Original Research Article

Lytic lesions of bone: a cytological and histopathological correlative study

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ABSTRACT

Background: Lytic lesions of bone are easier to aspirate and fine needle aspiration cytology aids in an earlier diagnosis. The findings are correlated with radiological findings and subsequent histopathological diagnosis. Sensitivity, specificity, positive and negative predictive value of fine needle aspiration cytology of lytic lesions of bone evaluated.

Methods: It was a descriptive study for 2 years. All types of lytic lesions of bone were aspirated with fine needle along with radiological assistance. The cytological diagnosis was correlated with histopathological diagnosis.

Results: A total number of 84 cases were studied with histopathological follow up in 51 cases. FNAC diagnosis was correct in 34 cases. In 8 cases, cytology diagnosis was malignant neoplasm, but correct typing was not possible. In 9 cases cytological diagnosis were inconclusive due to inadequate material. Sensitivity of the test was 70.83%, specificity was 50.12%, positive predictive value was 97.14%, negative predictive value was 6.67% and overall accuracy was 70.01%.

Conclusions: The role of FNAC in diagnosis of bone lesions is both promising and challenging. Because of simplicity, low morbidity and economical benefits, FNAC should be the first step in the diagnosis of bone lesions.

Keywords: Lytic lesions of bone, Fine needle aspiration cytology, Histopathological diagnosis

INTRODUCTION

FNAC has proved to be an accurate, cost effective and safe technique for diagnosing various inflammatory and neoplastic lesions. Lytic lesions of bone are commonly seen in orthopaedic patients. The differential diagnosis includes benign lesions, malignant lesions and metastatic deposits from tumors of other sites.1 Lytic lesions of bone are easier to aspire and cytology aids in an earlier diagnosis.2 Radiological evaluation aids in both aspiration and diagnosis. FNAC may be repeated from different sites if the material is inadequate.3

The present study is an attempt to evaluate the diagnosis accuracy of FNAC of lytic bone lesions in our situations and to assess its utility as a means of quick diagnosis which would otherwise require a long time, since bone biopsies require decalcification prior to routine paraffin processing. Aims of study included the usefulness of aspiration cytology in the lytic lesions of bone, to correlate the findings with the subsequent histopathological observation and also with the radiological imaging. Sensitivity, specificity, positive and negative predictive value of fine needle aspiration cytology of lytic lesions of bone also determined.
METHODS

Current study was a descriptive study. The study was conducted in the Government medical college hospital, Thiruvananthapuram. The material for this study was obtained from cytology lab, department of pathology and from department of orthopaedics, medical college hospital Thiruvananthapuram, from 2001 June to 2003 May. Aspirations were done with 18 gauge needle for deeper lesions and 20 to 22 gauge needles for superficial lesions. 10 cc syringes was attached for negative pressure. All aspirations were done after reviewing X-ray/MRI scan. All the procedures were done in cytology lab or in orthopaedic wards.

Inclusion criteria and exclusion criteria

An inclusion criterion in current study was, all the cytological samples getting histological follow up during the study period. Exclusion criterion was to exclude cytological samples showing only blood.

Procedure

The aspirated material was expelled on to a clean glass slide and smears were prepared using another glass slide. Slides were immediately wet fixed in 95% alcohol for papanicolaou staining. One or two slides were air dried for May Grunwald Giemsa staining. Two unstained smears were reserved for special stains. The smears were correlated with clinical and radiologic findings before arriving at a diagnosis. Histopathological correlation was done at a later time after receiving biopsy sample. Cell blocks were made whenever adequate material was available.

The slides were screened under scanner and low power of light microscope for studying adequacy of material and cytologic architecture. Cellular details were studied under high power with special attention to the staining of cytoplasm, amount of cytoplasm, nuclear-cytoplasmic ratio, nuclear membrane, characteristics of chromatin, presence of nucleoli, mitotic figures, giant cells, pleomorphism of component cells, arrangement of cells, arrangement of matrix and inflammatory cells. Cytohistopathologic correlation was made after ensuring those adequate biopsy samples were obtained. In case of doubt, repeat biopsies were advised. Multiple samples from different sites were examined for final diagnosis in some cases.

