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ORIGINAL PAPER

Primary Adamantinoma of the Rib. Unusual Presentation for a Bone Neoplasm of Uncertain Origin

Sergio Piña-Oviedo · Luis Del Valle · Rafael Padilla-Longoria · Hilda Mendoza-Ramón · Carlos Ortiz-Hidalgo

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Abstract Adamantinomas are rare, low-grade malignant intra-osseous tumors composed of epithelial and mesenchymal elements, which show a marked predilection for the tibia and fibula of young adult male patients. Although cases of adamantinoma located to the axial skeleton have been reported either as recurrent or metastatic disease, only two cases of primary adamantinoma located to the thoracic wall have been previously described. In this study we present the clinical, radiological and histopathological features of a 24-year-old male with a slow growing, solid-cystic, painful mass, located to the right 11th rib, which was morphological and immunohistochemically diagnosed as a primary classic adamantinoma. Radiological studies showed a multiloculated lesion with a solid component. The patient underwent a whole surgical resection of the lesion. Histologically, multiple foci of epithelial cells with basaloid and squamous components were found intermixed within a fibrous stromal tissue. Immunohistochemical analysis demonstrated expression of cytokeratins, EMA, vimentin and other epithelial markers. Primary affection of the rib is an unusual feature of classic adamantinomas.

Keywords Adamantinoma · Bone tumor · Bone epithelial neoplasm · Immunohistochemistry

S. Piña-Oviedo · C. Ortiz-Hidalgo
Laboratory of Tissue and Cell Biology, School of Medicine, Universidad Panamericana, Mexico City, Mexico

S. Piña-Oviedo
Instituto de Hematopatologia "The Anton van Leeukwenhoek Society" for Life & Exact Sciences, Mexico City, Mexico

L. Del Valle
Department of Neuroscience, Temple University School of Medicine, Philadelphia, PA, USA

R. Padilla-Longoria
Department of Surgical Oncology, The American British Cowdray Medical Center, Mexico City, Mexico

H. Mendoza-Ramón · C. Ortiz-Hidalgo (✉)
Department of Pathology, The American British Cowdray Medical Center, Calle Sur 132, No. 116. Colonia Las Americas, C.P. 01120 Mexico City, Mexico
e-mail: cortiz@abchospital.com

Introduction

Extragnathic adamantinomas (EA) are rare low-grade malignant intra-osseous epithelial neoplasms of uncertain histopathogenesis that microscopically resemble ameloblastomas (gnathic adamantinoma). They represent 0.4% of all primary bone tumors, and show a striking predilection for the anterior mid-shaft of the tibia in more than 80–90% of the cases, although some cases involving the appendicular skeleton have been published [1, 2]. The first description of this entity is attributed to Maier, who in 1900 published the case of a bone tumor with epithelial characteristics [3]. Thirteen years later, this entity was catalogued by Fisher as a 'primary adamantinoma of the tibia', because of the similar histopathologic features shared with ameloblastoma of the jaw [4]. Although cases have been reported with as wide range as 3 to 85 years of age, the mean age of presentation is 30 years, and it is rare in children, with only 3% of the cases diagnosed before the age of 10. EA has also been described in the femur, ulna, humerus, radius, fibula, ischium and small bones of the hand and feet [1]. Interestingly, simultaneous affection of

the tibia and ipsilateral fibula has been described in approximately 10% of the cases. Radiologically, these lesions are medullary, osteolytic, eccentric and expansile regardless of the location, and may have a prominent sclerotic margin indicative of a slow growth [5].

