Transplantable Chondrosarcoma in the Syrian Hamster (Mesocricetus auratus)  

Dee O. N. Taylor  
Viral and Rickettsial Disease Laboratory, California State Department of Public Health, Berkeley, California 94704

SUMMARY

A transplantable chondrosarcoma arose on the right humerus of a 6-month-old Syrian hamster in a breeding colony of 3000. After inoculating viable fragments by the cheek pouch route and administering cortisone in the first two passages, the neoplasm was transplanted successfully by subcutaneous inoculation, without the use of cortisone, in 220 of 251 animals through 17 passages over a period of 3.5 years.

The neoplasms were characterized by a well-defined capsule which enclosed a layer of anaplastic mesenchymal cells. These cells appeared to differentiate into neoplastic cartilage which underwent necrosis and developed mucus-filled cysts in the centers of the larger specimens.

The average rate of growth was variable among neoplasms, and no metastases were seen although local invasion was occasionally evident.

Antibodies were not found to the virions or tumor antigens of various onogenic viruses, and neoplasms did not develop in hamsters inoculated with cell-free filtrates.

INTRODUCTION

Numerous transplantable neoplasms of hamsters have been described or cited by various authors (3, 5—7, 10). Spontaneously arising transplantable neoplasms which produce bone and/or cartilage have been described in rodents other than the hamster (4, 8, 12, 13). The only report of a transplantable chondrosarcoma in the hamster was by Toolan et al. (14), who serially transplanted in hamsters various neoplasms from humans with the aid of X-irradiation and/or cortisone therapy.

This paper reports the occurrence and serial transplantation of a chondrosarcoma which arose spontaneously in a Syrian hamster.

MATERIALS AND METHODS

The original neoplasm was removed from the humerus of a 6-month-old Syrian hamster from a breeding colony of about 3000. For the first 2 passages, neoplastic tissue was minced with scissors and small fragments were implanted under the epithelial lining of the cheek pouches of 1 to 2-month-old hamsters. Two mg of cortisone acetate (The Upjohn Co., Kalamazoo, Michigan) were administered intramuscularly twice weekly. During passages 3-5, explants were transplanted both in the cheek pouches and subcutaneously. Cortisone acetate was not administered after the second passage.

Attempts to transmit the neoplasm with cell-free extracts were made by grinding the tissue in buffer to produce a 10% suspension. The larger particles were removed by light centrifugation. Initially attempts were made to use membrane filters to minimize adsorption of any virus present, but the tumor extract was too mucinous for adequate volumes of filtrate to pass. Therefore, the extract was forced through a type K5 Seitz filter pad (Republic Seitz Filter Corporation, P. O. Box 229, Milldale, Connecticut) with an average pore size of 200 µ. Five-hundredths ml of the filtrate were inoculated subcutaneously into 51 newborn hamsters. Fifty-seven newborn hamsters were inoculated with saline as controls.

Tissues from each passage were fixed in buffered formalin or Carnoy's fixative, embedded in paraffin, and stained with hematoxylin and eosin. 2 Other staining procedures used on selected tissues were: periodic acid-Schiff (PAS), periodic acid-Schiff alcian blue (PASAB), Masson's trichome, von Kossa's method for calcium, and methyl green pyronin Y (MGPY).

The average rate of growth of the neoplasms was determined by excising and weighing individual neoplasms, then dividing the weight by the number of days between implantation and excision.

Eighteen hamsters with large chondrosarcomas were bled during passages 3, 4, or 5. The sera were tested for complement fixing antibodies against SV40 and adenovirus types 12 and 18 tumor antigens. They were also tested for antibodies against the virion of the polyoma virus by hemagglutination inhibition.

OBSERVATIONS

The original neoplasm appeared to arise from the metaphysis of the right humerus. It encircled the diaphysis as a partially encapsulated nodular mass 2.5 cm in diameter. Disruption of the diaphyseal cortex was evident and neoplastic tissue extended into the marrow cavity. The subcapsular region of the
Dee O. N. Taylor

neoplasm was gray-white and mucinous while a central mass, about 1.5 cm in diameter, was white and cut with a firm consistency.

Transplanted neoplasms were also rounded nodular masses which were surrounded by a definite well-vascularized capsule (Fig. 1). Size varied from about 1.0 to 6.0 cm in the greatest dimension after 2 to 4 months’ growth. On the cut surface the neoplasms were gray-white, translucent, and mucinous around the periphery. There were varying amounts of more dense, often white, cartilaginous tissue in the centers of most specimens (Fig. 2). In some of the larger specimens mucus- and/or blood-filled cavities were present near the center.

