ABSTRACT

Aim: The present case aims to emphasize on the role of immunophenotyping in plasmacytic malignancies.

Introduction: Solitary plasmacytoma of bone (SPB) is a rare entity often encountered in vertebrae and less frequently in long bones. Its presence in jaws is extremely rare, accounting for 4.4% of cases only. About 5% of patients with plasma cell dyscrasias present with SPB.

Case report: An elderly male patient reported with a chief complaint of growth in the anterior region of the lower jaw since 3 months. The histopathological features following an incisional biopsy were suggestive of pyogenic granuloma. Serological investigations revealed seropositivity for human immunodeficiency virus (HIV)-1 antibody with hypergammaglobulinemia and hypoalbuminemia. Histopathology of excised tissue revealed a round cell malignancy with plasmacytic morphology. Further, to arrive at a specific final diagnosis, immunohistochemistry (IHC) was employed with a panel of markers CD45, CD20, CD3, CD138, and CD56. This panel enabled us to establish a final diagnosis of SPB with clinicopathologic correlation.

Conclusion: The present case posed a diagnostic dilemma as it presented with overlapping features of non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), extramedullary plasmacytoma (EMP), and plasmablastic lymphoma (PBL). A thorough clinical, radiological, serological, and IHC panel helped to diagnose the present case. The CD56 enabled differentiation between SPB and PBL. Thereby, this article emphasizes on the need for a panel of IHC markers that permit definitive diagnosis of lymphoproliferative malignancies.

Clinical significance: Timely diagnosis of malignant lesions is an essential concern for effective management. Thus, we emphasize that the IHC is a valuable investigative tool in the diagnosis of round cell tumors with plasmacytoid morphology.

Keywords: CD138, CD20, CD3, CD45, CD56, Enzyme-linked immunosorbent assay, Immunohistochemistry, Multiple myeloma, Plasma cell dyscrasias, Solitary plasmacytoma.

INTRODUCTION

A plasmacytoma is a distinct, solitary mass of neoplastic monoclonal plasma cells present within the bone marrow as SPB or EMP, which arises from plasma cells present within the mucosal surface. Plasmacytomas are monoclonal and this can be assessed in tissue sections or by biochemical evaluation of the type of immunoglobulin secreted by the neoplastic cells. Plasmacytomas are of significance because they may ultimately give rise to contemplative problems of MM. The SPB is a rare lesion which emanates from bone marrow-based B cells, explicitly those that have undergone terminal differentiation into plasma cells. The SPB exemplifies plasma cell dyscrasias involving a single bone in the localized form due to malignant plasma cell infiltrate.

It is essential to affirm the importance of HIV infection as a risk factor in cases of SPB, as it exhibits an aggressive and uncommon clinical presentation. The SPB documents a greater predilection in males and is more evident in the 5 to 7 decade of life presenting more commonly in the axial skeleton, particularly at the vertebrae. Korolkowa et al2 reported that 40% occur in the nasal cavity and paranasal sinuses, 20% in the nasopharynx, and 18% in the oropharynx. It rarely involves jaws, accounting for only 4.4% of cases in the mandible, most commonly in the bone marrow-rich areas of the body, angle, and ramus regions.3 SPB most frequently occurs at the posterior mandible. It can progress into MM in 50 to 60% of patients with a median overall survival time as 10 years.4

The SPB is an aggressive lesion that has the potential to transform into MM over a period of time. The expression of specific antigens by the neoplastic cells plays an important role in the diagnosis and definitive management.
CASE REPORT

A 78-year-old male patient reported to the dental outpatient department, Faculty of Dental Sciences, M. S. Ramaiah University of Applied Sciences, Bengaluru, India, with a chief complaint of growth in the front region of the lower jaw for 3 months. It was sudden in onset and increased gradually over 3 months. On inspection, a solitary pedunculated erythematous lesion with irregular borders was present in relation to lower anterior teeth region extending from 33 to 43 mesiodistally and from the labial vestibule to the floor of the mouth anteroposteriorly (Fig. 1A). On palpation, the inspectory findings were confirmed. The lesion was firm in consistency, mobile, nontender, fixed to the underlying tissues, and easily bled on touch. No palpable lymph nodes were observed in the head and neck region. A provisional diagnosis of pyogenic granuloma was made.

Computed tomography (Fig. 1B) revealed focal destruction of the outer and inner cortex of body of mandible in the midline associated with large heterogeneously enhanced soft tissue lesion measuring 40 × 30 × 30 mm APXTSXXC (anteroposteriorly, transversely, and coronal) abutting the tongue posteriorly and extending up to skin anteriorly with loss of central incisors. Ill-defined lytic areas of various sizes in regions of ramus, condylar process, hard palate, and alveolar process of the maxilla with focal-eroded regions were observed. Routine hematological investigations revealed a hemoglobin concentration of 11.5 gm%, white blood cell count of 5,260/mm³, platelet count of 2.09 lakhs/mm³, erythrocyte sedimentation rate of 13 mm/h, and packed cell volume of 35% respectively.

