Abstract

Osteofibrous dysplasia (OFD) is a rare, benign, fibro-osseous lesion that typically is seen within the cortex of the tibia in children. Adamantinoma (AD) is a rare, low-grade malignant primary bone tumor that occurs most often in the tibia and/or fibula of adolescent persons and young adults; however, it has been reported in other long bones, as well. Immunohistochemical and ultrastructural evidence has shown that the neoplastic cell in AD derives from an epithelial lineage. More recently, published reports have described another clinical entity—differentiated or OFD-like AD—that appears to lie between OFD and AD along a spectrum of disease. Controversy exists as to whether OFD is a precursor lesion to AD or whether OFD may be a residual lesion resulting from a spontaneously regressing AD. Management of OFD varies from observation to surgical intervention, depending on the age of the patient and the extent of the lesion. Management of AD requires surgical resection with wide margins, followed by appropriate reconstruction, to minimize the risk of local recurrence or metastasis.

Osteofibrous dysplasia (OFD) is a rare, benign, self-limited fibro-osseous lesion that is seen almost exclusively in the diaphysis of the tibia. The first case reported was by Frangenheim in 1921, although he termed the condition “congenital osteitis fibrosa.” Kempson reported two cases of “ossifying fibroma” in 1966, calling it such because it resembled fibrous dysplasia but was a histologically distinct entity. In 1976, Campanacci named the lesion “osteofibrous dysplasia of the tibia and fibula” in reference to its anatomic location, developmental origin, and histologic resemblance to fibrous dysplasia.

Adamantinoma (AD) of the long bones is a rare, low-grade, malignant, slow-growing primary bone tumor with a strong predilection for the midshaft of the tibia, with or without involvement of the ipsilateral fibula. The first described case is attributed to Maier in 1900. In 1913, Fischer named the lesion “adamantinoma” because it resembled AD of the jaw (now referred to as ameloblastoma). Similarities in location, patient age, radiographic appearance, and certain histologic features have led many to believe that OFD and AD are related lesions. More recent descriptions of an intermediate lesion, known as differentiated AD or OFD-like AD, provide further evidence for the likely existence of a spectrum of disease, with benign OFD at one end, malignant AD at the other, and differentiated AD somewhere in between. Identification of and distinction between these conditions is important for
management because untreated or undertreated AD can locally recur and/or metastasize, potentially with a fatal outcome.

**Epidemiology**

OOFD is rare, representing approximately 0.2% of all primary bone tumors. It most frequently occurs in the first two decades of life. In one review of 16 patients, patient age ranged from 8 months to 21 years (median, 9.5 years); 41% of patients were aged <6 years. OOFD is usually localized to the tibia, but the ipsilateral fibula is occasionally involved. In a review of 80 cases of OOFD, Park et al reported that the tibia was involved in 77 and that the fibula alone was involved in 3. In nine cases, the ipsilateral tibia and fibula were also affected. Within the tibia, the mid diaphysis is the most commonly affected area. Involvement of the radius and ulna has also been reported. Progression of the lesion generally halts with the achievement of skeletal maturity. Most published series of OOFD report a slight male preponderance, although the report by Park et al demonstrated a slight predilection for females (38 males, 42 females).

**Clinical Presentation**

Patients with OOFD most often initially present with lower leg swelling, with or without pain, or with anterior bowing. In rare instances, pathologic fracture brings the lesion to the attention of medical personnel. In their review of 16 patients with OOFD, Gleason et al reported that 31% of patients presented with pain, 19% with pathologic fracture, and 13% with tibial bowing. The other 37% had lesions noted incidentally on imaging studies obtained for other reasons. These data are similar to those reported by Park et al in their review of 80 patients with OOFD.

AD tends to present in a manner similar to that of OOFD. Pain, swelling, and deformity are the most common complaints at the time of diagnosis. Pathologic fractures have been noted in up to 23% of cases of AD at initial presentation. Thirty percent to 60% of patients may report prior trauma to the affected area, months or even years before diagnosis. Very advanced primary lesions or recurrent tumors may have a significant associated soft-tissue component. Spinal lesions may present with neurologic deficits. Instances of humerally mediated paraneoplastic hypercalcemia have been reported in conjunction with AD.

**Radiographic Features**

OOFD is nearly always found in the diaphysis of the tibia in patients aged <20 years. The lesion generally involves the anterior cortex and may cause anterior bowing of the tibia. OOFD typically manifests as an intracortical lytic lesion, which is generally well marginated and is often surrounded by a zone of sclerosis. Multiple luencies may be present within the cortex, with intervening sclerotic areas. The involved cortex may be expanded and/or thickened. Periosteal reaction is rare, but when present, it is thick, solid, and chronic-appearing. OOFD seldom progresses radiographically during childhood, and progression halts when the patient reaches skeletal maturity.