Histologically, two forms of EA are recognized: the "classic" adamantinoma (CA) and "osteofibrous dysplasia-like" adamantinoma (ODA), also known as 'regressing', 'juvenile intracortical', or 'differentiated' adamantinoma [2, 6]. Classic adamantinomas are composed of two intermixed components, epithelial and osteofibrous areas, which vary in proportion from case to case. The epithelial component exhibits four main patterns of differentiation: 1) tubular, the most frequently observed, with narrow cords of cells forming branches and anastomoses, 2) basaloid, with cells arranged in palisades, resembling of a basal cell carcinoma, 3) squamous with highly differentiated cells, including occasional florid keratinization, which resemble a squamous cell carcinoma, and 4) spindle cell, phenotype most frequently observed in recurrences. On the other hand, the osteofibrous component is characterized by mesenchymal, spindle cells [7]. The main differential diagnosis of EA is established with epithelial metastatic neoplasms. However, the bland cytological growth along with the 'soap-bubble-like' appearance of EA would be quite unusual for a metastatic carcinoma. Vascular neoplasms and synovial sarcoma may also enter into the differential diagnosis. The strict clinico-pathological correlation and the properly oriented immunohistochemical markers, as well as the image studies, will give helpful information for the recognition of this low-grade intra-osseous malignant tumor.

In this report, we present the clinical, radiological and histo-pathological features of a primary EA case located to the right 11th rib, in a 24-year-old patient, with a complete immunohistochemical analysis. In addition, a brief review about this uncommon bone tumor and a discussion of the recent findings regarding its osteofibrous dysplasia (OFD)-related histopathogenesis are presented. To the best of our knowledge, only two cases of primary EA originating from the rib have been previously reported in the English literature [8, 9].

Materials and Methods

Case Report

A 24-year-old man presented to the ABC Hospital in Mexico City because of a painful mass located in the right thoraco-lumbar region, which developed in a period of 5 months. The mass increased in size slowly and progressively, and was accompanied of moderate-to-severe pain. No history of a trauma was reported. On physical examination, the lesion measured approximately 5.0× 3.0 cm, and was apparently fixed to the postero-lateral face of the 11th right rib. The mass was of hard consistency and very painful to palpation. The rest of the physical examination was unremarkable and all laboratory values were found within normal range. X-ray analysis revealed the presence of an intra-osseous, multi-locular 'soap-bubble-like' lesion of approximately 5.0×2.3 cm located within the 11th right rib, which also displayed osteolytic defects and peri-lesional sclerosis (Fig. 1a,b). By USG, a hyper-echoic, 2.0 cm diameter, irregular mass was found within one of the cysts (Fig. 1c). A full-body CT scan revealed no evidence of tumor elsewhere. A surgical wide (*en bloc*) resection of the affected rib segment was performed with no complications. Two years after resection, the patient remains healthy, without signs and symptoms of either local or systemic recurrence.

Histology and Immunohistochemistry

After surgical resection, the tissue was fixed in formalin and embedded in paraffin after a decalcifying process. Sections of 4 μm in thickness were prepared, mounted in positively charged glass slides and stained with Hematoxylin & Eosin (H&E) for routine histological evaluation. Immunohistochemical analysis was performed using a biotin link-streptavidin peroxidase complex system, according to the manufacturer's instructions (Bio SB, Inc.). Our modified protocol includes deparaffination in xylene, re-hydration in descending grades of alcohol up to water, antigen retrieval with Citrate Buffer pH 6.0 heated to 95°C for 30 minutes, endogenous peroxidase quenching with 3% H2O2 in methanol, and blocking with normal horse serum. After rinsing with PBS, primary antibodies were incubated overnight at room temperature in a humidified chamber. Primary antibodies utilized for this study included mouse monoclonals against Vimentin (Clone V-9, BioGenex, San Ramon, California, 1:3000 dilution); low and high molecular weight Cytokeratins (clones AE-1 and AE-3, CellMarque, Austin, Texas, 1:100 dilution); Epithelial membrane antigen - EMA- (clone E29, DAKO, 1:150 dilution); CD31 (clone JC70A, DAKO 1:400 dilution); CD99 (MIC-2 antigen, clone H036.1.1, BioGenex, San Ramon, California, 1:50 dilution); E-cadherin (clone NCH-38, DAKO, 1:100 dilution); Epidermal Growth Factor receptor (clone H11, DAKO, pre-diluted); Calretinin (clone DAK-Calret 1, DAKO, 1:300 dilution); p53 (clone D0-7, DAKO, 1:300 dilution); and Ki-67 (clone SP-6, CellMarque, Austin, Texas, 1:100 dilution). After rinsing with PBS, anti-mouse biotinylated secondary antibodies and Avidin-Biotin complexes (ABC, Vector Laboratories, Burlingame, California), were incubated for 1 hour at room temperature each. Finally, sections were developed with diaminobenzidine, counterstained with hema-

