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# Spontaneous Chondrosarcoma in Wistar Rat

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**Case Report**

# Spontaneous chondrosarcoma in Wistar rat: a case report

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**Abstract:** In rats, chondrosarcomas have been reported to occur both spontaneously and secondary to chemical induction. In a rare case, a spontaneous chondrosarcoma was identified in the deformed femur of a young male Wistar rat. After gross examination of the femur and knee joint, tissue was collected and preserved. The formalin-fixed tissue was decalcified, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Microscopic examinations revealed a large, highly proliferative, noncapsulated growth of chondrocytic or chondroblastic origin in the femoral bone, with proliferating chondrocytes invading the bone and surrounding tissues in an infiltrative growth pattern. Based on its histomorphological features, the lesion was diagnosed as a malignant cartilaginous neoplasm of spontaneous origin. (DOI: 10.1293/tox.2020-0031; J Toxicol Pathol 2021; 34: 119–122)

**Key words:** chondrosarcoma, spontaneous, cartilaginous, femur bone, Wistar rat

Chondrosarcomas are malignant mesenchymal tumors in which the neoplastic cells produce variable quantities of cartilaginous matrix[1]; they are composed solely of chondrocytes and matrix[2]. Among domestic animals, the dog is the species most commonly affected; in other domestic and laboratory animal species, spontaneous chondrosarcomas of bone are relatively rare[3, 4]. However, they are the third most common primary malignant tumor of bone in humans[5]. They occur most commonly in the cartilages in various axial and appendicular skeletal sites; in mice, they also occur in extraskeletal sites, including the third eyelid, external ear, and larynx[6]. In humans, the most common skeletal location for conventional chondrosarcomas is in the long tubular bones, which account for approximately 45% of cases, with the femur being the most commonly affected (approximately 20–35% of cases), followed by the tibia[7].

Chondrosarcomas are derived from chondroblasts or pluripotent mesenchymal cells that undergo malignant transformation. Although they are often hypercellular, they maintain characteristic areas of differentiated chondrocytes surrounded by a cartilaginous or mucinous matrix[2], resulting in irregular, disorderly masses of immature cartilage. The cartilage cells in the lacunae of the cartilaginous matrix vary in size. As normal cartilage cells tend to hypertrophy during the process of endochondral ossification, cell and nucleus sizes are unreliable as indicators of malignancy for cartilage tumors. Aside from becoming enlarged, nuclei may become hyperchromatic, and other characteristics of malignancy may develop, such as double nuclei, large eosinophilic nucleoli, and multiple enlarged nucleoli; cellular disorganization may be one of the most helpful features for diagnosis. Malignancy is also evidenced by tumor invasiveness[8].

A total of 432 adult Wistar rats (HanTac:WH) were used in the study (equal sex ratio; weight 197–328 g). The animals were randomly divided into four groups (three experimental and one control) and housed separately in polysulfone cages. The animal room was maintained at 22°C (± 2°C) and 50% (± 10%) relative humidity, with a 12/12-h light/dark cycle. Food and water were available *ad libitum*. The experimental protocol was approved by the institutional animal ethics committee.

One male rat from the control group underwent unscheduled sacrifice at 11 weeks, at which time unilateral macroscopic deformity of the femur and knee joint was observed. The animal had exhibited an abnormal posture during routine in-life observation, and the bone was found to be swollen. Prior to necropsy, a blood sample was collected and submitted for clinical and pathological investigation. The animal was subjected to detailed gross pathological evaluation, and samples of both affected and normal tissues were collected and preserved in 10% neutral buffered formalin. After fixation, the tissue was decalcified, histologically processed, embedded in paraffin, sectioned to approximately 5 µm in thickness, and stained with hematoxylin and eosin (H&E). Histological processing and evaluation were per-

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formed according to standard guidelines and the standard operating procedures of the researchers' organization.

