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ORIGINAL STUDY

Aneurysmal bone cystic lesions: value of genomic studies

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Aneurysmal bone cystic (ABC) lesions can be primary or secondary (to a trauma or a pre-existing benign or malignant tumour). Specific translocations of the *USP6* gene are reported in about 70% of primary but never in secondary ABC lesions.

We report two cases of ABC lesions in which imbalanced genomic aberrations were detected at initial presentation and showed complex clonal evolution.

These demonstrative observations strengthen the guidelines regarding the diagnostic approach when an ABC is suggested by imaging. Biopsy is mandatory including genomic analysis. When a primary ABC is not clearly proven by the initial biopsy, an extensive curettage should be performed, with pathological examination of all removed tissue in order to exclude a secondary ABC. It also illustrates the added value of genomic analyses in the setting of an ABC lesion: complex clonal aberrations argues for a lesion secondary to a malignant proliferation whereas *USP6* rearrangement allows the diagnosis of primary ABC.

Keywords : aneurysmal bone cyst; malignancy.

INTRODUCTION

Aneurysmal bone cyst (ABC) is a very rare lytic lesion whose annual prevalence is about 0.32 per 100,000 individuals *(37)*, preferentially located in the long bone metaphysis, the pelvis and the spine. ABC may present several aspects, but is classically a primitive lytic bone lesion in metaphyseal position, composed of blood-filled spaces and solid tissue aggregates separated by fibrous septa. The solid ABC *(5,36)*, is a variant that is more compact and does not always contain any cavities. Another rare variant is soft tissue ABC *(3,34)*, which develops in

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the muscles, the perivascular spaces and the susclavicular or inguinal space, without bone involvement. Radiographically, it can mimic ossifying myositis *(3)*.

Secondary ABC *(32)* has been described after a trauma, a pre-existing benign and less commonly, a malignant tumour. Possible benign lesions are simple bone cysts, fibrous dysplasia, brown tumour (primitive hyperparathyroidia), giant cell tumour, but also osteoblastoma, non-ossifying fibroma, chondromyxoid fibroma, fibrous histiocytoma and eosinophilic granuloma. ABC may also be secondary to a malignant lesion such as osteosarcoma, angiosarcoma, chondrosarcoma or fibrosarcoma *(17,20)*. Telangiectatic osteosarcoma is an unusual variant of osteosarcoma presenting cystic haemorrhagic spaces lined by atypical cells, which may be misdiagnosed as a primary ABC *(17)*.

Several etiopathogenic theories have been proposed for ABC, with the most popular considering ABC as a reactive process *(8,9)* following intraosseous or subperiosteal haemorrhage due to dilatation of the local vascular network. This venous malformation could be primitive or secondary. Szendroï et al. *(30)* studied 20 ABC using angiography and found venous abnormalities but no arteriovenous fistulas. ABC may form in reaction to this haemorrhage, and involve osteoclast activation. This may explain secondary ABC: some tumours can produce this type of venous malformation and can be composed of cystic areas mimicking ABC. Some authors advocate an inherited predisposition. DiCaprio et al. reported a case of ABC of the twelfth thoracic vertebra in a father and an ABC involving the first lumbar vertebra in his daughter *(11)*. Power et al. reported cases of ABC in two monozygotic twins *(26)*. More recent studies propose a purely clonal neoplastic origin for ABC *(14–16)*. Panoutsakopoulos et al. first identified the recurrent chromosomal translocation t(16;17)(q22;p13) in primary ABC *(25)*. Others confirmed this chromosomal aberration in both bone and soft tissue ABC *(10,35)*. Oliveira et al. showed that this translocation places the entire coding sequence of the *USP6* (17p13) oncogene under the control of the *CDH11* (16q22) promoter *(22,23)*. Several alternative fusion partners for *USP6* have since been discovered. All the different translocations lead to *USP6* overexpression due to transcriptional up-regulation within the ABC spindle cells. *In vitro* studies suggest that USP6 overexpression explain many of the morphologic features of ABC *(24)*. *USP6* rearrangement is detected in around 70% of primary ABC but never in secondary ABC *(2)*. However, van de Luijtgaarden et al. report one case of metastatic ABC with *USP6* rearrangement without sarcomatous transformation *(33)*.

Malignant transformation of an ABC is very rare, with only a few cases reported and should be distinguished from secondary ABC to a malignant tumour, especially from the particular form of telangiectatic osteosarcoma. This paper reports two additional cases in which identification of the genomic alterations helped in the diagnosis of malignant aneurysmal bone cystic lesions and reviews the literature.

