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Late sarcoma development after curettage and bone grafting of benign bone tumors

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ABSTRACT

Background and aim: Rarely sarcomas develop in previous benign lesions, after a long term disease free interval. We report the experience on these rare cases observed at a single Institution.
Patients and methods: 12 cases curetted and grafted, without radiotherapy developed sarcomas, between 1970 and 2005, 6.5–28 years from curettage (median 18, average 19).

Age ranged from 13 to 55 years (median 30, average 32) at first diagnosis; tumors were located in the extremities (9 GCT, benign fibrous histiocytoma, ABC, and solitary bone cyst). Radiographic and clinic documentation, for the benign and malignant lesions, were available. Histology was available for 7 benign and all malignant lesions.
Results: To fill cavities, autogenous bone was used in 4 cases, allograft in 2, allograft and tricalcium-phosphate/hydroxyapatite in 1, autogenous/allograft in 1, heterogenous in 1. For 3 cases the origin was not reported. Secondary sarcomas, all high grade, were 8 osteosarcoma, 3 malignant fibrous histiocytoma, and 1 fibrosarcoma.
Conclusions: Recurrences with progression from benign tumors are possible, but the very long intervals here reported suggest a different cancerogenesis for these sarcomas. This condition is extremely rare accounting for only 0.26% of all malignant bone sarcomas treated in the years 1970–2005 and represents only 8.76% of all secondary bone sarcomas treated in the same years. This incidence is the same as that of sarcomas arising on fibrous dysplasia, and is lower than those arising on bone infarcts or on Paget's disease. This possible event must be considered during follow-up of benign lesions.

1. Introduction

Development of secondary bone sarcomas is a rare but well documented event. This can occur secondary to a predisposing benign condition and/or is endorsed by radiotherapy treatment.

Reported predisposing conditions are fibrous dysplasia [3,33], bone infarcts [19,32,8], intraosseous lipoma [18,6], chronic osteomyelitis [33,23], aneurysmal [2,5,12,35] and solitary bone cysts [15], and, more frequently, Paget's disease [14] and giant cell tumor of bone [26,4]. Regarding giant cell tumor, Hutter et al. [13] and Dahlin et al. [7] distinguished between primary malignant giant cell tumor, composed of sarcomatous growth associated to typical area of benign giant cell tumor, and secondary sarcomas where the malignancy develops later at the site of a previously documented giant cell tumor. This definition is also reported in the "WHO classification of tumours" [34].

Transformation is more frequent when radiotherapy is used [26,4], in the field of radiotherapy treatment also in areas without pre-existing conditions, and, in these cases, pathogenesis is obviously due to the oncogenic effect of treatment.

Reviewing the cases treated at the Rizzoli Institute, we noted a number of sarcomas developed on the site of previously curetted and grafted benign bone lesions after a long latency, in all cases radiotherapy had not been used.

Reports of similar cases in literature, without previous radiotherapy, are scarce [26,22,24,28,11,17]. Constantly, a long latency between the original benign- and subsequent malignant tumor is reported, and in spite of this, all authors have interpreted these sarcomas as secondary transformation of previous benign conditions, mainly giant cell tumors. Only sporadic and limited sentences suggest the possibility that grafts can be, as suggested for bone infarcts [19,32,2,24], or for infarction like changes [28], the irritative cause of transformation.

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2. Patients and results

Within the 4564 bone sarcomas treated at the Rizzoli Institute between 1970 and 2005, 12 cases developed a malignancy after curettage and grafting for a benign lesion, without the use of radiotherapy. Detailed characteristics of these patients are reported in Table 1. Five of these, all giant cell tumors, were previously reported [4].

Radiographic and clinic documentation for the benign and malignant lesions were available for all cases. Particularly, all patients had imaging examinations available after the graft and at the time of the sarcoma (all radiographs, eight CT and/or MR).

Histology was reviewed for seven of the benign lesions and for all malignant tumors.