Necropsy showed the affected femur to be enlarged, misshapen, and firm in consistency. The growth originating from the femoral surface was gray-white, with infiltration into the adjacent femoral bone and the articular surfaces of the knee joint. The growth was strongly mineralized and resistant to cutting prior to decalcification. No other gross lesions were observed in any other organ during the necropsy.

On microscopic examination of H&E-stained sections, the deformity was found to consist of a large, highly expansile, noncapsulated, and destructive growth of chondrocytic or chondroblastic origin. An elevated level of alkaline phosphatase was noted during the clinical and pathological investigation, which was considered to be associated with the growth. Abundant blue-gray cartilage matrix was noted, along with irregularly shaped lobules of proliferating cartilage, which varied in size and shape and showed high cellularity (Fig. 1 and 2). Large and well-differentiated basophilic cells with large nuclei and prominent nucleoli were observed in the lacunae, which were surrounded by a hyaline ground substance, frequently with multiple chondrocytes or multiple nuclei per lacuna. The cytologic features of the chondrocytes were generally similar to those of normal chondrocytes (Fig. 2); however, atypical and pleomorphic chondrocytes exhibiting disorderly arrangement and enlarged hyperchromatic nuclei were also frequent. Areas of less differentiated cartilaginous tissues were characterized by spindled (Fig. 3) or vacuolated cells. Binucleated and multinucleated giant chondrocytes and chondrocyte clusters were abundant (Fig. 4). Mitotic figures were variable, and chondroid matrix liquefaction was also seen occasionally. The proliferating chondrocytes were invading the bone and surrounding tissues in a disorganized and infiltrative growth pattern (Fig. 5 and 6). Infiltrative growth into the adjacent muscles was present, along with invasion of the femoral cortex and medulla, leading to multifocal osteolysis of preexisting bone, as well as a few areas of bone resorption and neovascularization accompanied by chondrocyte proliferation (Fig. 7). No evidence of metastasis to the regional lymph nodes or other organs was found. Areas of cartilage degeneration and erosion in the femur and knee joint (Fig. 8 and 9) were occasionally accompanied by foci of dystrophic mineralization. Chronic inflammation and edema were observed in the joint, along with synovial proliferation. Based on these histological features, the tumor was diagnosed as chondrosarcoma.

In rats, chondrosarcomas have been reported to occur both spontaneously and secondary to chemical induction.

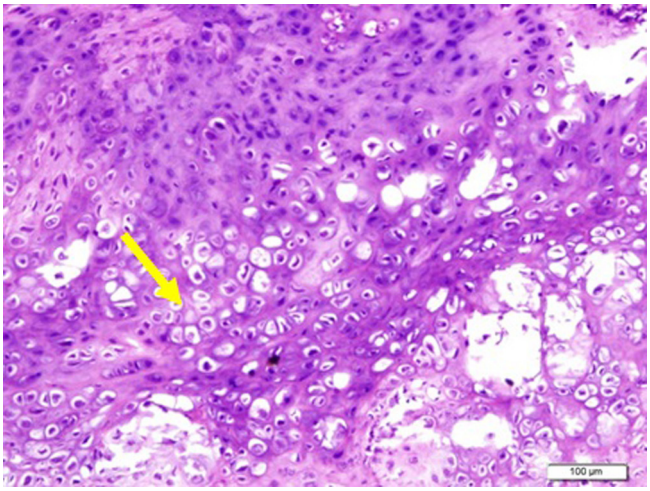


**Fig. 1.** Chondrosarcoma section showing irregularly shaped lobules of proliferating cartilage, varying in size and shape and exhibiting high cellularity (arrow). H&E, 10×.

