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Original article

Secondary chondrosarcoma in cartilage bone tumors: report of 32 patients

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Abstract

Background. Secondary malignancies arising from benign bone tumors are rare. Their recognition and diagnosis are difficult, and their slow growth and late recurrence require long-term follow-up. In this study, malignant transformation rates of various histological types of benign cartilage-forming bone tumors in large series were evaluated.

Methods. Between 1986 and 2004, a retrospective analysis of 627 cartilage-forming benign bone tumors revealed that 32 patients had malignant transformation. Of the 32 patients, 14 had solitary osteochondromas, 10 had multiple osteochondromas, 6 had a solitary enchondroma, 1 had Ollier's disease, and 1 had Maffucci's syndrome. The patient with Ollier's disease had two chondrosarcomas, and one patient with multiple osteochondroma had three chondrosarcomas. The cases were included in the study only when complete clinical documentation, radiological records, and histological analyses were available.

Results. The rate of malignant transformation for cartilage-originating tumors was 5.1% (solitary osteochondromas 4.2%, multiple osteochondromas 9.2%, solitary enchondromas 4.2%). The average time between the initial diagnosis and malignant transformation was 9.8 years. The most common site of involvement was the proximal portion of the femur. The tumors generally were well differentiated. The mean follow-up period was 57.3 months. Five patients (15.6%) died of tumor recurrence or metastasis at an average of 20.6 months. One patient is alive with tumor at 104 months.

Conclusions. Cartilage-forming benign bone tumors are rather prone to undergo malignant transformation. Although malignant transformation of a benign bone tumor is a rarely encountered situation, orthopedic surgeons should be cautious while following patients with a benign bone neoplasm. Early recognition and appropriate surgical treatment are required to achieve successful outcomes. The rate of local recurrence in secondary chondrosarcomas depends not only on adequate surgical treatment but also on the localization and histological grade.

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Introduction

Malignant transformation of benign bone tumors is rare, and the actual incidence has not been established.[1–4] Secondary sarcomas may arise in osteochondromas, multiple enchondromas, synovial chondromatosis, fibrous dysplasia, Paget's disease, and after radiation therapy.[1–3] Some tumors, such as hereditary multiple osteochondromas (HMOs) and multiple enchondromatosis, are more prone to malignant transformation, whereas in others, such as osteoid osteoma, no malignant transformation has been reported. The true incidence of malignant transformation remains unclear, as many osteochondromas and enchondromas, especially solitary lesions, are asymptomatic and have rarely been identified.[1,2,5,6] Malignant transformation leads to a chondrosarcoma (CS) in 90% of cases in the literature.[1–3] Secondary CSs are also rarely encountered, constituting approximately 1% of all malignant bone tumors and 8%–20% of all the patients with CS.[1–4] Osteosarcomas, fibrosarcomas, and malignant fibrous histiocytomas are encountered infrequently.[1–5]

Cartilage-forming benign bone tumors require long-term follow-up to understand the clinical course because of their slow growth and late recurrence. In this study, malignant transformation rates of various histological types of cartilage-forming benign bone tumors in large series have been reviewed.

Materials and methods

This retrospective study is based on a review of the case records and radiographs of 32 patients who had secondary CS of cartilage-forming benign bone tumors diagnosed between 1986 and 2004 in our department. A total of 627 patients with cartilage-forming benign bone tumors were treated during this period. The clinical data used in the study include the patient's age and sex,

the localization of the tumor, the time between the initial diagnosis of a benign tumor and the diagnosis of secondary CS, types of treatment, recurrence rate, distant metastasis, and the last status of the patient. For a case to be included in the study, histological slides had to be available for review and had to show evidence of malignancy. In addition, roentgenographic, gross tissue, or histological evidence of a preexisting benign lesion had to be present.

Among the 32 patients for whom radiographic imaging data were available, conventional radiographs were available for review for all of them, computed tomography (CT) scans for 18, magnetic resonance imaging (MRI) studies for 14, bone scintigraphy for 6, and angiographic evaluation for 4. The suspicion of secondary CS is indicated by growth of the tumor after puberty; the presence of pain, extensive calcifications, and irregularities in the cartilage mantle; erosions or destruction of the adjacent bones; extensive endosteal erosion; soft tissue invasion; and the thickness of the cartilage cap.[1–3] The demographic peculiarities of the patients are shown in Table 1.

