ANIMAL MODEL OF HUMAN DISEASE

Malignant Fibrous Histiocytoma

YOICHI KONISHI, MD, YOSHIO MII, MD, HIROSHI MARUYAMA, MD, and KENJI MASUHARA, MD

From the Department of Oncologic Pathology, Cancer Center, Nara Medical College and Department of Orthopedic Surgery, Nara Medical College, Kashihara, Nara, Japan

Biologic Features

Malignant fibrous histiocytoma (MFH) was first described by O'Brien and Stout[1] and subsequently characterized as a primitive, pleomorphic sarcoma with partial fibroblastic and histiocytic differentiation.[2] It has become evident that MFH develops in soft tissue in various sites of the body, including bone.[3] It is the most common soft tissue sarcoma of late adult life, and the prognosis is poor.[4,5] Therefore, an animal model of human MFH is needed for studying the pathogenesis of this malignant tumor.[6,7]

4-Hydroxyaminoquinoline 1-oxide (4-HAQO), a strong proximate carcinogen, which is a reduction product of the carcinogen 4-nitroquinoline 1-oxide,[8] has been shown to induce subcutaneous,[9] mesodermal,[10] and pancreatic tumors[11,12] in rats. Male Wistar or Fischer 344 rats weighing approximately 180 g were used. 4-HAQO, a yellow powder, was dissolved in 40% dimethylsulfoxide (DMSO) at 2 mg/ml and injected into the subcutaneous dorsal tissues or into the periosseous tissue of the left tibia. Alternatively, solid 4-HAQO was inserted into the bone marrow of the tibia as doses indicated in Table 1. The subcutaneous and bone MFH were induced in a dose-dependent manner by 4-HAQO. The highest incidence of tumors was 87% (13/15) in rats that received repeated weekly

Supported in part by a grant-in-aid for Cancer Research (401057, 501056, and 56010059) from the Ministry of Education, Science and Culture of Japan.

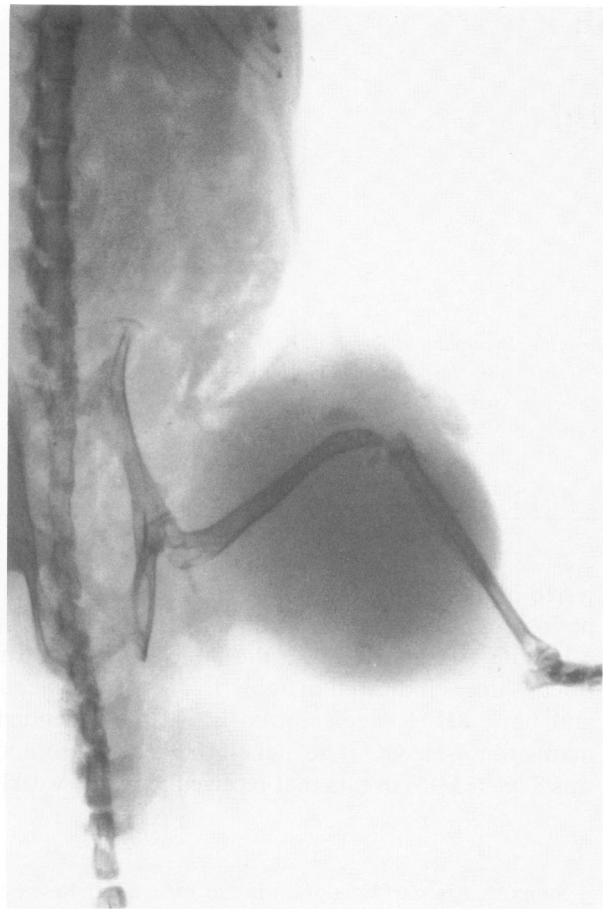
Publication sponsored by the Registry of Comparative Pathology of the Armed Forces Institute of Pathology and supported by Public Health Service Grant RR-00301 from the Division of Research Resources, National Institutes of Health, under the auspices of Universities Associated for Research and Education in Pathology, Inc.

