JBJA Journal of Bone and Joint Surgery - American 1996 - 1998
October 1997, Volume 79-A, Number 10
1545 Dedifferentiated Chondrosarcoma in Albright Syndrome. A Case Report and Review of the Literature*
Case Report

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J Bone Joint Surg [Am] 1997; 79-A; 1545-51

Fibrous dysplasia is a developmental condition in which the skeleton fails to mature normally. Albright syndrome, which was first reported in 1937 by McCune and Bruch[23] and by Albright[1], is characterized by polyostotic fibrous dysplasia, endocrine disorders, and brown patches on the skin (*café-au-lait* spots)[3,17,25]. It is seen more often in female than in male patients[35]. Malignant transformation in fibrous dysplasia was noted, in 1945, by Coley and Stewart[5], and since then it has been reported in more than 100 patients[12,19,33,43]. The most common secondary malignant lesion in fibrous dysplasia is osteosarcoma, followed by fibrosarcoma and chondrosarcoma[6,9,15,18,33,42]. The prevalence of malignant transformation in fibrous dysplasia is only 0.4 per cent (six of 1517 patients)[36]. However, the prevalence of malignant transformation in Albright syndrome is 4 per cent (four of 100 patients[36]), which is higher than that in other forms of fibrous dysplasia[36]. To our knowledge, we are the first to report the case of a patient who had a dedifferentiated chondrosarcoma secondary to Albright syndrome.

Case Report

A fifty-two-year-old man who had had polyostotic fibrous dysplasia and many *café-au-lait* spots since he was an infant was seen at our hospital because of mild pain and increased swelling of the left knee. There was no family history of bone tumors, skin pigmentation, or precocious puberty. During childhood, he had sustained multiple fractures of the long bones of the lower limbs. When he was five years old, acne, growth of pubic hair, and an increase in the size of the penis and testes were observed. During adolescence and adulthood, more fractures of the lower limbs occurred. Neither the lower limbs nor the pituitary gland had been treated with radiation therapy. Since the age of fifty years, he had been confined to a wheelchair because of the marked deformities and risk of fractures of the lower extremities.

On admission to our hospital, six months after he was first seen, the patient reported constant pain in the proximal aspect of the left tibia and marked tenderness was noted. The findings of laboratory tests were normal except for the level of serum alkaline phosphatase, which was 420 international units per liter (normal, 0 to 170 international units per liter).

Radiographs of both femora revealed lesions with characteristics ranging from lytic to a ground-glass appearance to sclerotic. Both hips had severe varus deformity (shepherd's crook deformity), which is typical of fibrous dysplasia. In the proximal aspect of the left tibia, several large osteolytic lesions and areas of osseous destruction were noted (Fig. 1). A bone scan showed increased uptake of isotope in the skull, maxillae, mandible, humeri, shoulders, ribs, forearms, hands, vertebrae, pelvis, femora, tibiae, and feet (Fig. 2). Computed tomography revealed disruption of the posterior cortex of the left tibia and an extraskeletal tumor mass (Fig. 3). T1-weighted magnetic resonance imaging after injection of gadolinium-diethylenetriamine penta-acetic acid showed a heterogeneous bone tumor with a soft-tissue component as well as areas of low and high signal intensity. On the basis of these clinical and radiographic findings, malignant transformation of the polyostotic fibrous dysplasia was suspected. Radiographs and computed tomography scans of the chest revealed no evidence of pulmonary metastases.

Incisional biopsies were performed on the left tibia, and core biopsy specimens were taken from different sites of tumor involvement in the right tibia and in both femora to exclude the diagnosis of polyostotic malignant transformation and to decide on a safe level of amputation. The histological findings revealed a malignant tumor only in the left tibia, and a through-the-knee amputation was performed. The initiation of chemotherapy was delayed at the request of the patient, and adjuvant chemotherapy was started two months after the operation according to the COSS-86 (Cooperative Osteosarcoma Study) protocol[41]. Pulmonary metastases developed fourteen months after the operation. At the time of writing, fifteen months after the initial operation, the patient was alive with disease.

Pathological Findings

The sectioned surfaces of the amputated specimen revealed multiple grayish-white granular lesions in the tarsus, first metatarsal, and phalanges. The proximal aspect of the tibia had a glossy blue-white cartilaginous tumor, measuring twelve by six centimeters, extending from the epiphysis into the diaphysis (Fig. 4). A white soft-tissue mass was seen in the posterior region of the proximal metaphysis and diaphysis, and a cystic lesion that measured four by five centimeters was found in the anteromedial region of the proximal part of the diaphysis. The distal part of the diaphysis had a lobulated area of firm cartilaginous tissue.

