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# Adamantinoma, osteofibrous dysplasia and differentiated adamantinoma

Received: 30 July 2002 Revised: 18 December 2002 Accepted: 20 December 2002 Published online: 22 March 2003 © ISS 2003

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# Introduction

#### Definitions

Adamantinoma is a low-grade malignant epithelial neoplasm of uncertain embryogenesis with a strong predilection for involvement of the mid-shaft of the tibia with or without involvement of the fibula. A stromal component with a fibrous dysplasia-like appearance is present in many cases.

*Osteofibrous dysplasia* (ossifying fibroma) is a benign deformity-inducing fibro-osseous lesion occurring in childhood with a strong predilection for involvement of the mid-shaft of the tibia with or without involvement of the fibula. Immunohistochemical studies demonstrate single or strands of keratin-positive cells in a majority of cases.

Abstract For just over 100 years, adamantinoma has been recognized as a primary bone tumor with epithelial characteristics and predominantly involving the tibia. Osteofibrous dysplasia is a fibro-osseous lesion also predominantly confined to the tibia with radiologic features similar to those of adamantinoma. This lesion has been shown by immunohistochemical studies to frequently contain cytokeratin-positive epithelial cells. More recently, a third group of cases with clinical and radiologic features similar to those of osteofibrous dysplasia have demonstrated more overt strands of epithelial cells within a fibro-osseous background and have been categorized as "differentiated", "regressive", "juvenile intracortical" or "osteofibrous dysplasia-like" adamantinoma. Cytokeratin subset immunohistochemical stains and cytogenetic studies performed in recent years suggest a common histogenesis for these three entities. This article reviews the clinical, radiologic and pathologic features of these entities as well as their prognostic significance. It also reviews the results of the immunohistochemical and cytogenetic studies which establish a common histogenetic relationship.

Keywords Adamantinoma · Osteofibrous dysplasia · Differentiated adamantinoma · Regressing adamantinoma · Juvenile intracortical adamantinoma · Osteofibrous dysplasia-like adamantinoma

*Differentiated adamantinoma* (regressing, juvenile intracortical, osteofibrous dysplasia-like adamantinoma) is a deformity-inducing fibro-osseous lesion occurring in childhood with a strong predilection for involvement of the mid-shaft of the tibia with or without involvement of the fibula. Strands of epithelial cells are present within the stroma and readily identifiable in routine hematoxylin and eosin stained sections.

As can be inferred from the above definitions, a probable histogenetic relationship exists between the three entities. Indeed, the only apparent difference between osteofibrous dysplasia (OFD) and differentiated adamantinoma is the presence of an epithelial component readily identifiable on routine hematoxylin and eosin stained sections and their identification only by immunohistochemical means in about 80% of osteofibrous dysplasia lesions. Cytogenetic studies have also demonstrated similar alterations in the two lesions. It would thus appear that OFD and differentiated adamantinoma represent a single pathogenetic process and that they exhibit only a quantitative difference in their epithelial content. There are only few isolated case reports of malignant behavior relating to either of these entities but the number of cases and length of follow-up is limited. Classic adamantinoma occurs over a wider age spectrum and behaves in a malignant fashion. However, some cases have a fibro-osseous component resembling OFD and even exhibit similar cytogenetic alterations also suggesting a histogenetic identity between adamantinoma, OFD and differentiated adamantinoma.

# Adamantinoma

#### History

The first case of a primary bone tumor with epithelial characteristics is attributed to Maier [1] in 1900. In 1913, Fischer [2] provided the first detailed description and named the lesion "primary adamantinoma of the tibia" because of its striking histologic resemblance to the jaw adamantinoma (ameloblastoma). In 1951, Schulenberg [3] suggested a unifying histogenetic concept for the gnathic ameloblastoma, pituitary adamantinoma and adamantinomas of the appendicular skeleton.

#### Incidence

Adamantinomas constitute only 0.1–0.5% of all malignant bone tumors [4]. There is a wide age spectrum but young adults are most frequently affected. The mean age at presentation is about 30 years with only about 3% of patients younger than 10 years. Some series report a slight male preponderance. A striking feature of this neoplasm is its predilection for involvement of the mid-shaft of the tibia, which accounts for about 85% of all cases. Synchronous involvement of tibia and fibula occurs in about 10% of all cases. Isolated case reports document involvement of ulna, femur, humerus, radius, rib, ischium, tarsal, metatarsal and capitate [5, 6]. There are also reports of extraskeletal pretibial soft tissue involvement [7, 8].

#### Clinical features

Swelling with or without pain is the usual presenting feature. The lesion may cause a pathologic fracture. A history of significant trauma has been noted in about 60% of 200 cases reviewed by Moon and Mori [5]. There have been two case reports of paraneoplastic hypercalce-



**Fig. 1** Adamantinoma. Osteolytic, eccentric, expansile lesion involving the cortex and medulla of the proximal third of the diaphysis of the tibia. Note the multiple radiolucencies surrounded by ring-shaped densities producing the characteristic "soap-bubble" appearance

mia associated with tibial adamantinoma and pulmonary metastasis [9, 10].