A positive cytohistopathological correlation was taken as true positive (TP) where as cytohistopathological disagreement was considered either as false positive (FP) when cytology is positive and histology is negative or as false negative (FN) when cytology is negative and histology is positive. Cases showing cytology as negative and corresponding biopsy also did not reveal any pathological lesion, were taken as true negative (TN).

Histopathology was the gold standard. Special staining was done in some cases.

The diagnostic indices like sensitivity, specificity, PPV (positive predictive value), NPV (negative predictive value) and diagnostic accuracy were calculated after exclusion of inadequate and unsatisfactory aspirates. Data was entered in Microsoft excel. Analysis of the data was done in SPSS.

Table 1: Diagnostic indices.

<table>
<thead>
<tr>
<th>Test positive</th>
<th>Gold standard positive</th>
<th>Gold standard negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>FN</td>
<td>FP</td>
<td>TP + FN</td>
</tr>
<tr>
<td>Test negative</td>
<td>FN</td>
<td>TN</td>
<td>FN + TN</td>
</tr>
</tbody>
</table>

*TP: True positive is both gold standard and test parameter positive, TN: true negative is both gold standard and test parameter negative, false positive (FP) is test parameter positive and gold standard negative, false negative (FN) is test parameter negative and gold standard positive. Sensitivity: (TP)/(TP+FN), specificity: (TN)/(TN+FP), positive predictive value (PPV): (TP)/(TP+FP), negative predictive value (NPV): (TN)/(TN+FN), accuracy : (TP+TN)/(TP+TN+FP+FN) = (number of correct assessments)/(number of all assessments).

RESULTS

A total of 84 cases were studied with histopathological follow up in 51 cases. The most frequently aspirated site was femur. Follow up of the patients revealed that the FNAC Diagnosis was correct in 34 cases. In 8 cases, cytology diagnosis was malignant neoplasm and further morphological typing was not possible with the available material. In 9 cases, cytological diagnoses were inconclusive due to inadequate material. Sensitivity of the test was 70.83%, specificity was 50.12%, positive predictive value was 97.14%, negative predictive value was 6.67% and overall diagnostic accuracy was 70.01%.

There were no complications after FNAC of the bone lesions. No adverse consequences have occurred as a result of any negative diagnosis. Close communications and cooperation among our clinical and pathology departments ensured that any clinically suspicious lesion was evaluated by a second diagnostic procedure if FNAC was unsatisfactory. No false positive diagnosis have been encountered in study.

Out of the 51 cases studied, 48 were primary bone lesions. The most frequent site of primary bone lesion was femur. 6 inflammatory lesions diagnosed. But only 3 cases obtained the histopathological follow up. In 2 cases, the cytological diagnosis was chronic inflammatory lesion and were confirmed by histopathology. But in 1 case, cytological examination showed only necrotic material. Then biopsy was suggested to rule out the
possibility of malignancy. Final histopathological diagnosis was chronic inflammatory lesion.

A case of aneurysmal bone cyst was diagnosed by FNAC in a 29 year old male with characteristic radiological findings. The smear was bloody with abundant osteoclasts and fibroblasts. Histopathology confirmed the diagnosis. One case of non-ossifying fibroma was proved histologically. In FNA smear, plenty of clusters of cells were present. Cells were spindly and polygonal with oval nucleus. Osteoclastic giant cells were frequent. There were no features of malignancy. Cytological differential diagnosis was non ossifying fibroma/aneurysmal bone cyst.

