IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 8 Ser.7 (August. 2021), PP 58-65
www.iosrjournals.org

Plasmacytoma of Mandible – A Case Report and Review

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Abstract:
Background*: Plasma cell dyscrasias are a formidable group of disorders among haematologic neoplasms. These are also termed as plasma cell disorders and plasma cell proliferative diseases. The medical term "dyscrasia" literally means "bad mixture," and can be traced back to the Greek physician Galen (A.D. 130 to 199). The clinical presentation of Plasma cell dyscrasias may vary from asymptomatic to life threatening malignant neoplasms. Monoclonal gammopathy of undetermined significance (MGUS), Malignant monoclonal gammopathies, Malignant lympho-proliferative disorders and immunoglobulin deposition diseases are among them. Plasmacytomas and multiple myeloma comes under the category of malignant monoclonal gammopathies. Plasmacytomas are monoclonal neoplastic plasma cell proliferations. The disease was first described by Schridde in 1905 (Chang et al, 2014)[1]. Plasmacytomas may present as a single lesion (solitary plasmacytoma) or as multiple lesions (as a part of multiple myeloma [MM]). Solitary plasmacytomas most frequently occur in bone, known as solitary bone plasmacytoma (SBP), but can also be found outside bone in soft tissues which are known as extramedullary plasmacytoma (EMP). EMPs are rare when compared to SBPs and commonly occur in head and neck region. In this case report we present a case of a 60-year-old male patient who reported pain and reddishfluid discharge from the lower right back tooth region of the jaw.*

Key Word*: Plasma cell, Plasma cell dyscrasias, Plasmacytoma, Extra medullary Plasmacytoma, Multiple myeloma*

Date of Submission: 06-08-2021 Date of Acceptance: 19-08-2021

I. Introduction

Solitary plasmacytoma (SP) of bone is a rare plasma cell proliferative disorder. SP shows an incidence of 2-5% of all neoplasms [2]. The common sites of development of solitary bone plasmacytoma (SBP) are marrow-rich bones, mainly in the axial skeleton and pelvic bones. Solitary extramedullary plasmacytoma (EMP) develop within the soft tissue, especially in the upper respiratory tract. In maxillofacial bones, SP is a relatively rare condition. Within the maxillofacial region, the rate of incidence of SP in mandible is reported as 4.4% [8]. The low incidence and lack of specific clinical symptoms makes the clinical diagnosis of SP in maxillofacial bones, quite difficult and may lead to misdiagnosis [9]. The aetiology is unknown; however chronic stimulation, radiation overdose, viral infections, and genetic factors may contribute to the development of the lesion. Solitary plasmacytoma of bone may transform into multiple myeloma with the involvement of multiple skeletal sites. This case report and review aims to report solitary plasmacytoma in the oral cavity.

II. Case Report

A 60 year old male patient reported to the outpatient department with a chief complaint of pain and reddish fluid discharge from the lower right back tooth region of the jaw since five days. The pain was gradual in onset, moderate, continuous, radiating to the right ear with no history of paraesthesia.

On general physical examination, the patient was moderately built; gait was normal and no other abnormality detected. The patient reported that he is not allergic to any drugs taken so far and he has been taking medication for diabetes since five years. Haematological findings were found to be within the normal limits and urine analysis had shown normal results.

On extra oral examination no gross asymmetry was found. The maximal mouth opening was 4cms without any deviation or clicking sounds of the temporomandibular joint. Lymph nodes in the head and neck region were not palpable.

On intra oral examination, the patient was partially edentulous with missing mandibular posteriors except 34, 35, and 38. In maxillary arch 25 & 27 were missing. The oral hygiene status was fair. On local examination expansion of buccal and lingual cortical plates with obliteration of buccal vestibule was observed.

{Figure1}.