#### Radiologic features

The typical mid-diaphyseal tibial lesion is osteolytic, eccentric, expansile and medullary in location. It is comprised of multifocal radiolucencies surrounded by ringshaped densities producing the characteristic "soap-bubble" appearance (Figs. 1, 2, 3). The entire lesion may have a prominent sclerotic margin indicative of slow growth. The lesion is longitudinally oriented with an average length in one series of 11.0 cm [11]. The expansile element tends to involve the anterior tibial surface and the lesion may produce a bowing deformity of the tibia. The periosteal reaction is variable from minimal to prominent. In about 15% of cases, there is extracortical extension into soft tissues. Additional CT and MRI studies are of limited diagnostic value but are helpful in assessing the extent and invasiveness of the lesion (Figs. 2B, 3B) [12].

<image>

**Fig. 2** A Adamantinoma. This osteolytic lesion is primarily cortical-based and has a well-defined sclerotic margin on its inner aspect. **B** Adamantinoma. The corresponding CT scan shows complete cortical disruption

#### Histogenesis

Immunohistochemical and ultrastructural studies have clearly established the neoplasm to be of epithelial derivation [13]. The origin of these epithelial cells remains an enigma. To date there have been no new theories to supplement those proposed by Fischer [2] in 1913 and Ryrie [14] in 1932. Fischer believed that the tumor originates from misplaced embryonic rests, whereas Ryrie suggested an origin from traumatic implantation of fetal basal cells resulting from the extreme flexed position of the fetus in utero and the intimate contact of the fetal



Fig. 3 A. Adamantinoma. Osteolytic lesion with less well defined margins involving both cortex and medulla. **B** Adamantinoma. CT scan showing cortical disruption, involvement of the medullary canal and soft tissue extension. (Courtesy of Dr. Howard Dorfman, Bronx, N.Y.)

head with the anterior tibial surface. The frequent history of significant trauma is of interest in regard to the possible traumatic implantation theory. However, this theory would fail to explain the occurrence of the lesion in bones other than the tibia.

#### Microscopic features

The neoplasm is comprised of epithelial cells surrounded by a fibrous stroma. In some cases the stroma contains woven bone spicules rimmed by osteoblasts resembling



**Fig. 4** Adamantinoma. Tubular variant. Anastomosing and branching cords of epithelial cells with central gland-like spaces resulting from loss of cellular cohesion. (Courtesy of Dr. Howard Dorfman, Bronx, N.Y.)



**Fig. 5** Adamantinoma. Basaloid variant. Nests of epithelial cells resembling those of a basal cell carcinoma. (Courtesy of Dr. Howard Dorfman, Bronx, N.Y.)

Fig. 6 A Adamantinoma. Squamous variant. Nests of squamous cells surrounded by a loose-textured fibrous stroma. Inset shows a nest of squamous cells at higher magnification. This lesion was diagnosed at age 40 years but a radiologic abnormality had been present from age 15 years. B Adamantinoma. Unusual pattern of poorly differentiated malignant neoplasm composed of nests of polygonal epithelial-type cells and spindle-shaped cells resembling a synovial sarcoma. This section was taken from a soft tissue mass adjacent to the osseous lesion shown in A and probably represents dedifferentiation of the depicted adamantinoma. (Courtesy of Dr. Peter Bullough, Manhattan, N.Y.)



**Fig. 7** Adamantinoma. Squamous variant. Cell separation has resulted in formation of the stellate reticulum identical to that seen in gnathic ameloblastoma (adamantinoma) and in craniopharyngioma. (Courtesy of Dr. Howard Dorfman, Bronx, N.Y.)

Fig. 8 Adamantinoma. Unusual squamous variant. In this unusual squamous variant, the squamous cells are distributed as isolated single cells in a loose-textured fibrous stroma. These cells are rounded with intensely staining, brightly eosinophilic cytoplasm (*arrows*)

