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Review Article

NONODONTOGENIC MALIGNANT TUMORS OF THE JAW BONE

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ABSTRACT

The malignant neoplasms affecting the maxilla and the mandible are categorized into primary tumors (originate within the mandible), secondary tumors, and metastatic lesions, (which involve the mandible secondarily) The most common malignant neoplasm represents the oral squamous cell carcinoma notably carcinoma of the floor of the mouth and gingiva that involved the mandible secondarily. Metastatic disease, such as those commonly arises from the breast and lung, are not uncommon malignant lesion of the mandible and regarded as the first manifestation of a malignant tumors outside the head and neck. The diagnosis of these neoplasms is important since these tumors have serious prognostic implications.

INTRODUCTION

Malignant tumors of the mandible and maxilla are grouped into primary tumors that originate within the mandible and secondary lesions, predominantly oral cancers and metastatic lesions, that involve the mandible secondarily. The most common malignant tumors of the mandible represent squamous cell carcinomas (**SCCs**) of the oral cavity, notably carcinoma of the floor of the mouth and gingiva that invade the mandible secondarily. [1]Metastatic disease, most commonly from the breast and lung, are not an uncommon malignant lesion in the mandible and may be the first manifestation of a malignant lesion outside the head and neck. Despite their infrequent occurrence, the recognition and diagnosis of a malignant jaw tumor is important since these tumors have serious prognostic implications.[1]

Chrondrosarcoma

Overview

"A malignant tumor characterized by the formation of cartilage, but not of bone, by the tumor cells. It is distinguished from chondroma by the presence of more cellular and pleomorphic tumor tissue, and by appreciable numbers of plump cells with large or double nuclei. Mitotic cells are infrequent[4]."- WHO

Chondrosarcoma is the third most common primary malignancy of bone, grow slowly and rarely metastasize[5].More often involve the maxillofacial area (60%) than the mandible (40%) and in the maxilla usually involve the anterior region and the palate. In mandible, occur in the premolar and molar regions, symphysis, and coronoid process, and occasionally in the condylar process.[6]The radiographic survey may show radiolucent, radiopaque, or mixed lesions that are relatively circumscribed or poorly demarcated.[6]Appearance varies from moth-eaten radiolucencies that are solitary ormultilocular to diffusely opaque lesions.[2]

Molecular Pathology

Studies have shown that various mutations of genes are identified in chondrosarcoma that includes IDH1 or IDH2 genes which are found in 86% of secondary central chondrosarcomas. Progression of enchondroma toward chondrosarcoma is characterized by aneuploidy and complex karyotypes with increasing histologic grade, with aberrationsin the p53 and Rb pathways. Mutations in COL2A1 gene, comprising insertions, deletions, and rearrangements, have been found in approximately 45% in secondary central chondrosarcomas. [7] NRAS (Q61K and Q61H) mutations have been identified in a subset of conventional central chondrosarcomas (12%). This activating NRAS mutation may be related with conventional central chondrosarcoma initiation, maintenance, or progression. In addition, mutations in TP53 (20%), the RB1 pathway (33%), and IHH signaling (18%) have been identified. [7]

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Histopathology

Chondrosarcomas are composed of cartilage showing varying degrees of maturation and cellularity. In most cases, lacunar formation within the chondroid matrix is evident, although this feature may be scarce in poorly differentiated tumors. The tumor often shows a lobular growth pattern.[8] The central areas of the lobules demonstrate the greatest degree of maturation, whereas the peripheral areas tend to exhibit immature cartilage and mesenchymal tissue consisting of round or spindle-shaped cells. Calcification or ossification may occur within the chondroid matrix.[8]

Grading

Grade I: Chondrosarcomas closely mimic the appearance of a chondroma, composed of chondroid matrix and chondroblasts that shows only subtle variation from the appearance of normal cartilage. The distinction between benign and well-differentiated malignant cartilaginous tumors is difficult. This tumor should be considered malignant when large, plump chondroblasts and binucleated chondrocytes are present. Calcification or ossification of the cartilaginous matrix often is prominent and mitosis are rare.

Grade II: Chondrosarcomas shows greater proportion of moderately sized nuclei and increased cellularity, particularly about the periphery of the lobules. The cartilaginous matrix tends to be more myxoid, with less prominent hyaline matrix. The mitotic rate is low.

