BENIGN METASTASIZING HEMANGIOMA

J. MAURICE ROBINSON, M.D., AND BENJAMIN CASTLEMAN, M.D.

BOSTON, MASS.

FROM THE DEPARTMENTS OF ROENTGENOLOGY AND PATHOLOGY, MASSACHUSETTS GENERAL HOSPITAL

A SMALL group of hemangiomata is characterized by extensive metastases, in spite of the seemingly benign histologic structure of both the primary and secondary tumors. Only four apparently authentic cases of this condition have been reported: Borrmann,[1] 1906; Shennan,[2] 1914; Ewing,[3] 1919; Geschickter and Keasbey,[4] 1935. They have given rise to considerable discussion because the existence of such a group has an intimate bearing on the question of the essential similarity of benign and malignant processes and because they are difficult to classify. Some authors (Jaffe,[5] Wollstein,[6] Taylor and Moore,[7] and others) have even attempted to discredit altogether the criteria on the basis of which these tumors have been grouped together.

We have recently had the opportunity to study a case which helps to clarify the paradox of a metastasizing benign tumor.

CASE REPORT

An 18 year old American girl entered the Tumor Clinic of the Massachusetts General Hospital complaining of a painless enlargement of the right breast of six months' duration. Three months after the lesion was first noted the breast became discolored and shortly afterward painful. Examination on admission showed that the right breast was about twice its normal size, forming a firm elastic mass with a purplish discoloration surrounding the nipple for about 8 cm. (Fig. 1). There was no increase in local temperature, no pulsation in the mass, and no discharge from the nipple. A small pigmented nevus was present on the opposite breast, but no other skin tumors were seen.

A preoperative diagnosis of hemangioma was made and a simple mastectomy performed.

Gross examination showed a right breast measuring 14.5 x 11.5 x 8.5 cm. covered by an elliptical piece of skin 14.5 x 8.5 cm. The nipple was negative. Just to one side of the nipple there was a mottled purplish discoloration of the skin over an area 5 x 3 cm. in size. Nearly all the breast tissue was replaced by a large, fairly well encapsulated, rather soft, mottled, purplish-gray tumor 10.5 cm. in diameter and 3 cm. in thickness. The capsule was quite adherent around the periphery and in places could not definitely be made out. The cut surface was edematous, light gray in color, and honeycombed with small cystic spaces filled with blood.

Microscopic examination showed a lesion consisting of small and large cystic spaces filled with blood and lined by small, uniform, apparently quite well differentiated endothelial cells. No mitotic figures were seen (Fig. 2). The lesion extended widely throughout the breast tissue, showed slight invasive properties, but no histologic evidence of rapid growth. Because of this tendency to infiltrate the breast tissue and in spite of the fact that its structure was that of simple angioma, the tumor was not considered entirely benign.

Eight months after the mastectomy the patient returned to the hospital. A keloid had developed in the scar and two small hemangiomata had now appeared, one over the right lower ribs posteriorly and the other in the right supraclavicular region. During

the following month two more lesions appeared, one on the chest, 1.5 x 1.3 cm. in extent, and the other on the scalp, 5 x 3 cm.

At this time roentgen therapy was started. During the next four months all the lesions except that in the scalp received three to four doses of .8 skin units* superficial therapy at monthly intervals. At the end of this period the treated lesions showed considerable flattening without, however, any definite decrease in width. The scalp lesion was then treated with monthly doses of .8 skin units for three months. Two new lesions appeared on the abdomen, followed rapidly by numerous others over the abdomen and back. An attempt to treat all of these was quite impractical. The scalp tumor began to grow rather rapidly, reaching three times its original size. It was then excised—one year after it was first noted, 20 months after the original mastectomy.

The pathologic diagnosis was hemangiosarcoma. This metastasis was quite different from the original tumor. The cystic angiomatous spaces had disappeared. The cells were quite spindle shaped, small, contained hyperchromatic nuclei, and were definitely

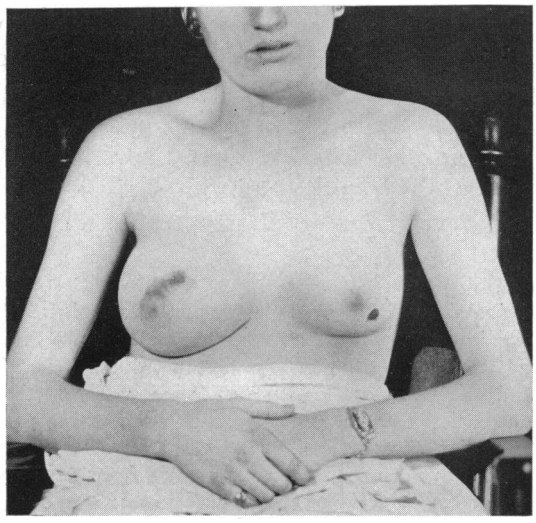

FIG. 1.—Showing the enlargement of the right breast, when first examined.

angioblastic. Mitotic figures were present and there was definite evidence of infiltration (Fig. 3).