OFD. Based on the pattern of the epithelial cell component and the presence or absence of the OFD-like element, several histologic variants have been described. The most frequent is the *tubular* variant in which narrow cords of epithelial cells form branching and anastomosing structures. A central gland-like space produces the tubular appearance and probably results from loss of cellular cohesion rather than true gland formation (Fig. 4). A basaloid variant resembles basal cell carcinoma with pallisading of its peripheral layer (Fig. 5). The squamous variant resembles a well-differentiated squamous carcinoma and may exhibit keratinization or cell separation may result in formation of the stellate reticulum pattern seen commonly in gnathic ameloblastoma (Figs. 6, 7, 8). There are frequently overlapping patterns between these variants in individual cases. The spindle cell variant is the most difficult to recognize as the spindle-shaped neoplastic epithelial cells may be difficult to distinguish from the mesenchymal cells and may produce patterns resembling those of mesenchymal neoplasms, namely, storiform, fascicular and "herring bone". A clue to their identification is their tendency to outline cleft-like or tubule-like spaces (Fig. 9). The osteofibrous dysplasia-like variant is usually composed of scant strands and single epithelial cells within a lesion otherwise indistinguishable from OFD. The relationship between this variant and OFD will be elaborated on in the sections dealing with OFD and differentiated adamantinoma. The least common variant has been described as Ewing's-like adamantinoma or adamantinoma-like Ewing's and is composed of anastomosing cords of small, uniform, round cells set in a myxoid stroma (Fig. 10). These cells have been shown by ultrastructural examination to exhibit features of both epithelial cells (namely well-formed desmosomes) and neuroendocrine cells (namely dense core granules and glycogen aggregates) [15, 16]. Immunohistochemical studies have shown the tumor cells to contain both epithelial and neural antigens including the Ewing's sarcoma-related antigen O13 [17]. Bridge et al. [18] recently documented three similar cases in which cytogenetic analysis demonstrated the presence of an 11;22 translocation in the nuclei of cytokeratin-immunoreactive cells, and therefore considered the tumors to be variants of Ewing's sarcoma rather than Ewing-like adamantinoma. They termed the lesion "adamantinoma-like Ewing's sarcoma". Further support for this interpretation is the result of an investigation of 14 cases of adamantinoma for T (11;22) and T (21;22) by reverse transcription polymerase chain reaction (RT-PCR). These translocations were found in cases of Ewing's sarcoma but not in any of the adamantinomas studied [19].

Α

Fig. 9 A Adamantinoma. Spindle cell variant. Histologically this tumor resembles a sarcoma and may be so misdiagnosed. B Adamantinoma. Spindle cell variant. Within the lesion depicted in A, note the presence of cleft-like spaces lined by a single layer of neoplastic cells and separated by bands of collagenous tissue. (Courtesy of Dr. Howard Dorfman, Bronx, N.Y.)



Fig. 10 A Adamantinoma-like Ewing's sarcoma. Lytic lesion involving the head of the radius. B "Adamantinoma-like Ewing's sarcoma". Cords and nests of small, fairly uniform polygonal cells. C "Adamantinoma-like Ewing's sarcoma". Soft tissue recurrence developed 19 years after resection of the radial head. Histologically, the cells are similar to those in the initial resection but in areas (inset) show greater pleomorphism. (Courtesy Dr. German Steiner, New York, NY)

#### Cytopathology

A cytopathologic diagnosis of a primary lesion based on tissue obtained from a fine needle aspirate is possible. It requires a knowledge of compatible clinical and radiologic features. The cellular population includes large or small polygonal epithelial-type cells admixed with a population of bland spindle-shaped cells, the latter derived from the stromal component [20]. Confirmation of the epithelial and mesenchymal nature of the two cell

types requires immunohistochemical studies. In stromalrich lesions such as the osteofibrous dysplasia-like variant, the epithelial cell component may be sparse or even absent in the aspirate, precluding the possibility of a definitive diagnosis. The diagnosis of pulmonary metastatic adamantinomas is also possible based on the cytomorphologic criteria described above, but would also require a knowledge of the prior history of an adamantinoma and especially such a history in the more distant past as metastatic disease may be delayed for many years [21, 22].

#### Electron microscopy

While some of the initial electron microscopic studies of adamantinomas suggested an endothelial or synovial origin for the neoplasm [23, 24], all subsequent studies demonstrated the presence of epithelial cells with tono-filament-desmosome complexes and stromal mesenchymal cells, clearly establishing an epithelial histogenesis [25, 26, 27, 28].

#### Immunohistochemical and cytogenetic studies

The initial immunohistochemical studies showed strong positive staining of the neoplastic cells with pan-cytokeratin antibody, confirming the epithelial histogenesis [13, 28, 29]. Recent studies by Hazelbag et al. [30] utilizing antibodies to cytokeratin subtypes have demonstrated an immunoprofile that differs from that of other bone and soft tissue neoplasms with known epithelial characteristics, namely synovial sarcoma, chordoma and epithelioid sarcoma, which exhibit immunoreactivity for keratins 8 and 18. By contrast, all adamantinomas studied, irrespective of histologic subtype, showed uniform positivity for keratins 14 and 19, 74% showed positivity for keratin 5 and 50% positivity for keratin 17. These findings suggest a histogenesis from basal epithelial type cells. Bovee et al. [31] examined the relationship between the epithelial and the stromal components of adamantinomas by comparing the immunohistochemical expression of the proliferation marker Ki-67, epidermal growth factor and epidermal growth factor receptor and fibroblast growth factor type 2 in the two cell populations. These antigenic factors were present either exclusively or predominantly in the epithelial component, suggesting that the epithelial component constitutes the primary proliferating neoplastic cell population that is able to stimulate a reactive fibrous growth. Additional studies by Hazelbag et al. [32] utilizing DNA flow cytometry and p53 immunohistochemistry demonstrated aneuploidy and significant p53 immunoreactivity only in nuclei of cells of epithelial phenotype. Furthermore, in several cases with pulmonary metastasis, only cytokeratin-positive epithelial cells and not the osteofibrous stromal component were detected in the metastatic lesions. Cytogenetic studies of adamantinomas have demonstrated trisomies in chromosomes 7, 8, 12, 19 and 21 [33, 34, 35].