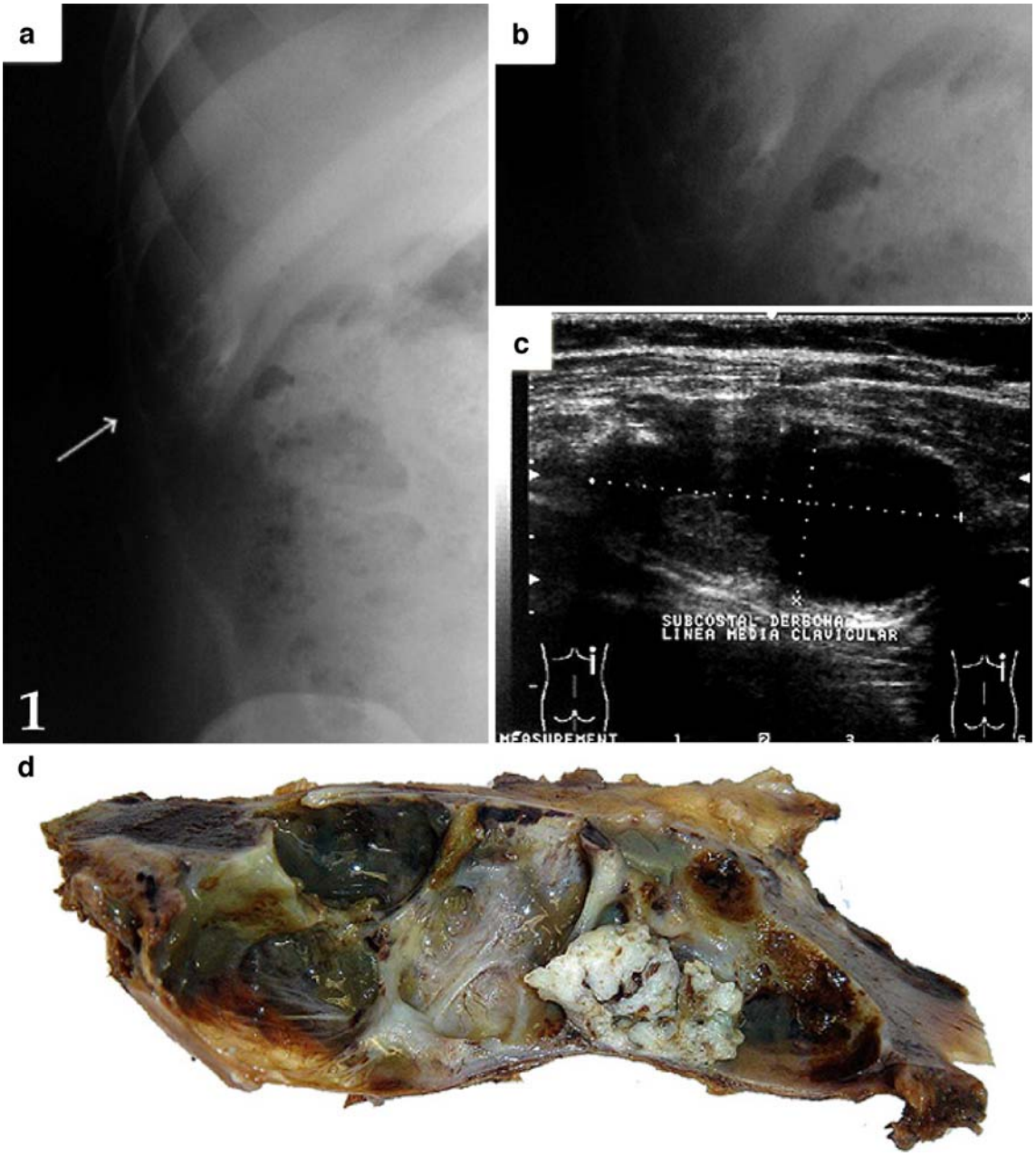

Fig. 1 Imaging studies and gross characteristics of the tumor. Radiographies of the thorax show an expanding mass with 'soap-bubble-like' appearance, affecting the right 11th rib (**a**, *arrow*). A close-up of the lesion corroborates the solid and cystic components of the tumor (**b**). An ultrasonogram highlights the presence of a multicystic component in the lesion (**c**). A section of the surgically removed segment shows an intra-osseous, multicystic lesion affecting the cortex and the medullary cavity of the rib. The lesion is irregular and heterogeneous with several white nodules and areas of fibrosis. Remnants of recent and old hemorrhages are present (**d**)

toxylin, dehydrated, cleared in xylene and mounted with Permount (Fischer Scientific).

Histopathological Findings

A specimen consisting of a whole surgical resection of a rib segment, measuring 10 cm in length, was analyzed. The tumor measured 7.0×4.5 cm, and presented a brown-pink rounded smooth lobulated surface. After middle sectioning, the tumor showed involvement of the cortex and the marrow cavity, and presented a multicystic gray-white mass, with solid bone and dense fibrous tissue. The cysts ranged from 0.9 to 5 cm in diameter, and were separated by multiple fibrous septae; they presented a glossy appearance, and some of them contained intra-tumoral hemorrhages. The solid component demonstrated a firm white-gray consistency *(*Fig. 1d).

Histologically, the intra-osseous lesion was composed of sheaths of epithelial neoplastic cells with a basaloid pattern,

and extensive areas of keratinization. No neoplastic cells were found beyond the periostium and the surrounding soft tissues. At low magnification, the neoplastic epithelial cells displayed different patterns, including a tubular, basaloid, and squamoid components (Fig. 2). The squamoid pattern was the most prevalent, and was conformed by clusters of epithelial squamous cells with small, dark nuclei, and clear-to-eosinophilic abundant cytoplasm that somewhat