Results

The rate of malignant transformation for cartilage-originated tumors was 5.1%. Of the 32 patients who had secondary CS on cartilage-forming benign bone tumors, 14 had solitary osteochondromas (43.8%), 10 had multiple osteochondromas (31.3%), 6 had enchondromas (18.8%), 1 had Ollier's disease (3.1%), and 1 had Maffucci's syndrome (3.1%) (Fig. 1). During the same period, 331 patients with solitary osteochondromas, 92 patients with multiple osteochondromas, 143 patients with solitary enchondroma, 15 patients with Ollier's disease, and 3 patients with Maffucci's syndrome received treatment at the authors' institution. The incidence of malignant transformation was 4.2% for the solitary osteochondroma group, 9.2% for the multiple osteochondromas group, and 4.2% for the solitary enchondroma group (Table 2). Of the 32 patients, 20 (62.5%) were male. Five patients presented because of local recurrence.

When secondary CS was diagnosed, the ages of the patients with solitary osteochondroma ranged from 18 to 55 years (average 34.8 years), which closely parallels the ages of the patients with multiple osteochondromas (range 15–69 years; mean 35.9 years). The average age was 49.8 years in the patients with solitary enchondromas, but patients with multiple lesions required surgery at a younger average age (mean 25.5 years). The overall average time between the initial diagnosis and the secondary CS diagnosis was 9.8 years. For solitary osteochondromas this period was about 8.9 years, for HMOs 11.8 years, and for solitary enchondromas about 7.7 years.

The most common site of involvement was the proximal femur. Two patients had more than one CS. One of the ten patients with multiple osteochondromas had three CSs (case 19) (Fig. 2), and the patient with Ollier's disease had two CSs at different locations (case 31).

Twelve patients had wide surgical margins, and three patients had marginal surgical margins. Two patients with marginal excision had local recurrence, whereas there was one recurrence after wide excision. Amputation was the primary procedure in nine patients. One recurrence was seen in 14 patients with solitary