Benign lesions consisted of typical benign giant cell tumors in 9 cases, and in 1 case each of benign fibrous histiocytoma, aneurysmal bone cyst, and solitary bone cyst. Age at diagnosis ranged between 13 and 55 years (median 30, average 32). All lesions were located in the extremities (proximal femur 2, distal femur 5, proximal tibia 3, distal tibia and proximal radius 1).

The type of bone used to fill the cavity after curettage was autogenous in 4 cases, allograft in 3 (in one of these tricalciumphosphate and hydroxihapatite was added), auto and allograft in 1, and heterogenous (Kiel bone) in 1. For the other 3 cases the type of bone was not reported. The 12 sarcomas that developed were all high grade. Histological diagnosis was eight times osteosarcoma, three so-called malignant fibrous histiocytomas of bone, and 1 fibrosarcoma. Radiographically, all cases showed a lytic lesion in the grafted area, with immediate signs of aggressiveness in 10 cases (cortical destruction, periosteal bone formations, soft tissue involvement), soon in the follow up in the 2 remaining. These developed 6.5–28 years from curettage (median 18, average 19). Patient age at diagnosis of sarcoma ranged from 33 to 77 years (median 44, average 51). Treatment consisted in palliation in 2 of the 3 patients who already presented disseminated disease, 8 amputations and 2 limb salvage procedures. Chemotherapy was given in 7 of the 10 surgically treated patients. Regarding surgery, it has to be noted that 3 of the 8 amputated patients had had a previous intralesional treatment, at the time of sarcoma, being the lesion considered a recurrence of the benign lesion. Probably, in these 3 cases, a different approach could have avoided *ablative* surgery. The three patients with disseminated disease died after 2, 3, and 8 months, respectively. One died of disease after a year, and another died of unrelated causes 10 years after treatment. Seven out of the other nine patients are continuously free of disease from 4 to 16 years from treatment of the sarcoma. Figs. 1–6 show some of these cases.

3. Discussion and conclusions

The development of these secondary sarcomas raises two important questions: (1) the real incidence, and (2) the possible pathogenesis.

It would be very interesting to know the real incidence of this transformation, but it is not possible to evaluate the exact number of benign lesions which were treated by curettage and grafting in those years. Moreover, some of these had had their first treatment, for the benign lesion, in other Institutions, thus making it impossible to calculate the denominator for the right proportion. A possible calculation of the risk can be obtained by comparing the frequency of other well known conditions of secondary bone sarcomas. In the same years, 1970–2005, we treated a total number of 137 secondary bone sarcomas, accounting for 3.01% of all 4564 treated patients with bone sarcomas. Table 2 reports these cases divided for the conditions in which they arose. The rarity of the

Table 1
Clinical characteristics of the 12 patients.

Case	Sex/age	Site	Month/year of 1st Diagn	Ben Diagn	Type of graft	Month/year of sarcoma	Years of latency	Age	Malig Diagn	Stage	Treat	Status	Date of last F-U	Years of F-U
C.R.	M/33	FEMUR DIST	1/1985	ABC	Unknown	9/1991	6.5	39	OS GR.4	LOC	AMPUT+CHEM	DEAD DOX	02/12/1992	1
C.P.	M/45	TIBIA PROX	8/1961	GCT	Allograft	04/1989	28	72	OS GR. 4	LOC	AMPUT	CNED	21/09/1998	9
C.S.	M/25	TIBIA PROX	7/1969	GCT	Heterogenous	10/1985	16	41	OS GR. 3	LOC	AMPUT	CNED[a]	20/01/1997	10
C.G.	M/13	FEMUR PROX	2/1970	SBC	Unknown	01/1990	20	33	MFH GR. 4	LOC	HIND AMP+CHEM	CNED	12/11/2004	13
L.P.	M/29	FEMUR DIST	6/1961	GCT	Unknown	01/1973	11.5	41	OS GR.4	METS	AMPUT	DOD	20/03/1974	0,8
M.G.	M/21	FEMUR DIST	4/1975	GCT	Autogenous	03/1991	16	37	MFH GR. 4	LOC	DISART+CHEM	CNED	18/10/2001	10
M.U.	M/25	FEMUR PROX	7/1967	GCT	Autogenous	12/1999	22	47	OS GR. 4	METS	NONE	DOD	08/01/1990	0,2
M.F.	F/55	RADIUS PROX	9/1991	GCT	Autogenous	10/1998	7	65	OS GR. 4	LOC	RESEZ+CHEM	CNED	27/03/2008	7
P.D.	F/31	FEMUR DIST	9/1988	BFH	Allograft+TCP/HA	03/1996	7.5	39	FS GR. 4	LOC	RESEZ+CHEM	CNED	27/04/2004	8
P.G.	M/50	FEMUR DIST	8/1969	GCT	Allograft	12/1996	27	77	OS GR. 4	METS	NONE	DOD	21/03/1997	0,3
S.M.	M/37	TIBIA DIST	7/1979	GCT	Autogenous	02/2005	26	63	OS GR. 4	LOC	AMPUT+CHEM	CNED	30/2/2009	4
V.F.	M/19	TIBIA PROX	4/1956	GCT	Auto+allograft	08/1983	27	46	MFH GR. 4	LOC	AMPUT+CHEM	CNED	01/03/1999	16