On histological examination, the tissue taken from the tarsus, metatarsals, and phalanges had the characteristic morphology of fibrous dysplasia with islands of woven bone in a fibrous stroma. Examination of the tibia revealed fibrous dysplasia as a pre-existing lesion in all areas that were not infiltrated by the tumor. Enchondroma-like nodules with a diameter of about two centimeters were found in the distal diaphyseal region, indicating a chondroid

differentiation in fibrous dysplasia (Fig. 5)[20]. These observations suggested that our patient had fibrocartilaginous dysplasia rather than typical fibrous dysplasia. The main lesion in the proximal aspect of the tibia was composed of cartilaginous tumor with low-to-moderate cellularity. At the periphery of the cartilaginous tumor, a destructive growth pattern was evident as the tissue had infiltrated cortical bone and the pre-existing fibrous dysplasia. In addition to the infiltrating growth pattern of the cartilaginous tumor, the findings included mild-to-moderate nuclear atypia, double nuclei, and some mitotic figures, which are features of a grade-1 or grade-2 chondrosarcoma (Fig. 6-A). The white soft-tissue area that was located posteriorly in the cartilaginous lesion in the proximal part of the diaphysis showed osteosarcomatous differentiation (Fig. 6-B), and the lytic lesion located anteromedially was a high-grade anaplastic sarcoma. These areas of high-grade sarcoma were immediately adjacent to the low-grade chondrosarcoma (Figs. 7-A and 7-B). This growth pattern led to the diagnosis of dedifferentiated chondrosarcoma with anaplastic osteosarcomatous components.

Discussion

The dedifferentiated chondrosarcoma in our patient developed in an area of pre-existing fibrocartilaginous dysplasia. In rare cases of fibrous dysplasia, the cartilage elements may be large and reach several centimeters in diameter[20,39]. The fibro-osseous lesion adjacent to the cartilage islands is the most important diagnostic criterion for fibrocartilaginous dysplasia[39,40]. Most dysplasias of this type involve the proximal part of the femoral shaft[40]. The main part of the tumor in our patient consisted of a low-grade chondrosarcoma juxtaposed with a high-grade anaplastic sarcoma or osteosarcoma. These histopathological features meet the definition of dedifferentiated chondrosarcoma as initially described, in 1971, by Dahlin and Beabout[7].

The main problem in the case of our patient was the differential diagnosis between dedifferentiated chondrosarcoma and chondroblastic osteosarcoma. The lesion first was regarded as chondrosarcoma because of the cytological findings of a low-to-moderate grade of malignancy, including double nuclei, and then because of the permeative growth pattern at the tumor margins. Chondroblastic osteosarcoma was unlikely because there were mostly areas of low-grade chondrosarcoma. In chondroblastic osteosarcoma, irregular neoplastic osteoid usually is intermixed with high-grade chondrosarcoma that has no grossly separated malignant elements[14]. The sharp transition between high-grade sarcoma and low-grade chondrosarcoma seen in our patient is typical of dedifferentiated chondrosarcoma.

It is probable that the dedifferentiated chondrosarcoma originated from fibrocartilaginous dysplasia with enchondroma-like nodules[25], which developed into chondrosarcoma and finally resulted in dedifferentiated chondrosarcoma. The interpretation that the enchondroma-like nodules transformed into chondrosarcoma is supported by the presence of enchondroma-like nodules in the distal part of the tibia, in which there was no tumor. To our knowledge, there have been only eight reported cases of malignant cartilaginous components in a sarcoma (usually an osteosarcoma[26,28,31,33,43] but also a chondrosarcoma[42]) secondary to fibrous dysplasia.

The prevalence of malignant transformation in fibrous dysplasia has been reported to be 0.4 per cent (six of 1517 patients)[36], and most of the patients were more than thirty years old when a sarcoma developed. Yabut et al.[42] analyzed the cases of eighty-three patients who had malignant transformation of fibrous dysplasia. Of the seventy-three patients for whom the histological diagnosis was described, forty had osteosarcoma; twenty-two, fibrosarcoma; and eleven, chondrosarcoma. The mean period of survival for the eighty-three patients was thirty-six months[42]. Ruggieri et al.[33] reported that, in twenty-eight patients who had malignant transformation of fibrous dysplasia, the secondary sarcoma was osteosarcoma (nineteen patients), fibrosarcoma (five), chondrosarcoma (three), or malignant fibrous histiocytoma (one). The most frequent sites of secondary sarcomas in these two reports were the craniofacial bone followed by the femur.

