Case Report

Solitary plasmacytoma of jaw bone: A case report and systematic review of fifty cases from literature

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Abstract

Solitary plasmacytoma of bone (SPB) is a localized form of plasma cell neoplasm where jaw involvement is rare. Distinguishing SPB from other plasma cell neoplasms is critical for treatment and survival. Here, a case of SPB of mandible in an elderly female is reported. Histopathological diagnosis of plasma cell neoplasm was confirmed immunohistochemically with MUM1 and CD138 positivity and multiple myeloma (MM) was ruled out on performing systemic workup. Prognosis of SPB worsens when it transforms into MM. A systematic review was undertaken with the objective to determine the factors affecting conversion of SPB to MM. An electronic search was undertaken with PubMed/MEDLINE, Web of Science and Science Direct. Fifty cases of SPB of jaw from 29 publications were reviewed. SPB commonly presents as a painless swelling. Radiographically, it is commonly seen as multilocular radiolucency with well-defined borders. Follow-up data showed that nine cases turned into MM in a mean duration of 1 year 9 months and 12 patients died after median disease-free survival of 6 years 9 months. Prognosis of SPB is found to be affected by tumor size (≥5 cm), anaplasia of tumor cells, Ki-67 labeling index, vascularity of the tumor, presence of clonal bone marrow plasma cells, serum immune globulin level, dose of radiotherapy and persistence of M protein after treatment. There is a need to identify prognostic subgroups in SPB based on these factors. Furthermore, studies are necessary for standardization of treatment protocol to halt or prolong the progression of SPB to MM.

Keywords: Multiple myeloma, plasma cell neoplasm, plasmacytoma of jaw bone, plasmacytoma, solitary plasmacytoma of mandible, solitary plasmacytoma, treatment of plasmacytoma

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Submitted: 14-Jun-2020, **Accepted:** 29-Jan-2021, **Published:** 14-May-2021

INTRODUCTION

Plasma cell neoplasms are relatively unusual malignancies of the head-and-neck region. The incidence of these tumors is about 2.6–3.3/100,000 populations.[1] These neoplasms are characterized by monoclonal neoplastic proliferation of plasma cells and are indistinguishable histologically. They may present as multiple myeloma (MM), solitary plasmacytoma of bone (SPB), or extramedullary plasmacytoma (EMP).[2] Behavior of each of these tumors is variable with the difference in prognosis. SPB and EMP are the localized forms of plasma cell neoplasms, while MM is a disseminated form. The prognosis of SPB is poorer than EMP and MM is the most fatal among them.

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.JOMFP_251_20

How to cite this article: Suryavanshi H, Patankar S, Dhumal S, Choudhari S. Solitary plasmacytoma of jaw bone: A case report and systematic review of fifty cases from literature. J Oral Maxillofac Pathol 2021;25:205-6.

SPB is localized plasmacytoma and is rare in the orofacial region.[3] Only 4.4% of SPB have been reported in mandible mainly in angulus and ramus area.[4] Prognosis of SPB worsens when it transforms into MM. Careful differentiation between SPB and MM is necessary. Distinguishing SPB from other plasma cell neoplasms is critical for treatment and survival. Here, we are reporting a case of SPB of mandible in an elderly female.

CASE REPORT

An elderly, partially edentulous female patient (of age 56 years) reported with a complaint of swelling in the left posterior region of mandible. Swelling gradually increased over a period of 4 months. Clinically, the swelling was of 5 cm × 3 cm in size and was extending from 33 to 36 with buccal vestibular obliteration, covered with normal intact mucosa. On palpation, swelling was found to be slightly tender and firm in consistency. There was no evidence of mobility with involved teeth. On extraoral examination, paraesthesia of the lower lip was noticed. On panoramic radiography, a well-corticated unilocular radiolucency extending from 33 to 36 was seen. Root resorption of 35 and 36 was also noticed [Figure 1]. Three-dimensional cone-beam computed tomography (CT) scan revealed diffuse to slightly clear radiolucency and loss of buccal and lingual cortical plates [Figure 2]. These features were indicative of an aggressive benign odontogenic tumor. An incisional biopsy was taken [Figure 3], and specimen was sent for histopathological examination.