Grade III: Chondrosarcomas are highly cellular and may show a prominent spindle cell proliferation. Mitosis may be prominent. Easily recognizable cartilaginous matrix containing cells within lacunae may be scarce.

Chondrosarcomas of the jaws are predominantly of histopathologic grades I and II tumors are very common.[9]

Mesenchymal Chondrosarcoma

Lichtenstein and Bernstein first described Mesenchymal Chondrosarcoma in 1959.[8] It is a rare form accounting for 0.33% to 0.5% of all primary malignant neoplasm of bone and histologically distinct and clinically unique compared with chondrosarcoma.[10] It can occur at any age, the peak incidence is in the second and third decades. characterized by a bimorphic pattern that is composed of highly undifferentiated small round cells and islands of well differentiated hyaline cartilage. Those that arise in bone show a predilection for the maxilla, mandible, and ribs.[10]

Osteogenic Tumors

Overview

Osteosarcoma is a malignant neoplasm characterized by direct formation of bone or osteoid by the tumor cells. Presents most commonly as a conventional intramedullary type or, less frequently, as rare variants, including periosteal, parosteal telangiectatic, small cell, and low-grade central types.[11] Approximately 80% of osteosarcomas are conventional intramedullary tumors and 80% to 85% arises in the long bones and they are relatively infrequent in the head and neck area. Studies have shown that it accounts for 6.5%involving skull, mandible or maxilla, facial bones, or cervical vertebrae.[9]Osteosarcoma may arise secondarily to some underlying condition, the most frequent include Paget's disease, usually in the polyostotic form; fibrous dysplasia (FD), bone infarct and irradiated bone. The craniofacial region is the most common site for osteosarcoma arising on the basis of preexisting fibrous dysplasia. [11]Osteosarcoma can also arise in two cancer susceptibility syndromes: hereditary retinoblastoma (Rb) and Li-Fraumeni syndrome. Osteosarcoma occurs chiefly in young persons, the majority between 10–25 years with decreasing incidence as the age advances. It is very rare in young children and the incidence increases steadily with age. [2] The most common presenting symptoms of the patients were swelling of the involved area, often producing facial deformity and pain, followed by loose teeth, paresthesia, toothache, bleeding, nasal obstruction and a variety of other manifestations. Mandibular tumors are more common than those in the maxilla.[12]Radiologically, osteosarcoma of the jaw has a purely lytic and destructive pattern in 35% to 45% of cases, a sclerotic pattern in 5% to 65% of cases, and a mixed pattern of lysis and sclerosis in 22% to 50% of cases.[11] A sunburst pattern, with radiating spicules of bone is considered a characteristic feature of osteosarcoma of the jaw, especially in mandibular lesions. An important radiologic feature of osteosarcoma of the jaws is symmetric widening of the periodontal membrane space that may also be associated with loss of the lamina dura. Although not specific for osteosarcoma, its occurrence is suggestive of an aggressive process.[13]

Histopathology

Microscopic features may vary considerably in different areas of a tumor:

Tumor is basically composed of sarcomatous, spindle-shaped cells exhibiting evidence of tumor osteoid production. Sarcomatous stroma is hypercellular and may exhibit osteoblastic, chondroblastic, fibroblastic, or malignant fibrous histiocytoma-like differentiation. Cells usually have obvious cytologic malignant features, including brisk mitotic activity with atypical forms. Some cells may exhibit epithelioid features.[14] Tumor osteoid is represented by eosinophilic, amorphous, fibrillary deposits between individual tumor cells or small aggregates of tumor cells. Early tumor osteoid forms a lacelike pattern around tumor cells, whereas the more advanced type is mineralized and has the appearance of woven tumor bone.[15]Some tumors exhibit prominent chondroblastic differentiation requiring careful search for tumor osteoid. Fibroblastic areas may exhibit a herringbone pattern; diligent search for tumor osteoid is sometimes required[16]

Small Cell Variant

May have features suggestive of Ewing sarcoma, mesenchymal chondrosarcoma, and lymphoma and require immunohistochemistry for differentiation and presence of tumor osteoid. Rare cases of small cell variant share genetic features of Ewing sarcoma. Preoperative chemotherapy may result in tumor necrosis represented by acellular tumor osteoid, acellular chondroid tissue, fibrosis, or hyalinized vascular stroma; preoperative chemotherapy is considered effective when greater than 90% of the tumor is necrotic[16]