As far as we know, there have been only eleven reports, including our report, of malignant degeneration in a patient who had Albright syndrome (Table I)[2,11,16,21,27,29,30,32,34,38]. All of the patients had Albright syndrome according to the reports, but the triad of the syndrome (polyostotic fibrous dysplasia, areas of pigmented skin, and precocious puberty) was noted in only two patients (Cases 10 and 11). Eight of the patients had secondary osteosarcoma; one, fibrosarcoma; and one (our patient), dedifferentiated chondrosarcoma. The type of sarcoma was not known for the eleventh patient. Two patients (Cases 2 and 4) had sarcoma in a previously irradiated area.

Early recognition of malignant transformation in fibrous dysplasia depends mainly on an accurate clinical history of symptoms such as pain and swelling[33]. As lesions of fibrous dysplasia show a high uptake of isotope[10,13], a bone scan has limited value for revealing malignant transformation. Unless a malignant change occurs[22,25,37,42], fibrous dysplasia usually remains contained within the bone[21]. Radiographically, the most constant feature of malignant transformation of fibrous dysplasia is infiltration of the tumor into the surrounding soft tissues[33]. If extraskeletal tumor growth is identified on computerized tomography or magnetic resonance imaging, malignant transformation should be strongly suspected.

The prognosis for patients who have a malignant lesion secondary to fibrous dysplasia is virtually the same as that for patients who have the corresponding primary tumor[33]. Dedifferentiated chondrosarcoma is likely to be followed by pulmonary metastasis, and the prognosis is poor[4,8,24]. After operative resection, our patient received chemotherapy with methotrexate, cisplatin, Adriamycin (doxorubicin), and ifosfamide

and had no sign of recurrent disease or metastases for thirteen months. However, pulmonary metastases developed fourteen months after the operation. The prognosis may be improved by early diagnosis and adequate treatment.

References: (1-43)