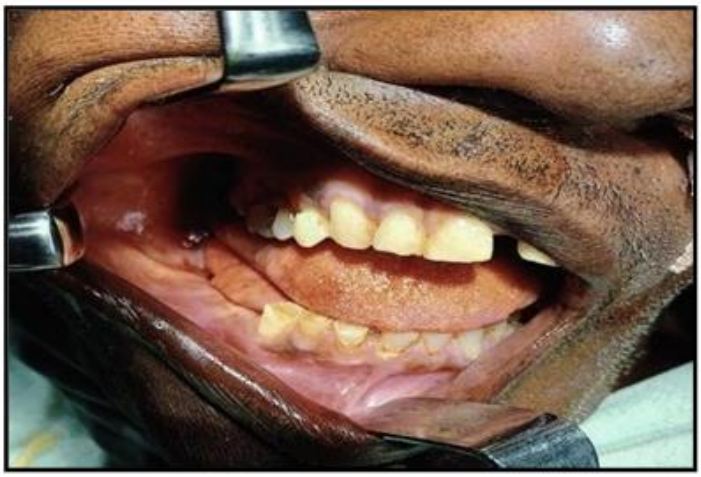


Figure 1: Clinical picture of patient showing lesional area in the right lower back tooth region

On radiological examination, the OPG showed irregular, ill defined multilocular radiolucency in right half of mandible from distal aspect of 42 extending into the ramus till coronoid process and sigmoid notch sparing the condyle, measuring approximately 4X9 centimeters with a horizontally impacted tooth surrounded by irregular soap bubble like radiolucencies {Figure2}.

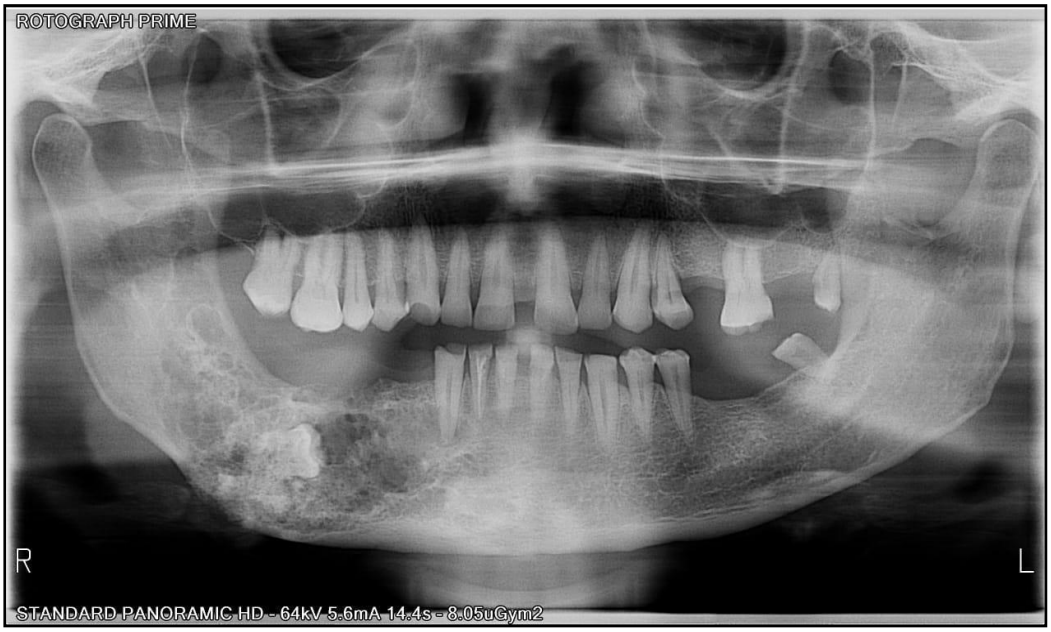


Figure 2: Orthopantamograph showing multilocular radiolucency located in the right mandibularregion.

The OPG findings were confirmed with Cone beam Computed tomography (CBCT). Based on these findings a clinical differential diagnosis of odontogenic keratocyst (OKC), dentigerous cyst, ameloblastoma, calcifying epithelial odontogenic tumor (CEOT) were suspected.

Patient's earlier reports revealed, an incisional biopsy done one month back from the date of reporting by the patient to our institution and was diagnosed as calcifying epithelial odontogenic tumour. As patient did not have biopsy block or slides of prior biopsy, the incisional biopsy was repeated before planning the excisional biopsy. Aspiration of the lesion was negative.

