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ORIGINAL PAPER

Adamantinoma of Long Bones: A Long-term Follow-up Study of 11 Cases

Miklós Szendrői · Imre Antal · Gabriella Arató

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Abstract The aim of this study was to evaluate the clinicopathological features and prognostic significances of 11 histologically proven adamantinoma cases based on an average 12,7 year long follow-up. The male: female ratio was 8:3, aged between 4 and 80 years (mean 29,3 years). The initial diagnosis at referral was other than adamantinoma in six patients (fibrous dysplasia, carcinoma metastasis, osteofibrous dysplasia, bone cyst, non-ossifying fibroma), referring to the differential diagnostic problems. All tumors were localized to the mid part of tibia. By histological evaluation, basaloid pattern on a background of fibrotic stroma dominated in six patients, while spindle and squamous features were less frequently seen. All adamantinomas were positive for cytokeratins often in coexpression with vimentin. No correlation was experienced between histology and clinical outcome. Intralesional curettage (2 pts) was followed by recurrence of the tumor. Wide resection was performed in eight patients with reconstruction using intercalary fibula autografts in seven patients. Reconstruction-related complications occurred in two third of the cases, all of them could however be controlled by repeated surgery. Six recurrences occurred in four patients, two of these recurrences occurred 20 and 16 years after initial surgery. One patient died 9 years after recognition of the tumor of pulmonary metastases. Adamantinoma of the long bones is a low grade malignant tumor, which clinical outcome is difficult to predict based on histology or surgical stage of the tumor. Wide surgical margin, e.g. resection the tumor reduces the rate of recurrence. This study underlines that recurrences do occur even decades after recognition the tumor, therefore a life-long follow-up of the patient is necessary.

Keywords Adamantinoma · Long bones · Histology · Surgery

M. Szendrői (✉) · I. Antal
Department of Orthopedics, Semmelweis University,
27 Karolina Rd., Budapest 1113, Hungary
e-mail: szenmik@orto.sote.hu

G. Arató
1st Department of Pathology and Experimental Cancer Research,
Semmelweis University,
Budapest, Hungary

Introduction

Adamantinoma of the long tubular bones is a rare primary malignant bone tumor with disputed histogenesis, first described and named by Fischer in 1913 [1] because of its close morphological resemblance to adamantinoma of the jaws. It accounts for 0,33% of all malignant bone tumors in the material of Dahlin [2] and 0,48% in that of Schajowicz [3]. Until 1994, Moon [4] collected 260 well documented cases from the world literature, mostly in the form of case reports. The number of cases which have been published in other series rarely exceeds ten-twenty [5–8] with the exception of some multicenter studies [9, 10]. In 85–90% of cases the tumor is localized to the tibia, firstly on the median third of the diaphysis, nonetheless it has also been described in the fibula, ulna, humerus, femur and the short bones of the feet [9–13].

Eleven histologically proven adamantinomas were treated between 1965 and 2003 and are recorded in the files of the Bone Tumor Registry of the Semmelweis University. This article reviews the clinical, radiological and pathologic features of these tumors as well as their prognostic significances and outcomes based on an average 12,7 years long follow-up.

Material and Methods

A total of 11 adamantinoma cases have been treated during the past 40 years in the bone tumor centre of a single institution. Radiographs and clinical data concerning demographics, location and size of the tumor, duration of the symptoms, type of biopsy, initial diagnoses, type of operative treatment, complications, prevalence of local recurrence, metastasis and survival were available for all patients.

CT or MRI were performed in six patients for evaluating the intraosseal extension of the tumor. The histological slides were reevaluated, immunohistochemistry using PAP standard procedures for cytokeratin, vimentin and Factor VIII (all Dako antibodies) were performed in nine cases. In two of the cases electronmicroscopic studies were also performed. Following surgical intervention the patients were regularly controlled, even in case of no complaints.