Immunohistochemistry

IHC is of limited value in the diagnosis of osteosarcoma. Can be positive for osteoblastic lineage biomarkers, including bone morphogenetic proteins, osteocalcin and osteopontin. S100 protein can be seen in the areas that exhibit cartilaginous differentiation. Occasional focal positivity for keratins,

epithelial membrane antigen and muscle markers (smooth muscle actin and desmin) [17]

Parosteal Osteosarcoma

According to the World Health Organization classification of tumors of soft tissue and bone: Osteosarcomas arising from the bone cortical surface are a spectrum of diseases and can be subdivided into parosteal, periosteal, and high-grade surface osteosarcoma.[14]This distinction isbased on the clinical presentation, histologic grade, and prognosis. Among the subdivisions, parosteal osteosarcoma represents the well-differentiated end. It is an uncommon malignant bone tumor, comprising 4% of all osteosarcomas. This entity was first characterized by Geschickter and Copeland in 1951 as "parosteal osteoma".[18]

Overview

Parosteal osteosarcoma differs in prevalence with regard to sex and age. It has a slight female predominance and most frequently occurs in the third decade of life peak incidence at 39 years.[3] The tumor is usually located at the posterior aspect of the distal femur in about 70% of cases, followed by the proximal tibia and proximal humerus. Rare locations, including cranial, mandible, rib, clavicle, and tarsal bone, have also been reported. Patients usually report a painless mass lasting for years, with decreased range of movement of the adjacent joint. Dull pain and local tenderness are the second most common symptoms. [18] Radiographically, the tumor often manifests as a lobulated, mushroomlike mass protruding from the underlying cortex with a broad base attachment. It has an irregular pattern of mineralization, and the periphery of the tumor is generally less radiodense than the center.[18]

Histopathology

The most prominent feature of parosteal osteosarcoma is its component of rather regularly arranged osseous trabeculae. Apparently, the more immature trabeculae undergo maturation in this slowly developing tumor and become "normalized." Between these nearly normal trabeculae are slightly atypical, proliferating spindle cells in which only occasional mitotic figures are found. The cellular proliferation is hypocellular, with abundant collagen between individual tumor cells. The spindle cells only show slight cytologic atypia.[9,19]

Periosteal Osteosarcoma

Periosteal Osteosarcoma was first recognized by Ewing in 1939 and further described by Lichtenstein as a periosteal counterpart of the conventional intramedullary osteosarcoma. The term periosteal osteosarcoma as a distinct clinicopathologic entity was first used by Unni *et al*. in 1976 due to its particular behavior that is distinct from those of conventional intramedullary osteosarcoma.[20]Periosteal osteosarcoma is a low- to intermediate-grade bone-forming sarcoma with predominantly chondroblastic differentiation that develops on the surfaces of long bones in children. It arises beneath the periosteum, elevating it and provoking prominent periosteal new bone formation. Some authors designated these extensively cartilaginous osteosarcomas as *juxtacortical chondrosarcomas.*[21]

Periosteal osteosarcoma is a rare tumor that represents than 2% of osteosarcomas. The peak incidence is during the second decade of life, and occurs more commonly in female patients, with a 1:1.7 maleto-female ratio. It occurs almost exclusively on the long tubular bones of a lower extremity. The tibia is most frequently involved, followed by the femur, with diaphyseal location predominating over metaphyseal. More rarely, the long bones of an upper extremity are involved, and individual cases have been reported in the acral skeleton and craniofacial bones (the mandible). Periosteal osteosarcomas of the mandible and maxilla are usually small, ranging from 2.7 to 3.5 cm.[11,21] Radiographical appearance shows radiolucent fusiform lesion that presents on the surface of a long bone. The periosteum appears to have been elevated by the tumor's expansion external to the cortex, which provokes prominent periosteal new bone formation in the form of both perpendicular striae and peripheral Codman's triangles seen on plain radiographs.[21]