Out of the 2 cases of Langerhan’s cell histiocytosis, one was correctly diagnosed cytologically. But in the other case, cytological diagnosis given was spindle cell lesion of bone. Benign and low grade lesions accounted 13 cases. 11 cases were giant cell tumour. In 8 cases, correct cytological diagnosis were given. In 1 case, cytological report was giant cell lesion. In 2 cases, cytological diagnosis were inconclusive mainly due to inadequate material. In our study, the age group for the giant cell tumour ranged from 19 to 45 years. Male, female ratio was 4: 7. Most common site was tibia followed by femur, metacarpals and radius. All cases showed radiologically diffuse osteolytic lesions. Classic soap bubble appearances were seen in 5 cases. The most striking feature in FNAC was high cellularity composed of clusters of ovoid to spindly mono nucleared cells and multi nucleated osteoclastic giant cells with uniform nuclei and abundant cytoplasm. Radiological features and clinical characteristics allowed a definite diagnosis in most cases.

In case of chondromyxoid fibroma, smear showed scattered plump spindly cells with ovoid dense nuclei. Background showed blood, inflammatory cells and myxoid material. Cytology diagnosis was spindle cell lesion with atypia. Excision was advised for definite diagnosis and it came out as chondromyxoid fibroma.

In a case of 22 year old female with fusiform osteo lytic lesion in fourth metacarpel, aspirate showed fragments of cartilage with cells having regular nuclei in lacunae. Amorphous material, macrophages and lymphocytes were also seen. Diagnosis given was benign cartilaginous neoplasm. Histopathology confirmed the diagnosis as enchondroma. Out of the 51 cases, osteosarcoma constituted 10 cases, Ewing’s-sarcoma; 5 cases, chondosarcoma; 5 cases, plasmacytoma; 6 cases, Chordoma; 1 case and haemangiopericytoma; 1 case.

Out of the 10 cases of osteosarcoma, correct cytological diagnosis was given in 6 cases. In 2 cases, the diagnosis given was malignant neoplasm. In 1 case, the cytological diagnosis was in conclusive. In that case, aspirated material was inadequate and showed scattered lymphocytes, macrophages, RBCs and benign looking cells. In 1 case of a 14 year old female with swelling right thigh, clinical diagnosis was osteomyelitis/ Ewing’s sarcoma. Cytological diagnosis given was malignant round cell neoplasm. The histopathological report was osteosarcoma-small cell variant.

In osteosarcoma, all the patients were in second decade. Male to female ratio was 4:1. Femur was the most common site affected, followed by humerus, tibia and ilium. X-ray showed lytic lesion. Characteristic Sun-ray appearance and Codman’s triangle was seen in only 1 case. FNA smears were moderate to hypocellular and were characterised by highly pleomorphic mononuclear to multi nucleate bizarre cells. A few osteoclastic giant cells were strikingly seen in some of the smears. In some cases, amorphous pink material closely associated with malignant cells were interpreted as osteoid with May Grunwald Giemsa stain.

Out of the 5 cases of Ewing’s sarcoma, 4 cases were correctly diagnosed cytologically. In 1 case of 32 year old female with lytic lesion tibia, the clinical diagnosis was giant cell tumour. Cytological diagnosis was malignant neoplasm. Excision biopsy was advised for the same and histopathology proved it as Ewing’s sarcoma.

The range of affected age group was from 1 to 32 years. Male female ratio was 2:3. Most common site affected was humerus. Radiologically diffuse osteolytic lesion with classic onion peel appearance was seen in 2 cases. FNA smears showed predominantly monomorphic population of clustres of round to oval cells with vacuolated cytoplasm and few small dark cells with scanty cytoplasm. Pseudo rosettes were seen in 3 cases. Nuclear chromatin was finely granular and bare nuclei were strikingly seen. Diagnostic accuracy was very high in Ewing’s sarcoma. 6 cases of multiple myeloma were encountered in the present study. Two of these were known cases of multiple myeloma. All cases were correctly diagnosed cytologically. Smear showed dispersed population of plasma cells with binculeated and pleomorphic forms. Classical eccentrically placed nucleus with clock face chromatin was also present. Diagnostic accuracy was 100%.

