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The Minimalistic Metamorphoses-Adamantinoma

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Mini Review

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Abstract

Adamantinoma is an exceptional, primary, malignant, low-grade bone, biphasic, fibro-osseous bone neoplasm of uncertain origin typically constituted of epithelial articulations embedded within a mesenchymal or osteofibrous dysplasia-like stroma. Adamantinoma commonly arises within diaphysis and metaphysis of tibia in addition to ulna, femur, fibula, humerus, radius, ribs, tarsal and metatarsal bones. Adamantinoma depicts a repetitive mutation of KMT2D (MLL2) gene along with fusion of somatic gene EPHB4-MARCH10. Expression of DLK1 gene is enhanced. Adamantinoma is subdivided into diverse categories such as classic subtype, osteofibrous dysplasia-like or differentiated adamantinoma and dedifferentiated adamantinoma. The neoplasm is comprised of epithelial cells with minimal atypia disseminated within an osteofibrous dysplasia -like stroma. Solid nests of basaloid cells with peripheral palisading, tubular structures, clusters of keratinized squamous epithelium or fascicles of spindle-shaped cells are exemplified.

Keywords: Adamantinoma; Osteofibrous; Mesenchymal; Histogenesis

Abbreviations: CT: Computerized Tomography; MRI: Magnetic Resonance Imaging; EMA: Epithelial Membrane Antigen; RANKL: Receptor Activator of Nuclear Factor Kappa-B Ligand; EGFR: Epidermal Growth Factor Receptor; FGFR: Fibroblast Growth Factor Receptor; FGF: Fibroblast Growth Factor.

Introduction

Adamantinoma is an exceptional, malignant, low-grade bone neoplasm which is thus nomenclated on account of histological similarity to ameloblastoma of the mandible. The exceptional, malignant, primary, biphasic, fibro-osseous bone neoplasm of uncertain origin is typically constituted of epithelial articulations embedded within a mesenchymal or osteofibrous dysplasia-like stroma. The neoplasm predominantly incriminates bones of lower extremity such as tibia or fibula. Although discernible by cogent imaging, adamantinoma is preponderantly categorized by pertinent histopathological evaluation. Concurrence of adamantinoma and osteofibrous dysplasia is debatable and is contingent to adequate tumour discernment, specific therapeutic options and prognostic outcomes of the neoplasm.

Disease Characteristics

Of obscure histogenesis, adamantinoma commonly arises within diaphysis and metaphysis of tibia and probably originates due to preliminary displacement of cutaneous basal epithelial cells during embryogenesis. It is thus posited that adamantinoma commonly emerges within anterior tibia, a site where endochondral bone is adjacent to cutaneous surfaces [1,2]. Possibly, epithelial component of adamantinoma is engendered directly from the mesenchyme with gradual quantitative enhancement. Emergence of an aggressive subtype may accompany transition from epithelial to mesenchymal tissue, also denominated as sarcomatoid dedifferentiation, a feature where epithelial

immune-phenotype is discernible. Osteofibrous dysplasia may pre-empt an adamantinoma. Contingent to specific immunohistochemistry and ultrastructural assessment, adamantinoma may contemplated to be of epithelial origin [1,2]. As an exceptional neoplasm, adamantinoma represents approximately 0.4% of primary malignant bone neoplasms. A slight male preponderance is observed with a male to female proportion of 5:4. Median age of disease emergence is 30.8 years although the neoplasm is observed between 4 years to 75 years. Generally, adamantinoma occurs within young to middle aged adults between 20 years to 40 years and rarely implicates paediatric or elderly population [1,2]. Common sites of neoplastic appearance are anterior metaphysis or diaphysis of tibia. Majority (~90%) of tumefaction are situated within median third of diaphysis of tibia where multifocal neoplasms are common. However, neoplasm can arise within the ulna, femur, fibula, humerus, radius, ribs, tarsal and metatarsal bones besides extra-skeletal, pretibial soft tissue. Synchronous incrimination of tibia and fibula occurs in around 10% subjects [1,2]. Adamantinoma depicts a repetitive mutation of KMT2D (MLL2) gene along with fusion of somatic gene EPHB4-MARCH10. DLK1 gene expression is enhanced. Repetitive anomalies of extra copies of chromosomes 7, 8, 12, 19 and 21 are discerned in osteofibrous dysplasia, osteofibrous dysplasia-like and classic adamantinoma thereby indicating a common genesis of the neoplasm [1,2]. The gradually progressive neoplasm is associated with localized tumour reoccurrence in around 30% to 35% subjects. Nearly 15% to 30% neoplasms metastasize through the lymphatics or blood stream to lymph nodes or pulmonary parenchyma. Metastasis to diverse bones and abdominal viscera are also discerned. Mortality associated with adamantinoma is roughly 6% to 18% [1,2].