Results

Clinical data of the eleven patients with adamantinoma are summarized in Table 1. Eight of the reported patients were females and three males aged between 4 and 80 years (mean 29,3 years). In all cases the tumor was found to be localized on the tibia, and open surgical biopsies were performed in every case prior to the definitive surgical intervention. The duration of symptoms before treatment varied between 6 months and 2 years. In one patient the tumor was discovered accidentally on x-ray examinations because of trauma, eight patients complained of pain,

Table 1 Detailed clinical datas of patient's cohort

Pts.	Sex	Age at diagnosis	Localization /size (cm)	Histology	Surgery	Recurrence	Complication	Follow-up (years)	Outcome
Case 1.	♀	21	tibia 6×26	basaloid	1. Resection + fibula pro tibia 2. Amputation	1×(2 yrs later)	none	9	Died on pulmonary metastases
Case 2.	♀	40	tibia 4×3	spindle cell recid: squamous cell	1. Resection + fibula pro tibia 2. Reresection 3. Curettage + cement + plate	2×(19 and 25 yrs later)	Infection	40	Died on other disease
Case 3.	♀	12	tibia 18×4	basaloid	Resection + fibula pro tibia (Huntington)	∅	∅	19	NED
Case 4.	♀	19	tibia 14×3	squamous	1. Curettage + spongiosa plasty 2. Resectio, fibula transp. + plate	1×(7 yrs later)	Fracture of graft	22	NED
Case 5.	♂	4	tibia 10×2	spindle	1. Curettage 2. Resectio + fibula transposition	1×(5 yrs later)	∅	13	NED
Case 6.	♂	12	tibia 14×2	spindle	Resection + fibula pro tibia	∅	Fracture of graft	12	NED
Case 7.	♂	54	tibia 20×3	squamous	Resection + fibula transpos, fibula pro tibia	∅	Fracture of graft, pseudoarthrosis, fracture of plate, infection	8	NED
Case 8.	♂	28	tibia 22×3	basaloid	Resection + fibula transposition, fibula pro tibia	∅	Pseudoarthrosis	7	NED
Case 9.	♀	68	tibia 9×3	basolaid	Resection, tumor endoprothesis	∅	Infection	4	NED + infection
Case 10.	♀	14	tibia 15×3	basaloid	Resection, fibula transposition + fibula pro tibia	∅	Fracture of graft	3	NED
Case 11.	♀	80	tibia 5×3	basaloid	Biopsy only	∅	∅	3	AWD

Comments: NED: No evidence of disease, AWD: alive with disease

swellings and/or palpable firm protrusion of the tibia, pathological fracture was the first symptom in two patients. The initial diagnoses at referral of the patients included fibrous dysplasia (2 pts), carcinoma metastasis (1 pt), osteofibrous dysplasia, bone cyst and non-ossifying fibroma (1–1 pt) apart from adamantinoma (5 pts).

Imaging Techniques

Radiographs revealed in most patient a multicystic, lytic, eccentric lesion in the mid-shaft of the tibia which localized to the cortex, affected, however, also the medullary canal (Fig. 1.). Exceptionally (1 pt), the tumor appeared as a single lytic mass without periosteal reaction, similar to bone metastases. The septa which divide the cysts, surrounding sclerosis and the thinned, partly disrupted cortical bone were best evaluated by CT (Fig. 2).

Pathology

The tumor size ranged from a few centimeters to a maximum 24 cm (mean 14,4 cm). The surface of the resected specimen was either firm or friable (Fig. 3.). On microscopic examination, all tumors contained epithelial elements surrounded by fibrous stroma. Frequently, two patterns occurred simultaneously. In most cases (6 pts) large clusters of basaloid epithel cells were present in the fibrous tissue (Fig. 4), in others squamous cells with focal keratinization (Fig. 5.) or spindle cell-like appearance of epithelial cells (Fig. 6) (2, and 3 pts, respectively) dominated the histological picture. In our material no tubular formation of the epithel cells could be demonstrated. The stroma surrounding the epithelial islands often showed different morphology. In some the fibrous tissue was loose myxoid, in others hyalinized and sclerotic. We did not find any differentiated or osteofibrous dysplasia-like morphology in any of our tumors, where osteoblast lined bony trabeculae appear in close relationship with the epithelial islands. By immunohistochemistry, the epithelial cells stained positively for cytokeratin, negatively for Factor VIII, while the stromal fibrous tissue showed positivity for vimentin.

