

# **The Adamantinoma Complex**

## **Osteofibrous dysplasia, differentiated adamantinoma, classical adamantinoma**

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The adamantinoma complex is a spectrum of lesions which contain epithelial cells imbedded in a fibrous proliferation. The proportion of epithelial cells varies. At one end of the spectrum is osteofibrous dysplasia, a lesion which consists mainly of fibrous tissue and rare epithelial cells which can only be seen with immunostains for keratin. At the other end of the spectrum is classical adamantinoma. This lesion consists of many islands of fibrous tissue clearly visible on H&E stains. The epithelial cells are proliferating and have the ability to destroy bone and metastasize. Classical adamantinoma is a low-grade malignant tumor. In the center of the spectrum is differentiated adamantinoma. This lesion has limited bone involvement but with clear nests of epithelial cells visible on H&E stains.

The remarkable feature of this lesional complex is that the lesions occur almost exclusively in the mid-portion of the tibia. This specific location is unique in bone and tumor pathology. Since all lesions of the adamantinoma complex are confined to this zone, it is likely that they are all related.

An unusual feature of lesions in this complex is that, although they are primary bone tumors, they contain epithelial cells. Only a few other primary bone and soft tissue sarcomas have epithelial cells. These include chordoma, synovial sarcoma, and epithelial sarcoma. However, the epithelial cells in the adamantinoma complex show specific keratins. These include keratins 14 and 19. Many also contain keratin 5 and keratin 17. These keratins suggest a basal and differentiation. This is in contrast to the other primary bone and soft tissue sarcomas which contain epithelial cells. Epithelial cells in these other tumors contain predominantly keratins 8 and 18. The histogenesis of the adamantinoma complex is a mystery. One theory is that lesions have their origin in misplaced embryonic rests. This might explain why these lesions are nearly exclusive to the tibia, a bone that lies directly below the skin and perhaps easily exposed to the implantation of rests.

The problem with lesions in this complex is that there is total confusion about the diagnoses and the treatment. Confusion is present not only in the radiographic and histopathologic interpretation, but also about the best advice for management. Unfortunately, most cases in this lesional complex are overtreated.

There appears to be a natural evolution for lesions on one end of the spectrum to the other. Perhaps adamantinoma is an advanced osteofibrous dysplasia. There have been reported cases of osteofibrous dysplasia which evolved to adamantinoma. The question is whether all cases of osteofibrous dysplasia have the potential to evolve to classical adamantinoma.

Osteofibrous dysplasia is the most common of any lesion in this spectrum. It also occurs in younger patients, usually early childhood. Occasionally, it is present at birth; rarely it is bilateral. Lesions appear as lytic intracortical bubbles in the anterior cortex of the mid-shaft of

the tibia. Often there is anterior bowing. The lesions may be small or they may be extensive and multifocal in the tibial cortex. Sometimes intracortical sites in the fibula may also be involved. Osteofibrous dysplasia very often seems to increase in size until skeletal maturity. Then, lesions stabilize with no further growth; sometimes they regress. Histologically, osteofibrous dysplasia consists of woven bone present in a cellular fibrous matrix. The lesion has a superficial resemblance to fibrous dysplasia although the bone in osteofibrous dysplasia is lined by differentiated osteoblasts, a feature not seen in fibrous dysplasia. There appears to be a zonal distribution of the woven bone and the fibrous tissue. The bone is denser at the edges of the lesion. Immunohistochemical stains for cytokeratin demonstrate isolated keratin positive cells in approximately 80% of the cases of osteofibrous dysplasia.

Other names for osteofibrous dysplasia in our many historical records of this disorder include: ossifying fibroma, congenital pseudoarthrosis, intracortical fibrous dysplasia, and Jaffe Campanacci disease.

Treatment for osteofibrous dysplasia is controversial. Some surgeons recommend an excision of every lesion. This is based on the notion that these are pre-malignant and surgery would prevent the development of a fully malignant adamantinoma. Other surgeons feel that the lesions should not be touched unless there is significant skeletal deformity or a certain likelihood of fracture. A third possible treatment consideration is observation alone.

In contrast to osteofibrous dysplasia which is not uncommon, classical adamantinoma is the rarest of all primary bone tumors. It occurs with a frequency of 0.1 to 0.4% of all primary malignant bone tumors. Even bone pathologists have very limited experience with this tumor.