resembled a well-differentiated squamous cell carcinoma. In some areas, these cell clusters exhibited extensive keratinization (Fig. 2c). The epithelial elements either formed narrow cords of epithelial cells forming anastomosing tubular structures, or presented a basaloid pattern, resembling a basal cell carcinoma (Fig. 2a,b). All the neoplastic epithelial cells were interspersed within a fibrous/mixoid stroma. In addition, multiple large and small cysts, lined by a squamous epithelium and filled with a mixture of cellular and/or acellular debris, were also found (Fig. 2d). There was no vascular invasion and mitotic figures were rarely found. No osteofibrous dysplasia-like areas were present.

Positive immunoreactivity in the epithelial component was observed for vimentin, cytokeratin (CK) AE1-3 and Epithelial Membrane Antigen (Fig. 3). Vimentin and CK-AE1-3 displayed immunoreactivity in the squamous cells, the keratinization areas, and in few scattered cells of the fibrous stroma; whereas EMA was strongly positive in the clusters of the squamoid component. E-cadherin and the EGF-R showed robust membranous positive expression in the epithelial components (Fig. 4a,b). Positive nuclear immunoreactivity for Ki-67 and p53 were found confined to the epithelial component in less than 3% and 15% of the tumor cells, respectively (Figs. 4c,d). In contrast, anti-CD31 enhanced the endothelial cells of blood vessels and was negative in the tumor cells. The anti-CD99 and calretinin immunolabeling was uniformly negative.

Discussion

To the best of our knowledge, only two cases of extragnathic adamantinoma have been described affecting the rib as a primary disease [8, 9]. Unlike the clinical presentation of these two previous reported cases – one with pleural and spine involvement, and the second with liver metastases – our patient only presented a solitary mass located to the 11th right rib. Seven months after the diagnosis a complete surgical resection was performed. Follow-up is being achieved with periodical visits, and thus far, after two