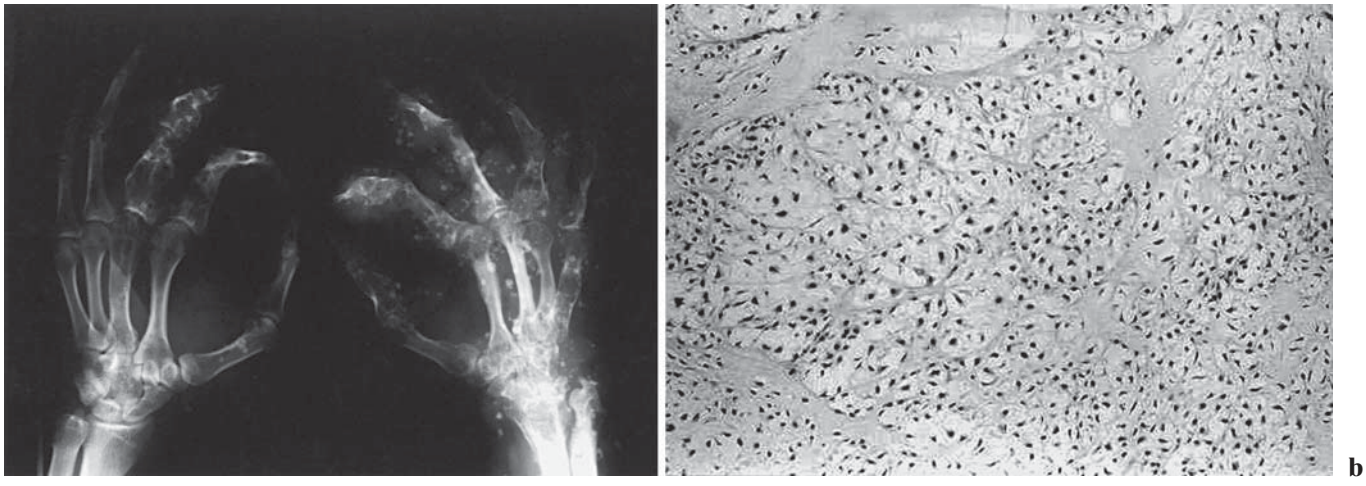


Fig. 1. a Multiple enchondromas in a 27-year-old-man with Maffucci's syndrome (case 32). Posteroanterior (PA) radiograph of the hand demonstrates multiple lytic expansile lesions and cortical disruption especially in the phalanges of the third digit of the left hand. Multiple phleboliths in the soft tissues are the mark of angiomas. **b** Low-grade chondrosarcoma (CS) with moderately hypercellular and some limited nuclear atypia, pleomorphism, and binucleate forms. × 100

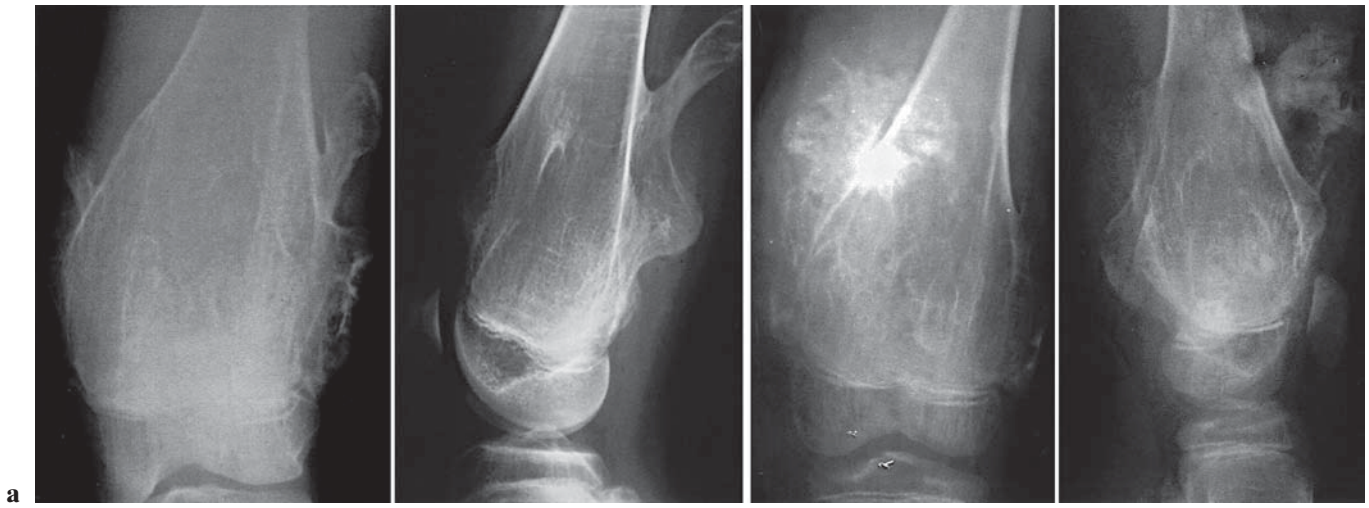
Table 1. Patients' characteristics

No.	Age (years)	Sex	Primary diagnosis	Localization	Malignant transformation	Grade	Time interval (years)	Surgery	Recurrences	Follow-up (months)	Distant metastasis	Last status
1	18	M	Osteochondroma	Humerus proximal	CS	1	4	Wide excision	—	140	—	NED
2	35	F	Osteochondroma	Tibia proximal	CS	1	12	Wide excision	—	84	—	NED
3	30	F	Osteochondroma	Femur proximal	CS	2	16	Hip disarticulation	—	84		NED
4	55	F	Osteochondroma	Femur distal	CS	1	6	High femoral amputation	—	36	Pulmonary	Exitus
5	27	M	Osteochondroma	Femur proximal	CS	1	3	Hip disarticulation	—	72	—	NED
6	23	F	Osteochondroma	Ischium pubic ramus	CS	1	3	Enneking type 3 + parsiyel resection + reconstruction	—	64	—	NED
7	36	F	Osteochondroma	Superior pubic ramus	CS		3	Wide excision	—	52	—	NED
8	26	M	Osteochondroma	Femur distal	CS	1	15	Wide excision	—	60	—	NED
9	36	M	Osteochondroma	Scapula	CS	1	10	1. Marginal excision 2. Marginal excision 3. Wide excision 4. Scapulectomy	3 times	71	—	NED
10	40	M	Osteochondroma	Femur proximal	CS	1	7	Wide excision + THA	—	48	—	NED
11	32	M	Osteochondroma	Tibia proximal	CS	1	2	Wide excision	—	33	—	NED
12	39	F	Osteochondroma	Femur distal	CS	1	25	Wide excision	—	48	—	NED
13	48	F	Osteochondroma	Femur proximal	CS	1	9	Hip disarticulation	—	32		NED
14	42	M	Osteochondroma	Femur proximal	CS	1	9	Wide excision	—	26	—	NED
15	41	M	HMO	Humerus proximal	CS	1	2	1. Shoulder hemiarthroplasty 2. Scapulectomy 3. Scapulotorasic disarticulation	2 times	119	—	NED

