PRIMARY MELANOCARCINOMA OF THE GALLBLADDER

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INTRODUCTION

The origin of melanoma in various parts of the body, although the subject of an extensive literature, is yet an unsolved problem in pathology. Every additional case, then, aids in strengthening one view or another.

Virchow, over a century ago, noted the marked pleomorphism of the tumors and believed them to be either carcinomatous or sarcomatous in origin. Each of these divisions has since been subdivided many times.

Under sarcomatous melanoma, the site of origin is variously recorded as the endothelium or perivascular histiocytes of the blood or lymph vessels (Jadassohn, Ribbert, Matsunaga, Lemmel); the mongolian and blue spots of the skin (Jadassohn, Tièche, Ribbert); choroid, ciliary body, and iris (Miescher, Roulet, Smith), and finally the chromatophores of Ribbert.

Ribbert believed that the chromatophores were specialized cells of mesenchymatous origin, whose function was pigment formation. He accepted only one type of melanotic tumor, that produced by the chromatophore. These cells he isolated from melanomas of various parts of the body, especially in animals, by teasing the tissue apart and staining the isolated cells. He described them as spindle-shaped cells with branching processes which surrounded the epithelial cells. The cytoplasm contained light to dark brown pigment granules, and the nuclei were round or oval and vesicular. From the histologic standpoint, melanotic tumors of the brain and choroid would seem to substantiate Ribbert’s contentions, but for the skin and other epithelial surfaces his theory fails (Ewing, Ribbert).

For melanoma of epithelial origin, almost every organ in the body has been reported as the primary source (Schmorl, Konjetzny, Kromayer, Cooke, Walthard and Albertini, Roulet). Of special
interest in relation to the case to follow are the cases reported by Wieting and Hamdi, a primary melanocarcinoma of the gallbladder; by Duval, a primary melanoma of the common duct; by Koch, a primary epithelial melanotic tumor of the liver.

The nervous origin of melanocarcinoma has recently been emphasized by Masson, who believes that the tumors are derived from the end apparatus of the sensory nerve filaments of the skin. These consist of the Merkel Ranvier tactile corpuscles in the epidermis and the Meissner corpuscles of the papillae. This conception is a modification of Erhmann's melanophore theory. The melanophore he believed to be of nervous origin, differing from Ribbert's chromatophore in that it was stationary.

The multitude of theories proposed failed to reveal the true nature of these tumors, and it was not until Bruno Bloch introduced his dioxyphenylalanin reaction (dopa) that a definite stride toward a solution was made. This reaction depended upon the capacity of cells to oxidize 3-4 dioxyphenylalanin, which was present in young pigment-producing cells. It was found that only epithelial cells had this property and that the chromatophores of Ribbert did not possess it. The later work of Matsunaga, Lemmel, and Lignac, however, revealed that both mesenchymatous and epithelial cells gave positive dopa reactions, and that similar reactions could also be obtained in fixed specimens.

Again the solution was jeopardized, and leading authorities were wont to discredit the work of Bloch, until Walthard and Albertini definitely showed that both the methods and the interpretation of the results of the opposing authors were questionable.

Walthard's method is as follows: Fresh tissues are placed in a one per cent dopa solution for twenty-four hours, at a pH of 7.3 and a temperature of 37° C. The reaction is specific for melanin-forming cells and is characterized by a gray-black, diffuse, finely granular appearance of the cytoplasm. The nucleus is dopa-negative. Pseudoreactions may be had if the solution is more alkaline or if the tissues are not fresh. In such instances large granules of a dark brown pigment become adherent to the surface of the cells and appear to be within them. Walthard discounts the work of Matsunaga and of Lemmel because at the time of their reports the importance of the hydrogen-ion concentration was not understood.

The case reported is that of a primary melanocarcinoma of the gallbladder. The histologic findings point definitely to its epithelial origin.
ABSTRACT OF CASE HISTORY

The patient was a colored man of forty-eight, whose history was obtained from his wife. She stated that for the past two months he had had sharp pains in the right lumbar region and that these were associated with the passing of blood by urethra. Two days before his entrance to the hospital he passed a great deal of blood. The same night he complained of severe headache, which was followed by several convulsive seizures. He then became disoriented as to time, place, and person, and was brought to the hospital on the second day of his acute illness.

Past History: No account of the patient's past history was obtainable.