1. Albright, F.; Butler, A. M.; Hampton, A. O.; and Smith, P.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. Report of five cases. New England J. Med. 1937; 216:727-746.
2. Bell, W. H.; and Hinds, E. C.: Fibrosarcoma complicating polyostotic fibrous dysplasia. Oral Surg., Oral Med., and Oral Pathol. 1967; 23:299-310.
3. Campanacci, M.: Bone and Soft Tissue Tumors, pp. 391-417. New York, Springer, 1990.
4. Capanna, R.; Bertoni, F.; Bettelli, G.; Picci, P.; Bacchini, P.; Present, D.; Giunti, A.; and Campanacci, M.: Dedifferentiated chondrosarcoma. J. Bone and Joint Surg. Jan. 1988; 70-A:60-69.
5. Coley, B. L.; and Stewart, F. W.: Bone sarcoma in polyostotic fibrous dysplasia. Ann. Surg. 1945; 121:872-881.
6. Dabska, M.; and Buraczewski, J.: On malignant transformation in fibrous dysplasia of bone. Oncology 1972; 26:369-383.
7. Dahlin, D. C.; and Beabout, J. W.: Dedifferentiation of low-grade chondrosarcomas. Cancer 1971; 28:461-466.
8. Dahlin, D. C., and Unni, K. K.: Bone Tumors. General Aspects and Data on 8,542 Cases. Ed. 3, pp. 227-259. Springfield, Illinois, Charles C Thomas, 1986.
9. DeSmet, A. A.; Travers, H.; and Neff, J. R.: Chondrosarcoma occurring in a patient with polyostotic fibrous dysplasia. Skel. Radiol. 1981; 7:197-201.
10. Döhler, J. R.; and Hughes, S. P.: Fibrous dysplasia of bone and the Weil-Albright syndrome. A study of thirteen cases with special reference to the orthopaedic treatment. Internat. Orthop. 1986; 10:53-62.
11. Dustin, P., Jr.; and Ley, R. A.: Contribution á l'étude des dysplasies osseuses. Description anatomo-clinique d'un cas d'ostéosarcoma polymorphe chez un enfant atteint de fibro-xanthomatose osseuse avec prematuration sexuelle. Rev. Belge pathol. 1950; 20:52-72.
12. Ebata, K.; Usami, T.; Tohnai, I.; and Kaneda, T.: Chondrosarcoma and osteosarcoma arising in polyostotic fibrous dysplasia. J. Oral and Maxillofac. Surg. 1992; 50:761-764.
13. Enneking, W. F.: Clinical Musculoskeletal Pathology. Ed. 3, pp. 267-272. Gainesville, Florida, University of Florida Press, 1990.
14. Fechner, R. E., and Mills, S. E.: Tumors of the bones and joints. In Atlas of Tumor Pathology, edited by J. Rosai and L. H. Sobin. Series 3, fasc. 8, pp. 26-28. Bethesda, Maryland, Armed Forces Institute of Pathology, 1993.
15. Halawa, M.; and Aziz, A. A.: Chondrosarcoma in fibrous dysplasia of the pelvis. A case report and review of the literature. J. Bone and Joint Surg. 1984; 66-B(6):760-764.
16. Hall, M. B.; Sclar, A. G.; and Gardner, D. F.: Albright's syndrome with reactivation of fibrous dysplasia secondary to pituitary adenoma and further complicated by osteogenic sarcoma. Report of a case. Oral Surg., Oral Med., and Oral Pathol. 1984; 57:616-619.
17. Huvos, A. G.: Bone Tumors: Diagnosis, Treatment, and Prognosis. Ed. 2, pp. 30-48. Philadelphia, W. B. Saunders, 1991.
18. Huvos, A. G.; Higinbotham, N. L.; and Miller, T. R.: Bone sarcomas arising in fibrous dysplasia. J. Bone and Joint Surg. July 1972; 54-A:1047-1056.
19. Immenkamp, M.: Die maligne Entartung bei fibröser Dysplasie. Zeitschr. Orthop. Grenzgeb. 1975; 113:331-343.
20. Ishida, T.; and Dorfman, H. D.: Massive chondroid differentiation in fibrous dysplasia of bone (fibrocartilaginous dysplasia) Am. J. Surg. Pathol. 1993; 17:924-930.
21. Jäger, M.: Osteoidsarkom auf dem Boden einer fibrös-polyostotischen Dysplasie (Jaffe-Lichtenstein) Zentralbl. Allgemeine Pathol. 1962; 103:291-298.
22. Lichtenstein, L.: Bone Tumors. Ed. 5, pp. 409-415. St. Louis, C. V. Mosby, 1977.
23. McCune, D. J.; and Bruch, H.: Osteodystrophia fibrosa. Report of a case in which the condition was combined with precocious puberty, pathologic pigmentation of the skin and hyperthyroidism, with a review of the literature. Am. J. Dis. Child. 1937; 54:806-848.
24. McFarland, G. B., Jr.; McKinley, L. M.; and Reed, R. J.: Dedifferentiation of low grade chondrosarcomas. Clin. Orthop. 1977; 122:157-164.
25. Mirra, J. M.; Picci, P.; and Gold, R. H.: Bone Tumors. Clinical, Radiologic, and Pathologic Correlations, pp. 191-226. Philadelphia, Lea and Febiger, 1989.
26. Mock, D.; and Rosen, I. B.: Osteosarcoma in irradiated fibrous dysplasia. J. Oral Pathol. 1986; 15:1-4.
27. Mogensen, E. F.: Fibrous dysplasia of bone. Report of an unusual case with endocrine disorders. Acta Med. Scandinavica 1958; 161:453-458.
28. Mortensen, A.; Bojsen-Møller, M.; and Rasmussen, P.: Fibrous dysplasia of the skull with acromegaly and sarcomatous transformation. Two cases with a review of the literature. J. Neuro-Oncol. 1989; 7:25-29.