Microscopically [Figure 4], it exhibited diffuse sheets of intensely basophilic cells infiltrating into surrounding connective tissue. The cells presented vesicular nuclei, prominent nucleoli and perinuclear halo. These histopathological features were indicative of plasma cell neoplasm. To confirm the diagnosis, panel of immunohistochemical markers was used which showed positive expression for CD138, MIB1 and MUM1 [Figures 5-7]. CD138 and MUM1 were suggestive of terminally differentiated plasma cells. MIB1 labeling index was about 25%–30% in the present case. The lesion was found to be negative for CD20, CD3, leukocyte common antigen (LCA), Mic-2 and synaptophysin. On performing systemic workup such as blood examination, radiographic survey and magnetic resonance imaging (MRI) of spine and pelvis, MM was ruled out. On the basis of these findings, final diagnosis of solitary plasma cell neoplasm of mandible was given. The patient was then referred to the oncology department for further treatment and is disease free for 1 year.

A systematic review was undertaken to integrate the available data on SPB of jaw to determine the factors which may affect the conversion of SPB to MM and to explore the therapeutic considerations which can prevent its conversion to MM. An electronic search was undertaken in August 2019. The search strategy was in agreement with the Cochrane guidelines for systematic reviews. PubMed/MEDLINE, Web of Science and Science Direct were searched using the keywords as SPB; solitary plsamacytoma of jaw OR mandible OR maxilla; and treatment for

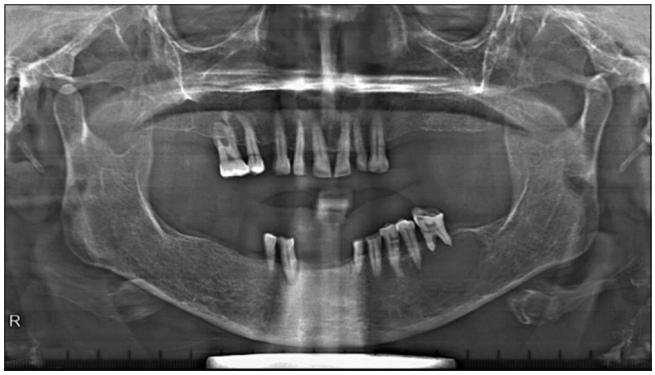

Figure 1: Panoramic radiograph showing unilocular radiolucency extending from 33 to 36

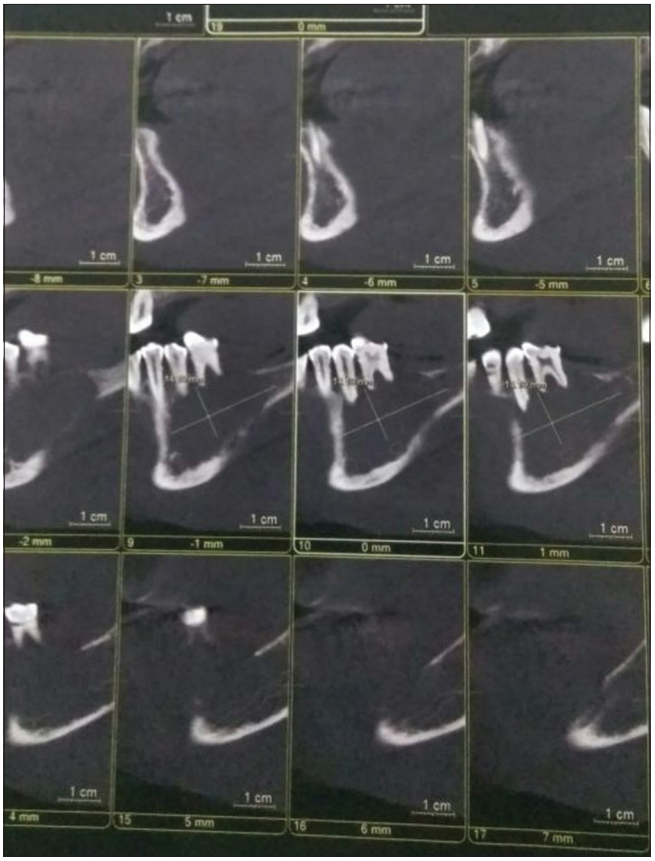

Figure 2: Three-dimensional scan showing diffuse to slightly clear radiolucency and loss of buccal and lingual cortical plates