Clinical Elucidation

The indolent neoplasm may depict nonspecific clinical features and cogent symptoms are pertinent to tumour location and extent of disease [3,4]. Adamantinoma exemplifies an insidious biological behaviour with gradual tumour progression. Tumefaction arises as a painless or painful, gradually evolving mass. Bone deformity and pathological fracture may ensue. Neurological deficits appear with incrimination of vertebral column [3,4]. Adamantinoma is subdivided into diverse categories such as

- classic subtype which is composed of distinctive epithelial constituents encompassed within a fibro-osseous stroma [3,4].
- osteofibrous dysplasia -like or differentiated adamantinoma exhibits inconspicuous aggregates of epithelial cells embedded within a fibro-osseous stroma.
- dedifferentiated adamantinoma exemplifies a sarcomatoid alteration along with decimated epithelial differentiation [3,4].

Histological Elucidation

On cytological examination, the biphasic neoplasm depicts epithelioid cells commingled with spindle-shaped cells. The cells are disseminated singularly or configure miniature fragments. Epithelioid cells demonstrate indistinct cytoplasmic boundaries, uniform spherical to elliptical nuclei, fine chromatin, distinct nuclear grooves and occasional micro-nucleoli. Spindle-shaped cells depict elliptical nuclei and are imbued with an abundant, clear cytoplasm [3,4]. Adamantinoma is a biphasic neoplasm configuring differentiating tumour patterns characteristically comprised of diverse proportions of commingled epithelial cells and osteofibrous components. Fibrous component appears as loosely cohesive, myxoid, hyalinized or sclerotic tissue. Mitotic activity is around 0 to 2 mitoses per 10 high power fields [5,6].

Classic adamantinoma manifests as a singular, well-demarcated, yellowish-grey, lobulated, firm or bony neoplasm with a sclerotic perimeter, confined to the bone cortex [5,6]. Majority of neoplasms are fleshy, firm, yellow-grey or greyish white. Lesions are occasionally multifocal. Infrequently, tumour parenchyma demonstrates cysts incorporated with straw coloured or haemorrhagic fluid. Characteristically, classic adamantinoma demonstrates distinctive epithelial cells admixed with osteofibrous components [5,6]. Classic adamantinoma depicts a significant epithelial component comprised of epithelial cells with minimal atypia disseminated within an osteofibrous dysplasia-like stroma. Solid nests of basaloid cells with peripheral palisading are prominent. Additionally, tubular structures, clusters of keratinized squamous epithelium or fascicles of spindle-shaped cells are exemplified [5,6].

Diverse proportions and differentiation of epithelial and osteofibrous components engender diverging tumour configurations designated as basaloid, tubular, spindle-shaped and squamous. Basaloid and tubular tumour architecture are frequently encountered. Spindle-shaped cellular component is predominantly delineated within layered cystic spaces, tumour reoccurrences and distant metastases [5,6]. Osteofibrous component preponderantly displays a storiform configuration engendered by spindle-shaped cells. Trabeculae of woven bone abut tumour centre or are centroidal and are prominently rimmed by osteoblasts. Transformation into lamellar bone appears within the tumour periphery [5,6]. Foam cells, foci of myxoid alterations, mast cells or multinucleated giant cells are exemplified. Mitotic activity is minimal [5,6]. Osteofibrous dysplasia-like variant typically represents a preponderance of osteofibrous tissue wherein miniature clusters of epithelial cells are discernible upon extended examination or specific immunohistochemistry. Adamantinoma necessitates

extensive tissue evaluation as differentiated neoplasms may focally exhibit the epithelial component [5,6]. Osteofibrous dysplasia-like adamantinoma typically exhibits miniature aggregates of epithelial cells, immune reactive to keratin, scattered amidst a prominent osteofibrous dysplasia-like stroma. Dedifferentiated adamantinoma manifests sarcomatoid features such as pleomorphic cells, significant mitotic activity, osteoid and chondroid accumulation or clear cell change. Sarcomatoid foci are immune non-reactive to keratin. On ultrastructural examination, epithelial cells display tonofilaments, hemidesmosomes and desmosomes [5,6].