Table 1. *Continued*

No.	Age (years)	Sex	Primary diagnosis	Localization	Malignant transformation	Grade	Time interval (years)	Surgery	Recurrences	Follow-up (months)	Distant metastasis	Last status
16	32	M	HMO	Femur distal	CS	1	15	1. Marginal excision + PMMA 2. Marginal excision 3. Above knee amputation	2 times	141	—	NED
17	29	F	HMO	Femur proximal	CS	1	2	Wide excision	—	125	—	NED
18	29	F	HMO	Tibia proximal	CS	1	26	1. Wide excision 2. Above knee amputation	+	115	—	NED
19	15	M	HMO	Femur distal, Scapula, Ilium	CS	1	4	Wide excision	+	104	—	AWD
20	28	M	HMO	Femur distal	CS	1	6	Wide excision	—	46		NED
21	31	M	HMO	Scapula	CS	2	4	Scapulectomy	—	57	Multiple	Exitus
22	36	M	HMO	Ilium	CS	1		Marginal excision		72		NED
23	69	M	HMO	Femur proximal	CS	1	14	Hip disarticulation	—	60	—	NED
24	49	M	HMO	Ilium	CS	2		Inoperable		3	Multiple	Exitus
25	31	M	Enchondroma	Femur proximal	CS	1	5	Inoperable	—	6	Multiple	Exitus
26	64	F	Enchondroma	Humerus proximal	CS	2	12	Scapulothoracic disarticulation	—	1	Pulmonary	Exitus
27	43	F	Enchondroma	Humerus proximal	CS	1	4	Curettage + PMMA	—	41		NED
28	36	M	Enchondroma	Femur proximal	CS	1	6	Curettage + PMMA	—	25	—	NED
29	80	M	Enchondroma	5. hand finger	CS	1	12	Ray amputation	—	13	—	NED
30	45	F	Enchondroma	Femur distal	CS	1	7	Curettage + PMMA	—	21	—	NED
31	24	M	Ollier's disease	1. hand finger, Humerus proximal	CS	1	10	Shoulder hemiarthroplasty + CMC disarticulation	—	22	—	NED
32	27	M	Maffucci's syndrome	3. hand finger	CS	1	14	Ray amputation	—	14	—	NED

CS: chondrosarcoma; NED: no evidence of disease; AWD: alive with disease; PMMA: polymethylmethacrylate; THA: total hip arthroplasty; CMC: carpometacarpal