An incisional biopsy was performed under aseptic conditions, which affirmed histopathological features of pyogenic granuloma like regions of inflamed vascular stroma comprising numerous dilated blood vessels with endothelial proliferation and dense inflammatory cells predominantly lymphocytes and plasma cells (Fig. 1C). Following the incisional biopsy, the patient reported with an enlarged lesion in a span of 10 days (Fig. 1D). Considering the size of the lesion and its immediate recurrent potential, thorough serological survey was performed. Investigations for HIV-1 and 2 antibodies by enzyme-linked immunosorbent assay, Tridot, and Vitros showed reactivity for HIV-1 antibody as per the National Aids Control Organization guidelines. Serological investigations for hepatitis B and C using surface antigen of the hepatitis B virus and hepatitis C virus were negative.

Excisional biopsy of the exophytic growth was performed; on microscopic examination, the sections revealed sheets of lymphocytes with varying sizes. The round cells exhibited atypical features, such as pleomorphism, large and hyperchromatic nuclei, numerous vesicular nuclei, prominent nucleoli, and bizarre morphology (Fig. 1E). With these observations, a diagnosis of malignant round cell tumor was suggested. Areas of plasmacytoid cells were also evident. The differential diagnosis included NHL, EMP, SPB, MM, and PBL.

Based on the radiographic features, MM was ruled out as multiple perforations of the mandible were found to arise from a single lesion. The serum albumin globulin ratio was found to be normal, and test for Bence Jones proteins was negative. Serum protein electrophoresis revealed hypoalbuminemia and hypergammaglobulinemia with the absence of monoclonal band (Fig. 1F). These observations were substantial to rule out MM. The EMP was also ruled out as the involvement of bone was evident radiographically.

For definite recognition of the neoplasm, a diagnostic workup was done with a panel of following IHC markers, namely, CD45, CD20, CD3, CD138, and CD56 described in Table 1. The IHC analysis for anti-CD45 showed a weak positivity (Fig. 2A), whereas negative immunostaining was obtained for anti-CD20 (Fig. 2B) and anti-CD3 (Fig. 2C) respectively, that enabled to rule out NHL. An intense membrane positivity was obtained with anti-CD138 (Fig. 2D) which further implicated a plasmacytic malignancy. This finding helped narrow down to two neoplasias of interest, namely, PBL and SPB. On obtaining a positive immunostaining with anti-CD56 (Figs 2E and F), a final diagnosis of SPB was made with clinicopathologic correlation.

Following the excision, the patient reported a month later, with a recurrent lesion. Although antiretroviral medication was prescribed, he had not started with the same. Following this, chemotherapy was planned.

DISCUSSION

Plasmacytic malignancies are deceptive and challenging to diagnose. The present case initially mimicked a pyogenic granuloma clinically. The same was confirmed histopathologically due to the superficial nature of biopsy. However, an appropriate deeper biopsy would have enabled to identify the lesion as a round cell tumor.

The SPB, EMP, and MM result from uncontrolled plasma cell proliferation that exhibits overlapping clinical and histologic features; it may often lead to a diagnostic dilemma and mislead the clinicians. However, the serological investigations and histopathology with IHC can be utilized to arrive at an accurate diagnosis to adopt the indicated treatment strategy to improve treatment outcomes.

The SPB affects <5% of patients with plasma cell myeloma with a predilection of 65% in males and
Diagnostic Panel of Markers CD45, CD20, CD3, CD138, and CD56 for Oral Solitary Plasmacytoma of Bone


35% in females, and the median age of presentation is a decade younger than that of subjects diagnosed with MM.\textsuperscript{5-7} The SPB may involve any bone, but it has a predisposition for the red marrow containing axial skeleton. Spinal disease is observed in 34 to 72% of cases. The thoracic vertebrae are most commonly involved, followed by lumbar, sacral, and cervical vertebrae. The rib, sternum, clavicle, or scapula is involved in 20% of cases with involvement of mandible being a rare event. An analysis of the surveillance, epidemiology, and end results database from 1992 to 2004 demonstrated that the incidence of MM (n = 23,544; incidence rate (IR) 5.35/100,000 person years) is 16 times higher than SPB overall (n = 1543; IR = 0.34), and incidence of SPB was 40% higher than that of EMP (p < 0.0001).\textsuperscript{5,8}