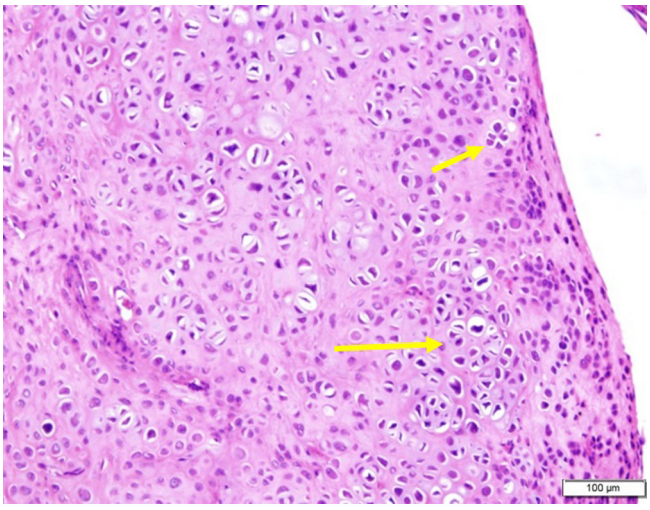


**Fig. 2.** Chondrosarcoma section showing large and well-differentiated basophilic cells with large nuclei (small arrow) distributed individually in lacunae and surrounded by a hyaline ground substance, with multiple chondrocytes per lacuna (large arrow). H&E, 10×.

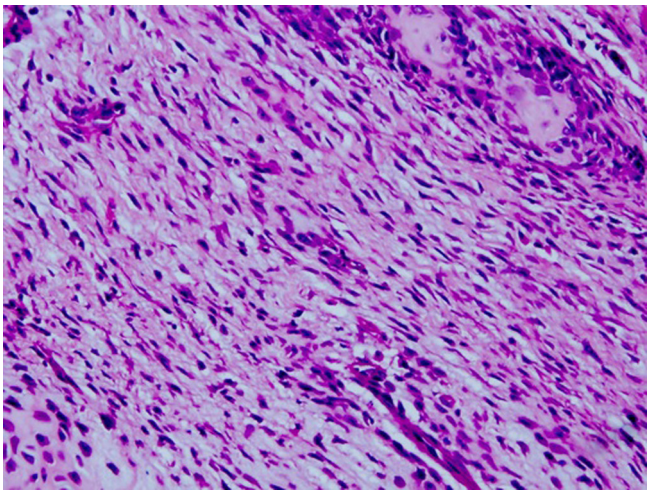

**Fig. 3.** Chondrosarcoma section showing areas of less differentiated cartilaginous tissues characterized by spindled cells (arrow). H&E, 10×.

While a few cases of chondrosarcoma have been found in older animals, cases in young animals have not commonly been reported. The current case, involving a spontaneous chondrosarcoma in a young rat, can thus be considered a rare finding.

Chondrosarcomas are highly pleomorphic, characterized by disorderly arrangement, multiple chondrocytes within lacunae, and the presence of less differentiated zones[9]. Nuclear pleomorphism, hyperchromasia, and the presence of more than one nucleus per lacuna are characteristic of chondrosarcomas; however, the cytologic features may be remarkably similar to those of normal cartilages[10]. The less differentiated areas may consist of spindled or vacuolated cells. Areas of osseous metaplasia should not be confused with bone produced by neoplastic osteoblasts[2]. Chondrosarcomas are distinguished from osteosarcomas in that the malignant stromal cells do not directly produce osteoid, instead entering an intervening cartilaginous phase[6].

All the characteristics of chondrosarcoma observed in this case have previously been reported by other authors, including the irregular growth pattern, presence of hypertrophic chondrocytes with hyperchromatic nuclei, binucleated or multinucleated giant chondrocytes associated with cellular disorganization, and infiltration of the malignant tissue into the adjacent tissue (femoral bone)[8]. However, no evidence of metastases in the lungs or other tissues was noted in this case.