Address reprint requests to Yoichi Konishi, MD, Department of Oncologic Pathology, Cancer Center, Nara Medical College, 840 Shijo-cho, Kashihara, Nara 634, Japan.

Table 1—Dose-Dependent Induction of MFH by 4-HAQO in Rats

4-HAQO		Site of Tumor induction	Time killed (weeks)	Tumor incidence (%)	Histologic subtypes (metastases)		
Route of administration	Dose (mg/rat)				Fibrous	Giant cell	Myxoid
Subcutaneous	0	Subcutaneous	55	0/13 (0)	0	0	0
	1	Subcutaneous	55	2/11 (18)	2 (0)	0	0
	4*	Subcutaneous	22–53	13/15 (87)	11 (0)	1 (0)	1 (0)
Periosseous	0		40	0/12 (0)	0	0	0
	2	Periosseous	35–40	3/13 (23)	3 (2)	0	0
	4	Periosseous	23–32	9/13 (69)	5 (1)	2 (0)	2 (0)
Bone marrow	0		40	0/13 (0)	0	0	0
	2	Bone	26–40	1/15 (7)	0	0	1 (0)
	4	Bone	20–37	11/18 (61)†	8 (3)	2 (0)	0
	8	Bone	20–31	12/14 (86)	6 (2)	2 (0)	4 (0)

* 4-HAQO at a dose of 1 mg/rat was injected once a week four times.
† One inflammatory subtype was observed.



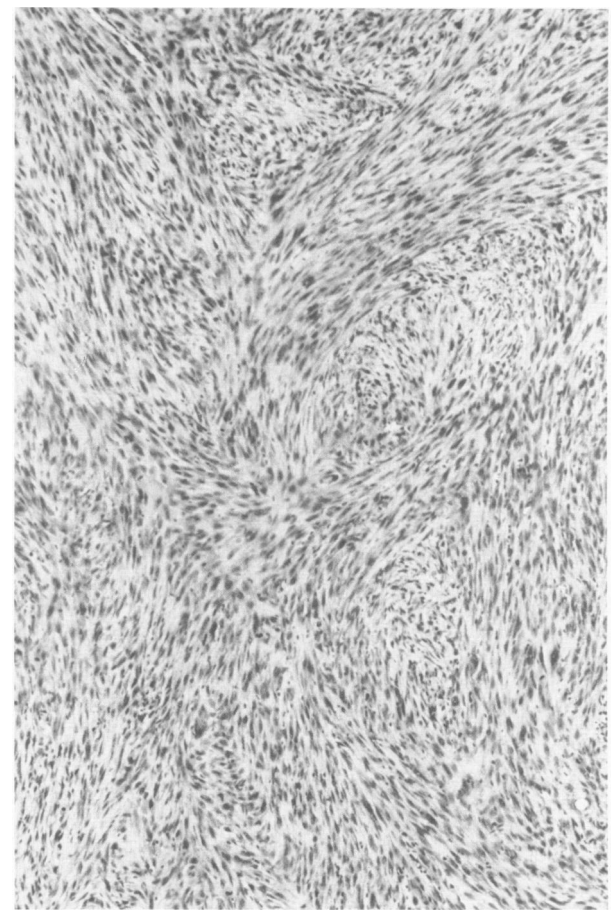


Figure 1 – Lateral X-ray demonstrating a large tumor shadow in the soft tissue of the left leg with associated bone destruction in a rat that received a periosseous injection of 4-HAQO. **Figure 2** – Fibrous type of subcutaneous MFH in a rat that received a subcutaneous injection of 4-HAQO (H&E, × 100)

injections of 1 mg of 4-HAQO/rat for 4 weeks, 69% (9/13) in rats that received a single periosseous injection of 4 mg of 4-HAQO, and 86% (12/14) in rats that received intraosseous insertion of 8 mg of 4-HAQO (Table 1).