Since there did not appear to be any involvement of the internal organs, an attempt was made to determine the radiosensitivity of some of the individual skin lesions. Two groups were selected: (1) the older lesions previously treated with superficial roentgen ray and (2) a few of the recent untreated masses. Each lesion received during a two week period 1,600 r (two erythema doses) of medium wave roentgen ray in one dose. A few received 3,200 r in two doses. Two months later the skin over the treated areas was flat and scaly; no masses could be felt. The untreated lesions, however, had grown slowly although no new tumors appeared. An hemangioma in the left breast

*A skin unit refers to a threshold erythema dose (350 r) of superficial or long wave roentgen ray delivered at 100 kilovolts, 5 milliamperes, 8 inch distance, .5 aluminum filter. "Medium wave therapy" refers to roentgen rays delivered at 140 kilovolts, 5 milliamperes, 4 Mm. aluminum filter, 50 inches. "Deep therapy" refers to short wave roentgen rays delivered at 200 kilovolts, 50 cm., 5 milliamperes, .5 Mm. copper filter. In the case of medium and deep roentgen ray therapy, 800 r measured in air is considered the equivalent of an erythema dose.

which was treated with 900 r right side and 900 r left side deep therapy through a 10 x 10 field, in divided doses of 300 r each, showed slight softening. The lesions were so numerous, however, that they could be counted only with difficulty. Many were barely perceptible and others appeared to be mere discolorations or spongy elevations. The attempt to treat them individually was therefore abandoned.

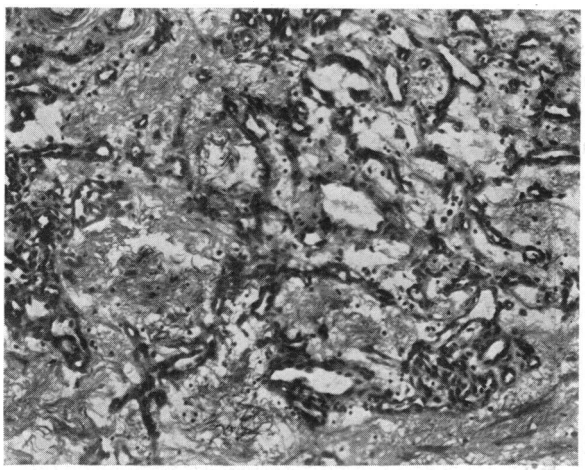

FIG. 2.—Photomicrograph of the primary tumor of the right breast, showing a fairly characteristic hemangioma.

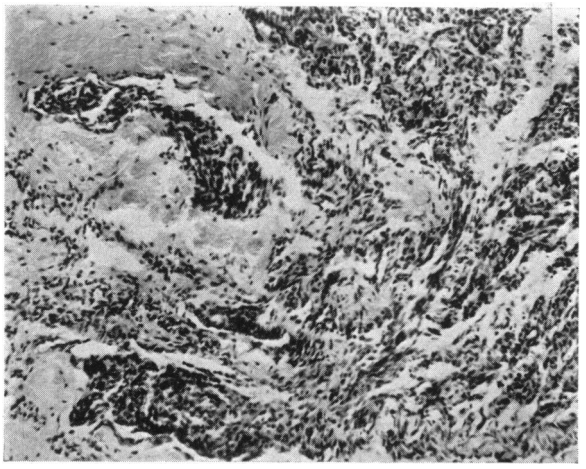

FIG. 3.—Photomicrograph of the metastatic nodule in the scalp, showing definite sarcomatous changes.

The patient left the hospital and did not return for five months. At this time the left breast was tremendously enlarged, discolored, and tense (Fig. 4). A palliative partial mastectomy was done. A large part of the tumor had invaded the chest wall and mediastinum. The histologic structure was similar to that observed in the scalp tumor; mitotic figures were fairly numerous. The patient was discharged and three months later died at home, three years after the first breast tumor was noted. An autopsy was not performed.