Histopathology

Microscopically, periosteal osteosarcoma consists of lobules of high-grade malignant cartilage that are separated by spindle-shaped mesenchymal cells in which eosinophilic lacelike ribbons of osteoid are found. However, these osteoid areas may be quite sparse and difficult to find and are best seen at the peripherally growing margin of the lesion. In some cases, fibroblastic or even osteoblastic foci may be found and even predominate, such that the tumor may be difficult to distinguish from a conventional high-grade surface osteosarcoma.[11]

Chondroblastic Osteosarcoma

Chondroid matrix is predominant in chondroblastic osteosarcoma. It tends to be high grade hyaline cartilage, which is intimately associated, and randomly mixed, with non-chondroid elements.[14] Myxoid and other forms of cartilage are uncommon, except in the jaws and pelvis. Grossly, an overt chondroid appearance is rare. This is probably secondary to the cartilage component being less well-formed, high grade, and mixing with non-chondroid elements resulting in a lack of large areas of pure chondroid differentiation and its attendant blue-grey lobulated appearance.[14]

Low Grade Central variant

A low grade osteosarcoma that arises from the medullary cavity of bone.[14] Low-grade lesions are rare and represent less than 2% of all osteosarcomas reported in the literature. Because of its rarity and well differentiation, low-grade osteosarcoma is usually misdiagnosed as a benign lesion. The clinical and radiographic presentation does not correlate well with the subtle histology picture of a low-grade osteosarcoma which makes the diagnosis difficult.[22] Low grade central osteosarcoma accounts for less than 1% of primary bone tumours and only 1-2% of all osteosarcomas. Males and females are equally affected. The peak incidence is in the second and third decades of life. Approximately 80% are located in the long bones with a distinct predilection for the distal femur and proximal tibia. The femur is the most frequently involved bone (approximately 50%), followed by the tibia, which is the second most frequently involved bone. Flat bones are uncommonly affected. Pain and / or swelling are the usual complaints. The duration of pain may be many months or even several years.[14, 22] Radiological features show large, poorly marginated intramedullary mass that either is sclerotic or exhibits trabeculations. Usually no evidence of periosteal reaction. Medullary tumor may extend along the length of the bone to the subarticular bone. May have cortical destruction with formation of a soft tissue mass.[16]

Histopathology

Common histologic features include a spindle cell proliferation with low cellularity, low mitotic rate, bland or minimal cytologic atypia, and variable osteoid production. Hypocellular to moderately cellular fibroblastic stroma with variable osteoid production. Intersecting bundles of spindle cells permeate through the preexisting bony trabeculae of the medullary cavity. Only minimal cytologic atypia, with some degree of nuclear enlargement and hyperchromasia. Rare mitotic figures may be seen. Osteoid production is variable, some resembling irregular trabeculae of woven bone, whereas others appear as parallel trabeculae. Cartilage production may also be observed rarely.[33]

Ewing's Sarcoma or Primitive Neuroectodermal tumor

Ewing's sarcoma is a sarcoma of the bone, classically describedunder small round cell tumors. First reported by James Ewing in 1921. There is considerable clinicaland histologic overlap between this tumor and the primitiveneuroectodermal tumor (PNET). Now with sophisticatedmolecular biological analysis, it turns out that both tumorssh are a common and unique chromosomal translocation.[12]

In general, Ewing's sarcoma arises within the bonewhile PNET arises within soft tissues. However, there areoverlap cases of Ewing's sarcoma arising within soft tissue (extraosseous Ewing's sarcoma) and PNET arising within thebone. Under the microscope, the tumors share a considerable homology though there are usually more neuroendocrinefeatures with PNET. Ewing's sarcoma is thought to be amore undifferentiated tumor.[12]

ES/PNET are highly malignant neoplasms of neuroectodermal derivation composed of small, round, generally uniform cells with small, round, lightly stippled nuclei and glycogen-rich cytoplasm. Some of the tumor cells may be arranged in Homer–Wright rosettes and pseudorosettes. Tumors characterized by sheets of uniform primitive cells with scant cytoplasm and cytoplasmic glycogen were classified as ES, whereas tumors featuring cells with more nuclear variability, more abundant cytoplasm, and rosette formation were classified as PNET.[23]