**Figure 1**

AP (A) and lateral (B) radiographs of the tibia and fibula in an 11-year-old boy who presented with a painless lump on the anterior tibia. Note the intracortical lytic lesions involving the anterior cortex and the resulting mild anterior bowing (arrow). Open biopsy confirmed the diagnosis of osteofibrous dysplasia.
AD is also typically located in the tibial diaphysis, generally in patients aged 20 to 50 years. The lesion tends to be eccentric, osteolytic, and expansile. The tumor often demonstrates multifocal lytic lesions with areas of intervening sclerosis, which can give the tumor a “soap bubble” appearance. Biopsy was consistent with adamantinoma.

MRI has proved to be very useful in the workup and staging of AD. AD generally shows a homogeneous, intermediate signal on T1-weighted images. On T2-weighted images, the signal intensity of an AD lesion is always high, whether homogeneous or heterogeneous. In a study of 22 patients with AD, Van der Woude et al found two main morphologic tumor patterns that could be distinguished by MRI: a solitary lobulated focus (41%) and a pattern of multiple small nodules in one or more foci (45%). The morphologic appearance on MRI did not correspond to the histologic subtype of AD. MRI was pivotal, however, in precise locoregional staging, providing critical information regarding distant cortical foci as well as intramedullary and/or soft-tissue extension. Such information is useful in determining tumor-free margins and planning surgical resection and reconstruction.

**Differential Diagnosis**

The differential diagnosis of a cortical, lytic, expansile lesion can be broad. In addition to OFD and AD, diagnostic considerations include fibrous dysplasia, nonossifying fibroma, unicameral bone cyst, aneurysmal bone cyst, chondromyxoid fibroma, Langerhans cell histiocytosis (ie, eosinophilic granuloma), osteomyelitis, osteosarcoma, chondrosarcoma, hemangiendothelioma, angiosarcoma, and metastatic carcinoma. Clinical information, including patient age and history, as well as location of the lesion in the tibial diaphysis, may help to narrow the differential.

It is most important, and perhaps most difficult, to differentiate OFD and AD. Even histologic differentiation between the two lesions can be difficult, and an ample tissue specimen is required for analysis. The
amounts of the fibrous and epithelial components can vary widely even within the same tumor, and sampling error is a significant concern with percutaneous or other limited biopsy specimens. Several cases have been published in which lesions that were initially diagnosed as OFD on limited biopsy were reclassified as AD after adequate diagnostic tissue was obtained.4

Pathologic Features

Microscopically, OFD is characterized by a loose, often storiform fibrous background containing spicules of woven bone trabeculae that are lined by a layer of osteoblasts2,8,9,13 (Figure 4). Although this histologic appearance is quite similar to that of fibrous dysplasia (hence, their similar names), fibrous dysplasia typically lacks the distinctive osteoblastic rimming of the bony trabeculae. Additionally, OFD demonstrates a zonal architecture, in which more immature woven bone trabeculae are located centrally; however, moving outward toward the periphery of the lesion, the trabeculae become more numerous, larger, and more mature and lamellar.2,8

AD is composed of islands of epithelial cells in a spindle-cell stroma4,5,32 (Figure 5). The relative amounts of the two components can vary considerably from one specimen to the next and even within one specimen. The epithelial nature of the tumor has been confirmed by immunohistochemical staining for cytokeratin, an epithelial cell marker (Figure 6), as well as by ultrastructural studies employing electron microscopy. These studies have demonstrated that the neoplastic cells contain desmosomes, tonofilaments, and microfilaments.6,33 Several histologic variants have been described, based on the pattern of the neoplastic epithelial cells. These variants include tubular (branching and anastomosing epithelial cells that resemble glands), basa-loid (with a palisading peripheral layer resembling basal cell carcinoma), squamous (resembling squamous cell carcinoma), and spindle cell (with spindle-shaped epithelial cells that may be difficult to differentiate from benign mesenchymal stroma).1,4,5,9,32-34 Although the basa-loid and tubular patterns are the most common, any or all of the subtypes may be seen, in differing proportions, even within the same lesion.6,34 The spindle cell variant is more commonly found in local recurrences and metastases.6,34 The neoplastic nature of epithelial cells is further confirmed by microscopic analysis of rare AD lung metastases,
which are composed only of the keratin-positive epithelial cells and which do not contain fibrous stromal tissue.3

