UNUSUAL CARDIAC AND CEREBRAL METASTASES IN MELANOSARCOMA

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Clinical interest in cases of generalized melanomas often becomes focused upon the extensive metastases in one or more organs. The primary neoplasm, if cutaneous, may have been forgotten by the patient or may show a relatively insignificant appearing recurrence at the site of the original tumor, which too often has been as much incised as excised, while the subcutaneous nodules and especially the luxuriant growth of the secondaries on hepatic soil are the outstanding features. Even at autopsy, the gross pathological picture may be such as to lead to serious misinterpretation of the primary site. There can be but little doubt that many of the reported instances of melanoblastomas arising in situations other than the eye and the skin are thus to be explained.

The case here presented is illustrative of the way in which the emphasis falls upon the secondary dissemination in cutaneous melanotic sarcoma. In addition, it presents an unusual coincidence of interesting features. The history of the case and the clinical findings failed entirely to indicate the extensive visceral metastases, and nothing in these suggested the remarkable meningeal involvement. A neoplastic nodule on the floor of the fourth ventricle, which had ruptured through the ependyma, did not influence the clinical findings sufficiently to attract attention. As for the heart, a moderate aortic regurgitation led a member (Dr. George R. Herrmann) of the Internal Medicine Staff to suggest the possibility of secondaries upon the aortic valve cusps, but this possibility was not taken seriously, and that the entire myocardium was studded with neoplastic nodules was unsuspected.
In retrospect, one might well ascribe the nausea and vomiting which were present, to a central nervous system origin; the muscle pains to the hundreds of metastases in the skeletal muscles and muscle fascia, many of which must have encroached upon nerves, or to the diffuse infiltration of the spinal meninges; the periods of irrationality to the meningeal involvement; and the lung signs toward the end, which were clinically considered to be due to a terminal broncho-pneumonia, to the failing pulmonary circulation from destruction of the myocardium or to the numerous pulmonary metastases. On the other hand, there is not one of these findings which might not well receive some other clinical explanation when found in a patient dying, as this one was, in a condition of marked tumor cachexia.

CASE REPORT

The following clinical notes are abstracted from the records of the Department of Internal Medicine, service of Doctor Newburgh.

E. B., male factory laborer, age thirty-three, entered the University Hospital January 10, 1922, as an emergency patient. He was brought in on a stretcher and was too ill to give his history. His chief complaints were pain in the abdomen and back, vomiting, and weakness. From his wife it was learned that he had been well up to nine weeks before. At that time he was taken with severe pains in the muscles of the arms, back, and legs, and the hands and arms were swollen. He went to bed for ten days and the swelling disappeared. Several days later he developed a severe pain in the mid-epigastrium which was thought to be due to a gastritis. At first food or soda relieved the pain but later they seemed to have no effect. He was nauseated but had not vomited until three weeks before entrance. The severe vomiting spells which began at that time had no relation to meals and from time to time the vomitus was mixed with altered or even bright red blood. He had been unable to retain any food for about a week previous to entering the hospital. Small tumors began to appear over the body about three weeks before entrance and they seemed to be growing somewhat larger.

Family and personal history were without incident except that the patient had had a large pigmented mole removed from his back about two years before. The exact date was not known. Some time before
this operation he had fallen and traumatized a portion of the mole and this accident was followed by infection in the mass of the tumor. According to the wife a pathological diagnosis of "pigmented cancer" was made after the operation.

Nine weeks before entrance the patient weighed 164 pounds. He lost 34 pounds in the first four weeks of his illness and loss of weight had continued. He slept poorly and had been receiving morphone for the past two weeks. He had been slightly irrational for the past week.

Abstract of physical examination by Doctor Hills

The patient is poorly nourished. He is lying in bed, is very drowsy and does not respond to questions. He appears rather unclear mentally. The hair is dark brown in color and coarse in texture. The skin over the face appears slightly flushed; over the remainder of the body it is warm, moist, and elastic. Immediately beneath the skin over the thorax, abdomen, thighs, and to a lesser extent over the back, there are numerous small tumor masses, ranging in size from that of a small pea to that of a pinhead. The tumor masses are freely movable beneath the skin, are hard, and have a slight bluish tinge. In the lower right back there is a large scar, slightly bluish in color, which is the site of the operation done about two years before. The eyes are negative except that the pupils react sluggishly to light. There is no apparent disturbance of hearing. The thorax is long and narrow. On palpation of the cardiac region there is a marked shock felt over the area of the apex impulse. On auscultation, immediately following the first sound there is a rough systolic murmur slightly heard at the apex and especially well heard at the left border of the sternum. The first sound is very loud. Over the aortic area there is a faint diastolic murmur. The lungs show some dullness over both apices, extending down into the interscapular region. Over the entire abdomen there is a tenderness with some muscle spasm upon palpation.