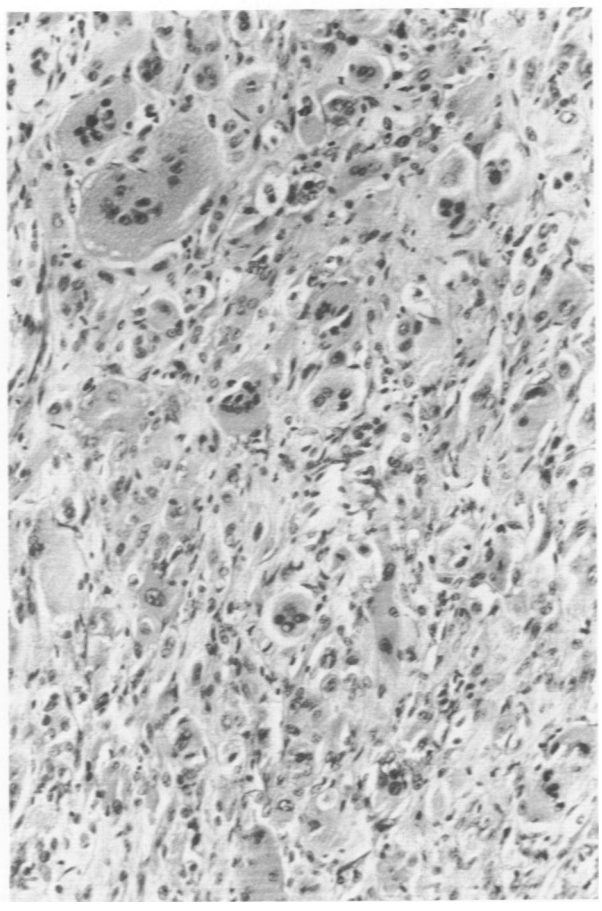
Radiologic examination performed during the experimental period revealed that a large tumor shadow developed in the soft tissue of the left leg in rats that received periosseous injections of 4-HAQO (Figure 1) and a small tumor shadow in the left tibia of rats that received an intrabone marrow insertion of 4-HAQO. The characteristic radiologic findings of bone MFH were an intramedullary lytic lesion, cortical destruction, and pathologic fracture.

Grossly, the subcutaneous and periosseous tumors were located in the tissue at the injection site. Bone tumors were present in the tibia where 4-HAQO had been inserted. Some large tumors had a diffuse or a partly jellylike appearance that corresponded to myxoid areas microscopically.

Histologic features of MFH permit differential diagnosis from other tumors.[2,5,13,14] Tumors induced by 4-HAQO were classified by light microscopy according to the description of Weiss and Enzinger.[2] The characteristic histologic features of each subtype of MFH are illustrated in Figures 2–4. The myxoid subtype stained positively with Alcian-blue but was PAS-negative. The fibrous MFH was the most common subtype (Figure 2), and inguinal lymph node and/or lung metastases were seen in this type.

Five different types of cells were identified in MFH by electron microscopy: fibroblastlike cells, histiocytelike cells, undifferentiated cells, xanthomatous cells, and multinucleated giant cells. Xanthomatous cells and multinucleated giant cells (Figure 3) appeared to be derived from histiocyte-like cells. Fibroblast-like cells predominated in the fibrous subtype of MFH; histiocytelike cells and undifferentiated cells predominated in the giant cell subtype; and intermediate cells predominated in the myxoid subtype.[15]

Each subtype of MFH was transplanted serially into the subcutaneous dorsal tissue of syngeneic rats



