular material derived from their breakdown. The tumor cells were arranged in compact clusters with a tendency to a perivascular rosette-like arrangement. Another characteristic finding in the tumor masses was reduplication and discontinuities of the vascular basement (Fig. 9). Usually, the connective tissue included a thick perivascular space of amorphous granular materials.

CASE 2

The patient was a 53-year-old woman whose clinical history dated back five years prior to her death, when she experienced episodes of intermittent headache. A complete work-up at that time failed to reveal the cause of this headache. Four years later, she experienced sudden unconsciousness, but appeared to be normal immediately afterwards. The episode lasted several minutes, but five months later she complained of diplopia and left ptosis. Over the next two days, the patient developed trouble thinking of word and a paresis of her right side, entering a lethargic state. The patient was admitted to another hospital with these symptoms. When carotid angiography was performed there, she entered a semicoma. Then she was admitted to the Emergency Center for Brain Disease for close examination. Physical examination revealed anisocoria (R$<$L), paralysis of the left oculomotor nerve, bilateral pupils reacting sluggishly to light, hemiplegia of the right side, right fundal hemorrhage, and a stiff neck. On neurological examination, lumbar puncture yielded blood-stained cerebrospinal fluid with an opening pressure of 160mm H_2O. Radical examination of the cerebral angiogram, RI scintigram, intracranial pneumogram, and CT scan indicated that there was a space-occupying lesion in the third ventricle (Fig. 2). On admission, the patient was given 5000 rads radiation to the third ventricle and an anticarcinogen. She developed a fever for which no infectious base could be found. The fever was considered to be of center origin. The patient died 15 months after admittance.

Postmortem Findings

The brain weighed 1159 g and was totally atrophic, appearing a slightly pale color because of the leptomeninges covering the brain except for the left cerebellum. The bilateral pons and temporal lobe were softened. There was left tonsillar herniation and subarachnoid hemorrhage around the midbrain region. In coronal sections, a tumor occupying the region of the third ventricle was disclosed without actual infiltration (Fig. 3). This measured $2\times2\times2$ cm. Its exact point of origin was impossible to determine, for it was attached to the floor of the third ventricle and the aqueduct. The rest of the brain, cranial cavity, spinal cord, and spinal canal were normal. The cut surface of the tumor was dark-red. There was complete obstruction of the third ventricle and the aqueduct. Histologically the specimen consisted of a large hemorrhagic area and the cerebral parenchyma, i. e., the part of tumor. The peripheral area of the hemorrhage was filled with melanin-pigmented cell, making several layers (Fig. 4). Perivascular invasion was also noted. All cells within the tumor appeared to be differentiated but no mitosis was present. The tumor had a uniform structure comprised of closely packed sheets of small cells with spindle-shaped, ovoid or rounded hyperchromatic nuclei and scanty indefinite cytoplasm (Fig. 5). This tumor was diagnosed as a benign melanoma.

DISCUSSION

Two cases of spontaneous intracerebral hemorrhage caused by unsuspected melanoma were reported. The usual cause of spontaneous intracerebral hemorrhage is aneurysm, A-V malformation, or hypertensive cerebrovascular disease. Brain tumor is an uncommon cause.

Recently we encountered a case of malignant astrocytoma which revealed itself acutely with subarachnoid hemorrhage. However the presence of the tumor was not established clinically before operating. The diagnosis was confirmed by histological examination of tumor tissue obtained at operation. Several months after the operation, the patient died due to a huge intracerebral rehemorrhage. Histological image showed an unusually rich vascularity immediately adjacent to the hemorrhage.

Padt *et al.* (3) stated that malignant tumors are more vulnerable to bleeding than benign ones, probably due to necrosis and vascularization in the tumor itself. Budney *et al.* (4) quoted papers of Jellinger and Slowick (5) and Skullerud and Löhen (6) who felt there may be some relationship between the histological criteria for recurrence and an increase in the mitotic rate and cortical invasion. It is to say from our cases plus the above case that malignant changes of tumor cell always induce recurrent intracerebral hemorrhage, although case 2 on adequate evidence suggests that the vessels were destroyed by angiography. Glass and Abott (7) reported that recurrent bleeding was not unusual and in 46.3% of their cases recurrent hemorrhage occurred. To date the relationship of blood vessels to tumor is relatively unexplored territory in spite of their fundamental

importance in the proliferation of the tumor and associated complications (8).