The histologic origins of AD have been a source of controversy for several decades. Some early investigators felt that because AD appeared to be a biphasic tumor, that is, one with epithelial and fibrous tissue, it was related to synovial sarcoma; others felt that AD had a vascular origin.35 Advances in immunohistochemistry and electron microscopy later proved conclusively that the neoplastic cell of origin in AD is epithelial in nature.5,33 That raised the question of how an epithelial neoplasm could make up a primary bone tumor. Because the most commonly affected bone is the tibia, in particular the anterior cortex (which is very superficial and subcutaneous in location), some authors believe that the tumor arises from epithelial rests that are congenitally implanted during fetal development.3,25 Others believe that, because up to 60% of patients with AD report an injury preceding diagnosis, the epithelial cells are traumatically implanted into the bone at the time of injury.25 This question remains unresolved.

More recently, another histologic subtype has been described—OFD-like AD or differentiated AD. This subtype differs from classic AD in its earlier presentation (within the first two decades of life), entirely intracortical location, and predominance of an OFD-like stroma, with only scant small nests of epithelial cells.78 In this subtype, the epithelial component may be subtle and, therefore, overlooked on routine histologic staining.3,7,8,36 However, immunohistochemical staining for keratin, an epithelial marker, highlights scant strands and single epithelial cells within a lesion that otherwise resembles OFD.3,8,36

Consensus has not been reached on the histologic criteria differentiating OFD, classic AD, and OFD-like AD.8 The current World Health Organization classification of soft-tissue and bone tumors states that an OFD lesion is devoid of epithelial differentiation and that “a tumor should be defined as OFD-like AD when keratin-positive epithelial cells are found.”98 Differentiating between OFD, OFD-like AD, and classic AD has proved to be even more difficult and controversial because immunohistochemical studies of lesions that are widely agreed to represent OFD also show scattered, isolated keratin-positive spindle cells within the stroma.1,12,14,15 However, most authors agree that the diagnosis of OFD-like AD requires the presence of nests of epithelial cells that are visible on routine staining, whereas lesions that have single, scattered epithelial cells seen only with immunohistochemical staining should be considered to represent OFD lesions.8 The criteria for distinguishing classic AD from OFD-like AD also varies, with some authors basing their decision on the size of the epithelial nests. Others consider a lesion to be classic AD when the epithelial component predominates over the stromal component.3,8,36

Even before OFD-like AD was recognized as a diagnostic entity, many researchers and clinicians believed that OFD and AD were related. Some authors felt that OFD was a precursor lesion that could progress to full-blown classic AD.1,3,12,13,15,24 The presence of an intermediate lesion such as OFD-like AD was felt to support that possibility, and there are sparse cases in the literature that report such a progression.37 However, in their review of 80 cases of OFD, for which the authors had follow-up information on 41 patients, Park et al2 reported that no case of OFD progressed to AD. Sweet et al13 reviewed 30 patients with OFD, and none progressed to AD. Others have proposed a contrasting theory, that differentiated or OFD-like AD represented a reparative process that was the body’s response to a spontaneously regressing AD.7,8,14 To date, however, there is a lack of well-documented cases of regressing AD.8

Other studies have been performed to explore a possible common histogenesis between OFD, OFD-like AD, and classic AD. Using immunohistochemistry, Maki and Athanasou10 demonstrated a common expression of several proto-oncogenes (eg, c-fos, c-jun) and bone matrix proteins (eg, collagen IV, laminin, galectin 3) in both OFD and AD. Some of these proteins are associated with mesenchymal-to-epithelial differentiation, which could explain the origin of the epithelial component of the tumor. These findings led the authors to conclude that OFD and AD are closely related and that OFD could represent a precursor lesion to classic AD. Bovée et al38 studied the expression of certain growth factors in the fibrous and epithelial portions of AD. They found that both the fibrous and epithelial components express fibroblast growth factor-2 and fibroblast growth factor receptor-1, whereas only the epithelial component expresses high levels of epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR). EGF and EGFR expression was higher in the epithelial cells in classic AD than in the epithelial cells of OFD-like AD. The authors also found high levels of Ki-67, a proliferation marker, in the epithelial component only. This helped to confirm that the epithelial portion is likely responsible for tumor growth and malignant activity, and that there are autocrine and paracrine mechanisms at play that allow the tumor to grow. It also lends support to the precursor lesion theory because the epithelial cells may acquire higher expression of fibroblast growth factor-2, EGF, and
EGFR, as well as higher proliferative activity, as the lesion progresses from benign to malignant.

