Original Research Article

Plasmacytoma of the mandible: A diagnostic conundrum

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ABSTRACT

Background: Plasma cell dyscrasias are neoplastic proliferation of monoclonal plasma cells that encompass a wide range of entities. Plasmacytoma may present as one of two distinct clinical entities: Multiple myeloma (MM) a disseminated type of disorder and solitary plasmacytoma (SP) a localized form of plasma cell neoplasm. In head and neck, MM comprises 1% of all malignancies and solitary plasmacytoma 2-5% among all plasma neoplasms. Solitary plasmacytomas present as two subtypes: extramedullary solitary plasmacytoma (ESP) and solitary bone plasmacytoma (SBP). SBP is considered to be a distinct entity and it can present as the first manifestation of the MM in 16% of cases and has a high risk of progression to MM. SBP commonly involves the long bones and vertebrae. Its occurrence in the jaw is extremely rare and only 4.4% are seen in mandible. Clinically, plasmacytoma of mandible presents as pain, tooth migration, hard and soft tissue swelling or pathological fracture. Radiologically, it presents as unilocular or multilocular lesion mimicking odontogenic tumour creating a diagnostic dilemma.

Materials and Methods: We report a series of 3 cases of plasmacytoma of the mandible with comprehensive details of clinico-radiological, histological, immunohistochemistry findings and treatment with a review of the literature.

Results: These three cases were clinically mistaken for Ameloblastoma, Odontogenic tumour and Oral cancer respectively. There was one case of Solitary Plasmacytoma and two cases on further workup proved to be multiple myeloma. All these cases were confirmed by immunohistochemistry.

Conclusion: Plasmacytoma of mandible is very rare. It is usually mistaken for other common mandibular lesions and oral cancers. Every attempt must be made to diagnose them precisely as management is quite specific. To best of our knowledge, this is the first series of plasmacytoma of the mandible in the Indian literature.

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1. Introduction

Plasma cell dyscrasias are neoplastic proliferation of monoclonal plasma cells that encompass a wide range of entities.1 Plasmacytoma may present as one of two distinct clinical entities: Multiple myeloma (MM) a disseminated type of disorder and solitary plasmacytoma (SP) a localized form of plasma cell neoplasm.2 In head and neck, MM comprises 1% of all malignancies and solitary plasmacytoma 2-5% among all plasma cell neoplasms. Solitary plasmacytomas present as two subtypes: extramedullary solitary plasmacytoma (ESP) and solitary bone plasmacytoma (SBP).2 SBP is considered to be a distinct entity and it can present as the first manifestation of the MM in 16% of cases and has a high risk of progression to MM.3 SBP commonly involves the long bones and vertebrae. Its occurrence in the jaw is extremely rare and only 4.4% are seen in mandible. Clinically, plasmacytoma of mandible presents as pain, tooth migration, hard and soft tissue swelling or pathological fracture. Radiologically, it presents as unilocular or multilocular destructive lesion.2 In this article,
we discuss 3 cases of plasmacytoma involving the mandible.

On extensive PubMed search, we found that till date 89 Cases of plasmacytoma of the mandible have been reported in the English literature, among these, 9 cases are from India, all of which are single case reports.

2. Case Summary

Total three cases of Plasmacytoma of mandible diagnosed by histopathology were analysed. The clinical details were obtained from the medical records. The Hematoxylin and Eosin slides were reviewed. In all three cases, diagnosis was confirmed by immunohistochemistry.

Case 1 was a 62-year old female presenting with a progressively enlarging swelling over lower half of the face on right side since 6 months. On examination, a swelling of size 4.5 X 8 cm was noticed over postero-lateral part of mandibulo-maxillary region with normal overlying skin. Intra-orally, bony swelling was seen in posterior mandible causing expansion of buccal cortex and obliteration of buccal sulcus. Her routine haematological examination was normal. X-ray showed a multilocular radiolucent lesion in the body, ramus and angle of mandible. On CT scan, it presented as a multilocular lesion with expansion and ballooning of the buccal cortex with a fleck of calcification involving body and ramus of the mandible and extending into infratemporal space. No mucosal ulceration or growth was noticed. In the view of clinic-radiological features, a provisional diagnosis of Ameloblastoma was considered. A tru-cut biopsy from the lesion was performed. It was reported as a low-grade neoplasm of minor salivary gland origin possibly Acinic cell carcinoma in the outside laboratory. For further differentiation immunohistochemistry (IHC) was advised. We received the blocks for opinion and IHC.