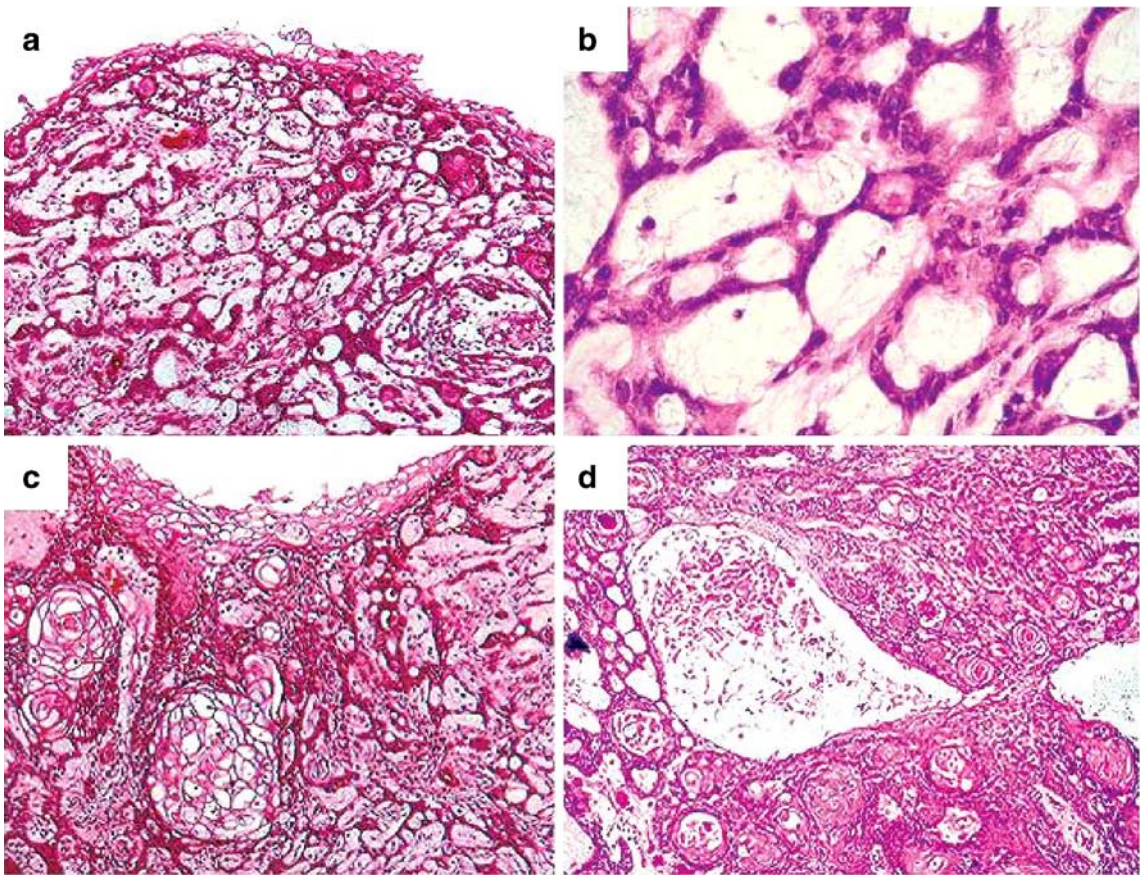

Fig. 2 Histological aspects of the tumor. Morphologically, different epithelial patterns can be identified; tubular (**a**, **b**) and squamous (**c**) areas. Cysts can also be observed (**d**). (**a**, **c**, and **d**, original magnification ×200, H&E; **b**, original magnification ×400, H&E)