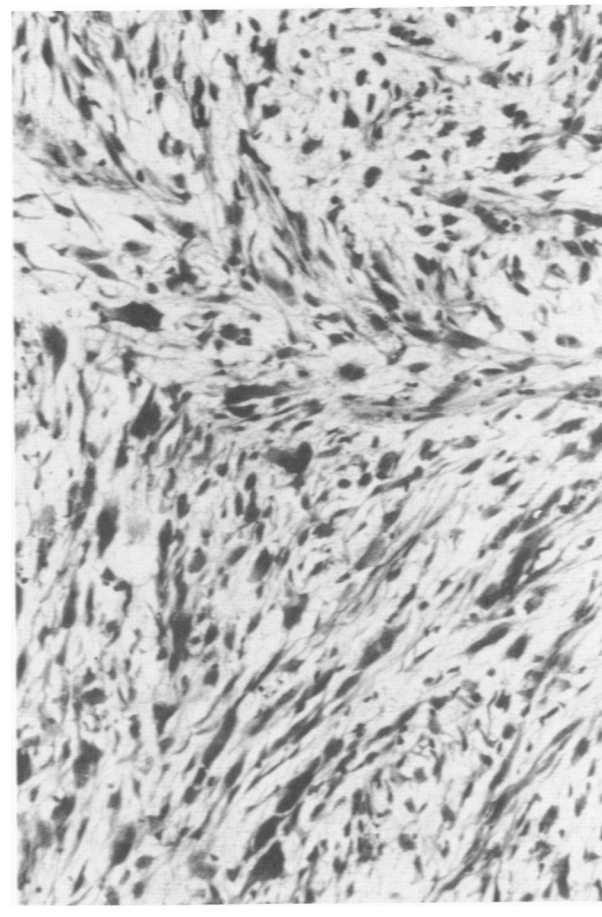


Figure 3 — Giant cell type of MFH in bone with multinucleated giant cells from a rat that received an intraosseous insertion of 4-HAQO (H&E. ×200) **Figure 4** — Myxoid type of MFH in bone with a diffuse myxomatous change and bizarre tumor cells. The rat had received an intraosseous insertion of 4-HAQO. (H&E. ×200)

(Fischer 344). Transplantability exceeded 80%; doubling time was 2.3–6.7 days in the fibrous subtype, 3.8–6.1 days in the giant cell subtype, and 3.0–5.7 days in the myxoid subtype. They are now 9th, 24th, and 5th generations. The original histologic features of fibrous and myxoid subtypes were not changed by serial transfer. In the giant cell subtype, the histologic features of the original tumor were retained until the 3rd generation; however, giant cells and xanthoma cells were no longer observed after the 4th generation, and the tumor was composed mainly of undifferentiated cells. This subtype transplanted serially is gradually transformed with a probable selection of stem cells and undifferentiated cells.[15]

Comparison With Human Disease

MFH induced by 4-HAQO is histologically similar to the neoplasm in humans, and its cell population was also similar by electron microscopy. MFH induced by 4-HAQO is classifiable into fibrous, giant cell, and myxoid subtypes similar to those in humans. Fibrous MFH showed lymphogenous and hematogenous metastases, which can be frequently seen in humans. The myxoid subtype was most frequently seen in MFH of bone. Thus, the morphologic appearance and biologic behavior of rat MFH induced by 4-HAQO are similar to those of human MFH. However, experiments for the study of the production of MFH by other carcinogens in other animal species are indicated, in spite of a report that is available.[16]

Usefulness of the Model

The present report gives information on the histologic appearance of MFH induced in rats by 4-HAQO and suggests that chemical carcinogens may be important in the development of human MFH. Spontaneous subcutaneous tumors occur in laboratory animals in long-term feeding experiments, and spontaneous MFH has been reported in rats[17–19] and in dogs and cats.[20] In this connection, histologic re-

evaluation of spontaneous tumors in laboratory animals may be required. Induction of MFH by 4-HAQO in rats and its transplantable lines provides useful experimental models for studying the histogenesis of MFH, the characteristic growth behavior, and effectiveness of chemotherapeutic agents on this malignant neoplasm.