The etiology is unknown however, the cell of origin uncertainand even the multipotentiality of antigenic expression controversial. Both Ewing's sarcoma and PNET have a common chromosome translocation t(11;22)(q24;q12) in approximately 85% of cases. This translocation results in juxtaposition of the *EWS* and *FLI-1* genes. Another translocation, t(21;22)(q22;q12), found in 10% to 15% of cases, fuses the *EWS* gene to the *ERG* gene.[24]

Most patients with Ewing sarcoma are adolescents, and the median age at diagnosis is 15 years. There is a slight male predominance. Osseous lesions most frequently involve the long bones, pelvis, and ribs. Only 1% to 2% of cases arise in the gnathic or craniofacial bones The most common clinical findings are pain and swelling. Fever, leukocytosis, and an elevated erythrocyte sedimentation rate also may be present in advanced disease.[25] Radiographically the tumor exhibits radiolucency that is poorly demarcated and never corticated. Its advancing edge destroys bone in an uneven fashion, resulting in a ragged border. The lesions are usually solitary and may cause pathologic fracture with adjacent radiographically visible soft tissue masses.[13] Ewing's sarcoma may stimulate the periosteum to produce new bone; this is usually the result of gross disturbances to the overlying periosteum and takes the form of Codman's triangle or "sunray" or "hair-on-end" spiculation.[26]

Histopathology

Ewing's sarcoma is an extremely cellular neoplasm composed of solid sheets or masses of smallround cells with very little stroma, although a few connective tissue septa may be present. The cells themselves are small and round, with scanty cytoplasm and relatively large round or ovoid nuclei with dispersed chromatin and hyperchromasia. The cell borders are indistinct. The sarcoma cells are arranged in Filigree pattern. Mitotic figures are common. The cells are positive for glycogen and are diastase resistant. Rosettes present in 10% of cases. Many tiny vascular channels may also be present. Hemorrhage with vascular lakes or sinuses may be seen. Geographic necrosis with perivascular sparing is a common feature. There is increased cellular pleomorphism and increased numbers of bizarre giant cells may be found in the lesions in patients treated with radiation and adjuvant chemotherapy. Encroachment of tumor cells on a bone trabecula causing its ragged resorption is apparent. Necrosis is also present on the opposite side of the fragment of bone. In some cases of Ewing's sarcoma, the cells are larger and may simulate the malignant lymphoma. Other tumors which have to be differentiated from Ewing's sarcoma are small cell osteosarcoma, PNET (peripheral neuroectodermal tumor of infancy), metastatic neuroblastoma, mesenchymal chondrosarcoma.[9,12,25]

Histopathologic classification and variants

Histologic classification of Ewing sarcoma includes three major subtypes: classic or conventional (typical) Ewing sarcoma, primitive neuroectodermal tumor (PNET), and atypical Ewing sarcoma. These tumors share the same immunohistochemical and molecular features, differing only in the extent of neural differentiation. Each subtype is considered a high-grade tumor.

Classic Ewing sarcoma is composed of small, round, uniform cells. The nuclei are round, and the nucleoli are inconspicuous. The nuclei have a rather smoky appearance. The cytoplasmic boundaries are indistinct, such that the cytoplasm of several cells seems to form a syncytium with the nuclei embedded in it. The cells are arranged in a diffuse sheet-like pattern, and necrosis varies from slight to extensive.[15] Mitotic activity is usually not prominent in typical Ewing sarcoma. PNET constitutes approximately 10% to 15% of Ewing sarcoma occurring in bone and soft tissue. The diagnosis requires the presence of Homer Wright rosettes with a central core of neutrophil, although the minimal number of rosettes is not firmly established. The background contains monotonous fields of conventional Ewing sarcoma.[15]

Atypical Ewing sarcoma accounts for approximately 15% to 20% of genetically proven Ewing sarcoma involving bone and soft tissue.[15] This is the most difficult group to recognize because these tumors have a greater degree of cytologic variability and/or unusual growth patterns, bringing a broad variety of primary and metastatic small round cell tumors into the differential diagnosis. Some tumors in this group contain large nuclei with irregular nuclear membranes and prominent nucleoli, whereas others have abundant eosinophilic cytoplasm

imparting a rhabdoid appearance. In most cases, the tumor cells grow in sheets. However, less common morphologic patterns, including adamantinoma-like, vascular-like, spindle cell, and sclerosing patterns, have been described, often occurring in combination with other areas resembling conventional Ewing sarcoma.[15]