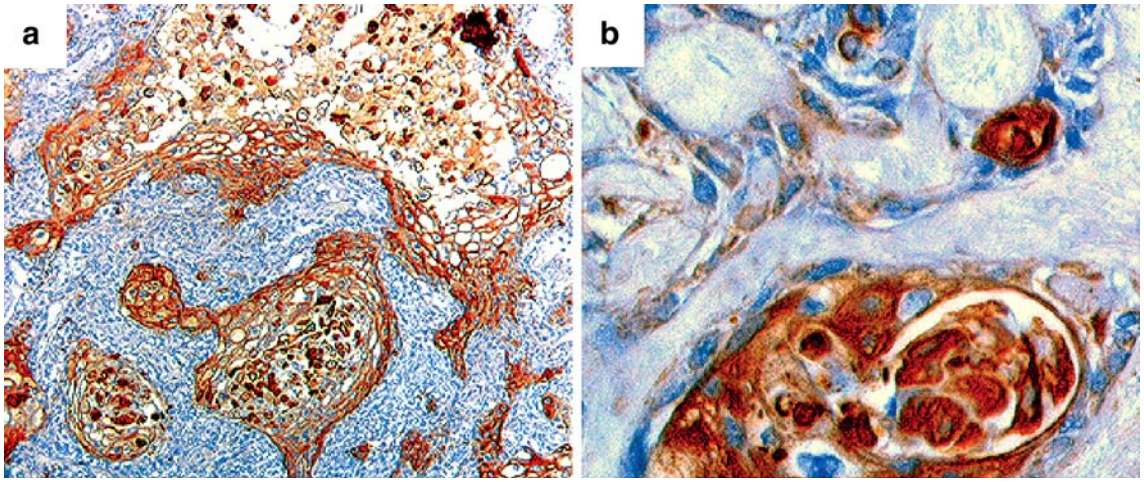

Fig. 3 Immunohistochemistry for Cellular Markers. The squamous pattern is highlighted by robust immunolabeling for Cytokeratin AE1–AE3 (**a**, ×200). EMA was also robustly expressed in the squamoid areas of the epithelial component (**b**, ×400)

years of the diagnosis, the patient still remains without local recurrence or any systemic manifestations.

As mentioned previously, classic adamantinomas, such as the one presented in this report, are closely related to a similar entity, osteofibrous "dysplasia-like" adamantinoma (ODA) and to another bone tumor of benign behavior and undefined nature, osteofibrous dysplasia (OFD). The ODA typically develops during the first decade of life in association with intra-cortical location, progressive anterior bowing deformity of the bones, and florid 'fibro-osseous' features, the latter composed of scant strands of single epithelial cells within a lesion, otherwise indistinguishable from OFD [2, 6]. The epithelial component is less conspicuous in ODA than in CA, although cytokeratin