Borrmann,[1] in 1906, reported the first case of this previously unrecognized

form of angioma, that of a female, aged 26, who had developed a walnut sized tumor in the right breast. It was excised a few months later but recurred five times during the following year, each recurrence being excised in turn. In addition a mass appeared in the scapular region which was also removed. The patient died 21 months after the tumor was first noticed, 17 months after excision. Autopsy showed another recurrence in the region of the primary site and a similar mass in the left buttock. Both lungs were filled with small hemangiomatous masses and the pleural cavities contained bloody fluid. The original tumor was not available for study, but all the recurrences and the metastases showed a structure fairly characteristic of

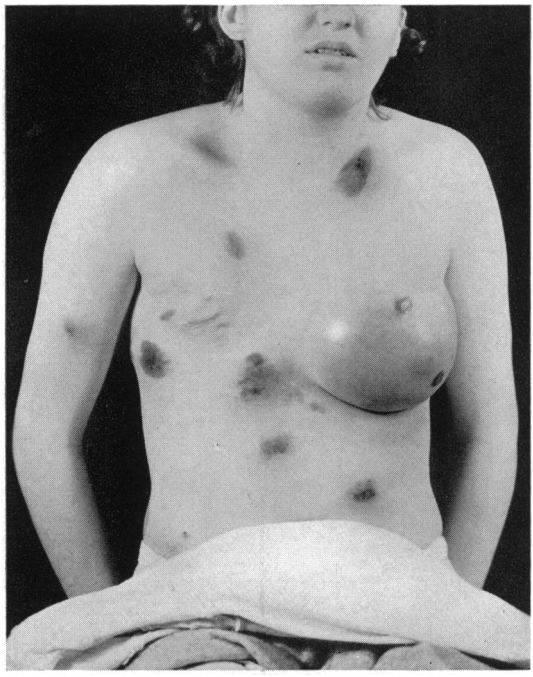

FIG. 4.—Appearance of patient two years and three months after her first admission, showing the numerous metastases in the skin and the marked involvement of the left breast.

telangiectasis or simple angioma. Borrmann emphasized the fact that there was nothing to distinguish any of them from benign hemangiomata without metastases.

The second case, reported by Shennan,[2] in 1914, was that of a female, aged 23, with a six year history, beginning with hemoptysis and later followed by splenomegaly, hemothorax and ascites. During her illness three small tumors appeared on the skin, one of which was excised and proved to be a cavernous hemangioma. At autopsy tumors of similar histologic structure were found in the spleen, lungs, thymus, bone marrow, liver and lymph nodes. The primary source was evidently in the mediastinum. In none of the organs did the histology remotely suggest sarcomatous change. While it cannot be denied that the internal tumors might possibly have been

slowly growing multiple benign angiomata, the skin lesions were presumably metastatic, and it is probable from the history that the larger tumors were, also.

Ewing[3] discusses the case of a middle aged woman with a bulky cavernous hemangioma of the breast with numerous metastases to the skin and lungs. The structure was similar to that described by Borrmann.

Geschickter and Keasbey[4] mention the case of a 62 year old man with angiomatous masses in both iliac fossae, lungs, pleura and spleen, all of which showed the histologic structure of an apparently benign angioma.

DISCUSSION.—Although varying in structure—Borrmann's case was a simple angioma; Ewing's was "quite similar"; Shennan's was a cavernous hemangioma; Geschickter and Keasbey's consisted of tightly packed spindle cells surrounding sinuses lined by endothelium—these four cases conform to the definition of this group: that is, they are metastasizing angiomata in which both the primary and secondary tumors are seemingly histologically benign. For this reason, they should be separated from two other large groups of hemangiomata. The first of these are the definitely malignant metastasizing hemangiosarcomata—*e.g.,* the cases reported by Pick, Stamm, Ullman, Kopf, Theile, and Jores (mentioned by Sonntag[8]), the cases of Wright,[9] Hall,[10] and others. The second are the multiple (not metastatic) benign hemagiomata, particularly those occurring in children, which by local invasive growth, location or hemorrhage may cause death, among them the cases reported by Homans,[11] Jaffé,[5] Wollstein,[6] Taylor and Moore,[7] and many others.