#### Therapy and prognosis

As a consequence of the rarity of the tumor, many of the published reports relate to small numbers of cases and isolated case reports. The larger series are derived from major cancer centers or national tumor registries. Admantinomas have a propensity to both local recurrence and metastatic disease, predominantly to the lung. Most authors have stressed the need for long-term follow-up as the mean duration to local recurrence may be as long as 7 years and metastases have been documented as occurring up to 27 years following diagnosis [36]. The largest series of 85 cases from the Mayo Clinic documented a 31% local recurrence rate, a 15% rate of pulmonary metastasis and a 13% mortality rate [37]. Twenty-eight patients followed up for a mean period of 10 years from the University of Leiden and the Netherlands Tumor Registry exhibited a 32% local recurrence rate after a mean period of 7 years, a 29% metastatic rate and a 25% mortality rate [38]. The most recently documented series involves 70 patients treated at 23 different cancer centers in Europe and North America, between 1982 and 1992 and with a median follow-up of 7 years [39]. Over 90% of these patients were treated by wide, local, limb-sparing resections. The local recurrence rate was 19% and the mortality rate 13%. These results indicate that wide local resection with reconstructive surgery is the treatment of choice, with results at least as good as those following amputation. Radiotherapy and chemotherapy have not been shown to be effective modalities of treatment.

# Osteofibrous dysplasia and differentiated adamantinoma

Osteofibrous dysplasia (OFD) was well categorized by Campanacci in 1976 [40]. In 1966, Kempson [41] termed the lesion "ossifying fibroma". In 1973, Johnson [42] used the terminology "congenital pseudoarthrosis" and in 1975 Semian et al. [43] coined the term "congenital fibrous defect". In 1981, Campanacci and Laus [44] reported 35 patients from their institution and reviewed 22 additional cases reported in the literature. OFD is a fibro-osseous process with a predilection for the diaphysis of the tibia. In the series of 80 cases reported by Park et al. [45], 77 involved the tibia and three the fibula. In nine of the cases, both tibia and fibula were involved on the ipsilateral side. Other reported sites of involvement are the ulna and the radius. The lesion occurs most fre-

Fig. 11A–D Osteofibrous dysplasia. Plain radiographs of cases of osteofibrous dysplasia. They are predominantly or exclusively cortical-based radiolucent lesions. In A–C, the lesions are well marginated. In D, the lesion is multilocular and has resulted in prominent cortical bowing. (B and D courtesy of Dr. Michael Klein, Manhattan, N.Y., and C courtesy of Dr. Peter Bullough, Manhattan, N.Y.)



quently in children under the age of 10 years. The clinical presentation is one of pain and swelling. The tibia may be bowed and pseudoarthrosis may develop. Radiologically, it first manifests as an intra-cortical, radiolucent, fairly well marginated lesion with marginal sclerosis and it may have a "ground-glass" appearance (Figs. 11, 12). The radiologic differential diagnoses include osteoid osteoma, Brodie's abscess, osteoblastoma, osteosarcoma and adamantinoma. Histologically, the lesion bears a superficial resemblance to fibrous dysplasia, being composed of variably shaped spicules of woven bone separated by a fibrovascular stroma. However, it differs from fibrous dysplasia in that the woven bone spicules are surrounded by a uniform rim of plump, po-





Fig. 13A-C Osteofibrous dysplasia. Branching and anastomosing trabeculae of woven bone rimmed by a uniform layer of polygonal osteoblastic cells and separated by moderately cellular fibrovascular stroma

lygonal osteoblasts (Fig. 13). Furthermore, the lesion exhibits a zonal phenomenon with maturation of woven bone to bone with a lamellar configuration at the periphery of the lesion. Based on the follow-up data from the two largest series of cases, from the Rizzoli Institute in

Milan and the Mayo Clinic, the process appears to undergo spontaneous regression at puberty [44, 45]. However, there is a local recurrence rate of about 25% following curettage or local resection, so that the authors of these series recommended delay in surgery until after puberty and only for extensive lesions. In none of these cases was there evidence of progression to an adamantinoma.