References

1. O'Brien JE, Stout AP: Malignant fibrous xanthomas. Cancer 1964, 17:1445–1458
2. Weiss WS, Enzinger FM: Malignant fibrous histiocytoma. Cancer 1978, 41:2250–2266
3. Feldman F, Lattes R: Primary malignant fibrous histiocytoma (fibrous xanthoma) of bone. Skeletal Radiol 1977, 1:45–160
4. Hajdu SI: Tumors of fibrous tissue, Pathology of Soft Tissue Tumors. Edited by SI Hajdu. Philadelphia, Lea and Febiger, 1979, pp 57–164
5. Enjoji M, Hashimoto H, Tsuneyoshi M, Iwasaki H: Malignant fibrous histiocytoma: A clinicopathologic study of 130 cases. Acta Pathol Jpn 1980, 30:727–741
6. Konishi Y, Maruyama H, Mii Y, Miyauchi Y, Yokose Y, Masuhara K: Malignant fibrous histiocytoma induced by 4-hydroxyaminoquinoline 1-oxide in rats. J Natl Cancer Inst 1982, 68:859–865
7. Mii Y, Maruyama H, Miyauchi Y, Yokose Y, Masuhara K, Konishi Y: Experimental studies on malignant fibrous histiocytomas in rats: I. Production of malignant fibrous histiocytomas by 4-hydroxyaminoquinoline 1-oxide in bone of Fischer 344 strain rats. Cancer 1982, 50:2057–2065
8. Nakahara W, Fukuoka F, Sugimura T: Carcinogenic action of 4-nitroquinoline-N-oxide. Gann 1957, 48:129–137
9. Endo H, Kume F: Induction of sarcoma in rats by a single injection of 4-hydroxyaminoquinoline 1-oxide. Gann 1965, 56:261–265
10. Shurgin A, Becker FF: Sequential events in induction of sarcomas by 4-hydroxyaminoquinoline 1-oxide: Fibroplasia, a premalignant phase. J Natl Cancer Inst 1974, 53:159–164
11. Hayashi Y, Hasegawa T: Experimental pancreatic tumor in rats after intravenous injection of 4-hydroxyaminoquinoline 1-oxide after partial pancreatectomy and splenectomy in rats. Gann 1976, 67:919–920
12. Konishi Y, Denda A, Inui S, Takahashi S, Kondo H: Pancreatic carcinoma induced by 4-hydroxyaminoquinoline 1-oxide after partial pancreatectomy and splenectomy in rats. Gann 1976, 67:919–920
13. Shimoda T, Yamashita H, Furusato M, Kirino Y, Ishikawa E, Miyagawa A, Ubayama Y: Liposarcoma: A light and electron microscopic study with comments on their relation to malignant fibrous histiocytoma and aminoquinoline 1-oxide in rats. Lab Invest 1983, 48: 187–198
14. Ushigome S, Hirota T: Malignant fibrous histiocytoma—With special reference to its differential diagnosis. Acta Pathol Jpn 1980, 30:779–813
15. Maruyama H, Mii Y, Emi Y, Masuda S, Miyauchi Y, Masuhara K, Konishi Y: Experimental studies on malignant fibrous histiocytomas induced by 4-hydroxyaminoquinoline 1-oxide in rats. Lab Invest 1983, 48: 187–198
16. Hirota T, Itahashi M, Kakizaki H, Oogaki H, Kawachi S: Comparative study between human soft tissue sarcoma, especially malignant fibrous histiocytoma, and rat sarcoma induced by 1-nitropyrene with light and electron microscopies. Trans Soc Pathol Jpn 1982, 71:396
17. Ward JM, Kulwich BA, Reznik G, Berman JJ: Malignant fibrous histiocytoma: An unusual neoplasm of soft tissue origin in rat that is different from the human counterpart. Arch Pathol Lab Med 1981, 105:313–316
18. Graves P, Faccini JM: Spontaneous fibrous histiocytic neoplasms in rats. Br J Cancer 1981, 43:402–411
19. Goodman DG, Ward JM, Squire RA, Paxton MB, Reichardt WD, Chu KC, Linbart MS: Neoplastic and nonneoplastic lesions in aging Osborne-Mendel rats. Toxicol Appl Pharmacol 1980, 55:433–447
20. Gleiser CA, Raulston GL, Jardine JE, Gary KN: Malignant fibrous histiocytoma in dogs and cats. Vet Pathol 1979, 16:199–208