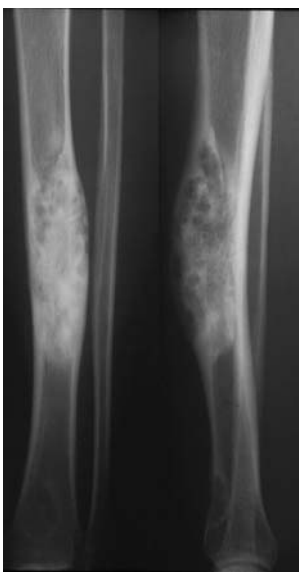

Fig. 1 Multicystic eccentric lesion in the mid-part of the tibia surrounded by sclerotic rims. (Radiographs, anterio-posterior and lateral views

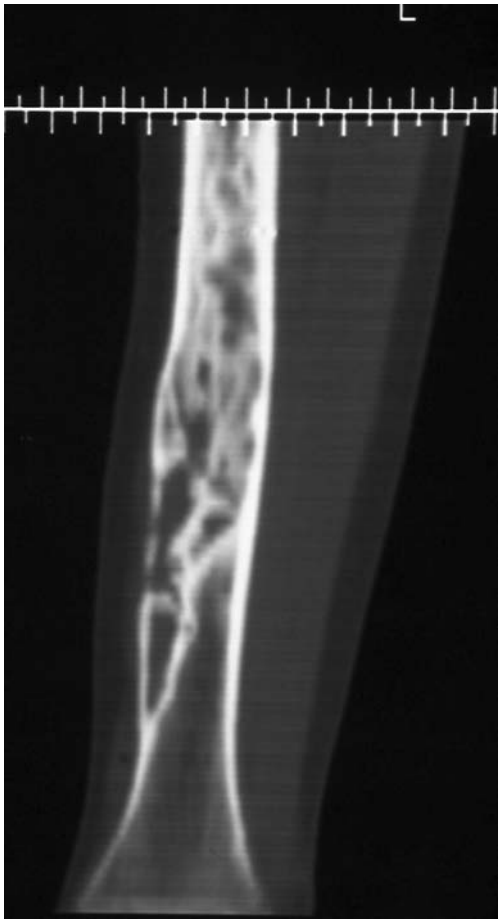

Fig. 2 The cortical destruction is clear visible on the reconstructive CT picture

Treatment and Follow-up

All 11 patients were treated by surgery without other adjuvant therapy (Table 1.). In three patients where the tumor was first misdiagnosed as fibrous dysplasia and bone cyst, a curettage and bone grafting was first performed. One patient (see Table 1. case 4 and Case reports, case 2) experienced pain 7 years later, but the size of the lesion did not change. The other patient (Table 1. Case 5) who was curetted, grafted and plated for a pathologic fracture of the initial "cyst", learned pain 5 years later and to that time the size of the tumor also increased significantly. Both of them were reoperated and the tumor resected widely in normal tissue. Non of them had developed further recurrences and

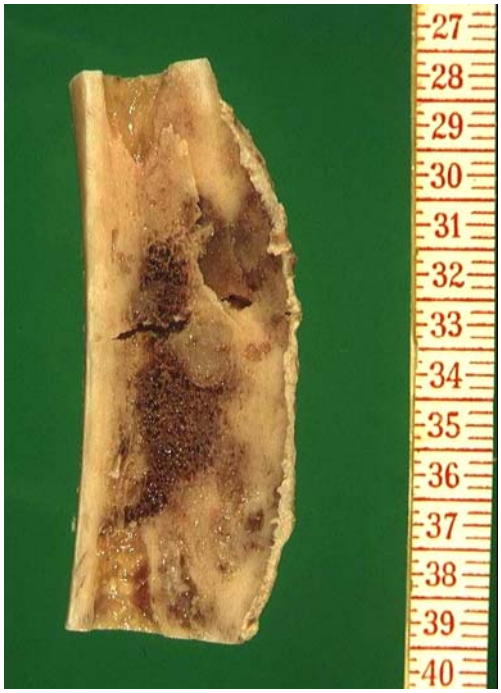

Fig. 3 The cut surface of the removed specimen: the defects are filled with yellowish-brownish firm fibrous tissue