The urine was practically negative except for a positive melanogen test. The blood showed 87 per cent hemoglobin, 4,300,000 red cells, and whites increasing from 17,000 to 26,200 during the stay of the patient in the hospital. The blood pressure was 160/60. The blood Wassermann was negative.

The provisional diagnosis was: Melanotic sarcoma, diffuse; aortic regurgitation; emaciation.

Following his admission to the hospital, the patient gradually grew worse, vomiting being so frequent that he retained practically no food.
He was irrational at times and very restless. On the morning of the 17th there were many râles on the right side and he was believed to be developing a broncho-pneumonia. He then grew rapidly worse and died the evening of the 18th.

**Autopsy findings**

*(Dr. C. V. Weller, prosector)*

Autopsy was done ten hours post-mortem. The more significant data are given in the abstract which follows.

The body is that of an adult male of slender build, 176 cm. long, showing marked emaciation. In the lower part of the right back there is a thin, freely movable, non-pigmented scar. At the upper end of this there is an elevated, deeply pigmented nodule, about 1 cm. in diameter, which has a bluish black color through the overlying epidermis. In the right axilla there is a smooth oval mass nearly the size of a hen's egg. Scattered everywhere in and beneath the skin there are very numerous small nodules, varying in size from shot-like grains, barely palpable, up to 1 cm. in diameter. These, in part, move freely with the skin but in part are more deeply situated and fixed, the skin moving over them. Most of these nodules show no pigmentation. Some of the larger, especially those which are situated near the epidermis, show a deep purplish or bluish color.

The spinal cord, examined only in the upper cervical region, shows no change except thickening of the meninges. Scalp and cranial vault are negative. The dura appears thicker than normal. The leptomeninges show everywhere a diffuse thickening, without pigmentation, and are more adherent to the cortex than normally. The cerebrum shows a moderate general congestion and edema. In the subcortical zone on the left side, about three cm. from the midline superiorly, there is a small area of softening in the brain substance. This has a pigmented, brownish border, not unlike that seen about areas of cerebral infarction with softening, and can not be positively known to be neoplastic by naked eye examination. On the floor of the fourth ventricle there is an elevated nodule, about 5 mm. in diameter and gray in color. This is evidently neoplastic.

The pericardial tension is normal, the pericardial fluid clear. The heart is somewhat larger than the cadaver's right fist. Scattered everywhere in and beneath the epicardium there are pale grayish-white to yellowish-white neoplastic nodules, ranging in size from minute
points, barely visible, up to 1 cm. in diameter. Most of these show no unusual pigmentation, although a few of the largest are brownish in the central portion. The right ventricular wall measures 7 mm. in thickness; the left, 14 mm. Metastatic nodules similar to those beneath the epicardium are found everywhere throughout the myocardium and in and beneath the endocardium. On the papillary muscles of the left ventricle they are very numerous, appearing elevated and slightly roughened on the surface. Here there is practically no evidence of pigmentation. Valvular orifices and valve flaps are negative except the aortic, which admits the thumb with ease. Near the edges of the aortic cusps there are several small nodular masses, possibly neoplastic. These are not pigmented and are firmer in consistency than the undisputed neoplastic nodules in the myocardium.

The autopsy findings in other organs may be summarized for the purpose of this report with the statement that the intercostal muscles, the substernal fascia, both lungs, omentum, peritoneum, spleen, pancreas, liver, kidneys, peri-adrenal tissue, bladder mucosa, and testes showed nodular metastases to the naked eye. The lungs showed no gross evidence of pneumonia, but there was a well marked congestion and edema.

Microscopical findings

(See below for detailed description)

Brain. Diffuse sarcomatous growth throughout the meninges. Large nodular metastasis in the floor of the fourth ventricle, showing central necrosis and a few pigmented cells. General congestion and edema.

Choroid plexus. Numerous metastases throughout.


Heart. Numerous metastases in the endocardium, throughout the myocardium and in the epicardium (detailed description below). To some of the endocardial metastases fresh thrombi are attached, and between the trabeculae of the left ventricular wall there are large masses of recent mixed clot containing several areas filled with apparently living neoplastic cells.