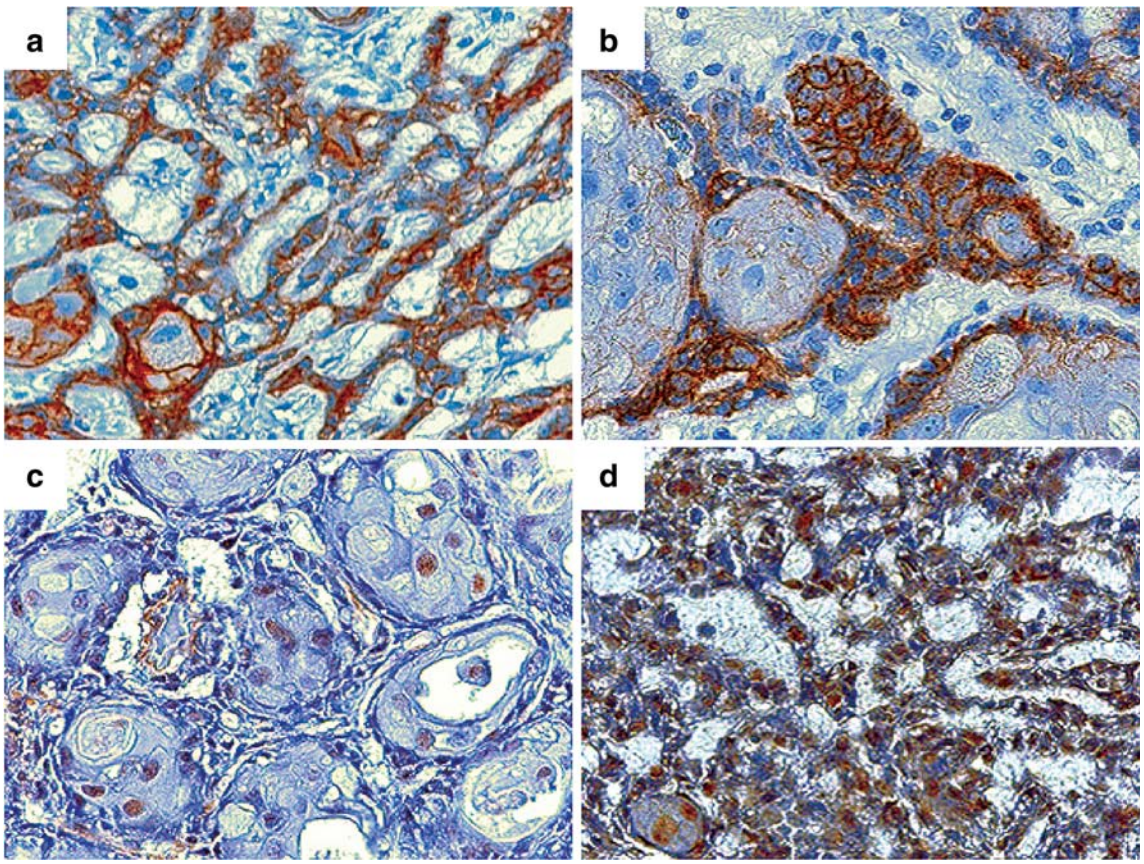

Fig. 4 Immunohistochemistry. E-cadherin in an area of the tumor with tubular pattern (**a**, ×200); EGF-R was positive in epithelial cell clusters within squamoid areas (**b**, ×400). p53 immunolabeling was less prominent in the squamoid areas (**c**, ×400), in comparison with the tubular areas, in which the positivity is robust and widespread (**d**, ×400)

positive cells are found in both 'classic' and 'OFD-like' areas of adamantinomas. Some authors have stated that ODA and OFD represent a single pathogenic process, and that they exhibit only a quantitative difference in their epithelial content [2]. To this extent, some authors have hypothesized that there may be a spectrum beginning with OFD evolving to ODA and to CA [1, 2, 10, 11].

Interestingly, cytogenetic studies have revealed clonal chromosomal abnormalities with trisomies 7, 8, and 12 in both OFD and adamantinomas, which supports that these two entities are closely related [6, 12, 13]. Trisomy 21 has also been reported as a recurrent cytogenetical finding in EA [13].

There are no substantial differences in the immunoreactivity pattern seen between the various subtypes of EA [14]. By immunohistochemistry, the neoplastic cells of EA show robust immunolabeling with pan-keratin antibodies such as CK AE1–3, and basal epithelial cell-type cytokeratins 5, 14, 17, and 19. Keratin 8 and 18 are absent in EA, which is an important issue to consider when synovial sarcoma, chordoma, and epithelioid sarcoma enter into the differential diagnosis, because those tumors have expression of keratins 5 and/or 18 as a common feature [14]. EMA and vimentin are also expressed in EA [14]. Cadherins, which are integral membrane glycoproteins with a single transmembrane domain, have been reported to be expressed in adamantinomas [11]. Expression of cadherins has been found to correlate with CA subtype, being the tubular, spindled, and basaloid patterns positive for E-cadherin, N-cadherin and P-cadherin, respectively [11]. Calretinin may also be expressed in adamantinomas, particularly in areas showing squamoid pattern, however, the importance of the biological expression of calretinin immunoreactivity is presently unknown [15]. Our case showed positive membrane-associated expression of EGF-R, as has been previously described, which further supports the established epithelial cell hypothesis of the proliferating tumor cells [16], and might be a potential therapeutic option, by using specific target-cell antibodies directed against this epithelial antigen.

Although it has been well established that EA is a neoplasm of epithelial derivation, the origin of these epithelial elements remains unknown [2]. Two scenarios have been proposed, one suggesting an origin from traumatic implantation of fetal basal cells, which has faded thanks to cytogenetic studies and which would also fail to explain locations other than the tibia for this tumor, and a most likely theory proposing the origin of these neoplastic cells in misplaced embryonic rests. When treated by surgical excision, EA of the tibia has a low rate of recurrences. Metastases may appear even 15 years after the initial diagnosis and may involve other bones, lungs, lymph nodes, liver and brain [17]. Chemotherapeutic regimens have not been successful [2].

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