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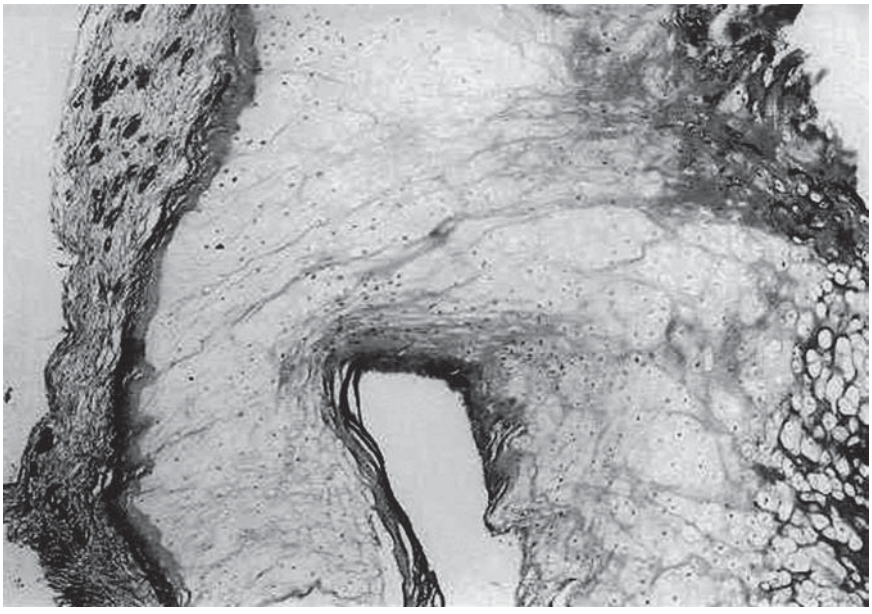

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Fig. 2. a An 11-year-old boy with hereditary multiple osteochondromas (HMOs) (case 19). Osteochondromas in the metaphyseal part of the distal femur. PA and lateral views. **b** PA and lateral views of the same patient after 4 years. Radiographs demonstrate a characteristic pattern of chondrosarcoma, which has calcification in the form of small, round, calcified bodies that resemble popcorn balls. **c** Panoramic view of the low-grade CS. Hypercellularity with relatively uniform-sized cells that demonstrate limited atypia. ×40

Table 2. Cartilage-forming benign bone tumors according to the World Health Organization[7] and malignant transformation rate of these tumors

Tumor	Total	Malignant	%
Osteochondroma	423	24	5.7
Solitary	331	14	4.2
HMO	92	10	9.2
Chondroma	161	8	4.9
Enchondroma	143	6	4.2
Multiple chondromatosis	18	2	11.1
Ollier disease	15	1	6.6
Maffucci's syndrome	3	1	33
Chondroblastoma	32	—	0
Chondromyxoid fibroma	11	—	0
	627	32	5.1

osteochondromas and three in 10 patients with multiple osteochondromas. The number of local recurrences ranged from one to three. Two patients had local recurrence during the first 5 years postoperatively; two had local recurrence after 5 years. Six patients received chemotherapy, and three patients had radiotherapy. Five patients died of tumor recurrence or distant metastasis (15.6%) at an average of 20.6 months (range 1–57 months), and one patient is alive with tumor at 104 months. The mean follow-up period was 57.3 months (range 1–140 months). The percentages of cartilage-forming benign bone tumors classified according to the World Health Organization[7] and the malignancy transformation rate of these tumors can be seen in Table 2.

