STUDIES ON BONE FORMATION DURING TRANSPLANTATION OF AN EXPERIMENTAL OSTEOGENIC SARCOMA

(Plate XXXIX)

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Synopsis

1) The successively subcutaneously transplanted osteogenic sarcoma, which was produced experimentally and forming little or no bone and which seemingly appeared as polymorphic cell- or fibro-sarcoma, showed evident osteoid formation in the 13th generation of transplantation.

2) An evident osteoplastic sarcoma developed when a non-osteoplastic sarcoma of the same origin as the above-mentioned tumor was transplanted into the medullary cavity of a Wister rat.

3) Based on the two experiments it was clarified that a sarcoma originating from the bone possesses latent capacity for osteoplasia even if it seemingly has lost osteoplastic ability during successive transplantations, and can develop into an osteoplastic sarcoma under certain circumstances. Definite bone formation of the sarcoma was found when the non-osteoplastic osteogenic sarcoma was transplanted into the intramedullary cavity of the bone.

INTRODUCTION

The old systemic classification of the tumors primary in bones was that proposed in the "Registry of Bone Sarcoma" of the American College of Surgeons. Recently, a classification of bone tumors was proposed by Lichtenstein and Jaffe, and by Herzog of Germany.

Diagnosis of osteogenic sarcoma when it shows relatively little osteogenesis is difficult as Jaffe states. There are questions of whether there is any morphological peculiarity in the sarcoma originating from bone and by what methods a tumor in question could be proved as a tumor originating from the bone. It is very difficult to answer these questions and more difficult to ascertain the latent capacity of bone formation by the usual examination methods.

An attempt was made to solve one of these questions, that is, the potentiality of bone formation which has close relationship to classification and diagnosis of osteogenic sarcoma by observing the changes first of sarcomas transplanted into the subcutaneous tissue successively from generation to generation, and second, the changes of the sarcoma after intramedullary retransplantation of the tumor, which had turned into non-osteoplastic sarcoma during subcutaneous transplantations.

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The evident osteoid formation took place in the 13th generation of subcutaneous transplantation which seemingly appeared as polymorphic cell- or fibro-sarcoma during successive transplantation. In the next examination, an evident osteoplastic sarcoma developed when a non-osteoplastic osteogenic sarcoma was transplanted intramedullarily.

**Experiment 1**

**Materials and Methods**

Wistar rats were used as experimental animals, radioisotopic $^{32}$P was administered intraperitoneally at monthly intervals and, 3 months after the first administration of $^{31}$P, methylcholanthrene or benzopyrene was administered intramedullarily just once. The osteogenic sarcomas developed as previously reported. These experimental osteogenic sarcomas were successively transplanted into the back of the same strain of rats. The transplanted tumors were examined by routine roentgenological and pathological examinations.

**Results**

On histological examination the subcutaneously transplanted sarcomas showed variable figures. Sometimes a little or no bone formation was observed in the course of successive subcutaneous transplantations but, bone and osteoid formation was observed in the specimen No. 864 on histological examination. No. 864 is the 13th generation of the rat treated with $^{31}$P and benzopyrene and which showed no osteoplasia on X-ray, but which was proved to be osteogenic sarcoma on histological examinations. Macroscopic findings of the tumor No. 864 six months after subcutaneous transplantation are as follows: Size of the tumor, $3 \times 3 \times 1$ cm; shape, hemispherical; consistency, elastic in general and hard in some parts. On histological examination it showed pathological bone and osteoid distinctly in some parts. The greater part of the tumor consisted of polymorphic cell sarcoma with giant cells, and mitosis was sometimes observed. Besides the pathological osteoid and bone formation, hyaline ground substance was seen mostly (Photo 1).

**Experiment 2**

**Materials and Methods**

Pieces of sarcoma No. 862 of the 18th generation, originating from the same tumor as No. 864, were transplanted into the medullary cavity of the tibia of homogeneous rats No. 903 and others (Photo 1). The intramedullarily transplanted tumors were examined roentgenologically and pathologically.
RESULTS

The histological findings of the sarcoma No. 862 were as follows: In the main, it showed spindle-shaped sarcoma cells or giant cells with mono- or poly-nuclei and sometimes mitotic figures, and the matrix showed hyaline or fibrous ground substance without bone formation (Photo 2). One piece of No. 862 sarcoma was transplanted into medullary cavity of the tibia of No. 903 rat and others. X-Ray figure 4 months after the implantation is shown in Photo 3. On radiographic examination it showed bone forming tumor, spicula formation, and pathological fracture. Macroscopically it was grayish white, and solid and firm in consistency. On histological examination it showed osteoplasia not only in the center of the sarcoma but also in the peripheral part outside the periosteum (Photo 4). In general, the sarcoma cells showed reticular structure besides bone formation, but the reticuline fibers were small in quantity. Necrosis and hematoma-like or sinusoid structures were observed in the sarcoma. Metastasis in the lung was also seen, as shown in Photo 5, indicating distinct bone structure with abscess formation.