Site: DIST, Distal; PROX, Proximal.
Ben Diag, benign diagnosis; ABC, aneurysmal bone cyst; GCT, giant cell tumor; SBC, solitary bone cyst; BFH, benign fibrous histiocytoma.
Malig Diag, malignant diagnosis; OS, osteosarcoma; MFH, malignant fibrous histiocytoma; FS, fibrosarcoma; GR. 3–GR. 4, broder's histological grade.
Stage: LOC, localized; METS, metastases at diagnosis.
Treat: treatment; AMPUT, amputation; CHEM, chemotherapy; HIND AMP, hindquarter amputation; DISART, disarticulation; F-U.
Status: DEAD DOX, dead due to doxorubicin toxicity; CNED, continuously no evidence of disease; DOD, dead of disease.
[a] Dead for unrelated causes at 122 months.

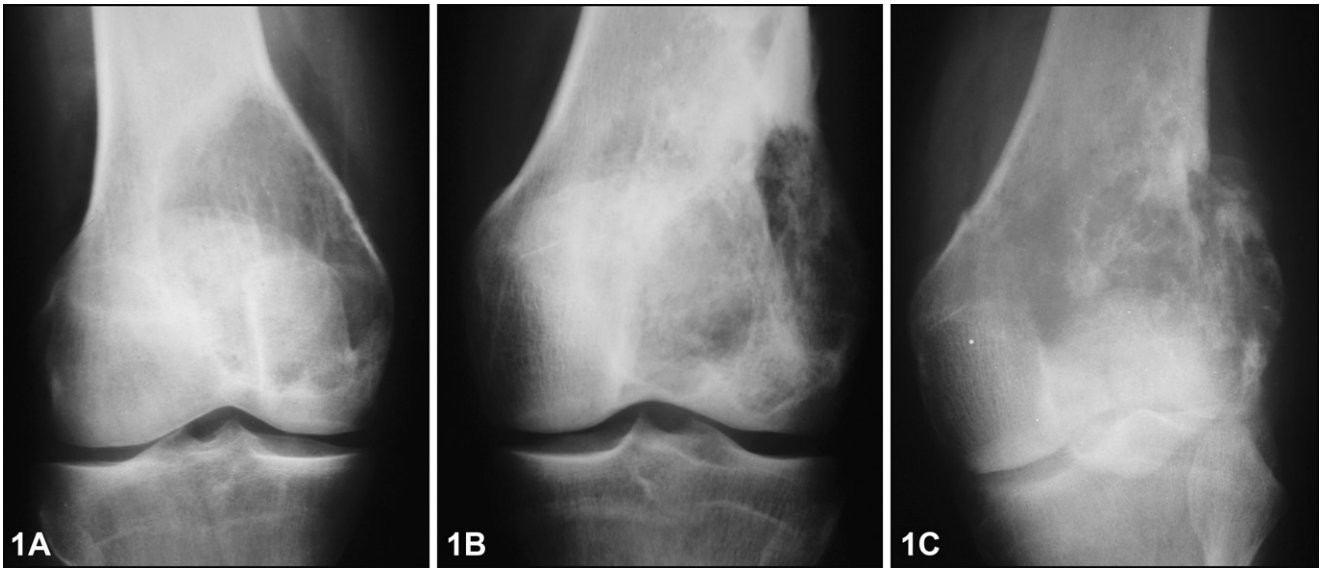

Fig. 1. Case 1: AP radiographs. (A) Aneurysmal Bone Cyst, January 1985: well limited lytic lesion. (B) September 1991: heterogeneous filling of the lesion by the graft. (C) December 1991. Cortical destruction and soft tissue involvement by the osteosarcoma.

transformation is evident, being similar to the percentage occurring on fibrous dysplasia or lower than that for sarcomas arising on bone infarcts or on Paget's disease.

Up to now, in similar cases reported in literature, it is hypothesised that the subsequent malignant tumors develop as a result of tumor progression from the underlying benign lesions [28,11,17].

The long latency between the original lesion and the clinical manifestation of the secondary sarcoma argues against this hypothesis, though possible late local recurrences in GCT have been reported [29].

Also against this hypothesis is the observation in our cases, when follow-up imaging was available, of the absence of a progressive recurrence in the years. The sarcoma appears to develop "*de novo*" with a very aggressive appearance and in a short period of time on an apparently healed lesion (Fig. 1).

To explain the development of these sarcomas new biological mechanisms, put forward in recent literature must be considered [31,21], as a hypotheses.

In the last years, tissue engineering has drawn attention for its possibilities to the so-called biologic treatment of bone defects. Bone grafts in this respect can be considered as scaffolds to promote healing of the lesion-baring bones.

One can foresee that these grafts, independently from their origin (auto, allo, or heterogenic), as other types of engineered scaffolds, attract bone marrow derived mesenchymal stem cells (MSC), which are the precursor cells of the newly formed bone bridging the bone-gap artificially created by curettage.

To explain the development of "de novo" sarcomas in these patients treated with curettage and grafting, the role of MSC should be considered, based on recent preclinical studies.