On microscopic examination, the H&E stained slides of incision biopsy specimen showed hyperplastic parakeratinized stratified squamous epithelium and underlying connectivetissue. The connective tissue is fibro edematous with haphazardly arranged thick collagen bundles interspersing with tumor cells exhibiting nuclear and cellular pleomorphism with round to oval-shaped centrally/ eccentrically placed nuclei. The presence of homogenous eosinophilic coagulum was evident in close proximity to tumour cells {Figure 3,4}. Based on the histopathological features of the Incisional biopsy a differential diagnosis of plasmacytoma, CEOT was given.

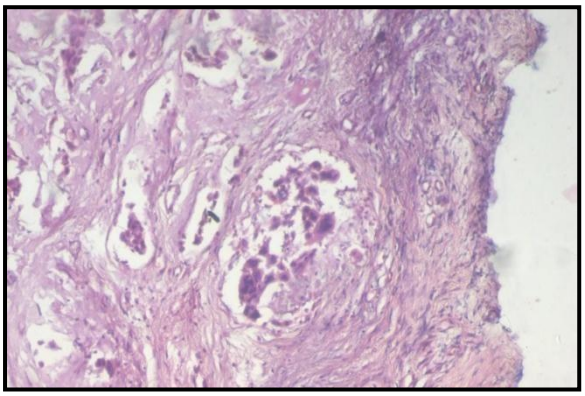


Figure 3: Microphotograph of H&E stained section showing haphazardly arranged thick collagen bundlesand loosely cohesive tumor cells exhibiting nuclear and cellular pleomorphism

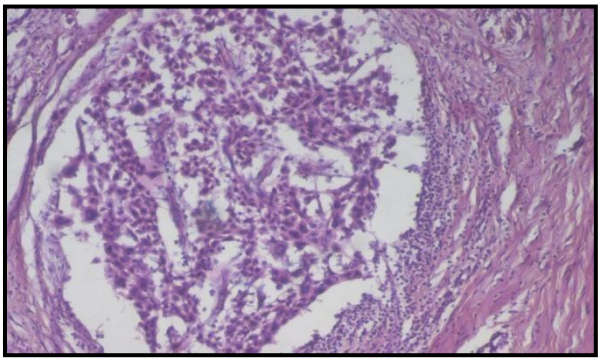


Figure 4: Microphotograph of H&E stained section of Excisional biopsy showing roundtumor cells with cytoplasmic extensions between the cells.

Hemimandibulectomy sparing the right condyle was done and the specimen was received for microscopic examination. The excisional biopsy specimen showed fibroedematous connective tissue with inflammatory infiltrate. Within the connective tissue, there were sheets of plasma cells exhibiting nuclear and cellular pleomorphism and increased abnormal mitotic figures. These features were more in favour of a plasma cell neoplasm whereas the presence of multilocular radiolucent lesion surrounding an impacted tooth and site of thelesion had enrouted us to think in terms that the lesion could be of odontogenic origin.

Therefore IHC analysis by immunostaining with cytokeratin, kappa, lambda and CD138 markers was done. Staining with KAPPA antibodies showed positivity in the tumor cell membrane and tumor secretion {Figure 5}. Staining with LAMBDA antibodies had shown faint positive staining in tumor secretions.

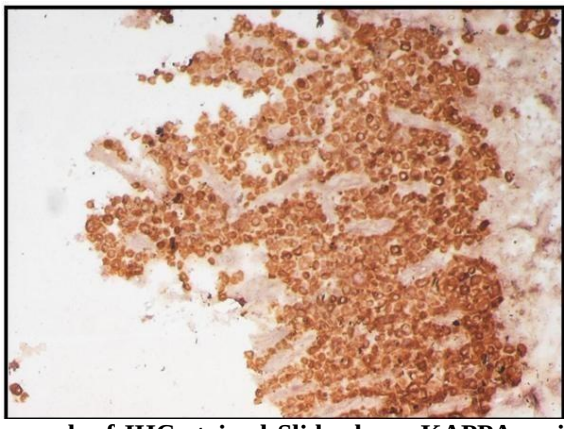


Figure 5: Microphotograph of IHC stained Slide shows KAPPA positivity in tumour cells.