On reviewing the slides, the tumour showed sheets of small round cells with moderate cytoplasm. In areas, the tumour cells showed plasmacytoid morphology. Hence, possibilities of myoepithelial neoplasm and plasmacytoma were considered. On IHC, tumour cells expressed CD138 and MUM-1 with Kappa light chain restriction. Tumour cells showed plasmacytoid morphology. Hence, a provisional diagnosis of oral malignancy, the patient underwent an incisional biopsy.

Diagnosis of oral malignancy was arrived at after histopathological examination showed infiltration of intertrabecular soft tissue by sheets of plasma cells showing a varying degree of differentiation. Plasma cells showed coarse nuclear chromatin and inconspicuous nucleoli. On IHC, the tumour cells expressed CD138, MUM1 and showed kappa light chain restriction. Hence, it was diagnosed as plasmacytoma of mandible.

The histopathological examination showed infiltration of the odontogenic tumour (Figure 4a). The patient underwent 50 Gy in 25 fractions of Intensity Modulated Radiation Therapy (IMRT). In the view of a significant reduction in gross tumour volume after 15 fractions, adaptive RT planning was done. Remaining 10 fractions were delivered using a revised adaptive plan. The patient is on programmed follow-up protocol and is presently disease-free for last 15 months after finishing the treatment.

Case 2 was a 51 years male presenting with a left lower jaw swelling of 4 months duration. On examination, he had hard bony swelling over the body of the mandible with normal overlying skin and intact mucosa (Figure 1a). On palpation, buccal cortical plate expansion with focal cortical plate erosion was noted. Teeth close to the swelling were mobile. X-ray showed a unicystic radiolucent lesion in the body of mandible. CT revealed, a well-defined unilocular radiolucent lesion measuring 4.3 x 4.6 cm, causing a breach in both buccal and lingual cortex giving an impression of the odontogenic tumour (Figure 1b). The patient underwent a diagnostic incisional biopsy.

The histopathological examination showed infiltration of intertrabecular soft tissue by sheets of plasma cells showing a varying degree of differentiation. Plasma cells showed coarse nuclear chromatin and inconspicuous nucleoli (Figure 2 a,b). On IHC, the tumour cells expressed CD138, MUM1 and showed kappa light chain restriction (Figure 2c,d). Hence, it was diagnosed as plasmacytoma of mandible. Serum electrophoresis demonstrated presence of “M” band (Figure 4b) and BM aspiration revealed a hypercellular bone marrow infiltrated by around 30% plasma cells (Figure 2e,f). On further workup, skeletal survey did not reveal any lytic lesion except jaw, and no CRAB features (Hypercalcemia, Renal failure, Anaemia, or Lytic bone lesions) were seen. As per guidelines of International Myeloma Working Group (IMWG), BM infiltration by 30% plasma cells and presence of “M” band qualified him for MM. The patient underwent 3 cycles of chemotherapy RVD regimen (Bortezomib- 1.3 mg/m² intravenously on days 1, 8 and 15 + Lenalidomide- 25 mg orally daily from day 1 to day 14 + Dexamethasone- 40 mg orally on days 1, 8 and 15) and 50 Gy in 25 fractions IMRT radiotherapy. He was lost to follow up 4 months after completing the radiation during the first wave of COVID 19 pandemic.

Case 3 was a 74 years male presenting with a proliferative growth on the right lower jaw since 3 months. It was associated with pain and occasional bleeding while chewing the food. The patient was a chronic tobacco chewer and Type 2 diabetic. On examination, an ulcerative proliferative lesion measuring 3.5 X 2.7 cm was seen on para-mandibular region of the right alveolus (Figure 3a). There was no associated cervical lymphadenopathy. With a provisional diagnosis of oral malignancy, the patient underwent an incisional biopsy.