Cytogenetic studies have provided further evidence that OFD and AD are likely related. Analyses of specimens from patients with OFD have demonstrated the presence of clonal chromosomal abnormalities, with trisomies of chromosomes 7, 8, 12, 21, and/or 22 occurring. In a review of AD cases by Kanamori et al, extra copies of chromosomes 7, 8, 12, 19, and/or 21 were found in seven of eight cases of classic AD and in two of three cases of OFD-like AD. These reports provide evidence not only that OFD may be a clonal neoplastic lesion rather than a developmental dysplasia, but also that OFD and AD are related lesions. It may be that multiple copies of chromosomes 7, 8, 12, 19, and/or 21 were found in seven of eight cases of classic AD and in two of three cases of OFD-like AD. These reports provide evidence not only that OFD may be a clonal neoplastic lesion rather than a developmental dysplasia, but also that OFD and AD are related lesions. It may be that multiple steps are required for the development of AD, involving growth factors and receptors and clonal chromosome abnormalities, and that OFD and OFD-like AD lesions have not undergone all of them. That the three lesions are related is well agreed on; whether one lesion can progress or regress to another remains controversial.

**Staging**

Diagnosis and staging begins with a thorough history and physical examination. The surgeon should obtain plain radiographs of the affected bone in at least two orthogonal planes. A CT scan through the area of the lesion can provide more information on the amount of cortical destruction and may reveal occult pathologic fracture.

MRI of the lesion is instrumental in determining diagnosis and planning treatment. Extension of the lesion into the medullary canal or extraosseous soft tissues can be detected and would influence the diagnosis toward AD versus OFD, in which the lesion is generally contained within the cortex. MRI is also critical in demonstrating the full proximal and distal extent of the lesion, allowing the surgeon to plan an appropriate operation with tumor-free margins in cases of AD. MRI can also aid in identifying the presence of multifocal disease, such as occult involvement of the ipsilateral fibula.

A well-planned biopsy should be strongly considered to confirm the diagnosis, even if the lesion is radiographically typical for OFD. The lesion may represent early AD. Alternatively, OFD may be a precursor to AD. In either case, a biopsy would facilitate a search for an epithelial component to the tumor. Ample diagnostic tissue is required for accurate diagnosis. The biphasic nature of classic AD (ie, benign fibrous and malignant epithelial) can lead to sampling error and to an erroneous diagnosis of a malignant AD as OFD. Therefore, extensive, and usually open, biopsy of the most radiolucent area of the lesion is recommended. Immunohistochemical staining for keratin can help in identifying the scattered epithelial cells in OFD-like AD and the nests of epithelial cells in classic AD.

When biopsy shows malignant AD, the patient should be evaluated for metastatic disease. The most common sites for metastasis are the lungs, regional lymph nodes, and other bones. Thus, physical examination for lymphadenopathy, high-resolution CT scan of the thorax, and nuclear bone scan should be performed.

**Treatment**

Because all of these lesions are rare and because most of the published literature is limited to case reports and small cases series, definitive treatment recommendations are difficult to determine. Even the largest published series include multiple institutions and/or occur over several decades, making it difficult to form definitive conclusions.

Management of OFD is somewhat controversial. Because it is a benign lesion that rarely progresses during childhood and never progresses after skeletal maturity, some authors recommend observation without surgical intervention (other than biopsy). Bracing may be done in an attempt to minimize deformity and prevent fracture. Surgical intervention is reserved for extensive or deforming lesions, or for pathologic fracture.

Recently, Lee et al recommended a more aggressive surgical approach for OFD—extraperiosteal resection in all cases. In their review of 16 patients diagnosed with OFD on initial biopsy, 3 ultimately were diagnosed with OFD-like AD or classic AD based on evaluation of the resection specimen. Thus, the authors concluded that because of the risk of sampling error, as well as the theory that OFD could progress to AD, all OFD lesions should be treated aggressively. An extraperiosteal approach was recommended because intralesion treatment often is inadequate, resulting in local recurrence. However, others feel that a better biopsy would have shown AD from the outset in those three patients and that they should not have been included in the study. Most authors feel that the benign nature of OFD is well established and that as long as the diagnosis is correct, observation and symptomatic treatment are sufficient.