The most striking finding in the literature (9) was the presence of numerous fenestrate in the endothelial cells of the tumor capillaries. They were covered by a diaphragm only 50 Å thick, which may indicate an inherent weakness in the endothelial lining. It was stated that changes in the vessels of a malignant melanoma may account for the predisposition of the tumors to bleed. According to Hirano (10), if separation existed antemortem, then one might expect a great deal of blood, including red cells to pour across the endothelial barrier and to permeate the parenchyma. This is not seen and one must, therefore, consider its reason. Unfortunately we could not illustrate the fine structure of the tumor capillaries due to huge damage of the tissue. However, melanoma, particulaly malignant melanoma, consists of tumor cells with pleomorphic shape and a number of cells containing melanosome complexes both of which enclose proliferative capillaries. Probably, tumor cells release a chemical factor which causes the formation of fenestrate and subsequent hemorrhage.

Although by custom tumors are designated either as benign or malignant, all untreated brain tumors are fatal and in this sense they must be treated as malignant. The term malignancy means progressive neoplasma. Scherbet and Lakshimi (11) pointed out that growth rates of astrocytoma cells in culture corresponded well with their histological grading. In agreement with the two cases here reported, this hypothesis may be an important criterion for malignancy. In addition, Fabiani *et al.* (12) proposed that atypical mitosis represent, as a single component, the most important expression of tumor growth, and hence of malignancy. It is necessary to consider the origin of cells giving rise to brain tumor. Most primary brain tumors consist of glioma. Glioma originates in neuroglia cells, spread throughout the brain and the spinal cord. Melanomas of the central nervous system arise from the pial melanin-bearing cells, melanocytes, which grow mainly in the neural crest of the embryo and subsequently migrate to various parts of the body. These melanocytes are normal constituents of the leptomeninges, particularly along the ventral aspect of the lower part of the medulla and upper part of the cervical spinal cord (1, 13). According to Bojsen-Møller (14), a scarce amount of melanin may sometimes be found in the leptomeninges of any of the lobe. Such cells are said to have a tendency toward malignant change (15—18). Consequently, the question arises, what causes malignant change ? The mechanism whereby melanocytes undergo a malignant change has not been adequately elucidated so far. Therefore, an attempt was made to compare two cases at the level of ultrastructure. Unfortunately, however, further cytological characteristics of case 2 could not be observed because of the disintegration of the autopsy specimen during cytological examination. The most striking finding in ultrastructually investigated specimens obtained at operation was nucleoli with various shapes. Nucleoli were generally enlarged, the reticular nucleolonema having various shapes. Ghadially (19) stated that nucleolar changes in malignancy include enlargement and margination of nucleoli,

irregularity of shape, and an increase in number of nucleoli. There is a close relationship between nucleoli and genetic information (20, 21). The results obtained from the ultrastructural images of case 1 are considered to support the view that the morphological modification of malignant melanocytes is influenced by genetic factors.

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LEGENDS

Fig. 1. Left carotid angiogram indicates right deviation of the anterior cerebral artery and lifting of the middle cerebral artery. (case 1)

Fig. 2. CT scan indicates that there is a space-occupying lesion in the third ventricle. (case 2)

Fig. 3. Coronal section of the cerebral hemisphere shows the tumor mass in the third ventricle. (case 2)

Fig. 4. The specimen consists of the hemorrhage area and part of the tumor. Peripheral area of the hemorrhage is filled with melanin-pigmented cells, making several layers. (case 2) × 200 H & E

Fig. 5. The tumor has a uniform structure comprised of closely packed sheets of small cells with spindle-shaped ovoid or round nuclei and melanin-pigmented cytoplasm. (case 2) × 400 H & E

Fig. 6. Note irregular nuclei of these tumor cells and the cytoplasm which contains numerous electron-opaque melanosomes in varying stages of melanization. (case 1) × 10,000

Fig. 7. Closely packed membrane-bound melanosomes are seen within the cytoplasm of a tumor cell. (case 1) × 10,000