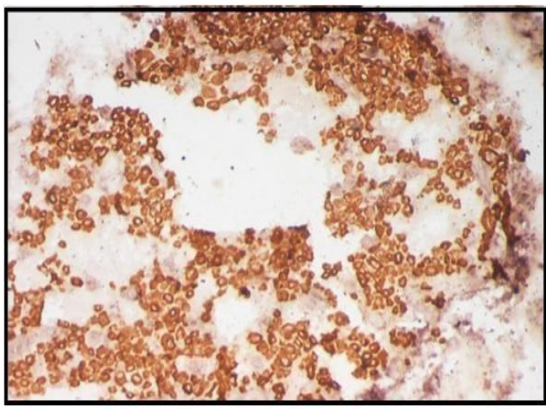


Figure 6: Microphotograph of IHC stained Slide shows Cytokeratin positivity in tumour cells.

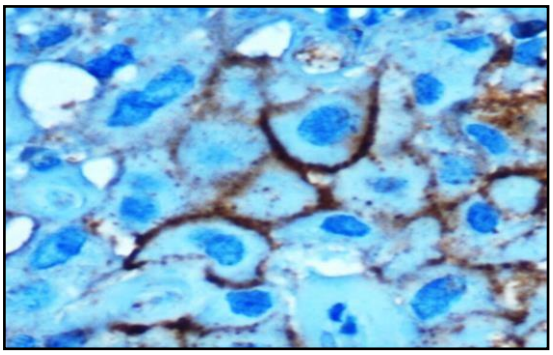


Figure 7: Microphotograph of IHC stained slide shows CD138 positivity in tumour cells.

Cytokeratin positivity was observed in the tumor cell cytoplasm {Figure 6}. CD138 positivity was observed in the tumor cell membrane and was negative for epithelial cells {Figure7}. These observations were supportive toconclude the lesion as plasma cell origin.

Skeletal survey with plain radiographs of skull, chest, long and pelvic bones was done to check for the involvement of other skeletal sites. No other osteolytic lesions were found. {Figures - 8, 9, 10}. Urine analysis for Bence jones proteins was negative. Hematological tests were within the normal range.