The treatment of differentiated or OFD-like AD is not well established either because this diagnosis has only recently been reported as a separate entity. Of the few cases that have
been reported, no instance of metastasis from an OFD-like AD lesion has been noted. That has led some authors to recommend observation of small OFD-like AD lesions in children but surgical wide resection for any lesion that progresses.\textsuperscript{12,36}

Classic AD is a malignant lesion with metastatic potential. Chemotherapy and radiation have not been effective in the treatment of AD.\textsuperscript{4,43} Thus, surgical management is necessary, with the goal of attaining clear margins.\textsuperscript{3-5,24,25,31,43}

Historically, amputation was the treatment of choice; however, more recently, good results have been achieved with en bloc resection with wide margins, followed by appropriate reconstruction.\textsuperscript{4,8,24,25,43-46} Reconstructive options include allografts, vascularized and nonvascularized autografts, metallic segmental implants, and distraction osteogenesis\textsuperscript{43-45} (Figures 7 and 8). In their report of 70 patients with AD, Qureshi et al\textsuperscript{43} attempted limb salvage surgery in 91%; 84% had preserved their extremity at final follow-up. However, as with most complex tumor surgeries, the complication rate was high (48%). Nonunion and fracture were the most common complications.

Prognosis

OFD is a benign lesion and thus it has an excellent prognosis. Although there seems to be a link between OFD and AD, several large series of patients with OFD with excellent follow-up have failed to show any case of OFD that has progressed to AD.\textsuperscript{2,8,10,13} Other published isolated cases have reported progression of OFD to AD, but these may represent biopsy sampling error and initial misdiagnosis.

AD is a low-grade malignancy with metastatic potential, and it can be fatal. In a review of 85 cases of AD from the Mayo Clinic, there was a 31% local recurrence rate at an average 4.7 years after initial diagnosis.\textsuperscript{32} The metastasis rate was 22%. In a review of 32 patients from The Netherlands, 9 patients who underwent intralesional or marginal resec-
tion developed local recurrence, and 3 of those 9 went on to develop metastases.\textsuperscript{24} Five other patients developed metastases without a preceding local recurrence, even as late as >10 years after initial resection. Significant risk factors for local recurrence included shorter duration of symptoms (<1 year), pain at the time of presentation, initial surgical treatment that was intralesional or marginal, and patient age ≤20 years. Significant risk factors for metastasis included classic AD, as opposed to OFD-like AD, duration of symptoms <1 year, and initial surgical treatment that was either intralesional or marginal.

The most recent large series, an international multicenter review of 70 patients published in the year 2000, showed a local recurrence rate of 8.6% at 5 years and 18.6% at 10 years.\textsuperscript{41} Wide surgical margins were attempted in 91% of patients, with a final limb preservation rate of 84%. Wide margins were obtained in 92%. The 10-year survival rate was 87.2%, and no significant relationship was found between survival and tumor stage, duration of symptoms, sex, or surgical margins. This is consistent with historical mortality rates of 13% to 18% reported in the literature. The overall rate of metastasis was 13%, which is comparable to historical reports of 15% to 30%.\textsuperscript{41}

Long-term surveillance is required for survivors of this low-grade, slowly progressing tumor. Local recurrence usually occurs 5 to 15 years after diagnosis, but it has been reported as late as 24 and 36 years after diagnosis.\textsuperscript{4} Metastases can also occur many years later, even after an initial resection with wide margins and a disease-free interval of ≥10 years.\textsuperscript{4} Metastases are managed with surgical resection.

### Summary

OFD is a benign, self-limited, deformity-inducing fibro-osseous lesion that occurs almost exclusively in patients aged <20 years and that nearly always occurs in the tibia. Observation is the typical form of management, with symptomatic management when necessary. Surgery is generally reserved for larger lesions with more pronounced deformities or functional problems.

AD is a low-grade malignant primary bone tumor composed of neoplastic epithelial cells within a benign fibrous stroma. AD typically occurs in patients aged 20 to 50 years, and it usually presents in the tibia. The low-grade nature of the tumor correlates well with the occurrence of very late local recurrence and metastases (indicating very slow growth) and relatively high 5- and 10-year survival rates.

Similar patient demographics, lesion locations, radiologic and histologic appearances, and cytogenetic abnormalities, as well as the more recent description of an intermediate lesion (ie, differentiated AD or OFD-like AD) lend strong support to the theory that all three lesions are related and lie along a continuous spectrum of disease. Whether one lesion can progress or regress to another is not yet definitively known.

Adequate biopsy and correct diagnosis are critical. Untreated or undertreated AD will slowly progress and/or locally recur, and it can ultimately spread to distant sites, sometimes with fatal consequences.

### References

**Evidence-based Medicine:** Levels of evidence are described in the table of contents. In this article, references 2, 3, 7-25, 27-41, and 43-46 are level IV studies. References 1, 4-6, 26, and 42 are level V expert opinion.

Citation numbers printed in **bold** type indicate references published within the past 5 years.

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