Immune Histochemical Elucidation

Epithelial cells are immune reactive to keratin, epithelial membrane antigen (EMA), vimentin, p63 and podoplanin. Fibrous tissue is immune reactive to vimentin. Classic adamantinoma demonstrates an epithelial component circumscribed by an intact basement membrane comprised of type IV collagen, laminin and galectin. Additionally, oestrogen, progesterone and N-cadherin molecules may be discerned [1,2]. Tumour cells are immune reactive to keratin, cytokeratin AE1/AE3, basal epithelial keratin specific reactivity to CK5, CK14 and CK19, vimentin, epithelial membrane antigen (EMA), p63 and podoplanin (D2-40). Tumour cells are immune non-reactive to CK8, CK18 and CD34 [1,2]. Osteofibrous dysplasia-like adamantinoma is composed of diffuse, interrupted epithelial islands with an absence of enveloping basement membrane. Epithelial component is immune reactive to epidermal growth factor and epidermal growth factor receptor (EGF/EGFR) [1,2]. Epithelial islands and fibrous tissue delineate fibroblast growth factor 2/ fibroblast growth factor receptor 1 (FGF2/FGFR1) [1,2]. Upon cell culture, tumour manifests macrophage colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL), molecules which engender osteolysis [1,2]. Differential Diagnosis Adamantinoma requires segregation from conditions such as •osteofibrous dysplasia is devoid of aggregates of epithelial cells and is immune reactive to keratin [7,8]. •metastatic carcinoma within the bone generally displays a diffuse dissemination of malignant cells. The neoplasm usually incriminates elderly population and is infrequent beneath the knee joint. Vascular invasion is associated with extensively malignant cellular component. Osteofibrous dysplasia-like stroma is usually absent [7,8]. •adamantinoma like Ewing's sarcoma is associated with significant epithelial differentiation. Tumour cells are diffusely immune reactive to cytokeratin and p63. Additionally, molecules such as NKX2.2, CD99 and FL1 may be detected. Pertinent chromosomal rearrangements such as genomic fusions between EWSR1 gene situated upon chromosome 22 and ETS family of transcription factors are observed. However, FUS gene situated upon chromosome 16 is uncommonly substituted for EWSR1 gene [7,8].

Differentiated adamantinoma or osteofibrous dysplasia-like adamantinoma may simulate osteofibrous dysplasia appearing within the tibia. Demarcation between the lesions can be challenging on histological and radiological grounds [7,8]. Additionally, clinical, radiological and morphological segregation of adamantinoma is necessitated from diverse bone tumours such as bone cysts, giant cell tumour or malignant neoplasms as chondrosarcoma, angiosarcoma and metastatic bone deposits [7,8].

Investigative Assay: Upon plain radiography, the osteolytic tumefaction situated within the bone cortex is well defined and multi-lobulated. Lesions may be multifocal, septate with intrinsic opacities and peripheral sclerosis. Radiolucent lesions are circumscribed by "ring-shaped" densities with consequent ''soap-bubble'' appearance. The cortical tumefaction expands longitudinally. However, infiltration of medullary cavity, encompassing periosteum and soft tissues may ensue secondary to destruction of bony cortex. A lamellar or solid periosteal reaction accompanies the osteolytic, cortical tumefaction [7,8]. Plain radiographs depict a singular or multiple lytic lesions of variable magnitude circumscribed by a sclerotic perimeter. A "soap-bubble" appearance of implicated diaphysis or metaphyseal cortex is discerned. Upon computerized tomography (CT), the cortical neoplasm exhibits expansion into circumscribing soft tissue. However, intraosseous extension of adamantinoma is absent. Computerized tomography can adequately detect occurrence of pulmonary metastases, incrimination of bone cortex and determination of bone metastases. Osteofibrous dysplasia and osteofibrous dysplasia-like adamantinoma is stringently confined to intra-cortical region [7,8]. Magnetic resonance imaging (MRI) can detect intramedullary or distant, cortical lesions or soft tissue invasion and may be adopted to assess loco-regional tumour metastasis for cogent tumour staging. Magnetic resonance imaging can appropriately determine a tumour-free surgical perimeter and is employed to assess strategies for reconstructive surgery. Upon MRI, adamantinoma can appear as a singular, lobulated neoplasm or as multiple, miniature nodules confined to a singular or multitudinous foci [7,8]. Adamantinoma depicts a minimal signal intensity upon T1 weighted imaging and enhanced signal intensity upon T2 weighted imaging. Although the neoplasm is detectable on diverse imaging procedures, definitive diagnosis is obtained by cogent tissue sampling. Open biopsy can be adopted for accruing additional tissue. Infiltration of medullary cavity or extra-osseous soft tissues is appropriately visualized with MRI [8,9].

Therapeutic Options: A comprehensive surgical extermination with a broad, perimeter of tumour- free tissue is efficacious in treating adamantinoma. Following a wide,

en bloc surgical resection, methodologies such as distraction allograft, osteogenesis, non-vascularized autogenous bone graft, vascularized autograft and metallic segmental replacement can be employed for limb reconstruction [8,9].