Physical examination revealed a well nourished colored male, lying comfortably in bed. Temperature: 100.2° F. Pulse: 100/min. Respiration: 22/min. Blood pressure: 134/80 mm. Hg.

The pupils were equal and regular, and reacted well to light and accommodation. The fundi showed a bilateral papilledema with hemorrhages. The heart and lungs were essentially negative. The abdomen was not tender. The liver, kidneys, and spleen were not palpable.

Over the shoulders and along the spine were several deeply pigmented areas some of them measuring 3 mm. in diameter. A pedunculated tumor measuring 6 mm. was present over the spine at the level of the fifth dorsal vertebra.

The right thumb was absent (removed surgically many years ago because of a crushing injury).

Neurologic Examination: Except for a questionable paresis of the right lower facial nerve, the cranial nerves showed no abnormalities. The abdominal reflexes were absent on both sides, and the cremaster was absent on the left side. Of the deep reflexes, the patellar was absent on the left side. There were no pathologic reflexes. Sensibility to pain, temperature, and touch was normal.

Co-ordination was poor. Muscle power was good, but there was a tendency to fall toward the left side. Romberg's sign was absent, but if the test was protracted over a long time the patient fell to the left side.

Laboratory Findings: The spinal fluid was under increased pressure and was bloody. The Wassermann reaction was 4 plus.

Hemoglobin was 90 per cent; the red blood count was 4,390,000, and the white count 9,400. The blood Wassermann reaction was 1 plus.

X-ray examination of the genito-urinary tract for stones gave negative results. Repeated examinations of the urine were without significance.

Clinical Diagnosis: A clinical diagnosis was made of taboparesis with secondary cerebral hemorrhage. The possibility of a brain tumor (metastatic?) involving the left frontal lobe and left cerebellar hemisphere was considered.

Subsequent Course: The patient went rapidly downhill, first into stupor, then coma. He developed a terminal temperature of 101° to 104° F. and died thirteen days after the onset of cerebral symptoms.
Abstract of Post-mortem Examination
(Performed by Dr. R. H. Jaffé)

Weight 151 lb. Length 176 cm. The external description corresponded to the clinical report given above.

The serous cavities were essentially negative.

Heart: The heart weighed 385 grams. The endocardium over the left side of the septum was thickened, the myocardium was purplish brown and firm. The aorta measured 78 mm., 1 cm. above the aortic cusps. In the ascending portion there were numerous whitish, scar-like

![Image of melanocarcinoma of the neck of the gallbladder]

Fig. 1. Melanocarcinoma of the Neck of the Gallbladder

Note the implantation metastases adjacent to the tumor. The remaining dark plaques are the result of small hemorrhages beneath the mucosa. To the left are the masses of clotted blood that were found within the gallbladder. About natural size.

placques measuring from 10 to 15 mm., with a fine longitudinal wrinkling. The coronary vessels presented discrete atheromatous plaques.

Lungs: The right lung was crepitant except for well circumscribed nodules in each lobe. These nodes varied in size from 3 to 14 mm. and were light pink-gray to deep brown. The left lung was similar to the right except that the cut surface was a mottled light purple-gray and moderately moist. The peribronchial lymph nodes measured up to 10 mm. in diameter and were black.
Stomach: The gastric mucosa was light pink-gray, with purple-red areas the size of a pin head along the folds. At the lesser curvature, 2.5 cm. above the pylorus, was a defect in the mucosa, 4 mm. in diameter.

Spleen: The spleen weighed 60 grams and was soft; the capsule was wrinkled and slate gray. On sectioning, the surface was purplish gray, mottled with darker red. The trabeculae were distinct.

Liver: The liver weighed 1510 grams. It was moderately firm; the surface was smooth and light purplish brown in color. The cut surface was light brown-gray with indistinct acinar markings.

Gallbladder: The gallbladder was distended and tense, measuring 13 × 5.5 × 6 cm. Upon opening, the fundus was filled with about 50 c.c. of a blood-tinged fluid. After removing this fluid, the mucosa was found to be covered by a layer of a soft, putty-like, deep reddish-brown substance, 3 to 4 mm. thick. This was easily removed and revealed the inner lining of the gallbladder, which was grayish white and studded by two black patches, 5 and 6 mm. in diameter, and a slightly raised, dark purple plaque measuring 5 mm. The neck of the gallbladder was filled by a soft, polypoid tumor mass, 4.5 × 4 × 2 cm., which was attached to the wall by a 4 mm. pedicle. The mass was dark brown and had an irregular, slightly granular surface. Its base and pedicle were rather firm, while its free portion was soft and friable. The adjacent part of the cystic duct was dilated, and the mass extended into it, filling the lumen completely.