On histopathological examination it showed a poorly differentiated malignant tumour composed of large round cells with nuclei showing blastic morphology (Figure 3b,c,d). Hence, IHC was performed for further
differentiation. On IHC, the tumour cells expressed CD138 and EMA with Kappa light chain restriction (Figure 3e,f). Other IHC markers like CK, CK7, S-100 and p63 were negative. Hence, a diagnosis of plasmacytoma with blastic morphology was made. On the skeletal survey, he had a solitary lesion in mandible and routine haematology workup showed anaemia. BM showed normal hemopoiesis with less than 1% plasma cells. Serum electrophoresis exhibited “M” band (Figure 4c). As per IMWG guidelines, he was labelled as MM. The patient underwent chemotherapy RVD regimen (Bortezomib- 1.3 mg/m$^2$ intravenously on days 1, 8 and 15 + Lenalidomide- 25 mg orally daily from day 1 to day 14 + Dexamethasone - 40 mg orally on days 1, 8 and 15). During treatment, the patient expired due to sepsis associated with severe febrile neutropenia.

Fig. 1: a: A clinical photograph of case 2 showing swelling in the Left lower alveolus; b: CT scan showing lytic lesion in the Left mandible with expansion of the buccal cortex & erosion of the both buccal& lingual cortex.

Fig. 2: Microphotographs of biopsy from the Left mandibular swelling (case 2). a & b: H &E sections showing sheets of plasma cells with abundant eosinophilic cytoplasm & eccentric nucleus. (a x100), (b x400); c: IHC image showing expression of CD138; d: IHC image showing kappa light chain restriction (c & d x400); e: Bone marrow aspiration (e x400) & f: biopsy (f x400) showed about 30% plasma cells.

3. Discussion

Plasmacytoma is a localized mass of neoplastic monoclonal plasma cells; first described by Schridde in 1905.4,5 Solitary plasmacytoma has been classified into 2 groups, the first being solitary bone plasmacytoma (SBP), which frequently occurs in the axial skeleton. The second group is the solitary extramedullary plasmacytoma (SEP).

The median age occurrence of solitary plasmacytoma is 50–70 years having a male predominance with a male:female ratio of 3:1.6,7 In our series, two patients were male and one was female.

The most common sites of SPB are long bones and vertebrae. In Head Neck region, about 40% of SP present in the nasal cavity and paranasal sinus, 20% in the nasopharynx, and 18% in the oropharynx. It rarely involves jaws and only 4.4% are seen in mandible.8 In the mandible, it is commonly seen in the bone marrow rich areas like the body, angle, and ramus.9 Pisano et al have noted that SBP most frequently occurs at the posterior mandible.10 In our series, two cases involved body of the mandible and the third presented in the body and ramus region.

The aetiology of SP is unknown. However, chronic stimulation, radiation, viral infection, and genetic modification could contribute to the onset of the lesion.11 One of our cases was diabetic and chronic tobacco chewer.

Clinically, SPB presents as jaw pain, paraesthesia, anaesthesia, mobility, migration of the teeth, haemorrhage, swelling in hard and soft tissues and pathological fractures.2 In our case series, two cases presented with asymptomatic swelling in the jaw and the third presented as soft tissue.
The detection of “M”proteins is usually done by serum or urine electrophoresis. In solitary plasmacytoma of mandible, the reported incidence of presence of “M”proteins is 38.09% with a range of 24-72%. In our series, all 3 cases showed presence of “M” band on serum electrophoresis.

According to the diagnostic criteria defined by the International Myeloma Working Group (IMWG), the diagnosis of SP is histological and requires evidence of clonal plasma cells in a single site, without or minimal bone marrow involvement (< 10% infiltration by plasma cells), absence of other lesions on the skeletal survey and end-organ damage as seen in symptomatic MM (anaemia, renal insufficiency, hypercalcaemia, multiple bone lesions, or amyloidosis).

On Histopathology, SP presents as clusters or sheets of atypical plasma cells with varying degree of differentiation and sparse stroma. Plasma cells are characterized by abundant cytoplasm with an eccentrically placed nucleus which may often show chromatin clumps typically arranged in cartwheel or clock-face pattern. Occasionally binucleated cells also noticed. Sometimes cells may also show paranuclear, pale staining area called as “hof.” On IHC, monoclonal plasma cells express CD138 and/or CD38 with either kappa or lambda light-chain restriction. The more sensitive techniques like flow cytometry which detect small clonal populations have a possible role in follow up and surveillance.