Immunohistochemistry

CD99 is a cell surface glycoprotein, the product of the MIC2 gene. Strong, diffuse membranous expression is seen in approximately 95% of Ewing sarcoma. MIC2 expression is unrelated to the gene products of the specific translocations found in Ewing sarcoma. CD99 expression is not specific for ES and has been seen in a large group of normal tissues and tumor types, including other round cell sarcomas. For example, between 71% and 93% of lymphoblastic lymphomas and leukemias express MIC2. Few neoplastic cells exhibit weak cytoplasmic staining in small cell osteosarcoma, as well as mesenchymal chondrosarcomas, between 10% and 25% of rhabdomyosarcomas, and approximately 20% of desmoplastic small round cell tumors (DSRCTs). In DSRCTs and rhabdomyosarcomas, CD99 usually shows a cytoplasmic staining pattern, in contrast to the membranous pattern typical of ES. Importantly, neuroblastomas lack CD99 immunore activity in all locations and age groups. Clearly, CD99 is a sensitive but not a specific marker for ES. Immunohistochemical detection of FLI1 has proven to be more specific for ES than CD99, with a somewhat lower sensitivity. Specificity of FLI1 is limited by its expression in lymphoblastic leukemias or lymphomas, Non Hodgkin lymphomas, and endothelial cells and derived neoplasms.[27]

Burkitt's Lymphoma

Burkitt's lymphoma has an important role in the understanding of tumorigenesis. It was the first humantumor to be associated with a virus, one of the first tumor shown to have a chromosomal translocation that activates an on cogene, and the first lymphomareported to be associated with HIV infection. Burkitt's lymphoma is the fastest growing human tumor, with acell doubling time of 24–48 h, and was the first childhoodtumor to respond to chemotherapy alone. It is the most common childhood cancer in areas where malaria isholoendemic example, equatorial Africa, Brazil, and Papua New Guinea. The so-called Burkitt's lymphoma beltstretches across central Africa.[28]

Burkitt lymphoma (BL) is defined by the World Health Organization (WHO) as a highly aggressive lymphoma often presenting at extranodal sites, or as an acute leukemia, composed of monomorphic medium-sized B-cells with basophilic cytoplasm and numerous mitotic figures. Chromosomal translocation involving *MYC* is the most frequent genetic feature. Epstein–Barr Virus (EBV) is found in a variable proportion of cases. Three clinical variants of Burkitt lymphoma are recognized; these differ in geographic distribution, clinical presentation, as well as association with infectious agents and cell biology.[29]

Three categories of BL are recognized currently: endemic, sporadic and immunodeficiency-associated. Endemic BL occurs in sub-Saharan Africa and New Guinea and is much less common elsewhere. It is a disease of children and adolescents, associated with EBV infection and malaria. It involves extranodal sites, particularly the jaw, gastrointestinal tract and gonads.[30]

Characteristics	Endemic BL (eBL)	Sporadic BL (sBL)	HIV associated BL
Epidemiology	· Equatorial · Median age 7 yrs · Associated with malaria / climate	· Median age 30yrs · Children (30%) · Older adults (1%) · Low Socio Economical Status	· HIV risk groups · Median age 10-19 yrs · Children in Africa?
Clinical Presentation	Facial skeleton (50%) CNS (33%) Other organs also affected	Abdominal, ileo-coecal (80%) Bone marrow (20%) Other organs also affected	Organ and nodal presentation
Geographic regions	Malaria belt	Worldwide	In endemic HIV areas in Africa

(Courtesy: Orem J, Mbidde EK, Lambert B, De sanjose S, Weiderpass E. Burkitt's lymphoma in Africa, a review of the epidemiology and etiology. Afr Health Sci. 2007;7(3))