In case of Ewing’s sarcoma, age group ranged from 41 to 67 years. Male female ratio in this was 1:2. In all cases of Ewing’s sarcoma, multiple osteolytic lesions were present. Sites of involvement included humerus, sternum, ilium, clavicle and frontal bones. Out of 4 cases of chondrosarcoma, only 1 case was cytologically diagnosed. In one case cytological diagnosis given was malignant neoplasm and biopsy was advised. Final diagnosis was chondrosarcoma. Two cases were inconclusive cytologically mainly due to inadequate sampling. Age group affected in chondrosarcoma was 40-62 years. Male female ratio was 1:3. Sites affected were femur femur, ilium and ribs.
Table 2: Lytic lesions of bone: number of cases, diagnosis, age group, male:female ratio, bones affected.

<table>
<thead>
<tr>
<th>HP diagnosis</th>
<th>N</th>
<th>Correct cytological diagnosis</th>
<th>Age group (years)</th>
<th>Male:female</th>
<th>Bones involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory lesion</td>
<td>3</td>
<td>2</td>
<td>30-50</td>
<td>1:2</td>
<td>Femur, tibia, clavicle</td>
</tr>
<tr>
<td>Aneurysmal bone cyst</td>
<td>1</td>
<td>1</td>
<td>29</td>
<td>Only males</td>
<td>Humerus</td>
</tr>
<tr>
<td>Non ossifying fibroma</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td>Only females</td>
<td>Tibia</td>
</tr>
<tr>
<td>Giant cell tumour</td>
<td>11</td>
<td>8</td>
<td>19-45</td>
<td>4:7</td>
<td>Tibia, femur, radius, metacarpal</td>
</tr>
<tr>
<td>Langerhan’s cell histiocytosis</td>
<td>2</td>
<td>1</td>
<td>2.17</td>
<td>1:1</td>
<td>Tibia, radius</td>
</tr>
<tr>
<td>Chondromyxoid fibroma</td>
<td>1</td>
<td>0</td>
<td>25</td>
<td>Only males</td>
<td>Metatarsal</td>
</tr>
<tr>
<td>Chondroma</td>
<td>1</td>
<td>1</td>
<td>22</td>
<td>Only females</td>
<td>Metacarpal</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>10</td>
<td>6</td>
<td>10-19</td>
<td>4:1</td>
<td>Femur, ilium, tibia, humerus</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>4</td>
<td>1</td>
<td>40-62</td>
<td>1:3</td>
<td>Femur, ilium, ribs</td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>5</td>
<td>4</td>
<td>1-32</td>
<td>2:3</td>
<td>Humerus, femur, fibula</td>
</tr>
<tr>
<td>Chordoma</td>
<td>1</td>
<td>1</td>
<td>63</td>
<td>Only females</td>
<td>Sacrococcyx</td>
</tr>
<tr>
<td>Haemangiopericytoma</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>Only females</td>
<td>Tibia</td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td>6</td>
<td>6</td>
<td>41-67</td>
<td>1:2</td>
<td>Humerus, sternum, ilium, clavicle, frontal bone</td>
</tr>
<tr>
<td>Metastasis</td>
<td>4</td>
<td>2</td>
<td>48-75</td>
<td>1:1</td>
<td>Humerus</td>
</tr>
<tr>
<td>Total cases</td>
<td>51</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Smears were cellular showing malignant chondrocytes arranged in small clusters and scattered singly. Individual cells were polygonal with moderate amount of cytoplasm and hyperchromatic pleomorphic nucleus. Some binucleate forms were seen in the lacunar spaces double and multiple forms were also seen. Background showed abundant myxoid ground substance. A 62 year old male was presented with lytic lesion of lower end of femur. Smear showed groups of cells with eosinophilic cytoplasm and spindle shaped nucleus. A multinucleated cell in a myxoid background is also seen. Diagnosis given was cartilaginous lesion with spindle cells possibly chondromyxoid fibroma. In this case, abundance of spindle cells misled our diagnosis. A 63 year old female was presented with swelling in sacro coccus region. X-ray showed irregular expansile osteolytic lesion of sacrum and coccyx with a large soft tissue compartment. Small calcification infiltrating perirectal fat and muscles were seen. FNA showed cellular smear showing sheets and clusters of round cells with abundant vacuolated cytoplasm with centrally placed uniform nuclei. Multivacuolated physaliphorus cells were also noted. Cytological diagnosis was chordoma. Histopathology confirmed the diagnosis. A single case of haemangiopericytoma was obtained in a 12 year old girl with recurrent swelling lateral aspect of knee. Radiological diagnosis was osteosarcoma. Cytology showed cellular smears composed of cells in cohesive clusters, sheets and singly. Cells were oval and spindly with vesicular nucleus and scanty cytoplasm.