Pancreas: The pancreas weighed 140 grams. It was firm, lobulated, and light yellow.

Intestines: In the jejunum, there was a button-like mass 14 mm. in diameter, with overhanging edges. It was covered by mucosa and situated at the mesenteric attachment.

Adrenals: The adrenals together weighed 20 grams. The cortex was light yellow and the medulla grayish white.

Kidneys: The kidneys weighed 340 grams; their consistency was diminished, and the capsule stripped with ease. In the cortex of the left kidney was a circumscribed, light gray nodule 3 mm. in diameter. The renal pelvis was pink-gray, smooth, and shiny.

Pelvis: The pelvic organs showed no significant pathology.

Brain: The brain weighed 1610 grams. The left temporal lobe was larger than the right, and the convolutions were flattened. On sectioning, numerous well circumscribed, dark brown to gray nodes were found throughout the cortex and medulla. The largest was in the left frontal lobe and measured 50 × 43 × 30 mm. The smallest was in the caput of the left caudate nucleus and measured 2 mm. in diameter.

Eyes: The eyeballs were free from pathologic changes.

Microscopic Examination

Gallbladder: The tumor originated from the gallbladder wall by a fibrous tissue pedicle which extended into the mass.

The cells of the tumor formed columns and small alveoli, which were separated by thin, branched septa, derived from the thicker connective-
tissue strands. The majority of these cells were cuboidal or polyhedral, of moderate size, with round, oval, kidney-shaped, or crescent-shaped nuclei, rich in finely granular and reticular chromatin. Many of these cells contained in their cytoplasm a light brown, dust-like pigment (seen best under oil immersion). Other cells contained uniformly coarsely granular, deep brown pigment. At times the membranes of these cells disappeared and the pigment was set free; their nuclei were pyknotic or absent.

Another type of cell, found between the cells just described and in the fibrous septa, was spindle-shaped or oval. These cells contained round or oval, vesicular nuclei and a cytoplasm filled with dark brown pigment granules of various sizes.

In some areas the cord-like or alveolar arrangement of the cells was less distinct, and the cells were diffusely scattered between thin bundles of connective-tissue fibers. Large portions of the tumor were diffusely

**Fig. 2. Cross-section through Tumor and Gallbladder Wall**

Note that the fibrous tissue pedicle originates in the gallbladder wall and that it is well incorporated with the tumor proper. × 6.
neerotic, and dark brown pigment granules were seen between the débris of broken down nuclei. Occasionally gland-like structures lined by a flat cuboidal epithelium, with pigment granules in their cytoplasm, were seen. The outer edge of the tumor presented disintegrated tumor cells.

An artery of medium size entering the pedicle was filled by a loose, fibrillar connective tissue. Adjacent to this artery was a solid cast of large, irregular cells with hyperechromatic nuclei of bizarre shape. Most of these cells were pigment-free. This cast seemed to be located in a preformed channel.

At the border of the tumor, the lining epithelium of the mucosa extended over the pedicle and for a short distance over the surface of the tumor.

Adjacent to the tumor, the wall of the gallbladder was thick, especially the part outside the muscularis, which consisted of dense, fibrillar connective tissue with small round-cell infiltrations. The lining epithelium was well preserved, high cylindrical, and free from pigment.

The black patches seen in the gallbladder outside of the tumor were composed of groups of polyhedral cells, as described in the primary tumor. Some of these cells contained a fine, light brown, dust-like pigment, while others were pigment-free. The cells were on the internal

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**Fig. 3. Section through a Metastatic Nodule**

Note the large polyhedral cells with their centrally located, deeply chromatic nuclei and the fine, dust-like pigment in the cytoplasm. × 2000.
surface and showed only a slight tendency to invade the gallbladder wall proper.

The purple-red plaque was composed of clumps of ill-defined erythrocytes, which often assumed a brownish hue. Between these cells, but especially in the periphery, were polymorphonuclear leucocytes and histiocytes, the latter stuffed with erythrocytes or their débris. There were a few cells containing iron pigment. This entire lesion was located inside the wall and was evidently the result of an old hemorrhage.