MATERIALS AND METHODS

1. Karyotyping and FISH

Karyotyping of tumour samples was performed according to standard procedures. Tissues were mechanically and enzymatically disaggregated and cultured in DMEM supplemented with 20% fetal bovine serum for 2-18 days. Cells were treated overnight with Colcemid (0.08μg/ml). Following hypotonic treatment (0.8% sodium citrate for 20 minutes), the preparations were fixed three times with methanol: glacial acetic acid (3;1). Metaphase cells were GTW-banded. Karyotypes are expressed according to the 2013 International System for Human Cytogenetic Nomenclature.

2. FISH

Bacterial artificial chromosomes (BAC) probes CTD-2367F23 and RP11-124C16 used to study the *USP6* locus by dual-color FISH were selected from the University of California, Santa Cruz (http://www.genome.ucsc.edu) database. The BAC clones were obtained from the BACPAC Resources Center at the Children's Hospital Oakland Research Institute, Oakland, CA, USA. Extractions, labelling and hybridizations were performed as previously re-

ported *(15)*. Additional dual-color FISH experiments were performed on fixed nuclei using the following commercial probes: ON SRD (1p36)/SE 1, ON 6q21/SE 6, ON MDM2/SE 12 (Kreatech, Amsterdam, The Netherlands) and LSI 9p21/CEP 9, LSI TP53/CEP 17, LSI SYT, LSI EWSR1 (Abbot SA, Wavre, Belgium). A minimum of 100 nuclei was examined in each sample, and all hybridized metaphases were captured.

RESULTS

1. Patient 1

This 16-year-old boy had been suffering from pain in his left shoulder for 6 months, before he sustained a pathological fracture. Radiograph and magnetic resonance imaging (MRI) showed a voluminous lesion with cystic cavities involving the epiphysometaphysis of the humerus with diaphyseal expansion (Figure 1A and 1B). A first surgical biopsy (biopsy A) was performed. The specimen was haemorrhagic and fibrotic, showing large haemorrhagic spaces and more cellular areas with some atypical mononuclear cells and multinuclear giant cells (Figure 2). Antigen Ki67 was highly expressed, indicating active proliferation. The lesion was considered as a primary ABC although radiological aspects of malignancy and atypical features within the biopsy.

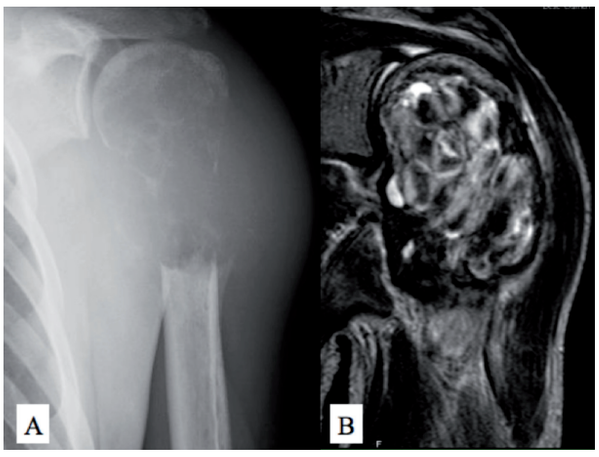

Fig. 1. — Patient 1. 1A: Radiographic image of the lesion of patient 1 at clinical presentation. 1B: T2-weighted MRI performed at the same time.

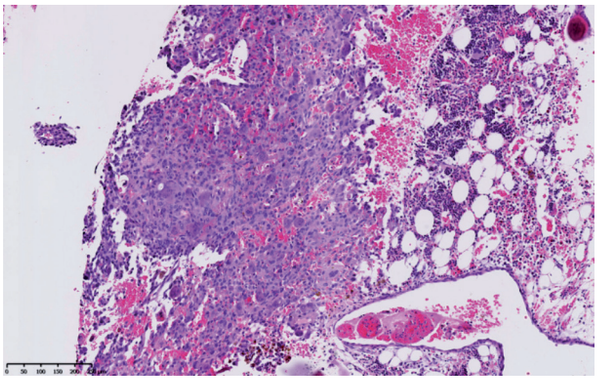

Fig. 2. — Patient 1. Histological aspect showing cellular area with mononuclear and multinuclear giant cells. Some atypical cells present (Hematoxylin and Eosin staining).

Fluorescent *in situ* hybridization (FISH) study (Table I) did not show any rearrangement of the *USP6* / 17p13 locus. The cytogenetic analysis detected a complex and hypodiploid karyotype with multiple clonal aberrations (Table I) (Figure 3A).