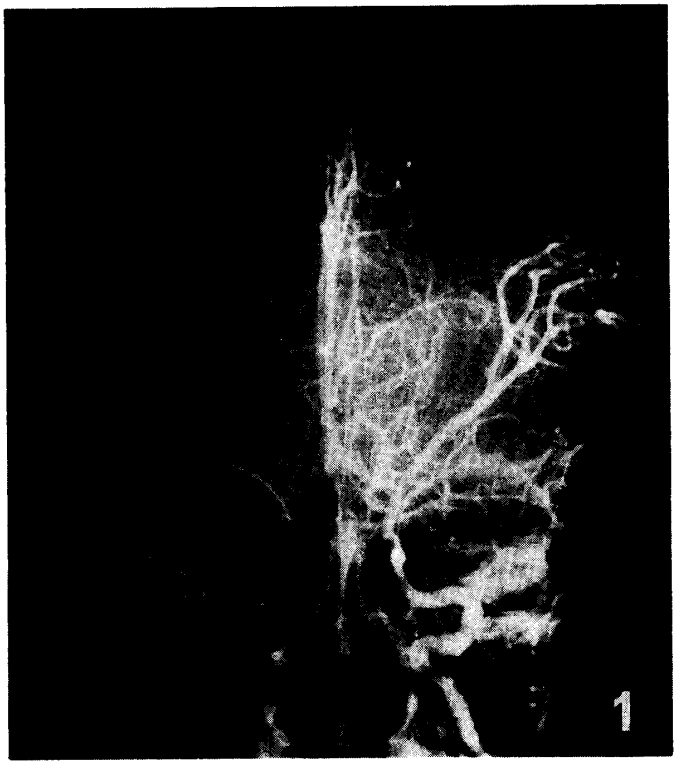
Fig. 8. Mitochondria are abundant in some areas. (case 1) × 10,000

Fig. 9. In the perivascular space reduplication and discontinuities of the vascular basement membrane and thick perivascular amorphous granular materials are seen. (case 1) ×10,000

Figs. 10–13. Various changes in nucleoli.