Microscopically, all of the neoplasms were comprised of basically the same cell type, although there was considerable quantitative variation among cell types in various neoplasms. Usually the periphery was surrounded by a distinct fibrous connective tissue capsule. Subjacent to the capsule there was a zone of loosely arranged plump mesenchymal cells which appeared to differentiate to cartilaginous tissue at the deeper margin (Fig. 3). Moderate numbers of mitotic figures, binucleate cells, and bizarre cells with large hyperchromic nuclei could be found in this zone. The matrix between the mesenchymal cells stained a very faint blue or not at all with hematoxylin and eosin. It was slightly PAS-positive and stained distinctly with alcian blue. A fine fibrillar pattern was apparent. In some instances the cells of this tissue had a myxomatous or fibrosarcomatous appearance. Frequently the mesenchymal tissue surrounded islands of hyaline cartilage in various stages of differentiation (Figs. 4, 5). The chondrocytes of such cartilage varied in size. The nuclei were sometimes large and hyperchromic with hypertrophic nucleoli (Fig. 5). The cytoplasm was intensely PAS-positive. Lacunae varied greatly in size and often contained several cells (Fig. 4). Mitotic figures were rare among cells in the cartilaginous matrix. In areas where the cartilage appeared well differentiated, the interstitial matrix stained deep blue with PASAB and orange with MGPY. Such areas often blended with poorly differentiated cartilage which had less affinity for alcian blue, none for the MGPY stain, and contained streaks of PAS-positive material. Large areas of necrosis and hemorrhage frequently were present in the centers of the larger neoplasms. Calcification occasionally was present in areas of necrosis, but fragments of bone were not seen after the second passage. Invasion of adjacent muscle rarely occurred (Fig. 6), and no metastases were seen.

Of the 8 hamsters initially inoculated with explants of neoplastic tissue, 2 had developed nodules of 6 and 10 mm in diameter at the sites of inoculation at the end of 3 months. During the subsequent 17 passages, 220 of 251 hamsters developed neoplasms over a period of 3.5 years.

At subcutaneous sites (Fig. 1) the neoplasms grew at an average rate of about 2 gm per month with a variation from 0 to 9.4 gm. The neoplasms were routinely passed at intervals of 2 to 4 months when the average weights were about 6 gm.

No significant titers were found in the sera of hamsters tested for antibodies against the virion of polyoma virus or the tumor antigens related to SV40 virus and adenoviruses types 12 and 18.

Cell-free filtrates extracted from transplantable chondrosarcomas have failed to induce neoplasms when inoculated into newborn hamsters.

DISCUSSION

Neoplasms arising spontaneously from cartilage apparently are rare in hamsters. We have found none reported in the literature, and the neoplasm described in this communication is the only one of its type seen in a breeding colony of 3000 during a period of 4 years.

The presence of the original neoplasm at the proximal end of the humerus, its mucoid to cartilaginous consistency, disruption of the diaphyseal cortex, and involvement of the bone marrow were gross evidence that it was a chondrosarcoma which had arisen “centrally” (1, 2, 11). Mucus- and/or blood-filled cysts, such as those seen in the larger transplanted neoplasms, are also typical of chondrosarcomas and are considered to be the result of mucoid degeneration of the cartilaginous matrix (1).

Histologically it was evident that portions of the original and transplanted neoplasms had the morphologic and tinctorial characteristics of hyaline cartilage in various degrees of differentiation. In addition, large bizarre nuclei, multinucleated cells, and mitotic figures in the poorly differentiated mesenchymal tissue at the periphery of the neoplasms were adequate to fulfill the criteria for chondrosarcoma (1, 2, 11).

Bone and areas of calcification are frequently found in chondrosarcomas and may make them difficult to differentiate from osteosarcomas (11). Therefore, lack of ossification in these neoplasms was a disconcerting feature since bone was not seen after the first two serial transplantations, although calcification was occasionally seen in areas of necrosis. In view of the anaplastic morphologic characteristics of the neoplasms, lack of metastases was also an unexpected feature. However, Lichtenstein (11) indicated that chondrosarcomas in humans are usually well encapsulated peripherally and, although they may invade bone marrow, they grow slowly and metastasize late with metastases often not occurring until after they have been surgically disrupted one or more times.