Adamantinoma subjected to amputation versus limb-sparing surgery is accompanied by identical survival rates. Simple curettage, marginal resection or intra-lesional excision of the neoplasm enhances proportionate localized tumour reoccurrence [8,9]. Radiotherapy and chemotherapy are ineffective in treating adamantinoma [8,9]. Adamantinoma demonstrates localized tumour aggression with possible occurrence of distant metastasis. Localized tumour reoccurrence is observed following inadequate surgical eradication. Tumour reappearance and distant metastasis is commonly observed in neoplasms arising in young individuals below <20 years, male subjects, duration of clinical symptoms below < 5 years, pain at initial representation of disease and preliminary therapy with simple curettage or surgical resection. Additionally, lack of squamous differentiation with enhanced epithelium to stroma proportion within the neoplasm is associated with tumour relapse or metastasis [8,9]. Classic adamantinoma is indolent with an unpredictable clinical course. Enhanced tumour reoccurrence upon incomplete surgical excision is contingent to elevated epithelium to stroma proportion [8,9]. Superior prognosis accompanies a comprehensive or radical surgical extermination [8,9]. Osteofibrous dysplasia-like adamantinoma is associated with a favourable outcome, in contrast to classic adamantinoma [8,9]. Dedifferentiated adamantinoma exhibits an aggressive clinical course [8,9].

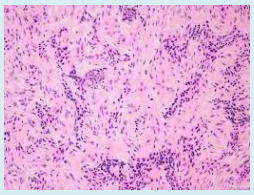

Figure 1: Adamantinoma demonstrating an epithelial component with cords and clusters of cells surrounded by a fibrotic stroma and minimal atypia [10].

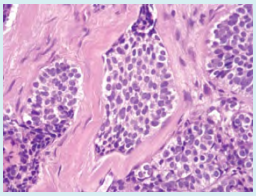

Figure 2: Adamantinoma exhibiting aggregates of epithelial cells with peripheral palisading scattered amidst a stroma rich in fibrous tissue [11].

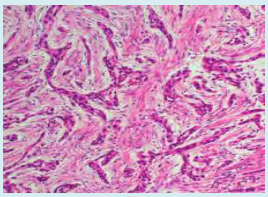

Figure 3: Adamantinoma exemplifying cords and fascicles of epithelial cells disseminated between a preponderantly fibrotic stroma [12].

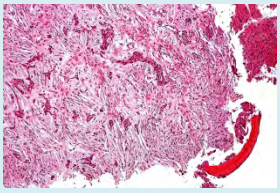

Figure 4: Adamantinoma delineating cords and bundles of epithelial cells intermingled within a fibrotic stroma and lack of atypia [13].

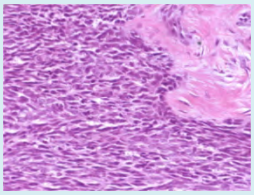

Figure 5: Adamantinoma depicting islands and clusters of epithelial cells surrounded by a dense fibrotic stroma with spindle-shaped cells [14].

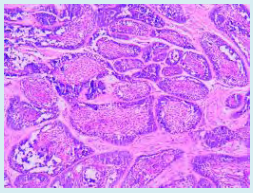

Figure 6: Adamantinoma displaying nests of epithelial cells with peripheral palisading intermixed within a spindly, fibrotic stroma [15].

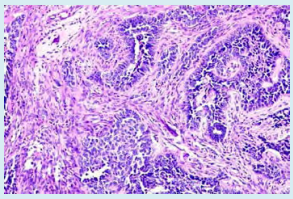

Figure 7: Adamantinoma demonstrating metastatic deposits within the tibia composed of islands of epithelial cells with peripheral palisading and a circumscribing fibrous tissue stroma [16].

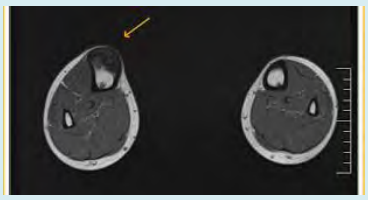

Figure 8: Adamantinoma demonstrating solitary, radiolucent lesion situated beneath the bone cortex in a across section of tibia [17].

Conclusion

Adamantinoma is immune reactive to keratin, cytokeratin AE1/AE3, vimentin, epithelial membrane antigen (EMA), p63 and podoplanin (D2-40). Keratin specific basal epithelium is immune reactive to CK5, CK14 and CK19. Adamantinoma requires segregation from conditions such as osteofibrous dysplasia, bone metastatic carcinoma, adamantinoma like Ewing's sarcoma, bone cysts, giant cell tumour or malignant neoplasms as chondrosarcoma and angiosarcoma. Plain radiography depicts an osteolytic, cortical, well defined and multi-lobulated tumefaction. Adamantinoma depicts a minimal signal intensity upon T1 weighted magnetic resonance imaging and enhanced signal intensity upon T2 weighted magnetic resonance imaging. Comprehensive, en bloc surgical extermination with a broad, perimeter of tumour- free tissue is efficacious in treating adamantinoma.

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10. Image1 Courtesy: Pathology outlines.
11. Image 2 Courtesy: Orthobullets.com.
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