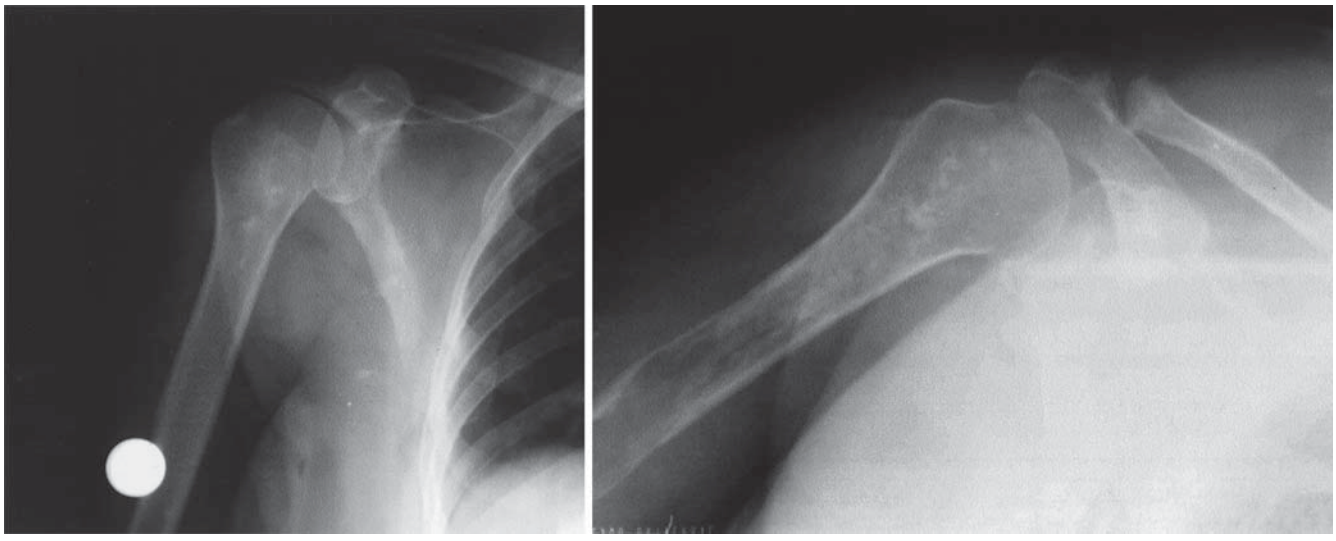

Fig. 3. a Solitary enchondroma in the metaphyseal part of the humerus (case 26). **b** Radiograph after several years shows an intramedullary, expansile-lytic lesion with increased punctate calcifications and cortical thinning. The patient died with pulmonary metastasis 1 month after scapulothoracic disarticulation

Histological evidence of a preexisting osteochondroma was present in five patients with solitary osteochondromas (35.7%) and in seven patients with multiple osteochondromas (70%). The remaining 12 patients (3 with HMOs, 9 with solitary osteochondromas) were initially operated on because of the suspicion of a secondary CS over the osteochondroma at the first admission. Histological evidence of a preexisting enchondroma was seen in one patient (case 25) with a solitary enchondroma who was referred from another center and evaluated as inoperable. There was an interval of 5 years between the histological diagnosis of the enchondroma and the secondary CS. Similarly, patient 26 was referred to our center after a diagnosis of secondary CS (Fig. 3). This patient died 1 month after scapulothoracic disarticulation with pulmonary metastasis. All radiological and clinical follow-up sessions for the other four patients until the occurrence of secondary CS were in our department. Three of these four patients were treated by curettage plus polymethylmethacrylate (PMMA) and one with ray amputation. No recurrence was seen in these patients during a mean of 25 months (range 13–41 months). Histologically, four tumors (one solitary osteochondroma, one enchondroma, two multiple osteochondromas) were considered grade II, and the rest were grade I. No grade III tumor was seen.

Discussion

Malignant transformation of benign bone tumors is a rare condition; and although there are numerous studies about specific bone tumors, none of the publications has reported malignant transformation rates of different histological types of benign bone tumors. However, malignant transformation of cartilage-forming benign bone tumors is not rare.[1,3,4,5,8,9]

Osteochondroma is the most common precursor lesion for secondary CS.[1–3,10] The true incidence of secondary CS is unknown because some of the patients are asymptomatic and do not visit a physician.[3,10–12] Many authors agree that the incidence is 0.4%–2.0% in patients with solitary osteochondromas and 1%–5% in patients with multiple osteochondromas.[2,3,6] The incidence of malignant transformation was reported from the Mayo Clinic as 7.6% for the solitary osteochondroma group and 36.3% for the HMO group.[2] This number might be elevated not only because of referral selection bias but also because of the longer follow-up period. In our series cartilage-forming bone tumors represent 37.5% of all benign bone tumors, and 5.1% of them are secondary CSs. The malignant transformation rate was 4.2% for solitary osteochondromas and 9.2% for HMOs. The syndrome-forming types of cartilaginous tumor especially tend to have malignant transformation.[2,3,6,9,12–18] When there is Ollier's disease, Maffucci's syndrome, or HMOs, the transformation rate increases about 10- to 15-fold based on the figures in the literature.[1,3,14,16] This may be because of the lower incidence of syndrome-forming cartilaginous tumors in the current series than is reported in the literature.

The average age of the secondary CS patient is 35 years, which is younger than patients with primary tumors.[2,10,12] In the Mayo Clinic series, 58% of patients with secondary CSs were in their third or fourth decade, with only 4.8% in their second decade.[2] In the current

study, there were only two patients in their second decade, whereas there were eight in their third, eleven in their fourth, and seven in their fifth decades, and the patients' average age was 37.4 years. Only four patients (12.5%) were over 60 years. This may indicate that secondary CS is less prevalent at younger ages than primary CS. It is possible that the apparent risk of malignant transformation increases as the duration of follow-up increases.