were free of tumor at the latest follow-up (22 and 13 years after recognition of the tumor).

Seven patients were treated by resection following the biopsy. Reconstruction was performed by intercalary autografts using the ipsilateral fibula with (6 pts) or without (3 pts) the contralateral one. In these latter three cases the so called Huntington procedure [14] was performed: the ipsilateral fibula was used alone and set into the proximal and distal tibia stumps in two steps. The graft was fixed by Ilizarov apparatus. No homografts were used. In one patient the defect was reconstructed by intercalary tumor endoprosthesis (Table 1. Case 9) and in another 80 year-old women biopsy and curettage was only performed because of her general condition, she is still alive with her tumor.

Six recurrences occurred in four patients: four recurrences following curettage and two after resection. Three patients could be cured by two resections and one recurettage. The fourth patient with recurrence was treated initially by above-knee amputation (Table 1, Case 1), she died, however, on lung metastases, which developed 7 years following the amputation!

Major complications occurred in eight of the 11 patients. There were fracture of the graft (five cases), infections (three cases), fracture of the plate (one case). In all but one patient the complications could be solved by one or repeated surgical intervention and all limbs could be speared.

Case Report

Case 1: (See also Table 1, case 2) A 40 years old female patient was first examined in 1957 due to left leg pain experienced over 2 years. Radiograph showed lytic de-

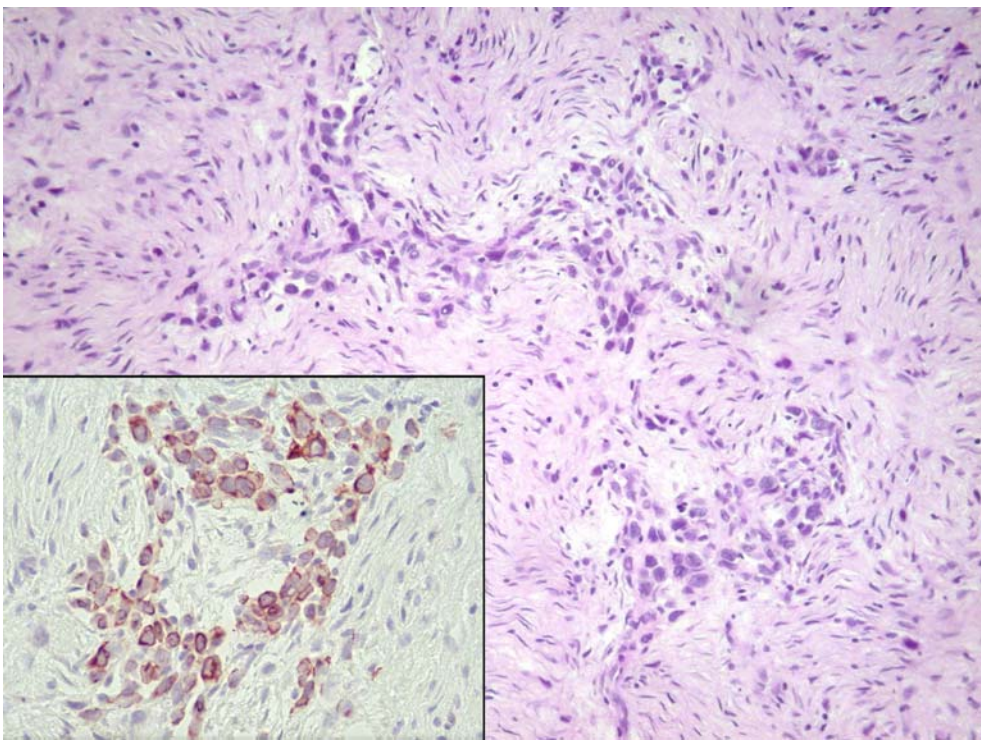

Fig. 4 Adamantinoma, basaloid cell subtype. Insert: Immunohistochemistric staining for cytokeratin