One month after biopsy, embolization was performed, with occlusion of two vascular pedicles. Two months later, a new biopsy was performed associated with a minimally invasive surgical procedure consisting of the introduction of demineralised bone matrix mixed with bone marrow *(33)*. At this time, pathological examination confirmed the diagnosis of telangiectatic osteosarcoma, showing numerous atypical cells with irregular and hyperchromatic nuclei (Figure 4) and a high Ki-67 proliferative index.

Genetic analysis (Table I) showed an important clonal evolution. The complex hypotetraploid karyotype corresponds to a duplication of the initial clone with multiple additional chromosomal abnormalities. This karyotype was compatible with a high-grade tumor (Figure 3B). Neo-adjuvant chemotherapy (cisplatin-adriamycin-methotrexate) decreased the tumour volume and was followed by surgical resection and reconstruction by inverted shoulder prosthesis 3-months later. Residual telangiectatic osteosarcoma was observed on the surgical specimen. The patient received adjuvant chemo-

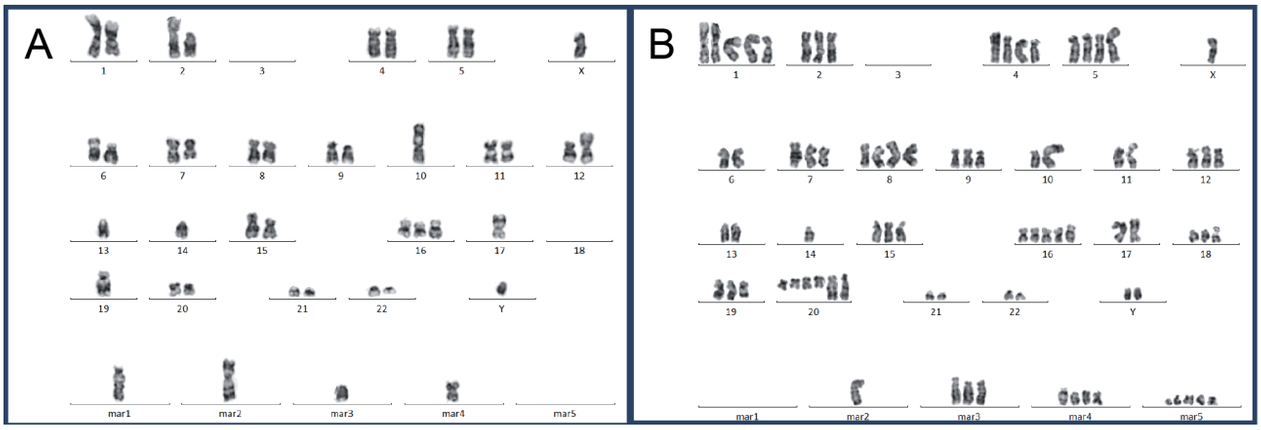

Fig. 3. — Patient 1. Karyograms on G-banded chromosomes at diagnosis (3A) and 3 months later (3B).

Table I. — Genetic abnormalities in biopsies from Patient 1

	Biopsy A	Biopsy B (3 months)
Karyotype	38~42,XY,-Y[4],del(2)(p11.2),-3,-3,-6[3],del(6)(p21)[2], del(7)(q31),del(9)(p21),add(10)(p15),add(12)(p11.2),-13[3], add(13)(p11.2)[3],-14,add(15)(p11.2),+add(16)(q12q13) or +add(16)(q22),add(17)(p11.2),-18,-18[3],add(19)(q13.3), add(20)(q?13.1),-21,-22,+2~5mars[cp7]/46,XY[10]	65~84<4n>,XY,*del(1)(p31)*,del(2)(p11.2)[2],-3,-3,*add(5)(p15)*, -6,del(7)(q31),*add(8)(p11.2)*,del(9)(p21),*add(9)(p12)*, add(10)(p15),add(12)(p11.2)[3],-14,add(15)(p11.2), *add(15)(p13)*,+add(16)(q12q13) or +add(16)(q22),-17, add(17)(p11.2),-18,add(19)(q13.3),*add(19)(q13.1)*, add(20)(q?13.1),*add(21)(p11.2)*,+6~21mars[cp10]/46,XY[8]
Interphase FISH	No significant alteration of the different tested probes : 1p36, CEP1, 6q21, CEP6, CDKN2A/CDKN2B/9p21, CEP9, MDM2/12q15, CEP12, USP6/17p13, TP53/17p13, CEP17, SYT/18q21, EWSR1/22q12	Homozygous deletion of the CDKN2A/CDKN2B /9p21) locus in 30% of nuclei Tetrasomies of CEP6, 6q21, CEP9, EWSR1/22q12 loci (7-14% nuclei) Monosomies of TP53/17p13, CEP17, SYT/18q11 loci (16-18% nuclei)

Italics: new chromosome alterations in biopsy B compared to biopsy A

therapy. He developed lung metastasis 3 years after the initial diagnosis and died 1.5 year later.