As described by other authors, chondrosarcomas in rats are often well differentiated, and distinguishing them from chondromas may be difficult, involving critical assessment of cellular pleomorphism and histologic evidence of invasion or metastases. In chondrosarcomas, invasion of

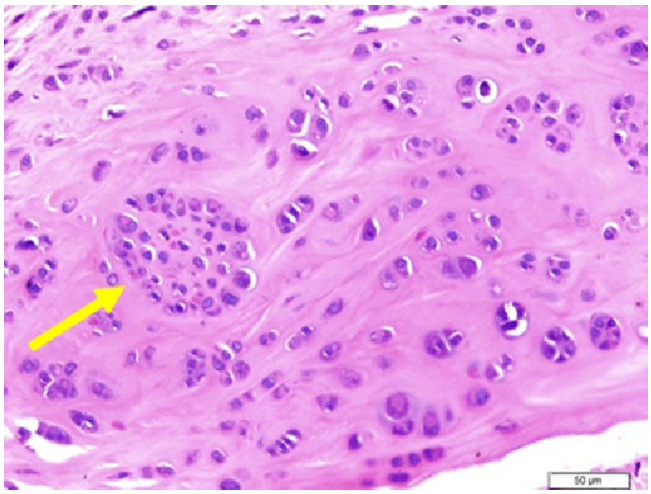


**Fig. 4.** Chondrosarcoma section showing multinucleated giant chondrocytes (large arrow) and angiogenesis (small arrow). H&E, 20×.