Osteoclastic giant cells were also seen. Cytological diagnosis was malignant neoplasm and excision biopsy was advised. Histopathology report was haemangiopericytoma. Out of all the metastatic bone lesion diagnosed, only 4 cases got histopathological follow up. Two cases with cytological diagnosis of adenocarcinoma were confirmed histopathologically. In two cases, cytology report was negative for neoplastic cells. But histopathology diagnosis was metastasis from poorly differentiated carcinoma in one case and metastasis from invasive ductal adenocarcinoma breast in another case (Table 2, Figure 1-3). Diagnostic indices were calculated for all cases after excluding inadequate samples. Sensitivity was 70.83%, specificity was 50.12%, positive predictive value was 97.14%, negative predictive value was 6.67% and diagnostic accuracy was 70.01%.

**DISCUSSION**

FNA is an important tool for the early diagnosis of bone lesions after evaluation of radiology and clinical findings. FNA using a 22 or 23 gauge needle is associated with lower risk of tumour seeding in comparison to core or open biopsy. FNAC is a simple and economical technique that can be performed as an OP procedure reducing patient hospitalisation and lowering the cost of patient care. Complications are seldom seen with FNA. Multiple samples can be taken to get adequate representative material. Treatment with radiation or chemotherapy can be started without any delay as the aspiration wound is not endangered. In addition, using FNAC as the diagnostic method, the
In the present study, 15 cases with positive cytological diagnosis of malignancy were directly referred to regional cancer centre before doing a biopsy. Even though this reflects the positive benefits of FNAC, these cases were excluded from the study as there were no histopathology to correlate. Similarly, in 18 cases, cytological aspirate were blood only and did not yield any diagnostic cells. These cases were also excluded from the study. A total of 51 cases had histopathological follow up. Cytological and histopathological correlations were seen in 34 cases. In 8 cases morphological typing were not possible. In 9 cases, cytological sample were inconclusive due to inadequate material.

In the present study, giant cell tumours were the most common lesions which constituted 11 cases. Cytological diagnosis was correct in 8 cases. In one case, cytological report was giant cell lesion. In 2 cases, cytological report was inconclusive due to inadequate material. The presence of giant cells in a bone aspirate should not imply diagnosis of giant cell tumour. Aneurysmal bone cyst, Giant cell reparative granuloma, metaphyseal fibrous defect, brown tumour of hyperparathyroidism etc. may show giant cells in aspirate. Hence it is necessary to correlate cytological findings with clinical and radiological features. In the present study, a case of aneurysmal bone cyst was diagnosed cytologically which showed characteristic radiological features. In a 22 year old female with fusiform osteolytic lesion in fourth metacarpal, aspirate showed fragments of cartilage with cells having regular nuclei in lacunae, amorphous material, macrophage and lymphocytes were seen Diagnosis given was benign cartilaginous lesion. Histopathology confirmed the diagnosis.

In current study, out of 10 cases of osteosarcoma, correct cytological diagnosis was given in 6 cases. Significant limitation of FNA is the inability to obtain osteoid in all
cases. Some variants of osteosarcoma can cause diagnostic problems. For instance, round cell variant of osteosarcoma closely mimics Ewing’s sarcoma and extensive chondroid differentiation in osteosarcoma make it difficult to distinguish it from chondrosarcoma.