2. Patient 2

This 13-year-old girl presented with right shoulder pain after a minor injury. Radiograph and MRI revealed an expansive tumour with cystic cavities involving the proximal humeral epiphysometaphysis with diaphyseal expansion (Figure 5).

Initial biopsies (biopsies A-B) taken at an interval of 8 months, were in favour of the diagnosis of a benign cystic lesion, possibly a solid variant of ABC. There were mononuclear stromal cells and multinuclear giant cells without cellular atypia (Figure 6 A and B).

The karyotype of the initial biopsy failed. FISH analysis did not show any rearrangement of the *USP6* / 17p13 locus but detected a high level amplification of the *MDM2* / 12q15 locus compared to the 3 copies of the centromere probe of chromosome 12, in 27% of the nuclei associated with an amplification of the chromosome 6 centromeric region. A minimal invasive surgical procedure with

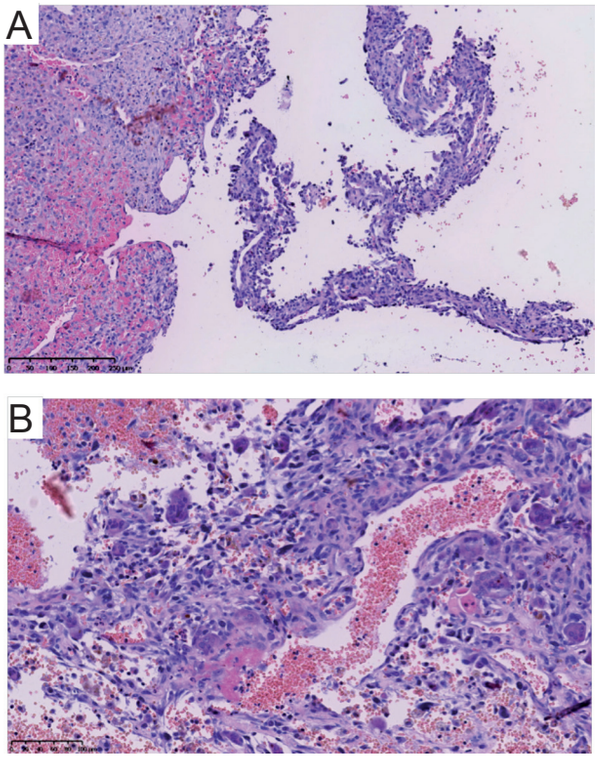

Fig. 4. — Patient 1. Cystic heamorragic areas and septa containing fibroblasts and giant cells. Numerous atypical cells with irregular and hyperchromatic nuclei (Hematoxylin and Eosin staining).

demineralised bone matrix and bone marrow was performed *(12)*. Four additional procedures of curettage, phenolisation and allografting were performed with the analysis of tissue fragments (biopsies C, D, E and F at 19, 30, 36 and 46 months, respectively; biopsies C and D not shown) (Table II). They showed atypical area leading to the diagnosis of malignancy, corresponding either to a malignant evolution of a previous ABC, either to a telangiectatic osteosarcoma (biopsies E and F : Figures 6C and 6D, respectively).

Karyotype performed on the second sample (biopsy B) identified complex chromosomal alterations in one pseudodiploid metaphase with a giant chromosome marker (Figure 7A). It evolved towards a more complex pseudotetraploid karyotype with clonal evolution, always containing one or two giant chromosome markers (biopsy F: 46 months later) (Figure 7B). FISH performed on biopsies B, C, D, E and F (8, 19, 30, 36 and 46 months later) detected the *MDM2* amplification (7-70% of interphase cells). FISH on metaphase cells showed that the *MDM2* amplification was located on the giant chromosome marker (Figure 7C). Immunodetection of MDM2 consecutive to the genetic results showed a high expression of the protein in fibroblastic cells in biopsies E and F (Figure 8).