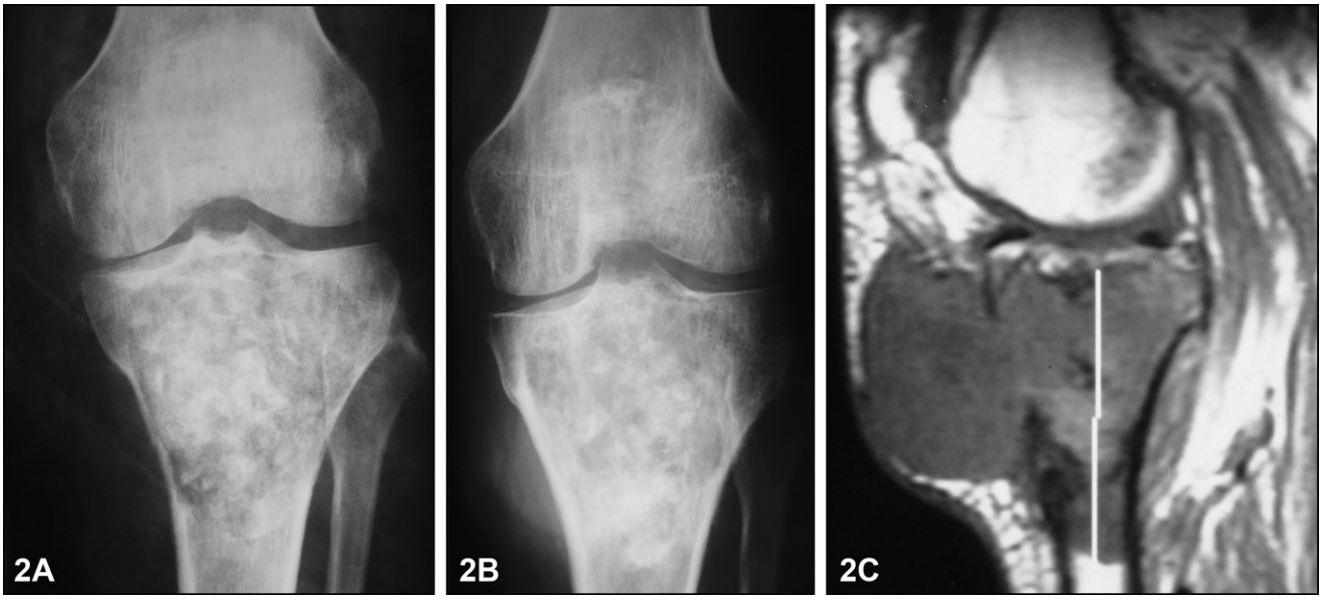

Fig. 2. Case 2: (A) Giant cell tumor after curettage and grafting with allograft bone, August 1961. (B) April 1989 (AP radiograph), and (C) (sagital T1W MR image): massive soft tissue involvement by the osteosarcoma.

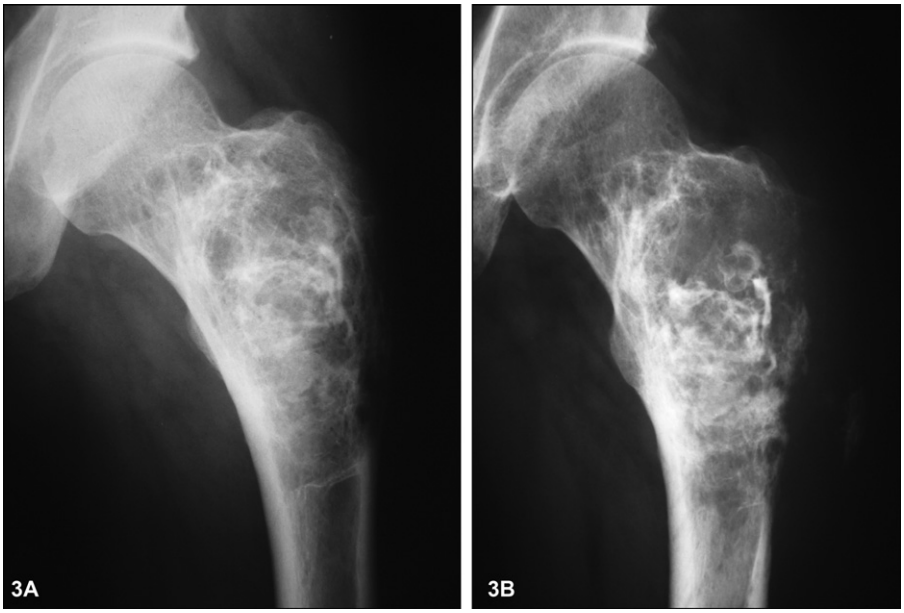

Fig. 3. Case 4: (A) Bone cyst curetted and grafted, February 1970. (B) January 1990. Malignant Fibrous Histiocytoma: on the lateral radiograph, the lateral part of the cortex has completely disappeared.

Recent reports have demonstrated the spontaneous transformation of MSC in sarcomatous cells after passages in culture [37,20,31,27], the development of sarcomas in mice injected with MSC [20,1,31], and the same process in mice when the MSC were seeded onto bioscaffold, independently from its origin (bioceramic or collagen) [30].

Tasso et al. [30] speculated that repair of bone tissue comes from interaction between three players: (a) progenitor cells which produce and are targets of growth factors, (b) scaffold that provides three-dimensional support, and (c) microenvironment. An unbalance between these three elements is foreseen to lead to adverse events.

It is well known that the remodelling process in bone is very slow and practically continues during the whole life span, as it is also demonstrated by the histological examination in patients, showing active remodelling after more than 7 years from grafting (Fig. 7). This might also explain the long latency of secondary sarcomas. Also experimentally [30], it is reported that sarcomas developed later when stiffer and less reabsorbable scaffolds were used, in comparison to collagen sponges. The type of scaffold and its elasticity directs stem cell lineage specification [10].

Another important role for MSC is related to their role in immune response, particularly in suppressing host anti-tumor reaction [9,25].