Molecular Studies

Approximately 75% of Burkitt's lymphomas carry the translocation t(8;14)(q24;q32), with the remaining cases having one of two variant translocations, the t(2;8)(p11;q24) or the t(8;22)(q24;q11). Common to each of these translocations is involvement of chromosome 8q24, the site of the *c-Myc*oncogene via these translocations, the *c-Myc*oncogene is juxtaposed with the Ig heavy chain (14q32), Igκ (2p13), or the Igλ (22q11) gene loci, resulting in *Myc* dysregulation. Increased Myc protein drives cell proliferation.[11] Other cytogenetic abnormalities are also common in sporadic Burkitt's lymphoma. Molecular studies have confirmed previous serologic studies that showed evidence of EBV infection. Approximately 90% to 95% of endemic, 50% of HIV-associated, and 25% of sporadic Burkitt's lymphomas contain EBV. The EBV is episomal, consistent with latent infection. The virus is often present in multiple copies per cell and is monoclonal, indicating that the virus is present before neoplastic transformation. EBV alone, however, is not sufficient to cause Burkitt's lymphoma. Other cofactors are operative.[11,24]

The median age of patients with endemic Burkitt's lymphoma is 7 years, with a male-to-female ratio of 3:1. The jaw is the best-known site of disease, involving the maxilla or mandible in 60% of patients, but large abdominal masses involving retroperitoneal structures, the gastrointestinal tract, or the gonads are also common. By contrast, sporadic Burkitt's lymphomas occur in industrialized nations. Other sites commonly involved include abdominal and peripheral lymph nodes, pleura, and pharynx. Bone marrow and central nervous system involvement is uncommon at presentation and are involved later in the clinical course. HIV-associated Burkitt's lymphomas commonly involve extranodal and nodal sites.[11] Oral manifestations include tooth mobility and pain, intraoral swelling of the mandible and maxilla, and anterior open bite. Mobile teeth may be present even in the absence of clinically detectable jaw tumors. Radiographic features on panoramic images include resorption of alveolar, loss of teeth lamina dura, enlargement of tooth follicles, destruction of the cortex around tooth crypts, displacement of teeth and tooth buds by the enlarging tumor, resulting in the impression of "teeth floating in air," and sun-ray spicules as bone forms perpendicular to the mandible from subperiosteal growth.[31,32] Radiographically is illdefined, noncorticated radiolucency, which later coalesce into larger, ill-defined radiolucency with an expansile periphery. They are of no specific shape, although they expand rapidly and have been likened to a balloon. This expansion breaches its outer cortical limits, causing gross balloon-like expansion with thinning of adjacent structures and production of a soft tissue tumor mass adjacent to the osseous lesion. Lesions that abut the orbital contents or the maxillary sinus may show a smooth surface soft tissue mass radiologically.[13,33]

Histopathology and Immunocytochemistry

Burkitt's lymphoma is a highly aggressive B-cell non-Hodgkin lymphoma characterized by monomorphic medium-sized cells with a very high proliferation rate. The cells are intermediate in size and contain coarse chromatin and prominent basophilic nucleoli. Some plasmacytoid and atypical variants show more nuclear pleiomorphism. In tissue sections, typically the cells seem to be molded and the cytoplasm is deeply basophilic with squared-off cytoplasmic margins. The proliferation index is almost 100%, with a high turnover shown by increased apoptosis. A "starry sky" appearance is due to scattered tingible-body-laden macrophages that contain apoptotic tumor cells.[3,28] The cells are always of B-cell lineage (CD20 positive and CD79a positive). CD10 and Bcl-6 are commonly coexpressed, but the cells are generally negative for Bcl-2. There is a scarcity of T cells in the background. Epstein-Barr-encoded RNA can be identified by fluorescence in-situ hybridisation.[3,28]

Metastatic Malignancy affecting the Jaw

Cancer is a complex disease characterized by variousbiological properties that develop through multistep processes. These properties include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis, in addition to reprogramming of energy metabolism and evadingimmune destruction.[24]However, the process of metastasis results in morbidity and eventual mortality in most patients. The jaws and mouth are uncommon sites for metastatic dissemination with only about 1 % of oral malignanciesattributed to metastases. Metastatic lesions may occur in the oral soft tissues or in both osseous and soft tissues. The common primary sources of tumors metastatic to the oral region are the breast, lung and kidney. Mandible is the most common location for metastases, with the molar area being the most frequently involved site. Frequently, they show non-aggressive clinical findings mimicking a reactive or benign lesions or even simple odontogenic infections. Nevertheless, the incidence is probably higher than suggested. [34, 35]Definition: Metastasis is the process whereby malignant tumors spread from their site of origin (*primary tumor*) to form other tumors (*secondary tumors*) at distant sites.[30]