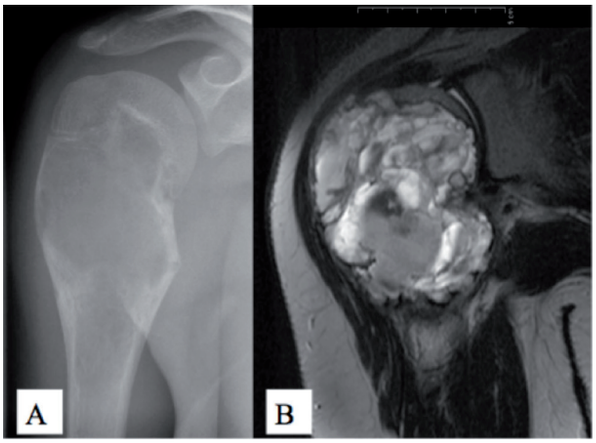

Fig. 5. — Patient 2. 1A: Radiographic image at presentation. 1B : T2-weighted MRI at the first recurrence (10 months later).

At the 6th recurrence (4 years and 10 months after the initial ABC discovery), the pathological aspects evolved in parallel with numerous atypical cells, TP53 protein expression and a high Ki67 proliferative index. The diagnosis of a high-grade osteosarcoma was then proposed (biopsy G). The giant marker with *MDM2* amplification was still detected in the setting of a non-complex hyperdiploid karyotype, either alone or in association with a subclonal trisomy 8 (Figure 7D). Treatment consisted of resection and reconstruction with inverted shoulder prosthesis. Adjuvant chemotherapy was performed (Cisplatin-adriamycin) and the patient remains in complete remission 10 years after the initial diagnosis.

DISCUSSION

Malignant aneurysmal bone cyst lesions can result from different tumoral processes. Cases of apparent malignant ABC transformation have been reported, in which review of the original histologi-

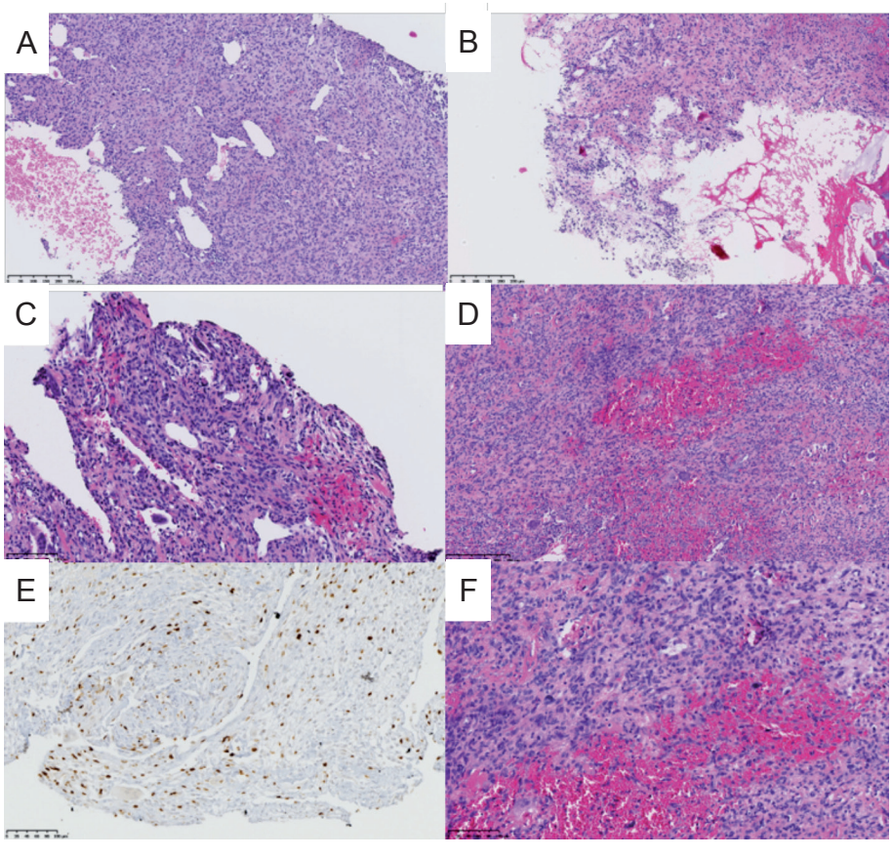

Fig. 6. — Patient 2. Histological aspects of initial biopsies A and B (6A, 6B) and of the latest biopsies : biopsy E at 36 months (6C) and biopsy F at 46 months showing haemorrhagic spaces containing focally atypical cells (6D and 6F at a higher magnification) (Hematoxylin and Eosin staining). 6E : Ki67 labelling performed on biopsy E showed positivity in atypical cells.

cal slides showed malignant features that were not initially diagnosed *(16)*. In this situation, the malignant tumour is usually a telangiectatic osteosarcoma discovered shortly after the ABC diagnosis *(7)*, such as the observation of patient 1. The genomic abnormalities were observed at first surgical specimen and confirmed the diagnosis of malignancy obtained with the curettage 3 months later.