29. Parrini, L.: The malignant transformation of fibrous dysplasia. Chirurgica 1957; 12:3-11.
30. Pons, A.; Arlet, J.; Alibelli, M. J.; Fabre, J.; Carton, M.; and Combes, P. F.: Deux cas dégénérescence maligne osseuse sur dysplasie fibreuse des os. J. Radiol. Med. Nucl. 1974; 55:268-269.
31. Present, D.; Bertoni, F.; and Enneking, W. F.: Osteosarcoma of the mandible arising in fibrous dysplasia. A case report. Clin. Orthop. 1986; 204:38-244.
32. Roze, P. R.; Mazabraud, A.; and Semat, P.: Dysplasie fibreuse des os et myxomes des tissus mous. Dégénérescence sarcomateuse localisée. J. Radiol. Med. Nucl. 1967; 48:527-536.
33. Ruggieri, P.; Sim, F. H.; Bond, J. R.; and Unni, K. K.: Malignancies in fibrous dysplasia. Cancer 1994; 73:1411-1424.
34. Ruggieri, P.; Sim, F. H.; Bond, J. R.; and Unni, K. K.: Osteosarcoma in a patient with polyostotic fibrous dysplasia and Albright's syndrome. Orthopedics 1995; 18:71-75.
35. Schajowicz, F.: Tumors and Tumorlike Lesions of Bone. Ed. 2, pp. 567-581. New York, Springer, 1994.
36. Schwartz, D. T.; and Alpert, M.: The malignant transformation of fibrous dysplasia. Am. J. Med. Sci. 1964; 247:1-20.
37. Simpson, A. H. R. W.; Creasy, T. S.; Williamson, D. M.; Wilson, D. J.; and Spivey, J. S.: Cystic degeneration of fibrous dysplasia masquerading as sarcoma. J. Bone and Joint Surg. 1989; 71-B(3):434-436.
38. Snapper, I.: Medical Clinics on Bone Disease, a Text and Atlas. Ed. 2, p. 202. New York, Interscience, 1949.
39. Unni, K. K.: Dahlin's Bone Tumors. General Aspects and Data on 11,087 Cases. Ed. 4, pp. 25-46. Philadelphia, Lippincott-Raven, 1996.
40. Unni, K. K.; McLeod, R. A.; and Dahlin, D. C.: Pathology Annual, pp. 91-131. New York, Appleton-Century-Crofts, 1980.
41. Winkler, K.; Bielack, S.; Delling, G.; Salzer-Kuntschik, M.; Kotz, R.; Greenshaw, C.; Jürgens, H.; Ritter, J.; Kusnierz-Glaz, C.; Erttmann, R.; Gädicke, G.; Graf, N.; Ladenstein, R.; Leyvraz, S.; Mertens, R.; and Weinel, P.: Effect of intraarterial versus intravenous cisplatin in addition to systemic doxorubicin, high-dose methotrexate, and ifosfamide on histologic tumor response in osteosarcoma (Study COSS-86) Cancer 1990; 66:1703-1710.
42. Yabut, S. M., Jr.; Kenan, S.; Sissons, H. A.; and Lewis, M. M.: Malignant transformation of fibrous dysplasia. A case report and review of the literature. Clin. Orthop. 1988; 228:281-289.
43. Yashima, S.; Ishikawa, T.; Nagahata, H.; Kiyomihara, M.; Nomura, M.; Yasui, R.; Shimosato, T.; Takata, T.; and Ijuin, N.: Osteosarcoma arising in the mandibular fibrous dysplasia of polyostotic type. A case

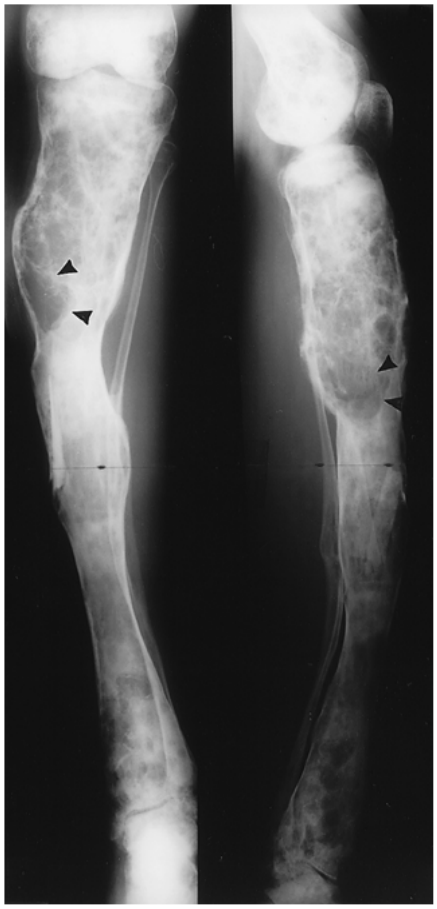

Fig. 1 Anteroposterior and lateral radiographs showing multifocal radiolucent areas, several osteolytic lesions (arrowheads indicate the largest lesion), ballooning, and deformity of the tibia.

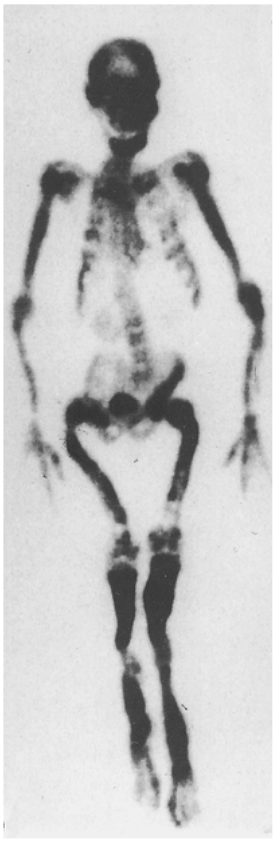

Fig. 2 Whole-body bone scan revealing polyostotic lesions and osseous deformity.