Aorta. Slight sclerosis. The para-aortic lymph nodes are filled with metastases.

Lungs. Multiple metastases. Pigmented cells are found in small numbers in the older and larger metastases. None elsewhere.
**Tonsils.** Moderate atrophy. Hyperkeratosis.

**Thyroid.** Excess of colloid. Colloid cysts. Numerous metastases.

**Spleen.** Chronic passive congestion. Lymphoid atrophy. Numerous metastases, some with central necrosis and hemorrhage.

**Pancreas.** Numerous metastases.

**Stomach.** Slight atrophic catarrhal gastritis.

**Intestinal tract.** Chronic atrophic catarrh. Peritoneal surface covered with metastases and metastases even in the muscularis.

**Mesenteric fat.** Small metastases everywhere.

**Adrenals.** Small metastases in both cortex and medulla. Numerous metastases in peri-adrenal tissue.


**Testes.** Diminished spermatogenesis. Some increase in stroma. Several metastases.

**Prostate.** Cystic glandular hyperplasia. Small metastases.

**Bladder.** Metastases in the mucosa and in the muscularis.

**Recurrence in scar on back.** A sarcoma of the type described below, showing relatively few pigmented cells in the greater part of its mass.

**Type of tumor.** In its recurrence and in the metastases, the neoplasm is an alveolar polymorphous cell sarcoma. Many areas have a highly vascular stroma and there are many large atypical giant cells. In portions of the recurrence there are numerous pigment-bearing cells. These are found in relatively large numbers, also, in the large axillary metastasis and in smaller metastases elsewhere, but a majority of the metastases show very little melanin. A chromatophoroma, but chiefly non-pigmented.

**Pathological diagnosis**

Recurrent melanosarcoma of the skin (primary in pigmented mole of lower right lumbar region, operated upon about two years previously). Multiple metastases in meninges, brain, lungs, bronchial nodes, heart, spleen, liver, kidneys, adrenals, bladder, prostate, testes, pancreas, peritoneum, intestinal wall, and all lymph nodes. Generalized sarcomatosis, chiefly non-pigmented. Atrophy, passive congestion, and parenchymatous degeneration of all organs. Aortic insufficiency due to sarcomatous infiltration of the myocardium. Tumor cachexia. General marasmus.
DISCUSSION

General character of the neoplasm

In view of the fact that the original pigmented mole was accidentally traumatized and then operated upon about two years before the patient entered the Hospital, it is of interest to note that the present illness was considered as of but nine weeks' duration. During the fore part of this long latent period the primary neoplasm may have been growing slowly without sufficiently heterotypic characteristics to give metastases. In view of the autopsy findings, however, another explanation can well be entertained. By far the largest metastasis found was that in the right axilla. It also showed the most marked degree of pigmentation. It is not at all unlikely that this may have been established before the original operation and that from it some, if not all, of the later general hematogenous dissemination may have been derived.

The extraordinary rapidity of growth, once numerous metastases were established, as shown by the clinical course, is indicated also by the relative lack of pigment. Many of the fairly good sized nodules might well be described as amelanotic, so that only the larger and older metastases fully reveal the pigment producing inheritance of the neoplasm. The foudroyant course of the overwhelming terminal sarcomatosis points to a sudden failure or exhaustion of some inhibiting power which had hitherto held blastomatous proliferation somewhat in check, or to a rapid exaltation of the proliferative energy of the blastoma cells.

In general, the type is that of an alveolar sarcoma exhibiting much variety in size and form of cells, but many of the smaller and presumably younger metastases and the emboli do not show the polymorphic type and are round celled. New formed blood vessels are abundant in some of the metastases, the appearance in such areas approaching that of an angio-sarcoma.
Brain and meningeal metastases

The neoplastic nodule on the floor of the fourth ventricle is of striking appearance, both in the gross and in microscopical sections. It was originally somewhat below the ventricular ependyma but with progressive growth ruptured through the overlying tissue, which is folded back upon itself on either side, the ependymal layer being otherwise intact (see fig. 1). After thus breaking through, the neoplasm presents a ragged surface from which free blastoma cells might well have been given off into the ventricular fluid.