However, a possible histogenetic relationship between OFD and adamantinoma has been suggested as a result of



**Fig. 14A–C** Osteofibrous dysplasia. Typical pattern of woven bone rimmed by polygonal osteoblasts. **B** demonstrates individual cytokeratin-positive cells in the stroma (*arrows*). However, careful examination of these cells in the hematoxylin-eosin stained section in **C** and in the Giemsa stained section in the inset to **C** shows the cytokeratin-positive cells to be mast cells

 Table 1 Osteofibrous dysplasia: frequency of cytokeratin-positive single cells

Authors	No. positive	% positive	No. of cases
Sweet et al. [46]	28	93	30
Ueda et al. [47]	10	77	13
Ishida et al. [48]	10	83	12
Park et al. [46]	2	33	6
Benassi et al. [49]	18	75	24
Total	68	80	85

the frequent demonstration of scattered, isolated cytokeratin-positive cells within the fibrovascular stroma of OFD, although these cells are usually not identifiable in routine hematoxylin and eosin stained sections. In a personal review of several series of immunohistochemical studies of OFD, cytokeratin-positive cells were identified in 80% of 85 cases (Table 1) [45, 46, 47, 48, 49]. This author has recently examined a case of OFD in which scattered, isolated cytokeratin-positive cells were clearly identifiable as mast cells and not epithelial cells in corresponding hematoxylin and eosin and Giemsa stained preparations (Fig. 14). This observation raises a concern regarding the histogenesis of all isolated cytokeratin-positive cells in previous studies. OFD of long bones should not be confused with the entity gnathic ossifying fibroma. Histologically, this jaw lesion resembles OFD but it is usually a well-circumscribed mass that can be shelled out from the surrounding bone and is considered to be a benign neoplasm. In an immunohistochemical study of eight cases of gnathic juvenile ossifying fibroma by Williams et al. [50] no cytokeratin-positive cells could be identified.

In a number of recently reported cases otherwise resembling OFD in young children, the presence of epithelial cells forming small nests or strands recognizable in routine hematoxylin stained sections has been identified (Figs. 15, 16, 17). These lesions have been designated as "differentiated", "regressive", "juvenile intracortical" or "osteofibrous dysplasia-like" adamantinomas [38, 48, 51, 52]. The follow-up information on these cases is limited but based on a review of the literature and personal communication with several of the authors of the larger series of cases, the overwhelming majority have pursued a benign course. However, there are a few well-documented cases in which patients initially diagnosed with OFD or juvenile adamantinoma have developed fullblown classic adamantinoma. In some instances this apparent evolution might be explained by inadequate curettage or sampling of the curetted material so that the more classic pattern of adamantinoma was missed [53, 54]. Hazelbag et al. [38] documented the occurrence of a thoroughly curetted lesion from a 13-year-old girl which showed features of OFD or juvenile adamantinoma with inconspicuous cytokeratin-positive cells occurring singly and in small aggregates in both the original surgical specimen and a recurrence which developed 3 years later. Five years later, the lesion had evolved into a classic spindle cell adamantinoma and 10 and a half years later, she developed pulmonary metastases. They reported a second lesion in a 16-year-old boy which was thoroughly curetted and showed features of OFD with isolated cytokeratin-positive cells. About 5 years later, the lesion had Fig. 15 A Differentiated adamantinoma. Plain radiograph showing an intracortical radiolucent lesion involving the mid-shaft of the tibia. (Courtesy of Dr. Michael Klein, Manhattan, NY). B Differentiated adamantinoma. In this example from a 6-year-old girl, a sclerotic lesion involving the cortex in the mid-diaphyseal region had initially been interpreted radiologically as an osteoid osteoma and biopsied. However, the lesion progressed over the next few months and showed proximal extension as seen in this radiograph



Fig. 16 A Differentiated adamantinoma. At low magnification of this fibro-osseous lesion from the tibia, the stromal element appears to be devoid of epithelial structures. **B** However, at higher magnification, nests of cells suggestive of primitive epithelial cell clusters are seen (*arrows*). Their epithelial origin was confirmed by immunohistochemistry. Same case as Fig. 15A



evolved into a classic spindle cell adamantinoma. Schneider and Enderle [55] reported a case of a lesion involving the tibia and fibula of a 10-year-old girl with histologic features that would be consistent with a juvenile adamantinoma. The patient developed pulmonary metastases and died 17 years later. Johnson [42] reported the case of an adult who developed an adamantinoma and who had had tibial bowing of the involved bone since infancy. Unni et al. [56] documented the occurrence of a tibial adamantinoma in a 35-year-old man who had had a biopsy of the lesion 16 years previously which showed features of OFD.