Figs. 10 and 11. Two nucleoli. (case 1) × 10,000

Figs. 12 and 13. Characteristic nucleoli and myelin-figured nucleoli. (case 1) × 12,000 and × 11,000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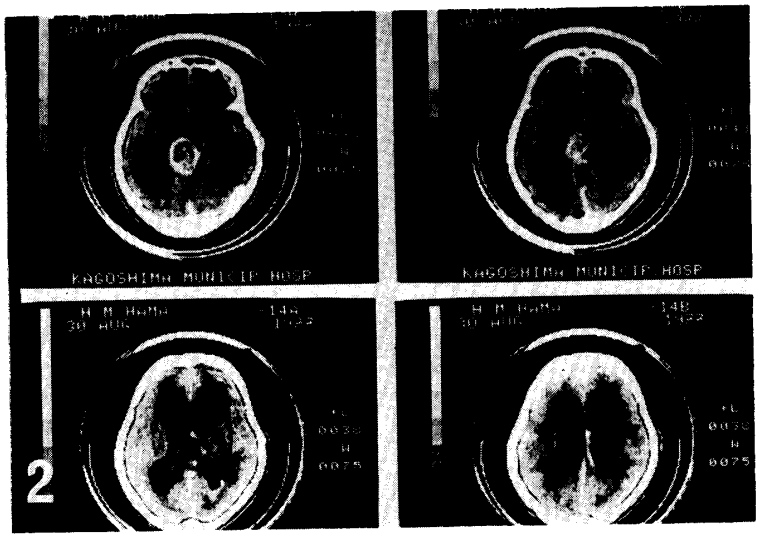
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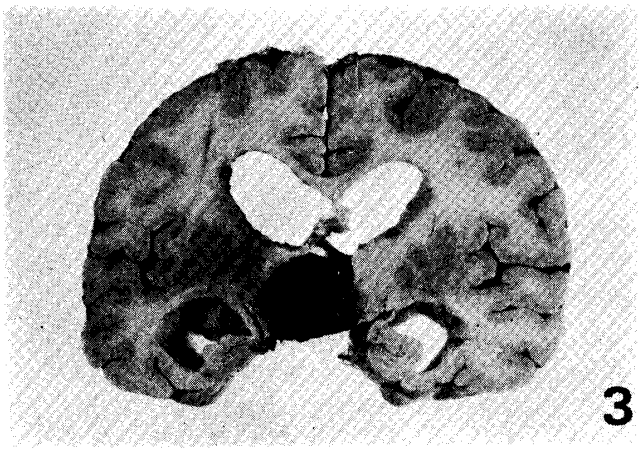
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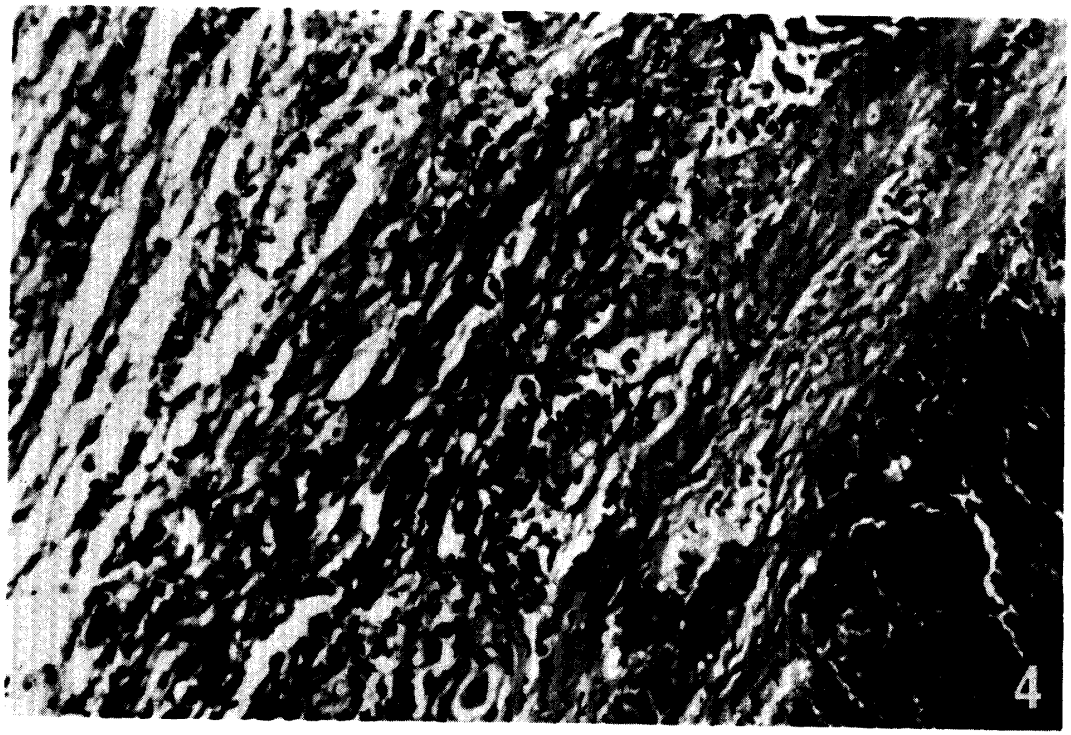
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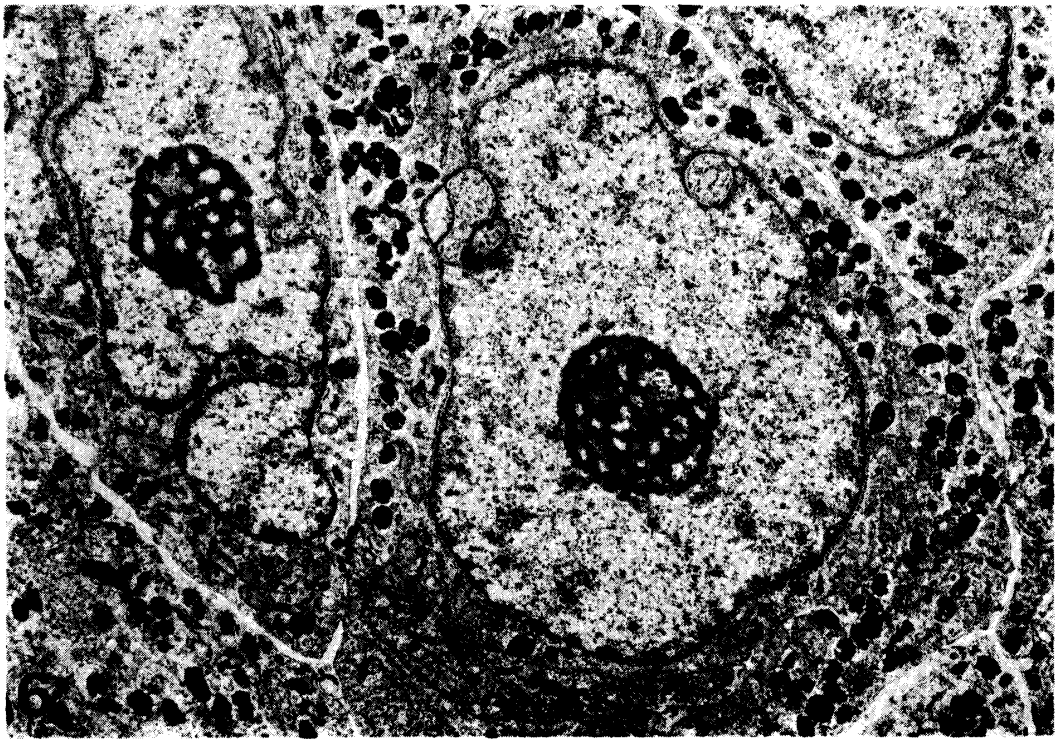