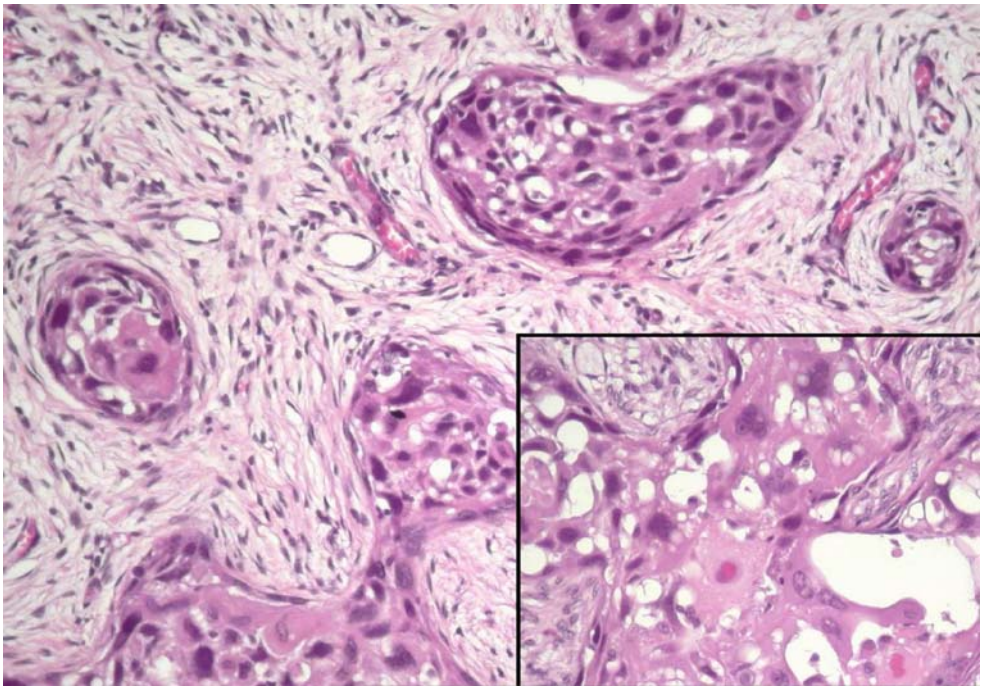

Fig. 5 Adamantinoma, squamous cell type. Insert: Squamous part, higher magnification

struction (Fig. 7) with sclerotic margin on the edge of the median-distal third of the tibia, involving the whole width of the bone. The lesion was found to be intersected by septa comprised of bone trabeculae. The histological study of the biopsy material demonstrated spindle-squamous cell type of adamantinoma. The tumor was cut out widely by means of a 13 cm long segment resection of the tibia. The defect was substituted with ipsilateral fibula. Infection arose as a late complication, therefore the wound was reopened, homologous bone implantation was performed and several sequestrotomies took place. Finally the inflammation healed, however, 20 years (!) after the initial surgical intervention tumor recurrence was manifest in the distal tibia stump (Fig. 8). Accordingly, repeated resection was carried out, which did not influence the life quality of the patient. Her knee function was intact, the tibiotalar joint exhibited moderately limited dorsal extension. Sixteen years later the patient was referred to us again (in 1993) with an 8×5×4 cm sized local recurrence (Fig. 9) in the median third of the transposed fibula, verified by both CT scan and histological examination. The radiographs and MR imaging