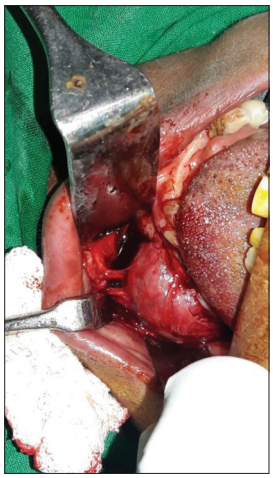

Figure 3: Intra operative photograph of tumour

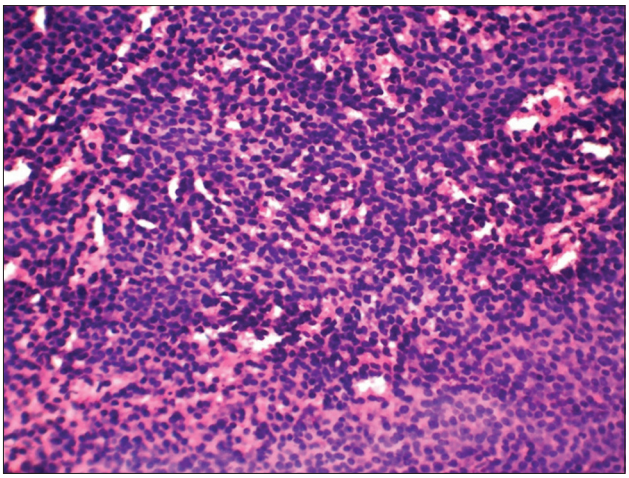

Figure 4: H&E stained section (×10) showing diffuse sheets of intensely basophilic cells infiltrating into surrounding connective tissue