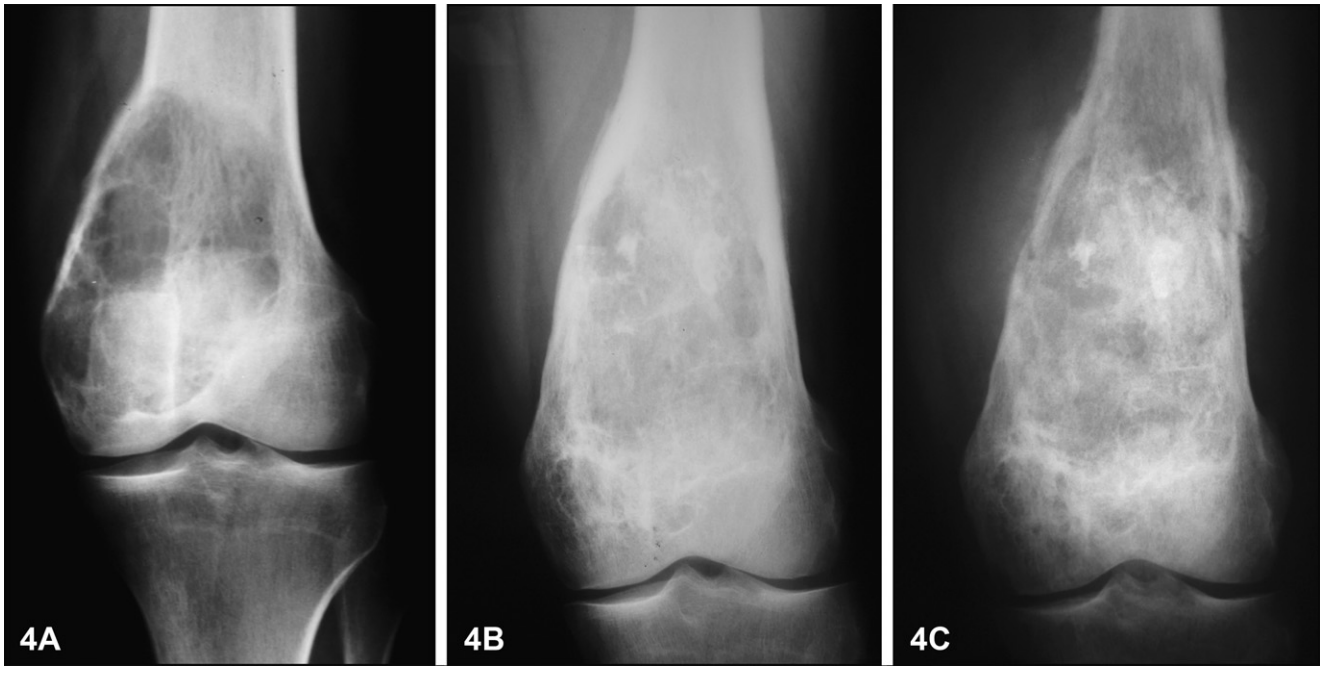

Fig. 4. Case 6: AP radiographs. (A) Giant cell tumor, after curettage and grafting with autogenous bone, June 1976. (B) and (C) Malignant Fibrous Histiocytoma in July 1991 (hardly visible limited osteolysis) and September 1991(massive lytic lesion), respectively.