Adamantinoma has the same distribution pattern as osteofibrous dysplasia - the mid-portion of the tibia. However, patients are older, usually either 20's or 30's. Also, adamantinoma shows evidence of growth. There is usually extensive involvement of the medullary canal or invasion of the soft tissue around the tibia. Also, a pattern of aggressive bone destruction is sometimes present. Based on KI67 staining, only the epithelial cells proliferate. Also, these are the cells that metastasize, usually to the lungs. Therefore, we must conclude that it is the epithelial cells that are the neoplastic cells.

There are many histologic variants of the epithelial cells. The classic histologic pattern is a basaloid appearance. However, a squamous, tubular, and spindle cell differentiation may also occur. There is also a lesion which has recently been described called an adamantinoid Ewing's sarcoma. This consists of basaloid cells in a fibrous stroma. These cells are positive for CD-99 indicating that this lesion is a variant of Ewing's sarcoma and not an adamantinoma.

The intermediate lesion in the adamantinoma complex known as differentiated adamantinoma. It is also called juvenile adamantinoma or osteofibrous dysplasia-like-adamantinoma. Differentiated adamantinoma often shows extensive bubbly intracortical involvement of the. There are nests of epithelial cells visible on routine H&E stains. This is the most problematic of these lesions because it is presumed, incorrectly, that this is a malignant tumor simply because of the presence of epithelial cells. However if followed, most differentiated adamantinomas have limited growth and may cease growing altogether.

There are two theories which attempt to explain the relationship of osteofibrous dysplasia, differentiated adamantinoma, and classical adamantinoma. One theory is known as

the **regression theory** which states that the epithelial cells are the neoplastic cells, and that the fibro-osteoid tissue is a reparative-reactive proliferation which may completely overgrow the epithelial cells. A lesion that got started out in this spectrum but was quickly overgrown by the fibrous tissue is what we know to be osteofibrous dysplasia. However, if the epithelial cells were not overgrown and continued to proliferate, classical adamantinoma would result.

The other theory is the **progression theory**. This theory suggests that the spindle cells of the fibro-osteoid proliferation may convert to an epithelial differentiation (although this is extremely rare given the proportion of osteofibrous dysplasia to classic adamantinoma). Once the cells are differentiated into epithelial cells, they have the capacity to behave as a malignant neoplasm.

How should one manage lesions in this spectrum? Rather than defining a specific treatment modality for each lesion in this complex, every case should be approached with the question, "Are the epithelial cells growing?" Although osteofibrous dysplasia may proliferate and, as the child matures, involve significant portions of the tibia, the vast majority of lesions will not metastasize. Patients with lesions in this complex should be closely followed. Evidence of growth of the lesion -- soft-tissue invasion, medullary canal involvement, aggressive bone destruction, and growth over time after skeletal maturity -- is the clue the lesion should be treated aggressively. Thus, a patient who has had long standing osteofibrous dysplasia and in adulthood has a new zone of destructive bone changes should be regarded as having classical adamantinoma. It should be emphasized, however, that this eventuality is extremely rare.

#### Suggested Readings

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6. Putnam A, Yandow S, Coffin CM: Classic adamantinoma with osteofibrous dysplasia-like foci and secondary aneurysmal bone cyst. *Pediatr Dev Pathol.* 6:173-178, 2003.

## Bullet Points

1. Lesions of the adamantinoma complex consist of osteofibrous dysplasia, differentiated adamantinoma and classical adamantinoma. These lesions are related. They all contain epithelial cells in varying proportions and are almost exclusively limited to the mid-shaft of the tibia.
2. Lesions in this complex are usually overtreated. This is due to occasional reports of osteofibrous dysplasia evolving into adamantinoma.
3. Most lesions of osteofibrous dysplasia are self limited.
4. The factor which should most decisively determine which lesions should get aggressive therapy are those in which it can be proven that the epithelial component is growing. This is because the epithelial cells are the neoplastic cells in lesions of this complex. Evidence of growth includes medullary canal involvement, soft-tissue invasion, an aggressive radiographic pattern, and a growth of the lesion after skeletal maturity.
5. Two contradicting theories are offered to explain lesions in the adamantinoma complex.
  - a. The fibrous tissue is a radioactive reparative response.
  - b. The epithelial cells result in a transformation of the fibroblastic cells.