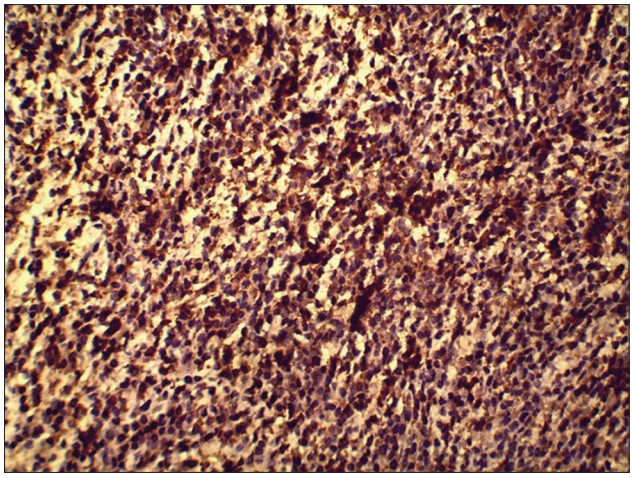

Figure 5: Immunohistochemical expression of CD138

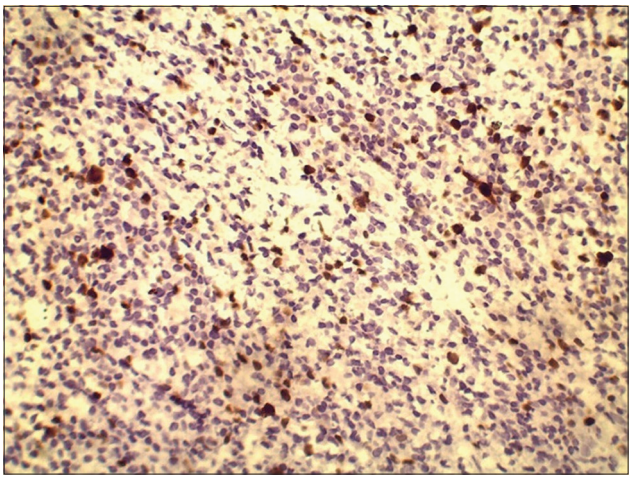

Figure 6: Immunohistochemical expression of MIB1

plasmacytoma. Case reports and reviews on SPB of jaw published from 2000 to August 2019 were searched. Inclusion criteria comprised cases of SPB of jaw bone with sufficient clinical, radiographical, histological and treatment details. Exclusion criteria composed of publications of MM, EMP and recurrent MM presenting as SPB.

Fifty cases of SPB from 29 publications which had sufficient clinical, radiological, histopathological and treatment details were included [Table 1]. Twenty-six cases of SPB were found to be reported in mandible and 24 in maxilla. The mean age of occurrence was found to be 55.8 years. In males, the mean age of occurrence was 48.87 years and in females it was found to be 57.94 years. Male-to-female ratio was 1.07:1.[1] The most common clinical appearance was of a painless swelling (46%). Pain was reported in 31.37% of cases, ulceration/red lesions in 3.9% of cases, mobility of involved teeth in 5.8% of cases and paraesthesia and pathological fracture in 5.8% cases. Presentation of nasal obstruction has been reported in 14.28% of cases of SPB of maxilla. Radiographically, SPB of jaw is commonly seen as multilocular radiolucency (47.7%) with well-defined borders (80.9%). While unilocular radiolucency is reported in 22.4% of cases with well-defined borders in 10.2% and ill-defined borders in 12.2% of cases. In 19.8% of cases, radio-opacity was noted mostly in lesions involving maxilla. SPB is diagnosed on histopathological examination which needs to be supported by immunohistochemistry to establish the confirmative diagnosis after ruling out MM.

According to this review of jaw SPB cases, 18 (36.73%) cases were treated by radiotherapy (RT) alone, 13 (26.5%) cases were treated by RT in combination with surgery, 6 (12.24%) cases by surgery alone, 4 (8.16%) cases by RT with chemotherapy (CHT), whereas 3 (6.12%) cases were treated by combination of surgery, RT and CHT and one case was treated by combination of surgery and CHT. In six case reports, treatment details are not available. Eleven cases which were treated by surgery followed by RT had no

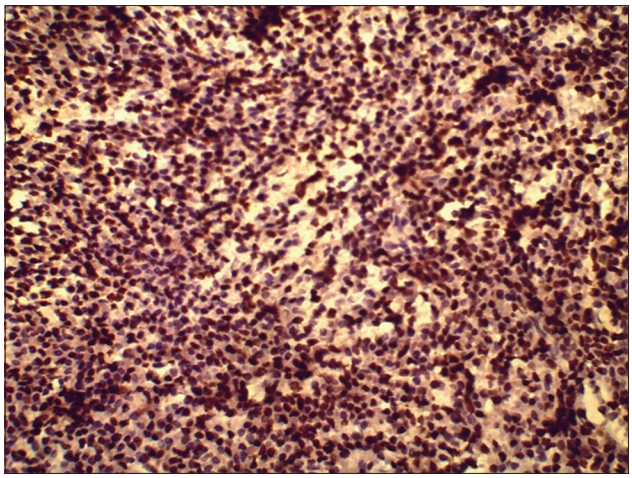

Figure 7: Immunohistochemical expression of MUM1

recurrence. Eight cases treated with RT of 40 Gray (Gy) dose did not show recurrence or progression into MM. Out of 50 SPB cases, nine cases (18.36%) turned into MM in a mean duration of 1 year 9 months and 12 cases of SPB (27.2%) died after median disease-free survival of 6.75 years.