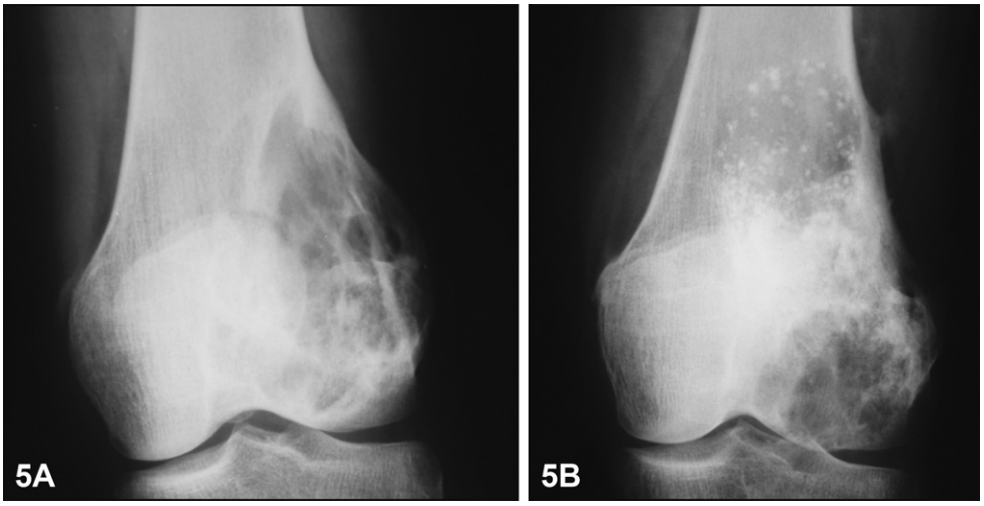

Fig. 5. Case 9: AP radiographs. (A) Benign fibrous histiocytoma: well limited lytic lesion. September 1988. (B) March 1996. Lytic aggressive lesion centered on the epiphysis: Fibrosarcoma.

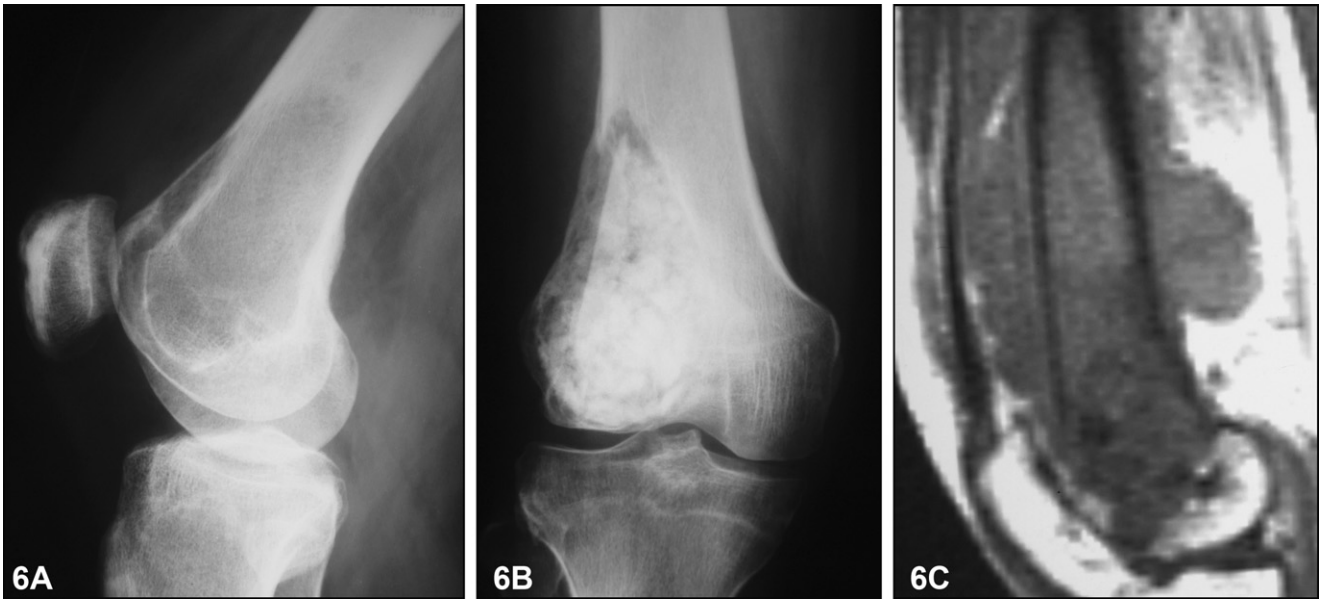

Fig. 6. Case 10: (A) Giant cell tumor, August 1969: on the sagital radiograph, well limited lytic lesion. (B) After curettage and grafting with allograft bone, December 1969. (C) December 1996, sagital T1W MR image: massive medullary and soft tissue involvement: osteosarcoma.