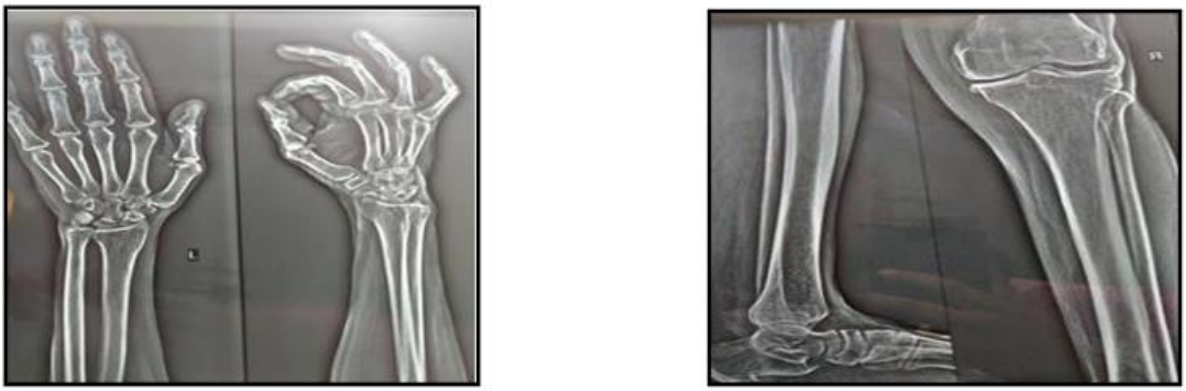


Figure 8: Plain radiographs of long bones

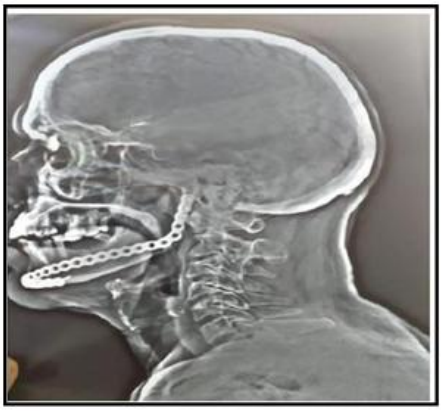


Figure 9: Plain Radiograph of skull

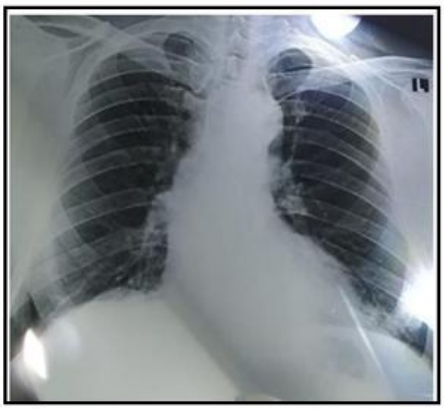


Figure 10: Plain chest radiograph

By correlating the clinical, radiological, histopathological features, biochemical test results and immunohistochemical staining pattern and also by taking the guidelines of International Myeloma Working Group (IMWG) {Table-1,2} into consideration, the diagnosis of "***Solitary bone Plasmacytoma"*** was concluded.

Table 1: International Myeloma Working Group diagnostic criteria and classification [11]

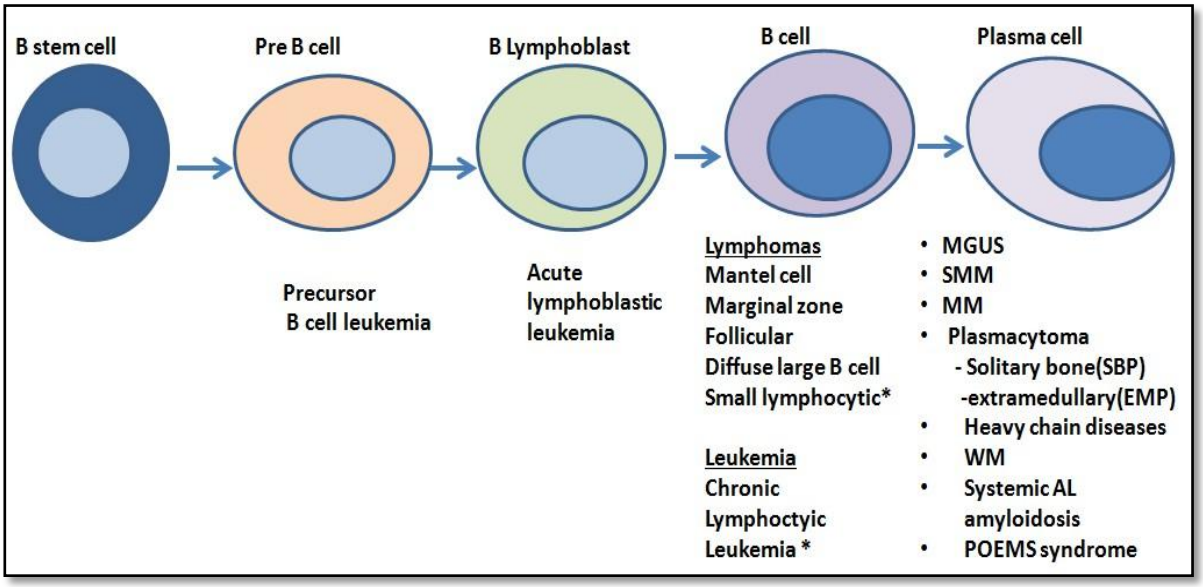
Solitary plasmacytoma • Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells. • Normal bone marrow with no evidence of clonal plasma cells. • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion). • Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, or bone lesions (CRAB) that can be attributed to a lymphoplasma cell proliferative disorder.
Solitary plasmacytoma with minimal marrow involvement • Clonal bone marrow plasma cells ≤10%. • Other criteria are similar to solitary plasmacytoma.