Borrmann discussed his case under the title of "Metastasenbildung bei histologisch gutartigen Geschwülsten" in order to clearly emphasize the vagueness of the boundary between benign and malignant tumors. He felt that the presence of metastases could no more be used to determine definitely the benign or malignant character of a process than, for example, the absence of a capsule, invasiveness, or rapid growth: these, we know, are not exclusively benign or malignant properties. Shennan, on the other hand, although agreeing with Borrmann with reference to the classification of these angiomata, calls attention to another problem which we consider more important; *viz.,* whether the histologic criteria, rather than the clinical, are not at fault.

Ewing feels that this group of angiomata is a borderline entity, "cavernous or more cellular angiomas possessing certain peculiar features of malignancy." Livingston and Klemperer[12] describe the histology of a single hemangioma invading the scalp. They considered the stroma, which simulated that of Borrmann's case, to be undifferentiated mesenchyme rather than simple connective tissue. They believed that the tumor reported by them and those reported by Borrmann, Shennan and Ewing possess similarities which justify their inclusion in a group by themselves—as malignant mesenchymal angiomata. Since the outstanding clinical feature of Livingston and Klemperer's case was the local invasive growth, their hypothesis, if true, might well explain the invasive properties not infrequently seen in solitary

angiomata. Their case, however, does not show the essential feature characterizing the other three: namely, the production of metastases. We are not certain, therefore, that the conclusions they have drawn from their case can be applied to these others.

Wright[9] divided metastatic hemangiomata into two general groups. He differentiates those with a histologically benign structure (cases of Shennan, Borrmann, and Ewing) from those with a histologically malignant structure (cases of Theile, Jones, Langlans, and his own, all of which were hemangiosarcomata of the spleen with metastases to the liver and other organs). He points out that the common feature of both groups was the formation of metastases, the histologic structure of which was similar to that of the primary tumor. In none did the primary benign hemangioma give rise to metastases with structural characteristics of malignancy.

It seems to us that the case we are reporting is a connecting link between the four cases cited in the literature and the true angiosarcomata. Ours is evidently an example of an apparently histologically benign tumor giving rise to malignant metastases. To assume that this is a case of multiple tumors one would have to admit that there were numerous hemangiomatous rests, such as Ribbert (quoted by Borrmann) describes, which began to grow under the influence of local or general factors. If this were true one would expect these secondary tumors to have been discernible either at the same time as the original tumor or certainly within a shorter period than one year. Since it is highly improbable that this is a case of multiple tumors, but rather that the lesions that appeared following the original breast tumor were really metastases, we must conclude that we are dealing with a process which was malignant from the onset and that the primary tumor, in spite of the absence of histologically malignant properties, was not benign. We feel that because the histologic structure of our case is very similar to the quoted cases, especially those of Borrmann and Ewing, it is probable that the latter were also primary malignant tumors. This is in agreement with Shennan's concept that it is the occurrence of metastasis which should be the deciding factor and not the histologic features.

In addition to its bearing on the classification of these angiomata, our case is also of interest because an opportunity was afforded to study the response of these tumors to various forms of treatment—surgical excision, suberythema doses of superficial roentgen rays, divided dose deep therapy, massive dose of intermediate therapy, and various combinations of these. In using suberythema doses of long wave length roentgen ray our aim was the production of an obliterating endarteritis in the tumor, comparable to the commonly accepted method of treating hemangiomata of the skin with small doses of radium at long intervals (Roesler,[13] Kaplan,[14] Baensch[15]). In using the deep and intermediate therapy an attempt was made to actually destroy the lesion. The response of the tumor, in spite of the large doses used for some of the lesions, was only temporary. There is very little doubt, therefore, that these tumors are highly resistant to radiation.

Before leaving the subject of radiation the remote possibility of the roentgen ray itself producing sarcomatous changes in the treated tumors should be mentioned. Sarcomatous degeneration as the result of radiation is extremely rare, and a *post hoc ergo propter hoc* element in the few reported cases cannot be excluded (Livingston and Klemperer). No case of such degeneration has ever been reported in a benign hemangioma treated by roentgen ray or radium, although radiation treatment of these is quite common. Other factors, such as the small amount of radiation which the masses in the scalp and left breast (both hemangiosarcoma) received, further reduce this remote possibility.

SUMMARY.—(1) So called "benign metastasizing hemangiomata" are defined and their classification and significance are discussed.

(2) An unusual case of an angioma of the breast with benign histologic characteristics which produced definitely malignant metastases is reported. Because of the histologic similarity of the primary tumor in this case to reported cases of so called "metastasizing benign angioma" the benign character of the latter must be questioned.

(3) The response of this tumor to various forms of radiation shows it to be highly radioresistant.

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