In SP, on Electrophoresis of serum and urine, (M)-protein levels should be < 3 g/dl; otherwise, one should suspect occult or extensive MM. The most common clonal immunoglobulin type is IgG followed by light chain. Case 1 presented M protein levels with 1.2 gm/dl and rest two cases had 3.7gm/dl and 5.9gm/dl respectively.

To distinguish SP from MM, a skeletal survey has a vital role. A plain radiograph can have at least 20% false-negative results hence it is rarely used. Low radiation dose whole-body CTscan (WBCT) is currently the imaging modality of choice in MM. MRI is less sensitive than CT in the detection of lytic bone lesions; however, it is appropriate for the detection of soft tissue lesions. The updated 2017 IMWG guidelines consider PET/CT as a valuable tool in multiple myeloma setting. Cavo et al have

| Table 1: The clinical details of all three cases are summarised |
|-----------------|-----------------|-----------------|
| Case No 1       | Case No 2       | Case 3          |
| Age /sex        | 62 /F           | 51/M            | 74/M            |
| Site            | Right mandible  | Left mandible   | Right mandible  |
| Presentation    | Bony swelling, posterior mandible | Bony swelling on the body of the mandible | Proliferative growth on the right alveolus, with occasion bleeding |
| Radiological findings | A multilocular lesion in body, ramus and angle of the mandible | Unicystic lesion with both buccal and lingual cortex erosion | Gross bony erosion |
| Provisional diagnosis | Ameloblastoma | Odontogenic bony lesion | Oral carcinoma |
| Paraprotein     | Present, κ-light chain 1.2 gm/dl | Present, κ-light chain 3.7 gm/dl | Present, κ-light chain 5.9 gm/dl |
| IHC findings    | CD138 and MUM-1 | CD138 and MUM-1 | CD138 and EMA |
| Bone marrow     | Normal          | Up to 30% PC    | Normal          |
| Skeletal survey | Solitary bone lesion | Solitary bone lesion | Solitary bone lesion |
| CRAB like feature | Nil            | Nil             | Nil             |
| Treatment provided | Definitive RT | “ RVD” Chemotherapy + RT | “ RVD” Chemotherapy |

On radiographs, tumours appear as unilocular or multilocular radiolucent and expansile lesion causing medullary bone destruction which may give an impression as odontogenic tumour. Some long-standing lesions may mimic as odontogenic cysts. In our case series, first case was provisionally diagnosed as ameloblastoma and the second one as aggressive odontogenic tumour and the third case presented as ulcero-proliferative tumour and hence was clinically mistaken for carcinoma.

Clonal plasma cells involved in plasmacytoma secrete a monoclonal immunoglobulin and either κ or λ light chains commonly described as monoclonal (M) protein, paraprotein or “M” spike. These monoclonal proliferation get localized in the bone marrow causing bone destruction. The Plasma cells produce osteoclasts activating factor which further promotes the growth of osteoclasts leading to bone resorption and contributing to further bone destruction. Bone damage alters the serum calcium levels which is more common in MM than SP. Among our cases, all three presented with a solitary bone lesion and none of them had altered calcium levels.

On treatment, for solitary plasmacytoma, definitive radiotherapy (RT) is used. However, in the presence of bulky disease, chemotherapy is also beneficial. A common treatment modality is “RVD” (Rituximab, Vinblastine, Doxorubicin). CD138 and MUM-1 are positive in plasma cells and EMA is positive in odontogenic cysts. In our series, all 3 cases shows presence of “M” band on serum electrophoresis.

Bone damage alters the serum calcium levels which is more common in MM than SP.
recommended that PET/CT should be part of initial SP investigation to exclude the presence of additional occult sites of clonal plasma cell proliferation. In our series, all three patients underwent a skeletal survey and all had a solitary mandibular lesion.