Wuisman et al. reported on 27 patients with multiple osteochondromas, 2 of whom each had two CSs.[12] Therefore, there are three, perhaps four, reported instances of multiple CSs in patients with multiple osteochondromas, Ollier's disease, and Maffucci's syndrome.[19–23] There was one patient with an HMO and one with Ollier's disease in our series who had multifocal secondary CSs.

A change in the size of an osteochondroma or new onset of symptoms warrants investigation, as each may herald malignant transformation.[1–4,6,8,12] Evaluation of the cartilage cap of an osteochondroma is important in this regard.[1–3,6,18] In the study by Hudson et al., the cartilage cap in benign osteochondromas averaged 9 mm (maximum 2.5 cm).[24] For secondary CS the mean cartilage thickness measurements of 3.9 cm (0.5–15.0 cm) and 4.6 cm (1–15 cm) were reported by Ahmed et al. and Wuisman et al. respectively.[2,12] We believe that a change in cap thickness in an adult with a cap of > 2 cm is worrisome regarding malignancy. In our study, the cartilage cap thickness was irregular, with a maximum measurement of 11 cm. Although changes in radiological appearance and clinical features of an osteochondroma (e.g., a rapid increase in size or local pain) suggest malignant transformation, they are unreliable. A definitive diagnosis requires biopsy.

Centrally located osteochondromas about the pelvis, hips, and shoulders are reported to be particularly prone to undergo malignant transformation.[1–3,6] The reason for this may be the delayed diagnosis of lesions in these areas. Two of our patients whose lesions were considered inoperable at the time of the initial diagnosis had giant masses over the ilium (case 24) or proximal femur (case 25). The low rate of malignant transformation of peripheral tumors may be related to their association with compression syndromes or deformities and so are removed at an earlier stage than tumors of the trunk. Garrison found equal distributions of malignant transformation in solitary osteochondromas between long and flat bones, with an 80% predilection for flat bones for multiple osteochondromas.[25] In the current study, 27 of 35 (77.1%) secondary CSs were in long bones, and 8 (22.9%) were in flat bones. Eleven (78.6%) and seven (70%) of the tumors that occurred after solitary osteochondroma and HMO, respectively, were in long bones. All of the tumors occurring after enchondroma were located in long bones. In the literature it was reported that the femur is the most frequently affected bone (30% of cases) for osteochondromas, with distal involvement being three times more common than proximal involvement.[1] Despite this opinion, in the current study proximal involvement was more frequent.

Solitary enchondroma represents close to 20% of all cartilage-forming benign bone tumors.[9,15] Malignant transformation in a solitary enchondroma is an uncommon but recognized complication.[9,26,27] In some cases, accurate distinction between enchondroma and low-grade CS is difficult for even skilled pathologists and clinicians (Fig. 3).[9,10,15,27] Pain seems to be a significant clinical symptom.[26] CS patients usually have a clinical history of pain. Among enchondroma patients, 43.8% reported pain, compared with 90.6% of all CS patients.[26] Also, small areas of stippled calcifications may be present in both enchondromas and CS; and if no radiographic areas of calcification are seen, it does not preclude the possibility of preexisting enchondroma.[8,26,27] The histological differentiation between benign enchondromas and low-grade CS depends on subtle criteria; and because malignant features are sometimes found in only limited areas of the tumor, a single small biopsy sample may erroneously indicate a benign lesion.[26] A major problem in the diagnosis of CS transformed from a preexisting enchondroma is the lack of unequivocal documentation by biopsy.[9,26,27] In these cases, a long medical history and radiological changes (Fig. 3b) of a preexisting tumor can be counted as a sign of malignant transformation. Permeation of cortical and/or medullary bone is an important characteristic of CS that can be used to distinguish it from enchondroma. Myxoid changes or chondroid matrix liquefaction is a common feature of CS.[10] Welkerling et al. found that nuclear features, such as nuclear size and nuclear polymorphism, were the most reliable criteria (Fig. 4).[26]