In addition, rare cases of true spontaneous ABC transformation (sarcoma arising *de novo* in the same site) have been reported, into malignant fibrous histiocytoma, chondrosarcoma, osteoblastic, pleomorphic, or fibroblastic osteosarcoma *(4,6)* (Table III). In these cases, it is unlikely that the diagnosis of sarcoma was initially missed for several reasons. First, an extensive surgical curettage of the ABC had been performed; all of the removed tissue had been subjected to histological examination, without obvious signs of malignancy. Second, the patient had a long disease-free period (Table III) before the occurrence of the sarcoma.

By using a minimally invasive treatment for ABC, such as demineralised bone matrix implantation, the whole volume of the ABC is not curetted and the cystic tissue is deliberately left in place because it is considered to initiate the healing process *(12)*. In case of initially misdiagnosed osteosarcoma, rapid progression would be expected *(19,21)*, although one case of late progression has also been reported in 2005 by Saito *(13)*. The authors presented the clinical, radiographic, and pathologic features of a telangiectatic osteosarcoma in a 20-year-old man, initially diagnosed and managed as a primary ABC. The first local recurrence was recognized 4 years

and 8 months after the first operation and was managed by curettage and bone grafting with internal fixation. The second local recurrence was observed 8 months after the second surgery and telangiectatic osteosarcoma was diagnosed. The patient underwent wide resection of the tumour with prosthetic replacement of the right proximal femur. The pathological features were compatible with a high-grade telangiectatic osteosarcoma. The retrospective review of the histologic section of the primary lesion showed features similar to ABC except for a few abnormal cells without mitosis in the tissue of cystic wall *(13)*. In our Patient 2, the time evolution appeared similar. No *USP6* rearrangement was present and could thus not confirm the diagnosis of a truly primary ABC. Moreover, genomic imbalances were initially detected (by FISH on the first biopsy, by both karyotype and FISH on the second biopsy) arguing for a secondary ABC to a pre-existing malignant proliferation, despite a histological aspect of benign cystic lesion.

The diagnosis retained for patient 1 is a telangiectatic osteosarcoma. It is a rare variant of osteosarcoma, accounting for less than 3% of all osteosarcomas. Radiographically, these tumours appear as lytic destructive lesions and occur in the metaphyseal region of long tubular bones. The location and x-ray appearance of telangiectatic osteosarcomas are reminiscent of an aneurysmal bone cyst and the differential diagnosis between these two entities can be microscopically quite challenging. Telangiectatic osteosarcoma shows dilated blood-filled spaces lined or traversed by septa *(1,31)*.

Three main histological components in the cystic walls are usually present in a typical ABC *(13)*: a cellular, a fibrillar and an osteoid component, the