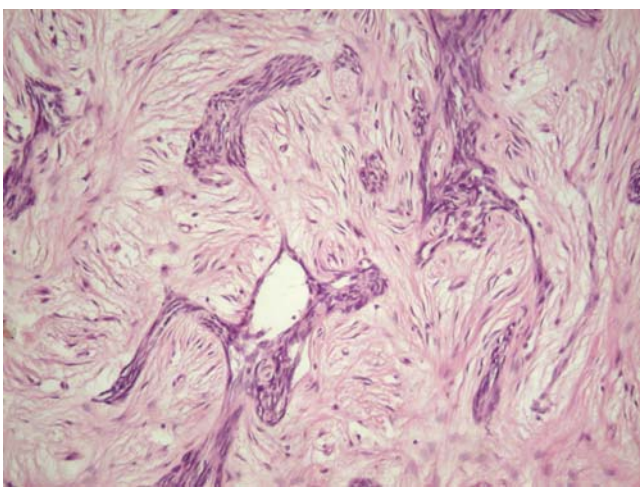

Fig. 6 Adamantinoma, spindle cell-like appearance

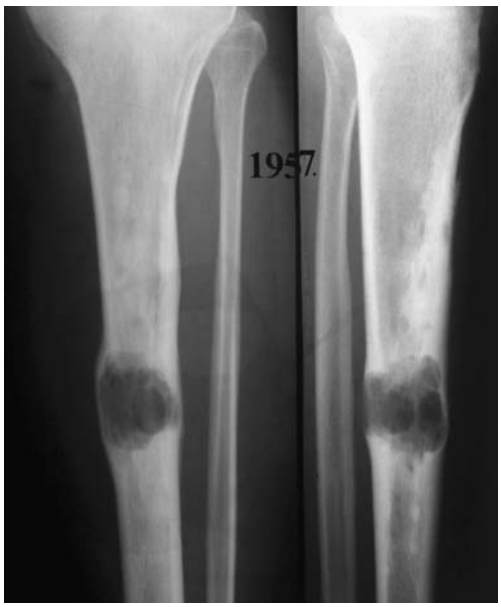

Fig. 7 See Table 1, case 2. Two-directional radiographs of the left tibia taken in 1957, cystic-lytic alteration can be seen in the diaphysis

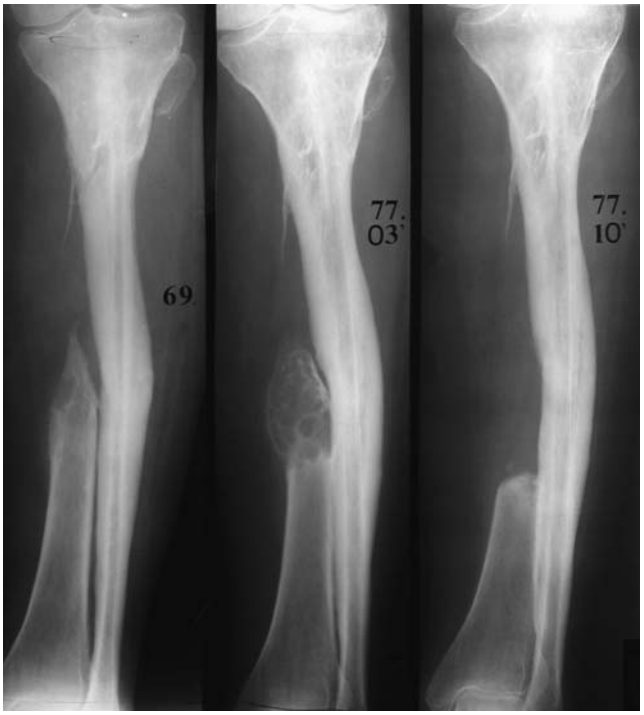

Fig. 8 12 years after transposition of ipsilateral fibula following resection of the tibia (**a**). Local recurrence in the distal tibia stump 20 years later (**b**). Resection of the recurrence wide in normal tissue (**c**)

showed the recurring tumor originating from the antero-medial side of the fibula and surrounded by thin bony shell. Considering the age of the patient - 76 years - as well as her current general condition, an intralesional resection and curettage of the defect was performed, then the fibula was strengthened by plate and bone cement (Fig. 9). The patient was able to walk until her death which occurred 2 years later at age 78, and was caused by cardiac failure.