- Lesion size of >5 cm
- Age (e.g., patients aged 40 years and over)
- Spine lesions
- Radiation Treatment dose
- High M protein levels
- Existence of light chains
- Persistence of M protein after treatment
- Anaplastic type plasmacytomas presenting a higher histologic grade
- Existence of a high level of angiogenesis

TABLE 2: Risk factors contributing to poor prognosis of Solitary Plasmacytoma of bone (SBP) [20]

III. Discussion

Plasma cells are antibody secreting cells that are differentiated from antigen activated mature B cells. Plasma cells, as a component of humoral immunity helps in protective responses of human immune system against pathogens and may become inimical to such an extent that life-threatening malignancies arise from the same cells when they are defective. The stages of differentiation from B cell to plasma cell and neoplasms occurring at each stage of plasma cell differentiation are shown in figure11.



Monoclonal gammopathy of undetermined significance (MGUS), Smouldering multiple myeloma (SMM), Multiple Myeloma (MM), Waldenstrom's macroglobulinemia (WM).

Figure 11: Schematic representation depicting stages of differentiation from B cell to Plasma cell and neoplasms occurring at each stage of plasma cell differentiation[1].

Solitary bone plasmacytoma (SBP) is rare and accounts for about 3-5% of plasma cell neoplasms[10]. Plasmacytomas are clonal proliferations of plasma cells that are cytologically and Immuno-phenotypically identical to plasma cell myeloma but manifest a localized osseous or extraosseous growth pattern (Jaffe, et al 2001).[3, 4]

An updated definition of SBP and EMP by the IMWG is as follows. SPB is defined by the presence of a single lytic lesion due to monoclonal plasma cell (PC) infiltration, with or without soft-tissue extension, and EMP consists of a soft-tissue mass that is not in contact with bone.[14]

The suggested aetiological factors for plasma cell neoplasams are radiation exposure, chemical exposure (formaldehyde, epichlorohydrin, Agent Orange, hair dyes, paint sprays, asbestos) and genetic predisposition[2]. Cytogenetic studies showed that the chromosomal aberrations seen in plasma cell disorders like recurrent losses in chromosome 13, chromosome arm 1p and chromosome arm 14q as well as gains in chromosome arms 1q 19p, 9q, are consistent with solitary plasmacytomas [13].

It shows male predilection with male to female ratio of 2:1 and is more common in 5th and 6th decade. The axial skeleton is more commonly involved than the appendicular skeleton. Thoracic vertebrae are more commonly involved than lumbar or cervical vertebrae. SBP involving maxilla and mandible is rare while 90% of EMP occurs in the head and neck region[12].

Most common symptom of SBP is pain due to destruction of bone at the site of lesion. In present case the patient had similar feature of pain in the right body of mandible radiating to right ear. Lae *et al* described three radiographic patterns in SPB, which include multilocular soap- bubble lesions, unilocular radiolucency with cystic appearance and ill- defined destructive bone resorption[16]. SBP is known to replace the trabecular bone, while the cortical bone may be partly conserved or even sclerotic. Advanced imaging modalities that contribute to diagnosis of solitary plasmacytoma include MRI, CT and PET. The lesion described in the present case showed radiolucency of multilocular soap- bubble appearance with extensive cortical destruction of posterior aspect of the right mandible.

The Bone Marrow (BM) of patients with plasmacytoma contains malignant plasma cells that directly, by the production of cytokines or indirectly, by stimulating BM cell secretion of other factors. Myeloma cells directly produce factors implicated in both Osteoclast (OC) activation and Osteoblast (OB) inhibition and this contributes to the imbalance between bone resorption and formation eventually resulting in the development of

osteolytic lesions. Among the factors implicated in OC activation, decoy receptor 3 (DcR3), interleukin-3 (IL-3), macrophage inflammatory protein-1α (MIP-1α), macrophage inflammatory protein-1β (MIP-1β), and tumor necrosis factor-α (TNF-α) , produced by malignant plasma cells plays important role.[15]

Histopathologically, SPB presents as clusters or sheets of atypical plasma cells with varying degree of differentiation interspersing with stroma. Plasma cells are 14 to 20 micrometers in diameter and characterized by abundant cytoplasm with eccentrically placed nucleus which may often show chromatin clumps typically arranged in cartwheel or clock- face pattern. Most plasma cells are uninucleated, few are binucleated or multinucleated. Hof, A pale perinuclear area (Peri nuclear halo) corresponding to the Golgi apparatus is seen. They may contain cytoplasmic inclusions called Russell bodies or multiple spherical inclusions packed in their cytoplasm (Mott, grape, or morular cells). Russell bodies and the inclusions of Mott cells are dilated endoplasmic reticulum cisternae containing condensed immunoglobulins.