Fig. 17A, B Differentiated adamantinoma. Histologic features appear typical of osteofibrous dysplasia with woven bone spicules rimmed by polygonal osteoblastic cells set in a fibro-vascular stroma. C, D Differentiated adamantinoma. In C, subtle nests of plump "stromal-type" cells raised the possibility of epithelial differentiation. This was confirmed by the positive cytokeratin staining demonstrated in a serial section in D (*arrows*)



The above observations have led several investigators to examine cases of OFD, juvenile adamantinoma and classical adamantinoma for cytokeratin subsets and, cytogenetically, to assess the presence or absence of any homologies. Benassi et al. [49] demonstrated strong cytokeratin (CK)19 expression in both adamantinoma and OFD and negativity for CK8 and CK18. Maki et al. [57] reported similar findings as well as a high incidence of CK1 positivity, a basal cell phenotype, in both entities. Cytogenetic studies of a small number of cases of OFD and adamantinoma have demonstrated trisomies 7, 8 and 12 in both entities [33, 34]. As noted previously, Bovee et al. [31] demonstrated that epidermal and fibroblast growth factor type 2, and their receptors, were present exclusively or predominantly in the epithelial components of classic adamantinoma. They also found that these factors and their receptors were expressed in OFD but were more intensely expressed and expressed in a higher percentage of cells in classic adamantinoma.

On the basis of the clinical, immunohistochemical and cytogenetics studies, a common histogenesis for OFD, juvenile adamantinoma and classic adamantinoma seems likely. Some authors have chosen to include lesions of OFD with identifiable cytokeratin-positive cells under the rubric "osteofibroma dysplasia-like variant of adamantinoma" [38].

In any event, such lesions, with a few notable exceptions as described above, have exhibited a relatively indolent course compared with the classical adamantinoma variants. It has been suggested that in such cases the fibrous element represents a reparative phenomenon associated with regression of the neoplastic epithelial cells. If this is indeed the case, this would be another example of spontaneous resolution of a potentially malignant tumor

## such as has been documented with spontaneous resolution of melanoma and other malignancies [51, 52].

# Conclusion

Adamantinoma, OFD and differentiated adamantinoma are histogenetically closely related lesions in which the epithelial cell components exhibit similar cytokeratin immunoprofiles and cytogenetic aberrations. However, the prognosis for classic adamantinoma is much less favorable than that for cases of OFD and differentiated adamantinoma. Consequently treatment of patients with a diagnosis of OFD or differentiated adamantinoma tends to be conservative while patients with classic adamantinoma are treated more aggressively. It is recommended that surgery for OFD and differentiated adamantinoma be delayed until after puberty and then only for extensive or deforming lesions.

### References

- Maier C. Ein primäres myelogenes platten epithelcarcinom der ulna. Bruns Beitr Klin Chir 1900; 26:553.
- 2. Fischer B. Über ein primäres Adamantinoma der Tibia. Virchows Arch [B] 1913; 12:422–441.
- Schulenburg CAR. Adamantinoma. Ann R Coll Surg Engl 1951; 8:329–353.
- Iravani S, Walling A, Gilbert-Barness E. Pathological case of the month. Arch Pediatr Adolesc Med 1997; 151:427–428.
- Moon NF, Mori H. Adamantinoma of the appendicular skeleton – updated. Clin Orthop 1986; 204:215–237.
- Plump D, Haponik EF, Katz RS. Primary adamantinoma of the rib: thoracic manifestations of a rare bone tumor. South Med J 1986; 79:352–355.
- Mills SE, Rosai J. Adamantinoma of the pretibial soft tissue. Clinicopathologic features, differential diagnosis and possible relationship to intraosseous disease. Am J Clin Pathol 1985; 83:108–114.
- Bertoni F, Zucchi V, Mapelli S, Bacchini P. Case report 506: Adamantinoma of the soft tissues of leg. S keletal Radiol 1988; 17:522–526.
- Altmannsberger M, Poppe H, Schauer A. An unusual case of adamantinoma of long bones. J Cancer Res Clin Oncol 1982; 104:315–320.
- Van Schoor JX, Vallaeys JH, Joos GF, Roels HJ, Pauwels RA, Van der Straeten ME. Adamantinoma of the tibia with pulmonary metastases and hypercalcemia. Chest 1991; 100:279–281.

- Bohndorf K, Nidecker A, Mathias K, Zidkova H, Kauffmann H, Jundt G. The radiologic findings in adamantinoma of the long tubular bones. Rofo Fortschr Geb Rontgenstrahl Neuen Bildgeb Verfahr 1992; 157:239–244.
- Young JW, Aisner SC, Resnick CS, Levine AM, Dorfman HD, Whitley NO. Case report 660: Adamantinoma of tibia. Skeletal Radiol 1991; 20:152–156.
- Rosai J, Pincus GS. Immunohistochemical demonstration of epithelial differentiation in adamantinoma of the tibia. Am J Surg Pathol 1982; 6:427–434.
- Ryrie BJ. Adamantinoma of the tibia: etiology and pathogenesis. BMJ 1932; ii:1000–1003.
- Lipper S, Kahn LB. Case report 235:. Ewing-like adamantinoma of the left radial head and neck. Skeletal Radiol 1983; 10:61–66.
- Ishida T, Kikuchi F, Oka T, Machinami R, Kojima T, Iijima T, Higaki S, Imamura T. Case report 727: Juxtacortical adamantinoma of humerus (simulating Ewing tumor). Skeletal Radiol 1992; 21:205–209.
- 17. Fukunaga M, Ushigome S. Periosteal Ewing-like adamantinoma. Virchows Arch 1998; 433:385–389.
- Bridge JA, Fuller ME, Neff JR, Degenhardt J, Wang M, Walker C, Dorfman HD, Baker KS, Seemayer TA. Adamantinoma-like Ewing's sarcoma: genomic confirmation, phenotypic drift. Am J Surg Pathol 2000; 24:322–323.