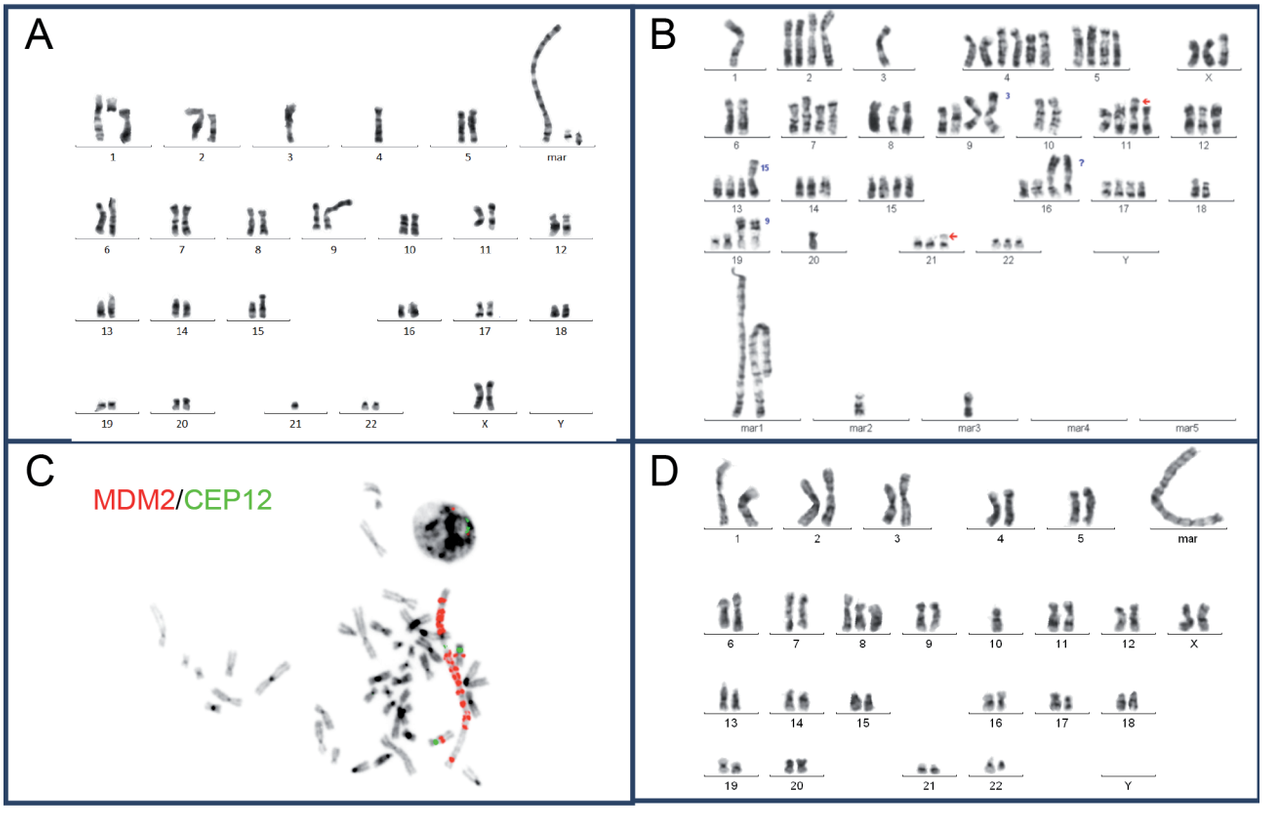

Fig. 7. — Patient 2. Karyograms performed on G-banded chromosomes at 8 months (7A : Biopsy B), 46 months (7B : Biopsy F) and 56 months (7D : Biopsy G). 7C : FISH analysis performed on fixed nuclei and metaphase cells of the biopsy F with the MDM2/CEP12 probes.

Table II. — Genetic abnormalities and evolution in Patient 2

	Biopsy A	Biopsy B (8 m)	Biopsy C (19 m)	Biopsy D (30 m)	Biopsy E (36 m)	Biopsy F (46 months)	Biopsy G (58 months)
Karyotype	Failure	46,XX,del(2)(p13p25),-3,-4, der(9)t(3;9)(q21;p23~24), der(11)t(9;11)(p13;p12), **+mar1**,+2mars[1]/46,XX[5]	Failure	Failure	Failure	36~98,XX,-3,+4[4],+add(4)(q21)[3], add(6)(q?21)[3],?dic(7;7)(q32;q11.2)[3], der(9)t(3;9)(q21;p23~24),dic(4;11)(q21;p15)[?], der(14;21)(q10;q10)[2],del(17)(p11.2)[1?], add(19)(p13.3),add(19)(p13.3)[3],**+1~2mar1**, +1~3mars[cp11]/46,XX[3]	47,XX,**+mar1**[5]/48,idem,+8[4]/46,XX[10]
Interphase FISH							
MDM2/12q15 amplification	27%	70%	27%	7%	63%	30%	57%
CDKN2A/9p21 deletion	N	ND	N	N	45%	35%	N
CEP6 amplification (copy number)	18% (6-7)	ND	N	F	77% (5-8)	N	75% (4-8)

Mar1: giant marker; ND: not done; F: failure; N: Normal; m: month

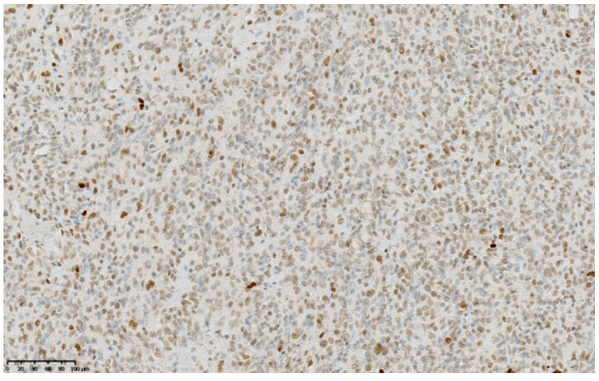

Fig. 8. — Patient 2. MDM2 immunostaining on histological sample showing a heterogeneous positivity within fibroblastic cells.