Discussion

In respect to the *histogenesis* of adamantinoma, the electron microscopic, the immune histochemical studies and cyto-genetic analyses of the past decade have presented significant results; ruling out angioblastic [7] and synovial cell origin [15] and proving the epithelial cell origin of the tumor [16–19]. Based on its histological appearance, Dorfman and Czerniak [20] and others [17, 21] described various histological sybtypes/pattern in adamantinomas, like spindle cell, basaloid, tubular (glandular/vascular), squamous and osteofibrous dysplasia-like forms.

Several authors point to the close relationship between the conventional adamantinoma, the so called differentiated adamantinoma (osteofibrous dysplasia-like adamantinoma) and osteofibrous dysplasia, which can cause serious differential diagnostic problems due to their similar radiological and histological appearances and typical location in the tibia. Cytokeratin subset immunohistochemical stains and cytogenetic studies performed in recent years suggest a common histogenesis for these three entities [13, 18, 22–24].

The clinical relevance is the different behavior of these entities: while the osteofibrous dysplasia is a benign process and active surgical treatment is disputed, the osteofibrous dysplasia-like adamantinoma can regress spontaneously but it is also regarded as precursor of a conventional adamantinoma [22, 25]. In case of osteofibrous dysplasia, histology reveals bony trabeculae with active osteoblasts rim, but the immunohistochemical study usually demonstrates single or strands of keratin positive cells in the fibrous stroma. These strands are more expressed in osteofibrous dysplasia-like adamantinoma.

Most of the *demographic data* of our adamantinoma patients are in accordance with the data of publications reporting on higher number of cases [9, 26]. In our material too, the tumor appeared mostly in young adulthood, the gender distribution was found, however, to the favor of females. In this material, the tumor was localized exclusively to the median third of the tibia, in one patient it has already involved two thirds of the bone at the time of referral.

In accordance with the literary data [7, 11, 27], the leading *symptoms* are slight pain, swelling, deformation of the tibia for a long period. This explains the long duration of the symptoms, 42 months (mean) in our material, however, Qureshi et al [9] reported on 62 months at 60

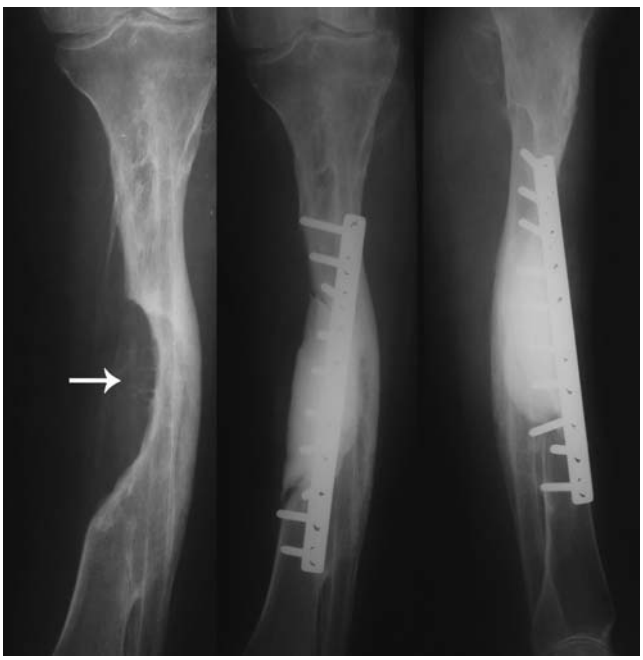

Fig. 9 Second recurrence in the area of the fibula 36 years later (*arrow, a*). Following curettage, the lesion was filled with bone cement, strengthened with plate (b and c)

patients. Pathologic fracture as first symptom can reach 20%. [9, 28].