Out of 5 histopathologically proven Ewing’s sarcoma, 4 cases were correctly diagnosed cytologically. Cytological smears of Ewing’s sarcoma revealed better cellular details than routine tissue section. Cytological diagnosis of malignant round cell tumour consistent with Ewing’s sarcoma is relatively easy along with clinico radiological correlation. In the present study 6 out of 6 multiple myeloma cases could be easily diagnosed cytologically. Two of these were known cases of multiple myeloma. Clinical features and findings of other investigations including radiology helped in the correct cytological diagnosis.

Diagnosis of chondrosarcoma by FNAC was difficult. Out of 4 histopathologically proven chondrosarcoma, only 1 case was correctly diagnosed cytologically. Two cases were inconclusive cytologically mainly due to inadequate sampling. In one case, cytological diagnosis given as malignant neoplasm. Cytological distinction of benign and malignant cartilage is also difficult.

A 63 year old female was presented with swelling in sacro coccygeal region. Irregular expansile osteolytic lesion of sacrum and coccyx with a large large soft tissue component was the radiological finding. FNA showed cellular smears showing sheets and clusters of round cells with vacuolated cytoplasm with centrally placed uniform nucleus. Characteristic multi vacuolated physaliphorous

In a biopsy proven case of hamangiopericytoma in a 12 year old girl, cytology showed cellular smears composed of neoplastic cells with spindly with vesicular nucleus. Cytological diagnosis was malignant neoplasm and excision biopsy was advised. Correct cytological diagnosis were not possible due to rarity of the neoplasm, lack of clinical suspicion and inadequacy of the material.

Out of the 2 cases of Langerhan’s cell histiocytosis, one was correctly diagnosed cytologically. Smear showed numerous large histiocytes with vesicular nucleus with nuclear folds and grooves in a background of eosinophils, lymphocytes and plasma cells. But in the other case, smear showed predominantly spindle cells with oval nuclei. Cytological diagnosis was given as spindle cell lesion of bone. In the present study, 4 cases of metastatic carcinoma diagnosed cytologically got histopathological follow up. 2 cases could be correctly diagnosed while 2 other cases missed the diagnosis due to sampling error.

In experienced hands, FNA of bone lesion has high positive predictive value, high negative predictive value and high accuracy. Since both false positive and negative reports have bearing on diagnostic indices, cytopathologist must be cautious in reporting negative for malignant cells on an insufficient aspirate. This will automatically reduce the number of false negative and increase the negative predictive value, sensitivity and diagnostic accuracy. Similarly, restraints on the over enthusiastic diagnosis of malignancy on a scanty aspirate will reduce the number of false positive, thereby increasing the positive predictive value, specificity and diagnostic accuracy. There was not even a single false positive case in our study. This proved that FNAC is a highly reliable method in the early diagnosis with good knowledge of clinical and radiological features.

The main limitation of FNA of bone lesions is the scarcity of material or blood only aspirate in some cases. In such cases, the interpretation of the case should be cautious. When clinical or radiological suspicion of tumour is present with negative cytological report, biopsy should always be advised for confirmation. Awareness of limitations and pitfalls of FNAC as well as knowledge of cytology of bone lesions improves the quality of reporting to a greater extend.

CONCLUSION

A concerted multi disciplinary approach including clinical and radiological features including FNAC can certainly overcome the problems in early diagnosis of bone tumors. Further contrary to the apprehension that bone is a hard tissue impenetrable by the fine needle, aggressive growth exhibited by many malignant bone tumor is often associated with cortical destruction and
soft tissue extension. These factors ensure that in most cases, it is easy to obtain sufficient FNAC material for objective evaluation. Thus the role of FNAC in diagnosis of bone tumors is both promising and challenging. Because of simplicity, low morbidity and economical benefits, FNAC should be in the first step in the diagnosis of bone lesions. A definite pathologic interpretation should never be rendered if diagnostic material is inadequate or radiological information is not compatible. Therefore, radiologist, cytopathologist and orthopaedic surgeon must work together for optimal results to avoid unsatisfactory smears. When correlated with clinical history and radiographic findings, FNA plays an important role in preoperative diagnosis and management of bone tumors.

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