Transplantable Osteogenic Sarcoma in Inbred AKR Mice

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SUMMARY

A transplantable osteogenic sarcoma occurring spontaneously in an inbred AKR mouse is described. The tumor has maintained its bone differentiation properties for 44 transplant generations.

INTRODUCTION

Spontaneous transplantable osteogenic sarcoma in mice is rare. Heiple et al. (6) have described an osteogenic sarcoma in C3H/Hes mice, which was maintained by serial subcutaneous transfer for over 100 transplant generations. Craig et al. (2) reported an osteogenic sarcoma arising in an adult Sprague Dawley rat; the tumor was successfully transplanted into Holtzman rats, and it retained its bone-producing capacity up to the 8th generation.

Pybus and Miller (9, 10) described a subline of inbred mice derived from the Sympsom stock which developed a high incidence of osteosarcomas and other bone tumors. However, spontaneous osteogenic sarcomas which are transplantable and retain the capability of bone production have not been described in inbred mice. In the present communication, we describe a spontaneous osteogenic sarcoma in the AKR inbred mouse. This tumor has been transplanted for 44 generations and has retained its original histologic differentiation pattern.

MATERIALS AND METHODS

The original tumor was found in a five-month-old inbred AKR mouse, obtained from Jackson Laboratories, Bar Harbor, Maine. The tumor arose in the hind extremity and measured 2 x 3 cm in 7 weeks. It was successfully transplanted into 6-week-old AKR mice. Successive transplantation of the tumor into groups of 6 to 10 AKR mice has been carried out for 44 generations. The tumor has a record of 100% takes. Mice were killed at various time intervals. The tissues recovered at autopsy were fixed in Zenker's solution and processed in the usual manner. Sections were prepared and stained with hematoxylin and eosin, periodic acid-Schiff (PAS), and von Kossa stains.

RESULTS

The tumor grew slowly and invaded locally at the site of implantation. At 11 days, the tumor measured 0.6 cm in diameter and reached a maximum of 4 cm at approximately 52 days. A slight regression was noted subsequently. No distant metastases were observed. Early in its development the tumor appeared solid, but later became cystic with extensive central hemorrhagic necrosis.

Histologic sections of the tumor at 11, 22, 38, 52, 92, and 134 days after transplantation were available for study. In its earlier stages (11 days) the tumor was very cellular and composed of plump spindle-shaped or oval cells which showed varying degrees of anaplasia (Fig. 1). Nuclei were in general large and eccentric with coarsely clumped chromatin and prominent nucleoli. Many mitotic figures were present, and some appeared atypical. The cells, for the most part, were loosely arranged in an edematous matrix. Formation of hyaline cartilage was apparent toward the center of the tumor. As the cartilage matured, the matrix was stained more deeply by the PAS reaction. The chondrocytes generally lay singly in the lacunae, but clusters of 2 or more cells within one lacuna were occasionally seen. No bone formation was observed at this stage. Although the tumor appeared solid on gross examination, cystic cavitation was noted microscopically. The cysts varied in size, occurred mainly at the center of the tumor, and contained a pale eosinophilic granular precipitate.

At 22 days the tumor was still quite cellular, the cells appeared more spindle-shaped and often arranged in bundles (Fig. 2). There was evidence of cartilage and bone formation with many areas of osteoid and well-mineralized bone, demonstrated by the von Kossa stain. Tumor cells were seen within the lacunae and at the periphery of the newly formed bone.

From the 38th day on, the tumor showed marked cystic cavitation and extensive necrosis. Bone and cartilage were present in variable amounts (Figs. 3, 4). The cellularity was reduced, and a variable amount of collagen appeared in the matrix. The number of mitotic figures was markedly reduced. In later stages, areas of the tumor showed regressive changes, such as necrosis of bone and cartilage. Such changes were scattered, and the tissues appeared viable in other portions of the tumor (Fig. 5).

These histologic features, including bone differentiation, have been observed continuously for 44 transplant generations.

DISCUSSION

Osteogenic sarcomas in inbred AKR mice have not been previously recognized. The tumor described in this report occurred spontaneously and has been successfully transplanted...
for 44 generations without losing its original characteristics of bone formation. Transplantable osteogenic sarcomas in mice have been reported by several investigators (1, 3, 6, 11). However, most of these tumors originated in hybrid strains and lost their bone formation after a number of transplant generations, eventually resembling an undifferentiated spindle-cell sarcoma or fibrosarcoma (1, 3).

Hilberg (7) described an osteogenic sarcoma arising in a C3Hb/HeN female mouse which lost its capacity of forming bone between the 6th and 20th generation. When the tumor was transplanted beneath the renal capsule, an appreciable amount of bone formation was again observed. No explanation could be given for the change, but it was suggested that the high alkaline phosphatase content of the renal tissue may be a contributing factor.

Distant metastases have developed in some of the reported tumors (1, 6, 11). Although the tumor of this report showed no evidence of metastatic spread, its malignant character was manifested by the histologic criteria and by local invasiveness.

Finkel et al. (4) have produced osteosarcomas in newborn CF1/ANL mice by the inoculation of a virus extracted from an osteosarcoma of a CF1 mouse. Osteosarcomas have also been induced by administration of $^{90}$Sr into mice of a CBA strain (8).

No causative agent has been identified in the tumor described in this report. The possibility that it may be related to the leukemogenic virus described by Gross (5) in AKR mice needs further investigation.

REFERENCES


Fig. 1. Histologic appearance of tumor at 11 days. Note cellular pleomorphism, mitotic figures, and loose arrangement of cells. H & E, × 400.
Fig. 2. Tumor at 22 days. The tumor cells are spindle-shaped and arranged in bundles around a large area of newly formed cartilage. H & E, × 160.
Fig. 3. Tumor at 52 days. Newly formed osteoid with beginning mineralization. Note tumor cells in the lacunae and at the periphery. H & E, × 160.
Fig. 4. Tumor at 92 days. Well-mineralized bone showing positive von Kossa reaction. × 160.
Fig. 5. Tumor at 134 days. Bone formation remains evident. Note cystic changes in right upper corner. H & E, × 160.
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