The location *and radiological appearance* of the tumor is characteristic in most of the cases. Adamantinoma appears as an eccentric area of destruction which is usually located in the anterior part of the diaphysis of the tibia. This part of the bone is slightly expanded, deformed, the tumor has a cystic or more often a multiloculated appearance with more or less sclerotic rim. The cortical bone is thinned, in other cases partially or extensively destroyed without any periosteal reaction [29].

CT is useful for evaluating the cortical destruction and demonstrate the sclerotic bony septa separating the cysts. The different tumor foci appear with high signal intensity on either T2 weightened images or with T1 weightened contrast enhanced images by MRI. Neither the CT nor the MRI is able to differentiate, however, between the differentiated and conventional forms of adamantinoma [30]. In the minority of the cases the adamantinoma appears as an intramedullary solitary lobulated focus resembling on bone metastasis [13].

Although the *histological examination* can also be difficult, the only reliable diagnostic criterion for adamantinoma is its typical histological appearance with clusters or nests of epithelial cells surrounded by spindle-celled fibrous tissue. The epithelial cells have mostly basaloid or spindle-shaped character. In our series we have only occasionally seen squamous cells rich in eosinophylic plasma and no tubular pattern. Sometime the stroma can contain areas of osteofibrous dysplasia or fibrous dysplasia-like fields. This can mislead the pathologist like in two cases in our material. Because isolated cytokeratin-positive cells can be found in these entities [26], the immunohistochemical result alone should be accepted with caution. Similarly to the literary data [16–18, 26], all of our cases showed cytokeratin positivity and factor VIII. negativity. The number of patients in our series is small, we agree, however, with many authors [9, 26] that no morphological parameters of the histology correlate with the clinical outcome of the adamantinoma.

Adamantinoma is known to be resistant for both radio- and chemotherapy [8, 13]. Opinions also vary in the literature in respect to optimal *surgical intervention*. Curettage and spongiosa plasty are not recommended because of the frequent recurrences [10, 11]. In the past, several authors [7, 31] advised amputation, emphasizing the multicentric nature of adamantinoma. Extensive resection in case of primary tumor, and amputation upon recurrence are suggested by Gebhardt et al. [32] and others [10, 11]. Deijkers et al. [33] reported good results after mere hemicortical resection. According to our experiences, wide segment resection gives good results not only in cases of primary adamantinoma, but in recurrences as well. Reconstruction techniques after *en bloc* resection of the tumor include the use of allografts, vascularized and non-vascularized autografts, distraction osteogenesis and segmental tumor endoprostheses [13]. According to our experiences, for replacing the median third of the tibia, transposition of the own ipsilateral and/or contralateral fibula as intercalary graft, appears to be the most successful method. As in our series (eight of 11 patients), the frequency of complications reported in the literature are still unacceptably high. Ortiz-Cruz et al [13, 34] observed infection, fracture, and nonunion with rates as high as 12%, 17% and 29% out of 104 patients, respectively. In our material at least, we could control these by further surgical interventions and no amputation was necessary for complications.

The *outcome* of the disease is difficult to predict. Mortality rates between 6% and 18% are reported and 12–29% of the tumors metastasize to the lung or lymph nodes [9–11, 13]. Negative prognostic factors for recurrences are young age, male sex, history of pain, aggressive growth [10, 11], while others did not found correlation between actual stage of the tumor or its histological subtype and survival [9, 26]. The recurrence rate is reported in the literature as high as 30– 35% [8, 26], which can significantly be reduced by an initial wide surgical resection of the tumor. As our study demonstrated, insufficient intralesional curettage with spongiosa plasty leads to local recurrence in nearly every case [9–11, 13, 16, 35].

In accordance with other authors [10, 13, 26], our long-term follow-up study clearly demonstrated that recurrences of adamantinoma do occur even after 10–20 years following the recognition of the tumor, therefore a life-long follow-up of the patient is necessary.

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