The meningeal dissemination constitutes the most remarkable feature of the case. The diffuse opacity, thickening and greater

Fig. 1. Photomicrograph of the Metastasis of Melanosarcoma in the Floor of the Fourth Ventricle

The main mass of the tumor nodule lies to the right. The more superficial neuroglia and ependyma have ruptured and are turned back toward the left. Note the nearly complete absence of pigment.
degree of adhesion of the leptomeninges, as noted at autopsy, proved to be due to a diffuse sarcomatous infiltration, spreading everywhere through the inner meninges of both brain and cervical cord, and from the pia streaming down into the cortical and even subcortical tissue (see figs. 2, 3, and 4). The infiltration is not quite so abundant over the gyri, but the sulci are completely

filled by the infolded blanket of new growth. The highly vascular meninges and outer cortex have furnished an exceedingly favorable soil for the growth of the tumor cells, and in the lower portion of the layer of sarcoma cells, actually in brain substance, a perivascular arrangement about the original cerebral vessels

Fig. 2. Low Power Photomicrograph of the Cerebral Leptomeninges to Show the Continuous Mass of Neoplasm Over the Surface and Streaming Down into the Cortex and Subcortical Tissue

Below, are older, heavily pigmented metastases having a very different manner of growth.
becomes very evident. In this zone, also, are to be found numerous groups of rather deeply pigmented cells which are almost entirely perivascular in position. Curiously enough, these melanin-bearing metastases are relatively small, and although undoubtedly older than the more superficial masses, as shown by the marked pigmentation, certainly exhibit a much feebler growth than that luxuriantly infiltrating from the diffuse meningeal layer.

It must be emphasized that the meningeal dissemination in this case is exactly like that described for certain of the so-called primary meningeal melanomas. It bears a very close resemblance, for instance, to the case reported by Lua (1) as primary in the meninges, and shows a much more diffuse extension than that in the case of Schopper (2). Such a case as this,
in which a primary cutaneous melanosarcoma is unquestioned, throws very grave doubt upon the supposed primary meningeal origin of similar diffuse meningeal melanosarcomas. The possibility of such an origin is accepted by many, including Ewing, the melanoblastoma supposedly having its origin in certain pigmented cells described as occurring normally in the lepto-

meninges. Here, however, the same gross and microscopical picture is presented as in some of the so-called primary cases, so that it must be concluded that the occurrence of a primary meningeal melanosarcoma has not been fully demonstrated.

FIG. 4. PHOTOMICROGRAPH OF THE DEEPER CEREBRAL EXTENSIONS FROM THE MENINGEAL METASTASES WITH A FEW OF THE SMALL, BUT MUCH OLDER, PIGMENTED CEREBRAL METASTASES
Fig. 5. Multiple sub-epicardial and myocardial metastases of melanocarcinoma
Heart

The occurrence of myocardial metastases in melanotic sarcomatosis is not unusual. The heart in this case, however, showed metastases in such extraordinary profusion (see fig. 5) that there is no difficulty in bringing a number of them into a single low-power field of the microscope. Metastases are especially numer-

Fig. 6. Photomicrograph of a sub-endocardial metastasis of melanosarcoma with a mass of tumor cells growing on the endocardium directly above the nodule

ous in and beneath the endocardium, and it is frequently noted that if a group of sarcoma cells lies just beneath the endocardium, it is capped by other cells lying without the original endocardial line and presenting themselves freely to the circulating blood (see figs. 6 and 7). To such plaques of cells mixed clot is often found adherent, and from them the masses of neoplasm and mixed clot lying nearly free in the ventricles were doubtless derived.
The small nodules on the aortic cusps could not be distinguished positively at autopsy from the endocardial metastases. On microscopical examination, they are found to be composed of hyaline connective tissue without neoplastic cells, and are therefore not metastases. In the myocardium about the aortic ring, however, relatively large metastases are found. To the result-

Fig. 7. Photomicrograph Showing Portions of Two Larger Sub-endocardial Metastases with a Large Mass of Neoplasm Growing from the Corresponding Endocardial Surface into the Intertrabecular Space of the Ventricle

ing relaxation of the ring, the aortic insufficiency must have been due. The sclerotic nodules doubtless represent the healing of some older infectious process, and are inadequate in size to explain the aortic lesion.
SUMMARY

In a case of diffuse melanotic sarcomatosis dying two years after mechanical trauma to, and operation upon, a pigmented mole, there are found in the brain a solitary metastasis in the floor of the fourth ventricle, innumerable older cortical and sub-cortical metastases and a diffuse meningeal sarcomatosis, none of which had influenced the clinical picture in such a manner as to call attention to its existence. The meningeal involvement is exactly like that described for certain cases of alleged primary meningeal melanosarcoma, and throws further doubt upon the possibility of such origin. Very numerous myocardial and endocardial metastases were present, producing a relative aortic insufficiency clinically evident.

REFERENCES