Up to now, there are no reports of malignancy in patients after the use of engineered scaffolds [16], but follow up is still very short and latency could be very long.

All authors involved in the evaluation of tumorigenic potential of MSC, with or without scaffolds, suggest caution in their use in patients [37,20,1,30,31,27,9], especially those who have a familial or a personal history of malignancy [25]. We support these suggestions, but we keep in mind that evolution of our cases suggest a risk also after benign conditions, where a particular genetic predisposition can be present due to the pre-existence of a lytic lesion. No reports of late malignancy after the use of methylmethacrylate (cement) for filling cavities after curettage are available in

Table 2
Secondary sarcomas observed in the years 1970–2005.

	Number of cases	Percentage on total treated bone sarcomas (4564 cases)	Percentage on total secondary tumors (137 cases)
After radiotherapy	51	1.12%	37.23%
On paget's disease	34	0.75%	24.82%
On bone infarcts	15	0.33%	10.95%
On fibrous dysplasia	12	0.26%	8.76%
On bone grafts	12	0.26%	8.76%
On giant cell tumors[a]	7	0.15	5.11%
On osteomyelitis	6	0.13	4.38%
Total	137	3.01%	100%

[a] Within 18 months from the diagnosis of giant cell tumor.

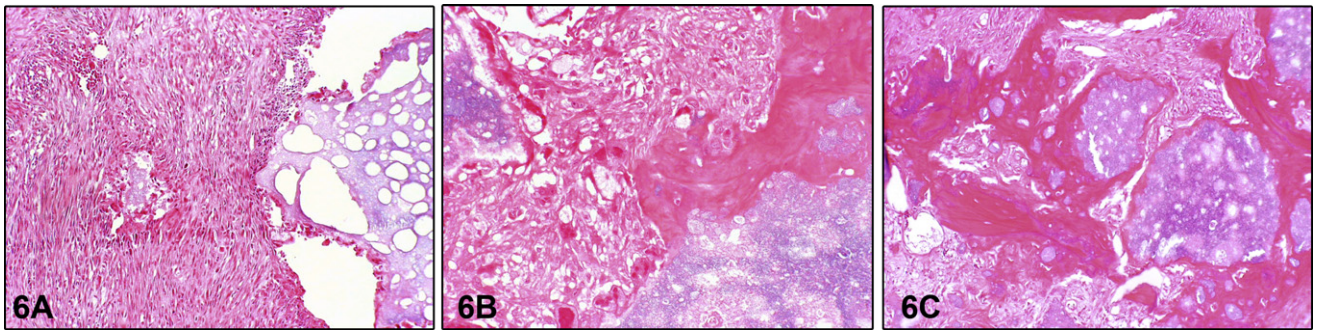

Fig. 7. Case 9: Histology at the time of surgery for malignant tumor, 7.5 years after curettage and grafting with allograft bone and TCP/HA. (A) H&E 10×. Panoramic view showing amorphous material encased by mature bone. (B) H&E 20×. Amorphous material in the right field, surrounded by the mostly spindle shaped and less frequently ovoid to round neoplastic cells with hyperchromatic and sometimes bizarre nuclei, showing predominantly fascicular, focally storiform pattern. Between that material and the sarcomatous component, reactive histiocyte like cells are evident. (C) H&E 20×. Mature bone encasing amorphous material, with reactive pleomorphic histiocytic type cells, with variation in size, some with giant bizarre nuclei.

literature, pointing to the consideration for this treatment. In fact, a three-dimensional scaffold, including bone grafts, could be the niche for MSC to develop tumors [25,36] which is absent when bone cement is used.

In conclusion, given the large size of our study population it is evident that the risk of late malignancy following bone grafting is very low, and the advantages of tissue engineering could justify this hypothetical risk. What has to be stressed is that any "late recurrence" must be approached considering the possibility of a secondary induced primary tumor. This means in practice renewed staging and consideration of tailored therapies, thus offering the patient the best chances of cure.

Conflict of interest statement

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The authors declare that they have no financial and personal relationships with other people or organizations that could bias their work. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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