In 2003, the International Myeloma Working Group (IMWG) published criteria for the classification of monoclonal gammopathies, MM, and related disorders recognizing SPB, EMP, and multiple solitary plasmacytomas (± recurrent) as distinct entities (Table 2). For SPB, the features considered are isolated area of bone destruction due to clonal plasma cells, bone marrow plasma cell infiltration not exceeding 5% of all nucleated cells, absence of further osteolytic bone lesions or other tissue involvement (i.e., no evidence of systemic plasmacytoma), absence of anemia, hypercalcemia, or renal impairment attributable to myeloma, low concentrations of serum, or urine monoclonal protein (i.e., myeloma protein), and absence of monoclonal band.\textsuperscript{6} The present case was in accordance with the above findings and MM was ruled out. The EMPs are localized plasma cell neoplasms that present as soft tissue lesions. The EMP was ruled out due to bone involvement that presented with lytic areas caused by a single lesion. Differences between EMP and SPB are shown in Table 3.

A noticeable feature in the present case was hypergammaglobulinemia and hypoalbuminemia, which is consistent with the investigation by Sharma et al.,\textsuperscript{7} who reported a case of SPB. Chronic infections may be a cause of hypergammaglobulinemia. Studies on animal models

### Table 1: Immunohistochemistry panel details employed in the present case\textsuperscript{5,6}

<table>
<thead>
<tr>
<th>IHC marker</th>
<th>Pathological state with positive staining</th>
<th>Region of stain localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD45</td>
<td>Pan lymphocytic marker\textsuperscript{11}</td>
<td>Cell membrane, cell surface\textsuperscript{11,21}</td>
</tr>
<tr>
<td>CD3</td>
<td>T-cell neoplasms\textsuperscript{11}</td>
<td>Cell surface</td>
</tr>
<tr>
<td>CD20</td>
<td>Normal and neoplastic B cells\textsuperscript{11}</td>
<td>Cell surface</td>
</tr>
<tr>
<td>CD138</td>
<td>Plasmacytic malignancy\textsuperscript{12}</td>
<td>Cell membrane</td>
</tr>
<tr>
<td>CD56</td>
<td>Plasma cells exhibiting cellular atypia\textsuperscript{15}</td>
<td>Cell membrane</td>
</tr>
</tbody>
</table>

Parameters | Observed values |
---|---|
Serum protein electrophoresis | Total protein: 6.6 g/dL; Albumin: 3.4 g/dL; Alpha 1 globulin: 0.3 g/dL; Alpha 2 globulin: 0.7 g/dL; Beta 1 globulin: 0.4 g/dL; Beta 2 globulin: 0.3 g/dL; Gamma Globulin: 4.5 g/dL |
AVG ratio (calculated) | 1.08 |
M band | Absent |

Figs 1A to F: (A) Solitary exophytic growth in the lower front tooth region; (B) computed tomography scan showing focal destruction of outer and inner cortex of body of mandible in the midline associated with large heterogeneously enhanced soft tissue lesion; (C) hematoxylin and eosin stain showing a fibrinous exudate with underlying dilated blood vessels and endothelial proliferation (100×); (D) recurrent lesion in the lower front tooth region following incisional biopsy; (E) hematoxylin and eosin stain showing sheets of round cells with plasmacytoid features like pleomorphism, large, and hyperchromatic nuclei (arrows indicate plasmacytoid cells with atypical features like pleomorphism, large, and hyperchromatic nuclei) (400×); and (F) serum protein electrophoresis showing hypoalbuminemia and hypergammaglobulinemia with absence of monoclonal (M) band.
have proved that lingering of viruses within the body can cause hypergammaglobulinemia, and if viruses are cleared quickly, they lead to only a transient increase in immunoglobulin G. Impairment in cytokine secretion can also cause hypergammaglobulinemia. Increased serological levels of interleukin (IL)-21, interferon-γ, IL-6, and IL-17 have been observed in numerous lesions associated with autoimmunity-related hypergammaglobulinemia.9

In the present case, the patient was seropositive for HIV-1 antibody. The NHL was considered as a differential diagnosis as it is the most common neoplasm in HIV-1

**Table 2: The IMWG diagnostic criteria of SPB, EMP, and multiple solitary plasmacytomas (± recurrent)6**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Solitary plasmacytoma of bone | No M-protein in serum and/or urine  
Single area of bone destruction due to clonal plasma cells  
Bone marrow not consistent with MM (plasma cells <5%)  
Normal skeletal survey (and MRI of spine and pelvis if done)  
No related organ or tissue impairment |
| Extramedullary plasmacytoma | No M-protein in serum and/or urine  
Extramedullary tumor of clonal plasma cells  
Normal bone marrow  
Normal skeletal survey  
No related organ or tissue impairment |
| Multiple solitary plasmacytomas (± recurrent) | No M-protein in serum and/or urine  
More than one localized area of bone destruction or extreme tumor of clonal plasma cells which may be recurrent |