The remainder of the wall was thickened. It was composed mainly of loose, fibrillar connective tissue and to a less extent of smooth muscle.

![Figure 4: Section through the Edge of the Primary Tumor](image)

**Fig. 4. Section through the Edge of the Primary Tumor**

Note the accumulation, about a blood vessel, of elongated spindle-shaped cells, whose cytoplasm is filled by coarse pigment granules of various sizes. The nuclei, where discernible, are vesicular and eccentrically located. $\times 1000$.

bundles. The epithelium was high columnar and intact. The folds, where present, were thickened by accumulations of large oval cells with granules of deep brown pigment, of various sizes.

The mass inside of the gallbladder consisted of disintegrated blood cells and a homogeneous material staining a pale brown. There were a few lymphocytes, leucocytes, pigmented tumor cells, and columnar epithelial cells.

**Brain:** In the section of the left frontal lobe examined there were two tumor nodes. One measured 13 mm. and the other 6 mm. in diameter. The larger node was sharply separated from the brain by a recent hemorrhage, which completely surrounded it and was in places as much as 3 mm. thick. Recent hemorrhages were also found inside of the node, which was composed of round, oval, and elongated cells. The round and oval cells contained fine, dust-like to coarsely granular dark brown pigment granules. The nuclei of these cells were centrally located and varied in size and shape, some being large and lobulated,
others round or oval. Their chromatin was dense, finely granular, with
a fine reticular network. The cytoplasm of the elongated cells was
filled by granules of various sizes, which were dark brown to black.
Their nuclei were small, pale, and eccentrically situated. Some of the
round or oval cells showed stages with disappearance of the membranes,
pyknotic nuclei, and coarsely granular cytoplasm free in the interstitial
tissue. About the node the brain tissue appeared loosened and showed
only a slight proliferation of the microglia with an occasional mitotic
figure.

The smaller node was composed of cords of cells arranged about
blood vessels. These cells were uniformly polyhedral or oval. Their
cytoplasm contained in some instances a dust-like, light brown pigment;
in other instances it was pigment-free. Their nuclei were large, rich in
chromatin, and centrally located. Occasionally elongated cells with
vesicular nuclei and oxyphilous cytoplasm were found. No pigment
was noted in these cells.

Nodules in the lung, jejunum, and kidney showed the same alveolar
arrangement and cell types observed in the brain and gallbladder. It
was noted that the lighter gray the nodule, the more immature were the
cellular constituents and the smaller the amount of pigment.

Small Nervus: The pigmented spots over the shoulders and along the
spine showed a thickening of the epidermis with central horny pearls
and slender branched papillae. In the stratum papillare of the cutis were
groups of uniform round to oval cells. The nuclei were round and rich
in chromatin; the cytoplasm was moderate in amount and at times was
filled by a granular, dark brown pigment. Between these cells, and also
in the stratum reticulosa, were long spindle-shaped cells with deep brown
granular pigment.

Nodule on the Back: The nodule on the back proved to be a firm
fibroma originating from the stratum papillare. It was covered by an
intact epidermis. The basal cells of the epidermis were rich in pigment.

Anatomic Diagnosis

The following anatomic diagnosis was made: melanocarcinoma of
the gallbladder with intravesical hemorrhage; metastases to the brain,
lungs, jejunum, and left kidney; syphilitic aortitis; atrophy of the spleen;
small peptic ulcer of the stomach; bronchopneumonia of the left lung;
papilloma and pigmented nevi of the skin.

COMMENT

Grossly, the origin of the tumor from the gallbladder wall by
a pedicle and its fan-like and irregular outline spoke for the
gallbladder as the primary source. The remaining melanotic
nodules were well circumscribed, giving the appearance of me-
tastatic origin. The nevi in the skin were entirely benign in
nature. Other possible foci of origin, as the eye, the meninges,
the rectum, were free from tumors.
Microscopically, two facts were brought out, the first that the tumor was primary in the gallbladder, and the second that it was epithelial in origin. The former was made evident by the fact that the pedicle was derived from the gallbladder wall and the fibrous strands extended from the wall into the tumor and were well incorporated with it. Also, there was found in a vessel of the pedicle a group of immature tumor cells which were much younger than the cells of the primary tumor. Finally, the metastatic tumor nodules were usually situated about vessels and were less mature than the cholecystic tumor.