DISCUSSION

Conner⁵) and Berg²) observed “spicula” formation after transplantation of chick endothelioma into the medullary cavity of a chick bone. From the spicula formation in the bone they concluded that the osteogenic sarcoma developed from the intramedullary transplantation of endothelioma. Their reports introduced the development of osteogenic sarcoma by intramedullary transplantation of endothelioma which in general has no bone-forming characteristic.

Brunschwig³,⁴) performed intramedullary transplantation of non-osteoplastic rat tumor which is composed of spindle and round cells and which produces collagen fibers, and observed the changes in the tumor after administration of calcium ion to the rats. Bone formation from the sarcoma cells which is an essential characteristic of osteogenic sarcoma was never seen, but periosteal reactive bone formation was seen between the periosteum and the cortical bone following a successful transplantation.

The spicula formation is one of the factors in diagnosis of osteogenic sarcoma. Conner and Berg observed spicula formation in a chick bone into the medullary cavity of which chick endothelioma was transplanted. Brunschwig's experiments do
not concur with the idea of Conner and Berg. These facts give doubts about the diagnosis of osteogenic sarcoma made by Conner and Berg. Taking Brunschwig's experiment into consideration, it is possible that what Conner and Berg saw in the development of the osteoplastic osteogenic sarcoma by intramedullary transplantation of the chick endothelioma was the development of false spiculae and not the true spicula.

The first transplantation of osteogenic sarcoma in mammals was performed by Barrett in 1944. He has successively transplanted sarcoma NCI No. 1 of mouse into subcutaneous tissue of C3H mouse. He described the result of this experiment as follows: "In the earlier generations of subcutaneous transplantation, the tumors form osteoid tissue and bone, and are characterized by a moderate growth rate, and in the later generations they grow with a rapidly increased growth rate. Further, the high alkaline phosphatase activity and the capacity of forming osteoid tissue characteristic of the early generations are either inhibited or lost."

Compared with these predecessors' descriptions, the present results have shown that experimental osteogenic sarcoma shows little or no osteoplasia macroscopically during their successive transplantations from generation to generation. In the present series of experiments, the histologic figures are more variable and show little or no osteoplasia in spite of possessing latent capacity for bone formation, even in the 13th generation of transplantation. However, when some unknown factor acts upon the subcutaneously transplanted sarcoma of a later generation, this sarcoma changes into osteoplastic osteogenic sarcoma during the transplantation, as in the case of No. 864 of the 13th generation of successive subcutaneous transplantation. On comparing the present experiment with that of Barrett, it is seen that Barrett's experiment merely showed the disappearance of osteoplasia during successive subcutaneous transplantation, while in the present experiment, non-osteoplastic polymorphic cell- or fibro-sarcoma which originated from the bone regained the osteoplastic power during continuous subcutaneous transplantations. It became clear that the seemingly non-osteoplastic polymorphic cell- or fibro-sarcoma which originated from the bone has a latent capacity for bone formation. The manifestation of osteoplastic character of the sarcoma may be the result of some changes in the environment, but the exact mechanism or factors causing the sudden osteoplasia is not clear.

The second is an experiment in which the subcutaneously transplanted non-osteoplastic osteogenic sarcoma was transplanted intramedullarily for the second time, and one concrete ossifying factor of the sarcoma was demonstrated clearly in this experiment. The non-osteoplastic tumor changed into osteoplastic tumor by intramedullary retransplantation and further it showed osteoplastic lung metastasis. It is interesting when this is compared and discussed with Brunschwig's experiment, in which the non-osteoplastic mesoblastic sarcoma was transplanted intramedullarily.
and did not developed into osteoplastic tumor.

The present series of experiments show that osteogenic sarcoma, even when it seemingly lost the bone-forming characteristic, can develop into osteoplastic sarcoma again when it is retransplanted intramedullarily, that is to say, when it is placed in a suitable environment. It is clear that the osteogenic sarcoma originating from the bone and showing appearance of fibrosarcoma or polymorphic cell sarcoma has a latent capacity for bone formation.

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REFERENCES


EXPLANATION OF PLATE XXXIX


Photo 5. Animal No. 903. Lung metastasis of osteoplastic osteogenic sarcoma induced by intramedullary transplantation.