- Hauben E, van den Broek LC, Van Marck E, Hogendoorn PC. Adamantinoma-like Ewing's sarcoma and Ewing's-like adamantinoma. The T (11;22), T (21;22) status. J Pathol 2001; 195:218–221.
- Galera-Davidson H, Fernandez-Rodriquez A, Torres-Olivera FJ, Gomez-Pascual A, Morena-Fernandez A. Cytologic diagnosis of a recurrent adamantinoma. Acta Cytol 1989; 33:635–638.
- Tabei SZ, Abdollahi B, Nili F. Diagnosis of metastatic adamantinoma of the tibia by pulmonary brushing cytology. Acta Cytol 1988; 32:579–581.
- Perez-Ordonez B, Bedard YC. Metastatic adamantinoma diagnosed by fine-needle aspiration biopsy of the lung. Diagn Cytopathol 1994; 10:347–351.
- 23. Yoneyama T, Winter WG, Mislow L. Tibial adamantinoma: its histogenesis from ultrastructural studies. Cancer 1977; 40:1138–1142.
- Lombart-Bosch A, Ortuno-Pacheco G. Ultrastructural findings supporting the angioblastic nature of so-called adamantinoma of the tibia. Histopathology 1978; 2:189–200.
- 25. Mori H, Shima R, Nakanishi H, Yoshida A, Fukunishi R. Adamantinoma of the tibia: a case report and a statistical review of reported cases. Acta Pathol Jpn 1981; 31:701–709.

- Knapp RH, Wick MR, Scheithauer BW, Unni KK. Adamantinoma of bone. An electron microscopic and immunohistochemical study. Virchows Arch [A] 1982; 398:75–86.
- Pieterse AS, Smith PS, McClure J. Adamantinoma of long bones: clinical, pathological and ultrastructural features. J Clin Pathol 1982; 35:780–786.
- Mori H, Yamamoto S, Hiramatsu K, Miura T, Moon NF. Adamantinoma of the tibia. Ultrastructural and immunohistochemical study with reference to histogenesis. Clin Orthop 1984; 190:299–310.
- Jundt G, Remberger K, Roessner A, Schulz A, Bohndorf K. Adamantinoma of long bones. A histopathological and immunohistochemical study of 23 cases. Pathol Res Pract1995; 191:112–120.
- 30. Hazelbag HM, Fleuren JG, van den Broek LJ, Taminiau AH, Hogendoorn PC. Adamantinoma of the long bones: keratin subclass immunoreactivity pattern with reference to its histogenesis. Am J Surg Pathol 1993; 17:1225–1233.
- Bovee JV, van den Broek LJ, de Boer WI, Hogendoorn PC. Expression of growth factors and their receptors in adamantinoma of long bones and the implications for its histogenesis. J Pathol 1998; 184:24–30.
- 32. Hazelbag HM, Fleuren GJ, Cornelisse CJ, van den Broek LJ, Taminiau AH, Hogendoorn PC. DNA aberrations in the epithelial cell component of adamantinoma of long bones. Am J Pathol 1995; 147:1770–1779.
- 33. Hazelbag HM, Wessels JW, Mollevangers P, van den Berg E, Molenaar WM, Hogendoorn PC. Cytogenic analysis of adamantinoma of long bones: further indications for a common histogenesis with osteofibrous dysplasia. Cancer Genetic Cytogenet 1997; 97:5–11.
- 34. Bridge JA, Dembinski A, DeBoer J, Travis J, Neff JR. Clonal chromosomal abnormalities in osteofibrous dysplasia: implications for histopathogenesis and its relationship with adamantinoma. Cancer 1994; 73:1746–1752.
- 35. Kanamori M, Antonescu CR, Scott M, Bridge RS Jr, Neff JR, Spanier SS, Scarborough MT, Vergara G, Rosenthal HG, Bridge JA. Extra copies of chromosomes 7, 8, 12, 19 and 21 are recurrent in adamantinoma. J Mol Diagn 2001; 3:16–21.