That the tumor was of epithelial origin was shown by the alveolar and glandular arrangement of the tumor cells. The stroma usually separated large groups of cells, but in some instances individual cells were surrounded by a delicate stroma. The significance of this latter finding will be discussed later.

The origin of the melanin could best be studied under oil immersion in the small metastatic nodule in the brain. The cells were more uniform and polyhedral in shape. Their cytoplasm was composed of a dust-like, light brown pigment, which was most concentrated about the nuclei. The nuclei themselves were first uninvolved but, with increase of pigment in the cells, they gradually became smaller and finally disappeared.

Histologically, it seemed that, although the cytoplasm was the source of the melanin, the nuclei, too, were involved in the process (von Szily, Smith). Hooker suggested that the nucleus acted as an oxidizing agent but did not actually produce the pigment, as stated by Rössle, Hertwig, Ritter and Kromayer. Bloch and Walthard and Albertini have shown that the nucleus is dopa-negative.

As the melanin-producing cells became older, as was seen in the large nodule in the brain and in the primary tumor, the pigment in the cytoplasm increased and became uniformly coarsely granular. Later, the nuclei became pyknotic and the cell membrane disappeared. With the pigment free in the interstitial tissue, numerous histiocytes were found in the vicinity, stuffed with granules of pigment of various sizes. This type of cell was not found in the metastatic tumor nodules poor in pigment. That these cells were phagocytic in character was shown by the fact that they contained, at times, granulocytes and red cells. These cells gathered about blood vessels, entered them, and carried their pigment to other parts of the body.
Granting that the tumor is derived from epithelium in the
gallbladder, the question still remains: What is its actual source?
Does it arise from the epithelium of the gallbladder; is it the
result of a metaplasia thereof, or does it have its source in an
embryonic rest? The literature contains no reference to the
formation of pigment by the epithelial lining of the gallbladder,
nor could such a process be found in studying the gallbladder
walls of patients of various ages (especially of the colored race).
Metaplasia of this columnar epithelium into squamous epithelium,
with malignant transformation, has been described by Konjetzny,
Herxheimer, and Speese. It is similar, for example, to that found
in the lung by Cohn.

Simmonds and Lubarsch believe that squamous-cell and mixed
tumors of the gallbladder are the result of misplaced embryonal
rests, rather than the result of metaplasia, as they were unable
to find an associated cholelithiasis or cholecystitis with these
conditions. The absence of stones or signs of inflammation in the
gallbladder in the case reported speaks for a misplaced embryonic
rest as the origin of the tumor. The slight round-cell infiltration
and fibrosis of the wall were rather a reaction to the tumor than a
primary infection, as the epithelium was intact.

The difficulties that arise in determining the epithelial or
mesenchymatous origin of the melanotic tumors are the pleo-
morphism that they at times assume and the marked intercellular
stroma that may be present. That these factors do not necessarily
mean that the tumors are sarcomatous in nature was shown by
Arnstein and Risel, who described cases of lung carcinoma in
miners, in which the cells were elongated and small, simulating
sarcoma. By various methods of connective-tissue staining (van
Gieson, Mallory, Bielschowsky) it was possible to demonstrate
the carcinomatous nature of these growths.

The intercellular connective-tissue stroma has been explained
either as arising from the perivascular connective tissue or by a
process of desmoplasia, as described by Kromayer, in which the
epithelial cells assume the properties of collagen formation.

The differentiation of melanosarcoma from melanocarcinoma
by the type of pigment granules in the cytoplasm, as described by
Duval, is erroneous. The experimental work of Smith and the
findings in this study have shown that epithelial cells may have
either finely or coarsely divided pigment granules of uniform size
in any given cell. The pigment granules of varying sizes are
usually found in elongated cells that have phagocytic properties and are mobile.

Conclusions

1. A case of primary melanocarcinoma of the gallbladder with multiple metastases is reported.

2. By studying the various metastatic nodules, it was found that the melanin was present in the cytoplasm in the early stages as a fine, dust-like, light brown pigment; in the later stages as a uniformly granular, dark brown pigment. The latter was usually associated with death of the cell and liberation of the melanin, which was in turn found in the cytoplasm of elongated mobile cells, as dark brown to black pigment granules of various sizes.

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