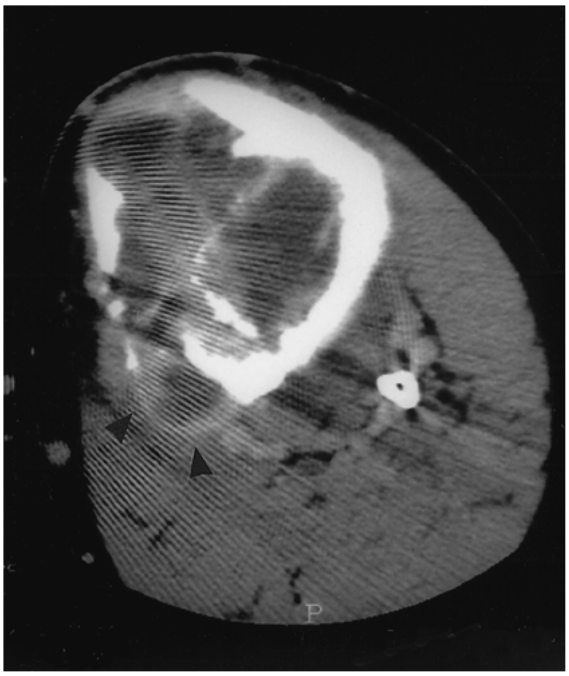

Fig. 3 Computed tomography scan showing an osseous lesion, disruption of the tibial cortex, and an extraskeletal tumor mass (arrowheads).

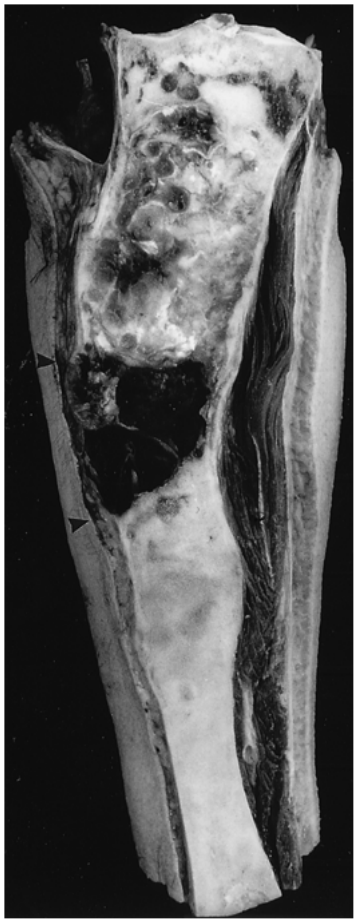

Fig. 4 Resected specimen of the proximal and diaphyseal region of the tibia, showing mainly cartilaginous tumor tissue in the proximal aspect of the tibia. There is complete destruction of the cortex by hemorrhagic tumor tissue with extraosseous extension of the tumor into the soft tissue on the medial side (arrowheads).

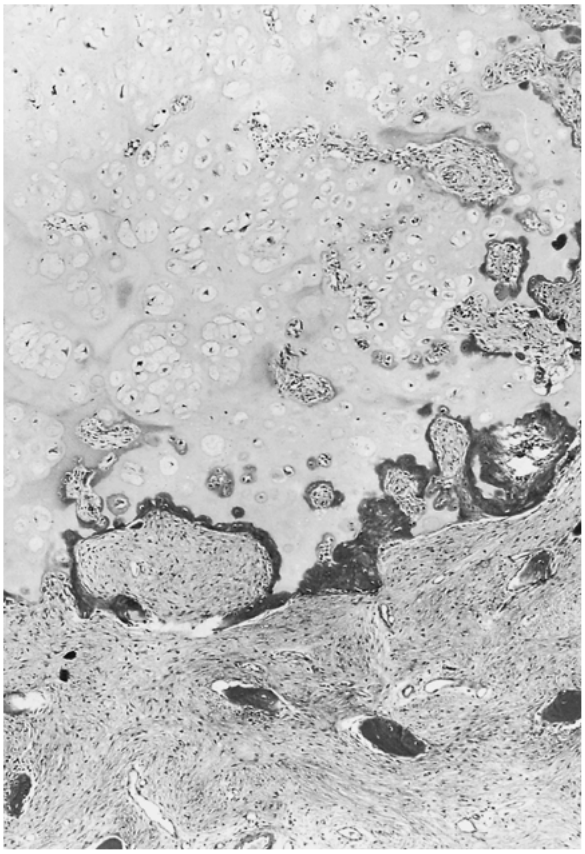

Fig. 5 Photomicrograph of a specimen taken from an area of fibrocartilaginous dysplasia, showing highly differentiated cartilaginous tissue with marginal ossification, consistent with enchondroma-like nodules (x 64).