Most cases of metastases to the oral cavity are found in the presence of a widespread disease; can be assumed that these develop as a result of secondary spread from other sites, especially from the lungs. However, in almost a quarter of the cases, oral metastasis was found to be the first indication of an occult malignancy at a distantsite.[34]

Presentation in the Oral Sites

Due to differences in presentation, site of origin and probable pathogenesis, oral metastatic lesions were divided into mucosal and jawbone metastases. The jawbones are twice as common for metastatic colonization than the oral mucosa. Metastatic lesions can be found anywhere in the oral cavity, however, in jawbones, the mandible was more frequently involved than the maxilla, with the molar area being the most frequent site (50 %) followed by premolar area (38 %) and the angle-ramus (29 %). In the oral soft tissue, the attached gingiva is the most commonly affected site (60 %) followed by the tongue (18 %)[11, 34]

Clinical Presentation

Oral metastases can grow rapidly causing pain, difficulty in chewing, dysphagia, disfigurement and intermittent bleeding, leading to poor quality of life. The clinical presentation can be variable, which may lead to erroneous diagnosis or may create diagnostic dilemma. In soft tissues, the attached gingiva is the most frequently involved site preceded by the tongue.[3] In the early stages, metastases to gingiva resemble hyperplastic or reactive lesions such as pyogenic granuloma, peripheral giant cell granuloma, fibrous epulis and periodontal abscesses. The metastatic lesion in other locations of the oral soft tissues manifests as a sub-mucosal mass particularly in the tongue with few cases presenting as ulcers.[11]

With the progression of the disease, oral metastatic lesions cause progressive discomfort, pain, bleeding, superinfection, dysphagia, interference with mastication, and disfigurement are some of the main complaints of patients. The clinical manifestations in bone include a bony swelling with tenderness, pain, ulcer, hemorrhage, paresthesia, and pathological fracture. Sometimes, tooth mobility and trismus are also present.[35]

Radiographic Features

Radiographically, metastatic lesions are most often found with ill-defined border and usuallyare osteolytic (radiolucent), but they may be osteoblastic (radiopaque) or mixed radiopaque and radiolucent lesions. The radiographic appearance of lesions has been attributed to a disruption of balance between osteoclastic and osteoblastic activity that occurs during normal bone turnover. Tumor type may affect the radiographic appearance of the lesion, prostatic carcinoma metastases are classically osteoblastic while metastatic breast or renal carcinoma may be osteolytic, osteoblastic or mixed.[36,13]

Histopathology

The histologic appearance is poorly differentiated, making it challenging in determining the location of the primary lesion. A thorough medical history canfacilitate in diagnosing. On suspicion of a metastatic tumor referral for complete oncologic work up is required.[3] Advanced imaging, scintigraphy, screening using panel of immunohistochemicalstains and regional investigations based on the suspected source should be done to find out or confirm the origin and identify the other areas of secondary spread. The diagnosis of such lesion is based on pathology but it is still difficult because they often show varied indifferent histological findings than primary tumor.[34,35]

Immunohistochemistry

Tumor specific markers for determination of tissue of origin metastatic breast carcinomas typically are positive for cytokeratin 7, but negative for cytokeratin, thyroid transcription factor-1(TTF1) and Prostate specific antigen (PSA). In contrast, metastatic colorectal carcinomas are typically CK20 positive, but CK7, TTF1 and PSA negative. A metastatic lesion that stains positively for CK7 and TTK1 likely would be from a lung carcinoma.[35,36]

CONCLUSION

This review illustrates varieties of malignant tumors occurring in the jaw bone. The clinician who is responsible for diagnosis and treatment of patients with jaw swellings should realize the considerable overlap in clinical, histological, as well as

radiological features. Malignant tumors of the mandible and maxilla are grouped into primary tumors that originate within the mandible and secondary lesions, predominantly metastatic lesions that involve the mandible secondarily. Metastatic disease most commonly from the breast and lung, are not an uncommon and may be the first manifestation outside the head and neck. The osteogenic sarcoma is the most common sarcomatous lesion in the mandible and is suggested when a bone-forming matrix with sclerosis is found within the tumor. Diagnostic errors can have big consequences and it can cause difficulty in establishing optimal treatment protocols for this diverse group of tumors.

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