Optimal therapeutic strategy for SPs should aim to achieve durable long-term local control with minimal morbidity, effective pain control, and in certain instances stabilize weight-bearing bones. As per the National Comprehensive Cancer Network (NCCN) clinical practice treatment guidelines in oncology 2017, SP is a radiosensitive tumour, radical radiotherapy is the treatment of choice. It has been illustrated as an index of local disease control of 80% with durable remission and even a cure. The International Lymphoma Radiation Oncology Group (ILROG) panel recommends following dose guidelines (with 1.8-2 Gy daily fractions):

1. SBPs <5 cm: total dose 35 to 40 Gy  
2. SBPs ≥ 5 cm: total dose 40 to 50 Gy  
3. SEPs: total dose 40 to 50 Gy.

In head and neck area, it is reasonable that the clinical tumour volume (CTV) includes the gross tumour volume (GTV) plus a margin of 0.5 to 3 cm expanded in all directions, respecting anatomic boundaries.

We employed adaptive radiotherapy in one of our cases. Adaptive radiotherapy refers to a change in the radiation therapy plan in order to accommodate changes in the tumour volume during the course of radiation therapy. In the case 1, there was a significant reduction in the tumour volume noted after delivering a dose of 30 Gy in 15 fractions. To account for this decrease in tumour volume, we revised the radiation plan so that the high doses would be restricted to the tumour and do not spill into the surrounding healthy tissues. The remaining 20 Gy in 10 fractions was delivered using the revised plan.

Surgical treatment is elective in those selected cases where entire tumour can be removed with a minimal cosmetic or functional deficit or those to prevent or stabilize a pathologic mandibular fracture.

Though the role of chemotherapy is safeguarded, some authors have limited its usefulness to disseminated diseases. The European expert panel states that adjuvant chemotherapy can be considered for those patients with evidence of persistent disease post radiotherapy.

The combination of RT with novel agents is attractive theoretically. Adjuvant novel agents such as proteasome inhibitors or immunomodulatory drugs (eg. lenalidomide) may be useful in enhancing local control and possibly eradicating the subclinical disease in patients with SP to prevent the development of systemic MM. It needs further studies.

In our case series, case no 1 presented as Solitary plasmacytoma, hence she underwent upfront definitive radiotherapy. She had responded well to radiotherapy and is disease free after 15 months of follow up. Rest two cases were plasmacytoma with myeloma defining events; hence, they underwent chemotherapy in the form of RVD regimen. In Case No 2 after chemotherapy patient received radical RT to the residual solitary lesion. Case 3 was administered RVD regimen but due to chemotherapy complications, he succumbed to death during treatment.

The median survival rate of a solitary plasmacytoma is longer than in multiple myeloma due to the localised nature of the disease. However, clinical remission is unusual. SBPs have a high risk of progression to MM (65% to 84% in 10 years and close to 100% by 15 years) and in contrast, SEPs have a lower risk (10% to 30% over 10 years) of progression to MM but a higher risk of local recurrence. Scientific evidence suggests that patients with SBP larger than 4-5 cm in size have a higher risk of developing MM.

Due to the progressive nature of SP and prolonged time (6-8 months) to achieve maximum RT response; periodic surveillance is mandatory. Routine complete blood count, serum chemistry (calcium and creatinine) and evaluation for potential biomarkers like persistent M-protein, clonal expansion of free light chains (FLC) and presence of clonal plasma cells are common practices. PET/CT scanning when available can be particularly useful in follow-up setting for a skeletal survey.

After extensive PubMed search using Meshword, “plasmacytoma” and “Mandible”, we could retrieve 89 cases of plasmacytoma of the mandible reported in the English literature, among these 9 cases are from India all of which are single case reports. Recently Suryavanshi et al have done an extensive review of 50 cases of SBP of mandible. Kulkarni et al described a unique case of plasmacytoma of mandible with rare bilateral involvement. To best of our knowledge, this is the first series of plasmacytoma of the mandible in the Indian literature.

4. Conclusion
Plasmacytomas involving mandible are quite unique and rare tumours which are usually mistaken for other more common odontogenic lesions and minor salivary gland neoplasms. Every attempt must be made to diagnose them precisely as its management is quite specific.

5. Conflict of Interest
The authors declare that there are no conflicts of interest in this paper.

6. Source of Funding
None.


References


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