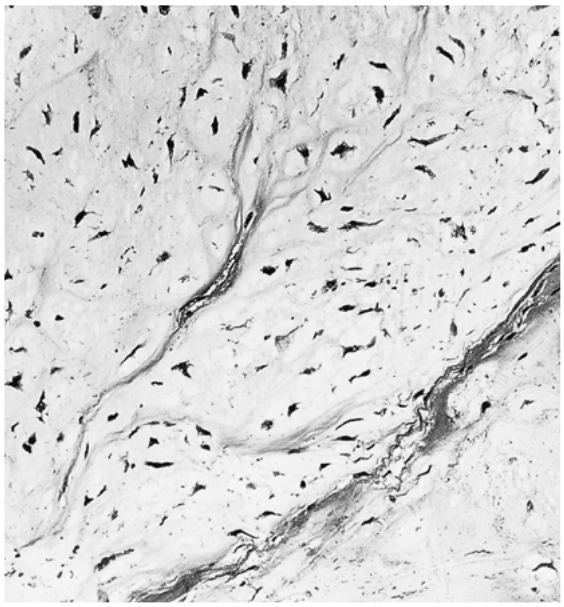

Fig. 6-A: Photomicrograph showing low-grade (highly differentiated) chondrosarcoma (x 400).

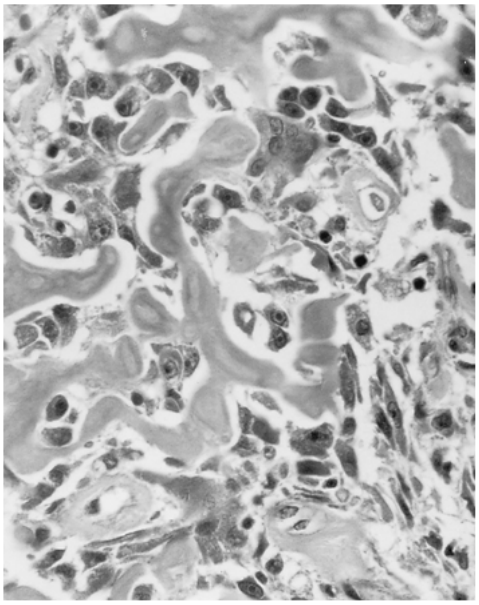

Fig. 6-B: Photomicrograph showing an area of osteosarcoma with osteoid production (x 400).

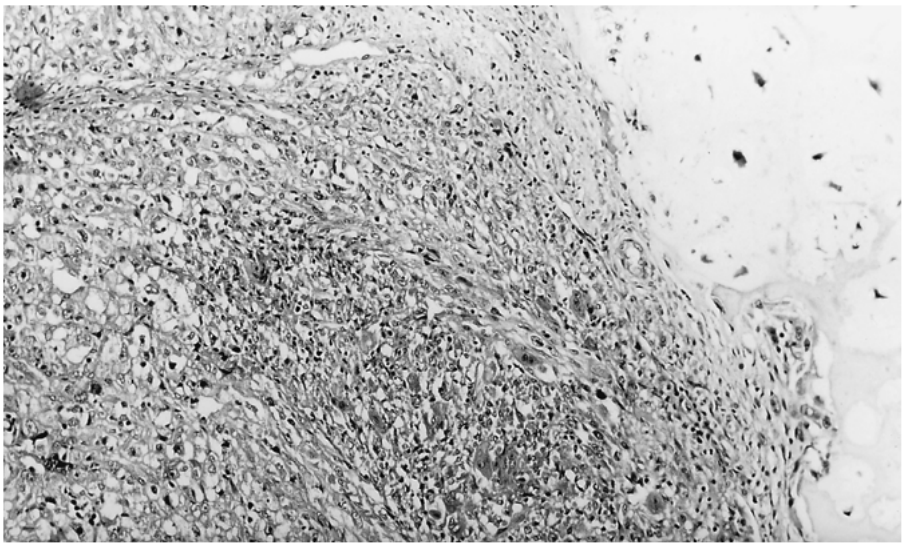

Fig. 7-A Photomicrograph showing the sharp transition between low-grade chondrosarcoma and high-grade sarcoma, which is a characteristic feature of dedifferentiated chondrosarcoma (x 100).