The size of the enchondroma may be an important factor.[9,15,26,27] Brien et al. believed that the chance of a modestly sized solitary enchondroma (3–7 cm) becoming malignant is not minuscule, but they estimated the risk to be about 2%–3%. They estimated that a large solitary enchondroma (8–15 cm in maximum dimension) has, during an entire lifetime of the patient, an approximately 5% chance of undergoing malignant transformation.[9] Given the above theoretical considerations concerning the malignant potential of a solitary enchondroma, we advise, as did Brien et al., complete curettage of any enchondroma >7 cm. In the present study, three patients in whom secondary CS occurred after solitary enchondroma (cases 27, 28, 30) were diagnosed early while the tumor was still small and without cortical destruction or soft tissue invasion; they were treated by curettage and PMMA with no need for more radical procedures.

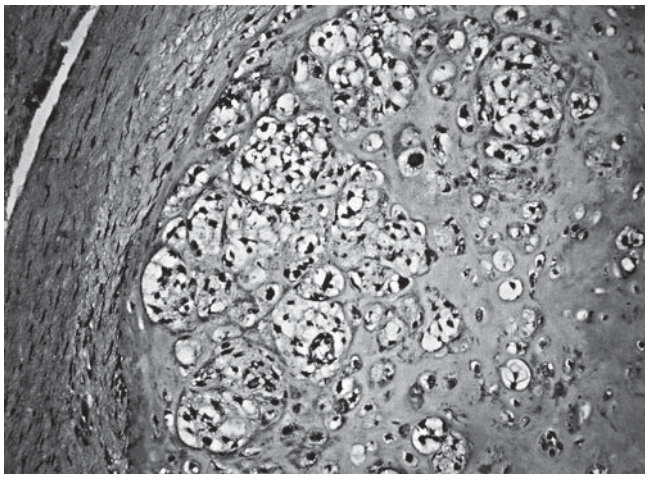

Fig. 4. Low-grade CS with moderately hypercellular and nuclear atypia, pleomorphism, and binucleate forms. ×200

Patients with multiple enchondromatosis carry a significantly higher risk of transformation to secondary CS.[9,10,16,18,26] The rate of CS in conjunction with Ollier's disease has been estimated to be as high as 50%.[9,10,16,26] Of the 15 cases reviewed in our series, one patient developed CS (6.6%). Similar to Ollier's disease, Maffucci's syndrome may undergo malignant transformation.[9,28,29] There have been varied estimates of secondary CS in Maffucci's syndrome, and it has been suggested that secondary CS is more commonly seen in Maffucci's syndrome than in Ollier's disease.[9,10] Lewis and Ketcham reported secondary CS in 16 of 105 patients with Maffucci's syndrome, with an overall malignancy rate of 23%.[30] In the current study, one of three patients with Maffucci's syndrome had secondary CS. We believe that the true secondary CS rate in Maffucci's syndrome can be estimated when the quantity of patients with Maffucci's syndrome who had long follow-up periods increases.

Even though the rate of local recurrence is reported to be primarily dependent on the adequacy of the surgery rather than the histological grade,[1–3,12] we believe that not only adequate surgery but also the location and the histological grade have an influence on the survival of the patient. Although most secondary CSs are low grade, their size and location may make wide excision difficult, especially with intrapelvic tumors. In the current study, four tumors (cases 3, 21, 24, 26) were histologically considered grade II, and the rest were grade I. Three of the patients with a grade 2 tumor died, whereas only 2 of 28 patients with a grade 1 tumor died, and one of these patients (case 25) was deemed inoperable when diagnosed. The results of the current study confirm the belief that a secondary CS is a low-grade neoplasm, and higher histological grades worsen survival. If complete removal of the tumor is possible, the patient may have a long disease-free survival.[2,12,25] Ahmed et al. reported that patients with secondary CS who undergo no treatment or inadequate treatment die within 10 years after diagnosis.[2]

Conclusion

Although malignant transformation of a benign bone tumor is a rarely encountered situation, orthopedic surgeons should be cautious when following patients with a benign bone neoplasm, especially cartilage-forming tumors associated with syndromes. The patients in this study with secondary CS were one to two decades younger than the patients with primary CS. Early recognition and appropriate surgical treatment are necessary for successful outcomes.

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