Osteosarcoma is a primary bone tumour composed of cells, which at least focally produce tumoral bone (osteoid). It is, with the exception of plasmacytoma, the most frequent primary malignant bone tumor having an incidence of 2.5 per million populations per annum. Children and young adults are the most affected age group with a second incidence peak around the age of 60. More than 90% of osteosarcomas are of the conventional highly malignant type and the majority of them occur around the knee followed by the humerus and pelvic bones. Approximately 7-10% arise in the craniofascial bones (maxilla and mandible). Osteosarcoma is rare in the spine and in the small bones of hands and feet. The most common symptoms are bone mass, often with soft tissue involvement and pain.

The prognosis of osteosarcoma and the life quality of survivors has improved greatly in the last 20 years mostly due to the introduction of neo-adjuvant chemotherapy and to advances in limb-sparing surgical techniques. A reliable and speedy diagnosis in cases of osteosarcoma is crucial in order to quickly initiate adequate chemotherapy before surgical excision of the tumors.

Osteosarcomas show a wide variation in regard to their morphological appearance. Most common is the conventional intramedullary subtype. Less common variants are periosteal osteosarcoma, parosteal or juxta cortical osteosarcoma, central low-grade osteosarcoma, high grade surface osteosarcoma and small cell osteosarcoma.

Cytologic features of high-grade osteosarcoma

**Osteoblastic subtype**

Variable cellularity
A mixture of single cells and clusters in moderately cellular smears
Moderately to highly pleomorphic rounded, ovoid, polygonal tumour cells
Osteoblast-like tumour cells with eccentric nuclei and a cytoplasmic ‘Hof’
Clusters of epithelioid tumour cells with distinct cytoplasmic borders and rounded nuclei with prominent nucleoli
Multinucleated tumour giant cells
Strands of osteoid matrix (red or purple in MGG, pale pink in HE) between Mitoses, often atypical
Benign osteoclast-like giant cells; numerous in giant cell rich osteosarcoma
Occasional necrosis and calcifications

**Chondroblastic subtype**

Myxoid back ground matrix (red; red-violett in MGG)
An admixture of atypical mono- or binucleated chondroblast-like cells in addition to cells seen in osteoblastic osteosarcoma
Occasionally fragments of hyaline cartilage with atypical cells in lacunae

**Differential diagnosis**

Reactive osteoblastic proliferations as in fracture callus
Pseudomalignant myositis ossificans
Osteoblastoma
Giant cell tumour (giant cell rich osteosarcoma, teleangiectatic osteosarcoma)
Aneurysmal bone cyst (telangiectatic osteosarcoma)
High grade malignant chondrosarcoma
Pleomorphic sarcoma (MFH-type, pleomorphic leiomyosarcoma)
Conventional Ewing's sarcoma (small cell osteosarcoma)
Mesenchymal chondrosarcoma (small cell osteosarcoma)
Primary large cell anaplastic lymphoma in bone
Metastatic carcinoma
Metastatic melanoma

Comments

Reactive osteoblastic proliferations such as fracture callus and pseudomalignant myositis ossificans are the most important benign lesions that can be mistaken for OS. Reactive osteoblasts in these entities may be pleomorphic showing anisokaryosis and prominent nucleoli, but their chromatin pattern is regular and the cytoplasmic ‘Hof’ clearly visible. When the yield is poor and haemorrhagic as may be the case in aspirates from telangiectatic osteosarcoma, osteoclast-like benign giant cells may predominate and scattered obviously malignant cells may be overlooked and there is a risk that the lesion could be misdiagnosed as an aneurysmal bone cyst. The multinucleated benign giant cells present in giant cell rich osteosarcoma may be as numerous as in smears from giant cell tumours. It is important to look for obvious malignant cells and atypical mitoses. Osteoblastoma-like osteosarcoma is a diagnostic challenge in biopsy samples and even more so in FNA material. When the radiologic features in these cases are not unequivocally malignant, the cytological diagnosis is better reported as inconclusive than suspicious for osteosarcoma. The tumour cells of conventional osteosarcoma may exhibit epithelioid features such as distinct cell borders and rounded or ovoid nuclei with prominent nucleoli and when they are clustered they can mimic cells from metastatic carcinoma. Especially metastatic renal carcinoma can produce an extracellular matrix which can be easily confused with osteoid. Anaplastic large cell lymphoma can arise primarily in bone and may feature large cytoplasm-rich, rounded cells with eccentric nuclei and prominent nucleoli resembling highly atypical osteoblast-like tumour cells. Antibodies to keratin, S-100-protein, HMB45, Melanin A, EMA, ALK, CD45 and CD30 are suitable markers in the differential diagnosis of carcinoma, malignant melanoma and ALCL, respectively.

The clue to the cytological diagnosis of conventional osteosarcoma in routinely stained smears is the presence of intercellular osteoid and osteoblast-like tumour cells. Osteoid is best appreciated in MGG-stained smears. To confirm diagnosis it is at times necessary to supplement the routine stains with ancillary techniques. Strong intracytoplasmatic alkaline phosphatase staining (ALP) in tumour cells confirms their osteoblastic differentiation. ALP-staining is of great help in the differential diagnosis between chondroblastic osteosarcoma and high grade malignant (Grade III) chondrosarcoma as well as in the distinction from metastatic carcinoma or melanoma and from anaplastic large cell lymphoma. Differentiating osteoid from collagenous matrix can occasionally be difficult. Electron microscopic examination, is another well-established method to define osteoid in fine needle aspirates.

Cell blocks preserved the architecture of the tumor tissue including calcification and osteoid. Cell block can help in the clarification of diagnosis, especially when one can see both malignant cells and strands of osteoid in the cellblock section.
Conclusions

FNAC is an efficient method in the diagnosis of high-grade osteosarcoma. The final conclusion must be based on the combined evaluation of clinical and radiographic data and the cytologic examination, often supplemented with ancillary techniques.

Primary investigation and treatment including cytologic or histopathologic diagnosis of osteosarcoma, should be preferably performed at multidisciplinary centers. The optimal use of fine needle aspiration as a pre-treatment diagnostic tool requires the referral of patients to such centers where the cytopathologist is a member of the team, and where there is close cooperation between cytopathologist, radiologist, surgeon and oncologist.

References