Lae *et al* [16] observed Classic histological features in 67%; Anaplastic cells in 33 %; presence of amyloid deposits in 38 %; and sinusoidal pattern in 5 %. in their study on SBPs.

SS Susnerwala *et al* [17] implemented the grading criteria originally devised by Bartl *et al* (1987) for multiple myeloma (MM) for histological grading of extramedullary plasmacytomas.

Histological grading criteria devised by Bartl et al (1987) for multiple myeloma (MM) [17] includes a three-tiered grading system containing ***marschalko type, asynchronous type and plasmablastic type*** of plasma cells corresponding to Grade 1 (low grade), Grade 2 (intermediate grade) and Grade 3 (high grade) respectively. In the present case, the plasma cells in the lesional areas are of ***asynchronous type.***

Immuno-histochemical analysis will be of great help in diagnosing the plasma cell disorders. The present case showed positivity for CD 138, kappa and lambda and cytokeratin IHC markers. There was strong positivity for kappa and faint positivity for lambda. This indicates differential expression of kappa and lambda proteins by the neoplastic cell.

Abberent Cytokeratin expression in plasmacytomas:

The finding of aberrant expression of cytokeratin by plasma cells in the present case is concordant with the positive expression of cytokeratin mentioned in the literature by **Wotherspoon A.C. *et al* (1988) (**reported 37%) [19]**, Adam *et.al* (2007) (**reported 10% positivity) [20] , **Rohit *et.al* (2015)** [21] , **Suzuki *et.al* (2017)** [22], **Bharani V *et al*** (2017) [23]. Among them **Rohit *et.al* (2015)** in their study found that 21.4% of plasmacytomas of their study sample expressed positivity for modern day cytokeratin cocktails [21].

Differential Diagnosis

The differential diagnosis of Plasmacytoma includes Reactive plasma cell proliferation, Malignant melanoma and MALT lymphoma. Reactive plasma cell proliferation is difficult to differentiate in H&E sections. IHC studies reveal polytypic plasma cell populations while plasmacytoma shows monotypic plasma cells. Malignant melanoma lacks Ig expression and is positive for S-100 protein in IHC analysis in contrast to plasmacytoma. MALT lymphoma will show a spectrum of cells ranging from small lymphocytes to plasmacytoid lymphocytes and plasma cells and infiltrating neoplastic cells of follicular epithelium resemble lymphoid cells.

Prognosis of SBP and EMP

Development of multiple myeloma, local recurrence or development of new lesions contributes to poor prognosis. Progression to Multiple myeloma is seen in about 65-85% of patients with SBP and 30% of patients with EMP within 10 years after the initial diagnosis, for this reason early diagnosis, regular follow ups and meticulous treatment is mandatory. [25]

IV. Conclusion

Posterior mandible is the most common site for many cystic/lytic lesions of diverse origin. The occurrence of plasmacytoma in this region may create dilemma and become an enigma for oral pathologists to conclude the diagnosis. The involvement of jaw bones by plasmacytomas may manifest as soft tissue mass (EMP) / lytic (SBP) lesions in the jaw bones and this presentation reinforce the fundamental role of oral and maxillofacial pathologist in recognition and early diagnosis of the systemic condition. Comparing, contrasting and correlating all i.e., clinical, histopathological, radiological (including skeletal radiographs) features, biochemical, urine analysis and immunohistochemical analysis with respective markers will help in concluding the diagnosis, when SP occurs in jawbones. Immunohistochemistry, cytogenetics, molecular genetics and other ancillary techniques will be great help in diagnostic accuracy.

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Navya Hadassah Tadiparthi, et. al. "Plasmacytoma of Mandible – A Case Report and Review." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 20(08), 2021, pp. 58-65.