latter being not always present. The cellular component in the septa includes stromal cells, which are mononuclear, with a round or oval nucleus, and giant cells, easily detected as they contain several nuclei. Cystic spaces are not delimited with atypical cells. The fibrillar component is composed of fibroblasts embedded into a more collagenous extracellular matrix. Dense collagen is occasionally present, with an abundance of enlarged thick collagenous fibres, which was present in the first biopsy of the second observation. The osteoid component corresponds in ABC to reparative organic bone matrix deposited by osteoblasts, without atypia. The histological presentation of a telangiectatic osteosarcoma shows the presence of atypical cells at the edge of the septa and atypical cells can be seen isolated in the blood filled spaces. Mitotic activity is often present. Production of osteoid or immature bone by the malignant cells can be absent.

Genomic aberrations in conventional high-grade osteosarcomas are usually complex *(27)*. The genetics of telangiectatic osteosarcoma is not well described but is usually less complex than the genetics of conventional osteosarcomas *(29)*. Patient 1 exhibited an unexpected complex karyotype from the beginning confirming the malignancy of the lesion and the increased complexity during the follow-up was in favour a high grade of the telangiectatic sarcoma.

A *MDM2* amplification was observed in all analysed samples of patient 2, in a wide range of proportions [7-70%] and associated with variable subclonal chromosomal aberrations. Overexpression of MDM2 was confirmed at the protein level (Figure 8). *MDM2* amplification is reported as a frequent genomic event low-grade osteosarcomas (parosteal osteosarcoma and low-grade central osteosarcoma), but not in telegiectatic osteosarcoma. It is also reported in some high-grade osteosarcomas which have been demonstrated to be dedifferentiated central low-grade osteosarcomas *(16)*. These low-grade osteosarcomas are usually associated with a good prognosis, as for patient 2 who is in complete remission with a follow-up of 10 years *(14)*.

In the first case, the diagnosis of osteosarcoma was not clearly made at the initial biopsy probably due to sampling heterogeneity. Atypical cells were not numerous enough to ascertain this diagnosis. The second observation raised the question whether it corresponds to a low-grade form of osteosarcoma or to a slow malignant transformation of an ABC. The two initial biopsies showed no obvious sign of malignancy in the whole removed tissue and were in favour of a benign ABC, with subsequent biopsies showing more atypical cells. However, the fact that in both patients (i) no *USP6* rearrangement characteristic of primary ABC was detected and (ii) complex chromosomal aberrations were initially present, similar to those detected at the diagnosis of osteosarcomas, and clonally evolved during the follow-up towards a higher grade pattern, is in favour of the initial presence of a small proportion of malignant sarcoma cells having a growth advantage.

CONCLUSION

When imaging suggests the diagnosis of ABC, a biopsy is mandatory, including genomic analysis. In case of non-clearly proved ABC by the initial biopsy, an extensive curettage should be performed with pathological examination of all of the removed tissue. Genomic studies (at least FISH, but if possible conventional or molecular karyotyping) on biopsy and curettage may be useful to detect genomic aberrations characteristic of a primary ABC (*USP6* rearrangement) or arguing for a malignant proliferation complex structural and numerical chromosomal aberrations.

Table III. —Malignant transformation of ABC (review of literature)

Authors/Year	Patient sex/ age (years)	ABC location	Initial treatment	Recurrence	Delay before transformation (years)	Malignant transformation
Kyriakos et al. 1991	F/11	Distal tibia	CBG	3	4	Telangiectasic osteosarcoma
Wuisman et al. 1993	M/19	Distal femur	CBG	0	4	Surface osteosarcoma
Barnhart et al. 2002	Dog/5	Distal ulna	CBG	0	2.5	Chondrosarcoma
Anract et al. 2002	M/28	Distal femur	CBG+ osteosynthesis	0	12	Malignant fibrous histiocytoma
Hsu et al. 2005	M/19	Proximal tibia	CBG+ phenol	0	6	Osteosarcoma
Brindley et al. 2005	M/13	Proximal humerus	CBG	0	5.5	Telangiectasic osteosarcoma
	M/36	Proximal tibia	CBG	0	12	Fibroblastic osteosarcoma
Saito et al. 2005	M/20	Proximal femur	CBG	2	5.5	Telangiectasic osteosarcoma
Mei et al. 2009	M/40	Proximal humerus	CBG	3	10	Malignant fibrous histiocytoma

F=female; M=male; CBG=curettage and bone grafting

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