Adequate explanations for lack of ossification are speculative, but they may be related to some of the following factors: (a) removal of the neoplasms before they reached a critical size; (b) selection of tissues for transplantation which did not have potential for ossification, or (c) inoculation of the transplants in unusual anatomic sites (cheek pouch and subcutis) which may have altered the physiologic environment. Lack of metastases may also have been related to some of the above factors. Of those listed, inoculation of transplants at unusual anatomic sites would seem most likely to affect potential for metastasis, since the numerous thin-walled vascular channels of the bone marrow no longer would be exposed to neoplastic tissue. Lack of surgical disruption of established neoplasms also may have averted introduction of tumor emboli into the blood stream. Neither lack of ossification nor lack of metastases seem to be sufficient criteria to disqualify these neoplasms as chondrosarcomas in light of the positive histologic evidence. Such dissenting features do indicate, however, that additional experiments should be done to determine if these deficient criteria...
are fulfilled when experimental conditions are more analogous to those under which the human counterpart exists.

The rate of growth of these neoplasms varied from 0 to 9.4 gm per month. There was also considerable variation in the proportion of poorly differentiated mesenchymal tissue to cartilage, with mesenchymal tissue being most abundant in the more rapidly growing neoplasms. Therefore, it would seem likely that the rate of growth was related to the selection of tissue for transplantation, since one would expect explants from the actively growing poorly differentiated mesenchymal tissue at the periphery to grow faster than explants selected from the more differentiated cartilaginous tissues. Experiments are now in progress to determine if the growth rate of these neoplasms can be influenced by such selection.

Finkel et al. (4) have reported that a viral agent can induce osteosarcomas in mice. Lack of antibodies to polyoma virus and the tumor antigens related to SV40 virus and adenoviruses types 12 and 18 plus the failure of cell-free extracts to induce osteosarcomas in newborn hamsters are indications that the chondrosarcoma described here is not virus induced. However, Huebner et al. (9) recently reported that a defective virus can be recovered from rhabdomyosarcomas in hamsters with the aid of various murine leukemia viruses. Therefore, our findings do not necessarily preclude the possibility of a viral etiology for this transplantable chondrosarcoma which is also derived from the mesoderm. Consequently, additional virus isolation techniques will be applied as they are developed in this laboratory.

ACKNOWLEDGMENTS

The author wishes to thank Miss Anna Wiener and Mr. S. Edward Brock for their capable technical assistance.

REFERENCES


Fig. 1. Syrian hamster with well-encapsulated transplantable chondrosarcoma in the subcutis of the right lateral thoracic region. This animal was sacrificed 48 days following inoculation.

Fig. 2. Surfaces of the chondrosarcoma in Fig. 1 cut along two parallel planes. They are off-white, translucent, and have a glistening surface. The section on the right has an opaque central mass which cut with a cartilaginous consistency.

Fig. 3. Edge of a transplantable chondrosarcoma. A well-defined connective tissue capsule is evident at the top of the picture. Subjacent to the capsule is a zone of loosely arranged plump mesenchymal cells in which mitotic figures are present (arrows). The bottom half of the photomicrograph is comprised of poorly differentiated cartilage. The cytoplasm of the chondrocytic cells is PAS-positive and the intercellular matrix is stained with alcian blue. Periodic acid-Schiff alcian blue. X 290.

Fig. 4. Nodule of poorly differentiated cartilage from a transplantable chondrosarcoma. The lacunae contain one or more cells of various shapes and sizes. Fibrocytes and bizarre mesenchymal cells with differentiation toward cartilage forming cells are at the periphery. Hematoxylin and eosin, X 195.

Fig. 5. Poorly differentiated cartilage from a transplantable chondrosarcoma. Some of the chondrocytic cells have large bizarre nuclei with hypertrophic nucleoli. Hematoxylin and eosin. X 400.

Fig. 6. Unencapsulated margin of a transplantable chondrosarcoma where striated muscle is being infiltrated by spindle-shaped mesenchymal cells. Two mitotic figures are evident in the center of the photomicrograph (arrows), and a nodule of cartilage is present at the right. X 160.
Hamster Chondrosarcoma
Transplantable Chondrosarcoma in the Syrian Hamster (*Mesocricetus auratus*)

Dee O. N. Taylor


Upgraded version

Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/28/10/2051

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/28/10/2051. Click on “Request Permissions” which will take you to the Copyright Clearance Center's (CCC) Rightslink site.