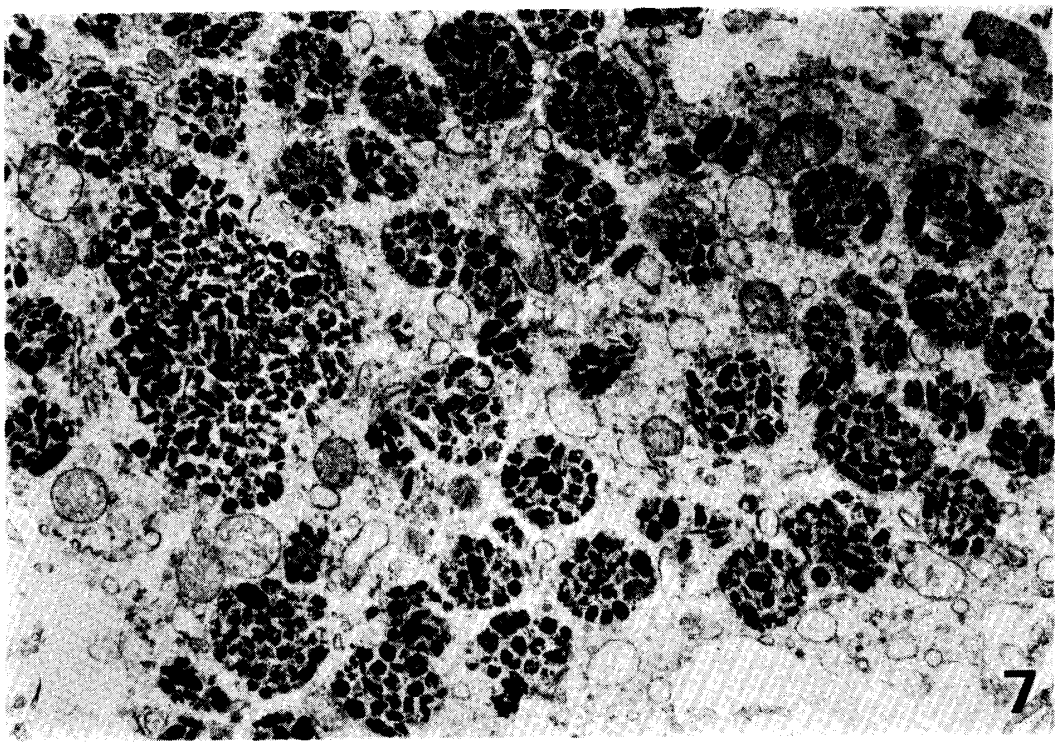
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