- 36. De Keyser F, Vansteenkiste J, Van Den Brande P, Demedts M, Van de Woestijne KP. Pulmonary metastasis of a tibial adamantinoma. Case report and review of the literature. Acta Clin Belg 1990; 45:31–33.
- Keeney GL, Unni KK, Beabout JW, Pritchard DJ. Adamantinoma of long bones. A clinicopathologic study of 85 cases. Cancer 1989; 64:730–737.
- Hazelbag HM, Taminiau AH, Fleuren GJ, Hogendoorn PCW. Adamantinoma of the long bones. A clinicopathologic study of thirty-two patients with emphasis on histological subtype, precursor lesion and biological behavior. J Bone Joint Surg Am 1994; 76:1482–1499.
- 39. Qureshi AA, Shott S, Mallin BA, Gitelis S. Current trends in the management of adamantinoma of long bones. An international study. J Bone Joint Surg Am 2000; 82:1122–1131.
- Campanacci M. Osteofibrous dysplasia of long bones, a new clinical study. Ital J Orthop Traumatol 1976; 2:221–237.
- Kempson RL. Ossifying fibroma of the long bones, a light and electron microscopic study. Arch Pathol Lab Med 1966; 82:218–233.
- Johnson LC. Congenital pseudarthrosis, adamantinoma of the long bone and intracortical fibrous dysplasia of the tibia (abstract). Lab Invest 1973; 28:387.
- Semian DW, Willis JB, Bove KE. Congenital fibrous defect of the tibia mimicking fibrous dysplasia. A case report. J Bone Joint Surg Am 1975; 57:854–857.
- 44. Campanacci M, Laus M. Osteofibrous dysplasia of the tibia and fibula. J Bone Joint Surg Am 1981; 63:367–375.
- 45. Park YK, Unni KK, McLeod RA, Pritchard DJ. Osteofibrous dysplasia: clinicopathologic study of 80 cases. Hum Pathol 1993; 24:1339–1347.
  46. Sweet DE, Vinh TN, Devaney K.
- 46. Sweet DE, Vinh TN, Devaney K. Cortical osteofibrous dysplasia of long bones and its relationship to adamantinoma. A clinicopathologic study of 30 cases. Am J Surg Pathol 1992; 16:282–290.
- 47. Ueda Y, Blasius S, Edel G, Wuisman P, Bocker W, Roessner A. Osteofibrous dysplasia of long bones – a reactive process to adamantinomatous tissue. J Cancer Res Clin Oncol 1992; 118:152–156.
- 48. Ishida T, Iijma T, Kikuchi F, Kitagawa T, Tanida T, Imamura T, Machinami R. A clinicopathological and immunohistochemical study of osteofibrous dysplasia, differentiated adamantinoma and adamantinoma of long bones. Skeletal Radiol 1992; 21:493–502.

- 49. Benassi MS, Campanacci L, Gamberi G, Ferrari C, Picci P, Sangiorgi L, Campanacci M. Cytokeratin expression and distribution in adamantinoma of the long bones and osteofibrous dysplasia of tibia and fibula. An immunohistochemical study correlated to histogenesis. Histopathology 1994; 25:71–76.
- 50. Williams HK, Mangham C, Speight PM. Juvenile ossifying fibroma. An analysis of eight cases and a comparison with other fibro-osseous lesions. J Oral Pathol Med 2000; 29:13–18.
- Ueda Y, Roessner A, Bosse A, Edel G, Bocker W, Wuisman P. Juvenile intracortical adamantinoma of the tibia with predominant osteofibrous dysplasialike features. Pathol Res Pract 1991; 187:1039–1043.
- 52. Czerniak B, Rojas-Corona RR, Dorfman HD. Morphologic diversity of long bone adamantinoma. The concept of differentiated (regressing) adamantinoma and its relationship to osteofibrous dysplasia. Cancer 1989; 64:19–34.
- 53. Kim JY, Kang GH, Chi JG. Adamantinoma of the tibia with predominant features of fibrous dysplasia : a case report. J Korean Med Sci 1996; 11:444–448.
- Konrad EA, Meister P, Stotz S. "Adamantinoma" of the tibia and reactive bone changes. Arch Orthop Trauma Surg 1978; 92:297–301.
- Schneider H, Enderle A. Differential diagnosis of a metastasizing adamantinoma of the tibia and fibula. Arch Orthop Trauma Surg 1979; 94:143–149.
- Unni KK, Dahlin DC, Beabout JW, Ivins JC. Adamantinomas of long bones. Cancer 1974; 34:1796–1805.
- 57. Maki M, Saitoh K, Kaneko Y, Fukayama M, Morohoshi T. Expression of cytokeratin1, 5, 14, 19 and transforming growth factors beta 1, beta 2, beta 3 in osteofibrous dysplasia and adamantinoma: a possible association of transforming growth factor beta with basal cell phenotype promotion. Pathol Int 2000; 50:801–807.