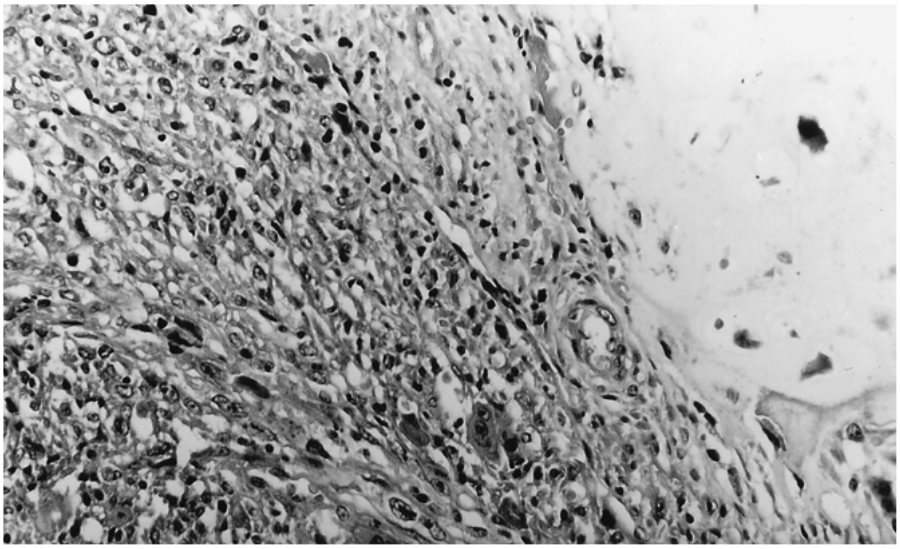

Fig. 7-B High-magnification photomicrograph of the area of transition (x 200).

TABLE I
REVIEW OF THE LITERATURE

Study	Case	Gender, Age at Onset *(Yrs.)*	Symptoms
Snapper[38] (1949)	1	F, 7	Pathological fracture, precocious puberty, mental deficiency
Dustin and Ley[11] (1950)	2	F, 7	Pathological fracture, precocious puberty
Parrini[29] (1957)	3	F, 6	Precocious puberty
Mogensen[27] (1958)	4	F, 19	Pigmented skin, acromegaly, delayed menarche
Jäger[21] (1962)	5	F, 6	Pigmented skin, pathological fracture (femur)
Bell and Hinds[2] (1967)	6	F, 6	Pigmented skin, sinusitis, bronchial pneumonia
Roze et al.[32] (1967)	7	F, infancy	Pigmented skin, myxoma
Pons et al.[30] (1974)	8	M, 12	Pigmented skin
Hall et al.[16] (1984)	9	M, 4	Pigmented skin, acromegaly, hyperthyroidism, pathological fracture
Ruggieri et al.[34] (1995)	10	F, 7	Pathological fracture, pigmented skin, precocious puberty, hypertension
Ozaki et al. (present study) (1997)	11	M, infancy	Pigmented skin, pathological fracture, precocious puberty

	Age at Onset *(Yrs.)*	Affected Bone	Symptoms	Diagnosis
	14	Femur	Not reported	Osteosarcoma
	13	Pelvis	Pain, mass, dysuria	Osteosarcoma
	8	Calvarium	Recurrent mass	Osteosarcoma
	36	Orbita	Visual impairment, exophthalmos	Not reported
	22	Maxilla	Swelling	Osteosarcoma
	16	Rib	Pain	Fibrosarcoma
	72	Tibia	Pain	Osteosarcoma
	21	Mandible	Swelling	Osteosarcoma
	37	Mandible	Swelling	Osteosarcoma
	40	Ilium	Swelling, pain	Osteosarcoma
	51	Tibia	Swelling, pain	Dedifferentiated chondrosarcoma

	Outcome
	Died with metastasis at <12 mos.
	Died with metastasis at <12 mos.
	Not reported
	Died at 7 mos.
	Died with pulmonary metastasis at 9mos.
	Died, after local relapse, at 14 mos.
	Died with metastasis at 18 mos.
	Died with pulmonary metastasis at 8 mos.
	Not reported
	Died with pulmonary metastasis at 5 mos.
	Alive with disease at 15 mos.