MRI: Magnetic resonance imaging

**Table 3: Differences between SPB and EMP19**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Solitary plasmacytoma of bone</th>
<th>Extramedullary plasmacytoma</th>
</tr>
</thead>
</table>
| Site of occurrence of MM      | Axial skeleton—vertebra and skull  
Poor prognosis—significantly high 65–84% in 10 years and 65–100% in 15 years, median time to progression to MM is 2–3 years |
| Effect of RT application      | Long-term disease-free survival is observed in 30% patients |
| Diagnostic criteria           | Solitary bone lesion confirmed by skeletal survey, plasma cell infiltration proven by biopsy, normal bone marrow biopsy (<10% plasma cells), and lack of myeloma-related organ dysfunction |
| Treatment                     | Surgical excision and RT  
Surgical excision  
RT: Radiotherapy |

In the present case, the patient was seropositive for HIV-1 antibody. The NHL was considered as a differential diagnosis as it is the most common neoplasm in HIV
patients in India affecting about 10% of the individuals.10 Thereby, CD45, CD3, and CD20 were considered for evaluation. However, a negative immunostaining by CD45, CD3, and CD20 helped to rule out NHL. Expression of CD45 is observed in hematopoietic cell lines, unnoticed in nonhematopoietic cell lines and also in normal and malignant nonhematopoietic tissues. Therefore, CD45 aids to identify lymphoid neoplastic cells from nonhematopoietic undifferentiated neoplasms. The CD3 marker is highly specific for T cells; it is appreciated in majority of T-cell neoplasms; CD20 is a differentiation antigen of B cells with its expression being restricted to normal and neoplastic B cells.11

In addition to the above investigations, we also performed an IHC staining with CD138 to identify if the neoplastic lesion was of plasmacytic origin. An intense membrane positivity was observed, and similar findings were identified by Baad et al3 in their report of SPB in the mandible. The CD138 is expressed on the surface of mature epithelial cells and normal and neoplastic plasma cells. It plays an important role in the evaluation and characterization of plasma cell dyscrasias.12

The PBL was also considered as a possible differential diagnosis. It exhibits characteristic clinical features like affinity toward oral cavity with a predilection to sites, such as jaw and palate. Histologically, it presents features like large polygonal plasmablastic cells with abundant basophilic cytoplasm and large eccentric nuclei. It is a high-grade B-cell lymphoma and does not express CD56.13,14 The present case showed moderate positivity with CD56, which supported with the diagnosis of SPB excluding the possibility of PBL. The CD56 aids to identify atypical plasma cells in SPB by its expression in the lesional tissue when compared with EMP and other plasma cell dyscrasias.15 Studies conducted by Corti et al13 and Komarchanth et al14 were in favor of the present case.

The neoplasm in the present discussion exhibited a skeletal immunophenotype with negative CD3, CD20 expression and weakly positive CD45 expression. It showed a predominant plasma cell differentiation and expressed intense membrane positivity for CD138 and positive membrane staining for CD56. This enabled to establish a conclusive diagnosis of SPB with clinicopathologic correlation.

Cytogenetic findings in SPB show recurrent losses in chromosome 13, chromosome arm 1p, 1q, and gains in chromosome arms 19p, 9q, and 1q.16 Occasionally, patients with SPB may present with peripheral polyneuropathy or with features that are consistent with POEMS syndrome—polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes. Minimal criteria to diagnose POEMS syndrome are sensorimotor peripheral neuropathy and evidence of a monoclonal plasma proliferative disorder.6 The SPB is an antecedent to MM, with its progression to the latter lesion usually within 3 years that is indicative of a poorer prognosis and can exhibit an unusual involvement of soft tissues. The EMP is usually encountered in the head and neck, with less aggressive features when compared with SPB.17 It is essential to diagnose SPB accurately; the monoclonal or aberrant plasma cell phenotype should be demonstrated with useful IHC markers18 and serological investigations. According to the Durie and Salmon staging system, SPB is regarded as Stage I myeloma wherein hemoglobin is >10 g/dl, with normal level of serum calcium, normal bone structure, and low M component.19

The SPB can be treated with surgical excision, radiotherapy, and chemotherapy to reduce the size of the lesion. A regular skeletal survey is essential to assess the prognosis due to the rarity of SPB.20

CONCLUSION

Immunophenotyping plays a pivotal role for a precise diagnosis in rare neoplasias like the plasmacytic malignancies. The CD3, CD20, and CD45 are known as the Pan Lymphoma Cocktail. A weak expression of CD45 is observed in plasma cell dyscrasias compared with B- and T-cell lymphomas. The CD138 expresses intense staining with the plasma cell population. The CD56 is frequently used to distinguish abnormal plasma cells from the normal counterparts as it stains the former positive and can be correlated with poor disease prognosis. Serological investigations can aid in distinguishing among plasma cell dyscrasias combined with an IHC panel.

REFERENCES