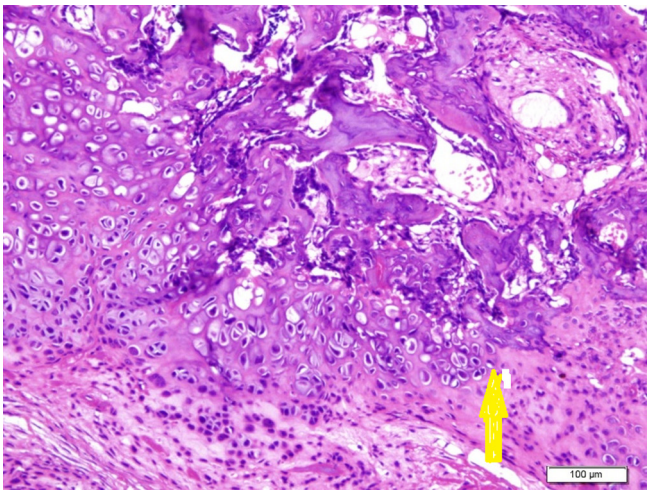


**Fig. 5.** Chondrosarcoma section showing invasion of bone by chondrocytes (arrow). H&E, 10×.

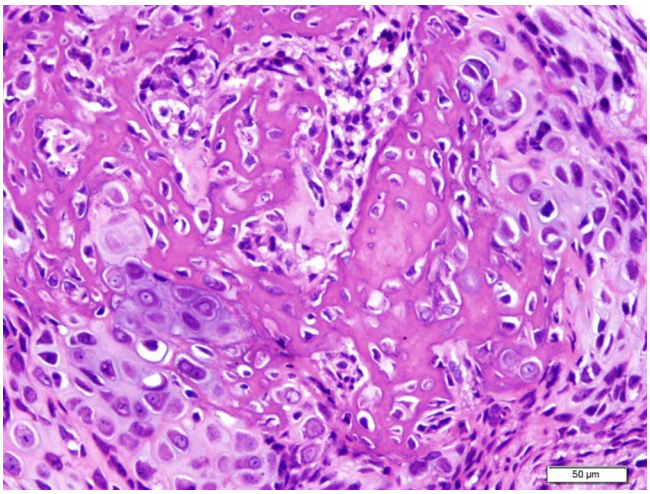


**Fig. 6.** Chondrosarcoma section showing invasion of bone by chondrocytes. H&E, 20×.

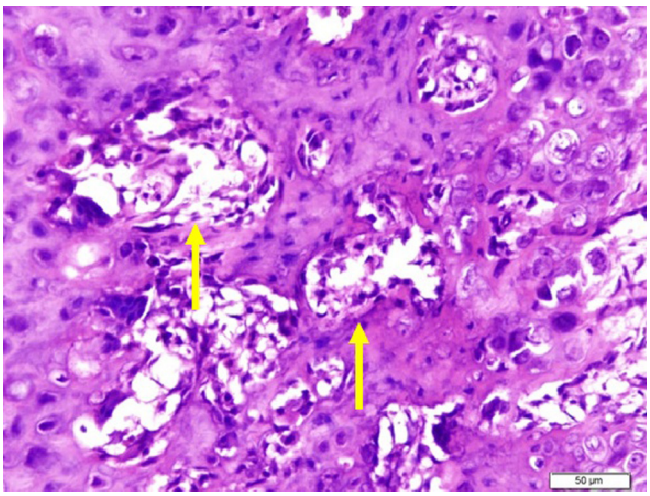


**Fig. 7.** Chondrosarcoma section showing areas of bone resorption and cartilage formation (arrow). H&E, 20×.

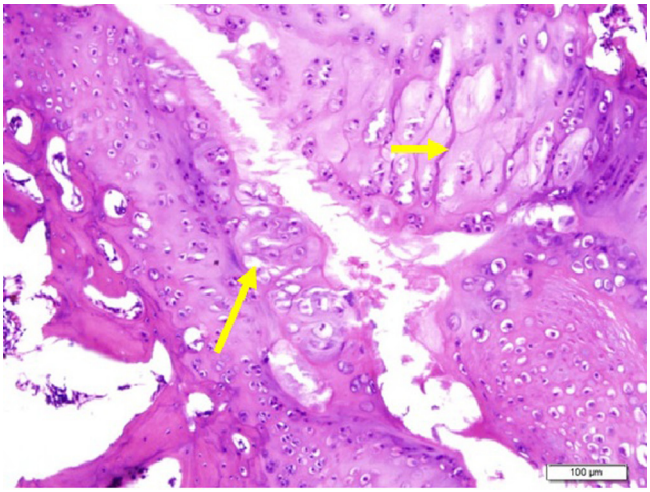

**Fig. 8.** Chondrosarcoma section showing areas of cartilage degeneration (large arrow) with matrix liquefaction (small arrow). H&E, 10×.

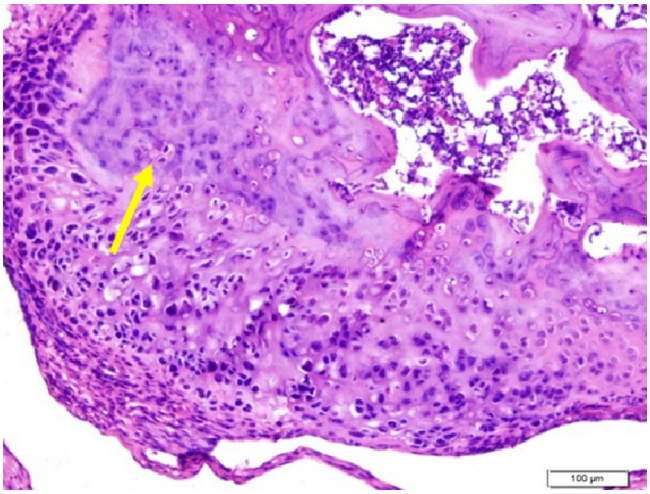

**Fig. 9.** Chondrosarcoma section showing cartilage degeneration in the knee joint (arrow). H&E, 10×.

cartilaginous tissue into the cortical bone and the marrow space may result in entrapment of bony trabeculae[6]. In the present case, chondrosarcoma was diagnosed by the presence of highly pleomorphic chondrocytes and by clearly observable invasion of the proliferative cartilaginous tissue into the bone and surrounding tissues, enveloping areas of normal bone and extending into the marrow space.

In chondrosarcomas, the neoplastic cells do not directly produce osteoid or bone; instead, endochondral ossification or osseous metaplasia of entrapped mesenchyme may occur[2]. In this case, no evidence of osteoid formation by proliferating cells or osseous metaplasia was observed. However, areas of endochondral ossification and dystrophic mineralization were present in close proximity to the degenerating cartilage, as also reported in a previous case[11].

**Disclosure of Potential Conflicts of Interest:** The authors declare that they have no known competing financial interest or personal relationship that could have appeared to influence the work reported in this paper.

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