DISCUSSION

SPB as defined by International Myeloma Working Group (IMWG) is the presence of single lytic lesion due to monoclonal plasma cell infiltration, with or without soft-tissue extension.[33] It manifests as single osteolytic lesion without plasmacytosis of bone marrow and constitutes approximately 3% of all plasma cell neoplasms.[34] In head-and-neck region, SPB is very rare with incidence of 12%–15% and 4.4% in mandible.[4] It most commonly involves the posterior body of the mandible and can extend to angle and ramus which are marrow rich areas.[35] Although the etiology remains uncertain, etiologic agents such as radiation, exposure to chemicals and genetic factors have been implicated. Recently, several hypotheses have been underlined including a possible role of viral infection.[36] In SPB of jaw bone, chronic irritation or preceding trauma can also act as trigger for plasma cell proliferation and infiltration.

In the present case, patient's chief complaint was painless swelling in the left posterior region of mandible. As per the review, the most common clinical presentation of SPB was found to be painless swelling [Table 1]. Lombardo *et al*. in their review reported painless increase in volume as the most common clinical finding in SPB of jaw.[37] Pisano *et al*. in their study of 13 cases of SPB reported ulceration and hemorrhage as primary symptom along with pain and swelling.[38] In the present review, male-to-female ratio was found to be 1.08:1 and mean average age of occurrence was found to be 55.8 years.

Radiographically, SPB presents as a well-defined, unilocular or multilocular destructive lesion. Lae *et al*.,[7] in their study on 21 SPB cases, reported unilocular radiolucency with cystic appearance as the common radiographic presentation of SPB. Moulopoulos *et al*.[39] reported that most of their patients with SPB had lytic destructive lesion on conventional radiograph. SPB clinically and radiographically mimics an odontogenic tumor which makes the diagnosis even more difficult. Kanazawa *et al*.[40] have categorized the variable radiological features of SPB into three categories as multilocular radiolucent area resembling ameloblastoma or myxoma, unilocular radiolucent area with an odontogenic cyst such as appearance and third, i.e., irregular destructive bone resorption suggestive of malignant bone tumor. Therefore, SPB could be misdiagnosed on radiological features as odontogenic tumor or cyst. According to 2017 IMWG guidelines, positron emission tomography/CT (PET/CT) scan is mandatory for diagnosis of SPB.[41] CT is helpful to detect the extent of bone destruction accurately. According to IMWG, the updated criteria for the diagnosis of SPB are single area of bone destruction due to clonal plasma cells, absence of M-protein in serum and/or urine, bone marrow not consistent with MM (plasma cells <10%), normal skeletal survey (and MRI of spine and pelvis if done) and no related organ or tissue impairment.[41]

A definitive diagnosis of SPB based solely on the hematoxylin and eosin light microscopic findings is difficult because of the frequent absence of distinguishing features. Ancillary techniques such as immunohistochemical, ultra-structural, cytogenetic and molecular techniques may be used to aid in the confirmative diagnosis of SPB. Homogenous infiltration of plasma cells can be proved on histopathology and on immunohistochemistry where cells show unequivocal positivity for CD138 and/or CD38. Monoclonal proliferation of plasma cells can be confirmed by the presence of kappa/lambda light chain restriction or by polymerase chain reaction-based approach. Histopathologically, it is necessary to differentiate SPB from plasmablastic lymphoma (PBL). Features such as neoplastic cells exhibiting abundant cytoplasm, vesicular chromatin and central nuclei with prominent nucleoli are commonly observed in PBL. Neoplastic cells of PBL are positive for CD38, MUM1, CD138 and VS38c, while CD20 is not expressed in PBL. In our case, immunohistochemical analysis showed CD138, MIB1, MUM1 and Ki67 positivity, while the tumor was negative for CD20, CD3, LCA, Mic-2 and synaptophysin which ruled out lymphoma, leukemia, Ewing's sarcoma and neuroendocrine metastasis. CD138

Table 1: Review of 50 cases of solitary plasmacytoma of jaw with clinical and radiographic features, immunohistochemical findings, treatment and follow-up details

Author, year	Age/sex	Site	Clinical features	Radiographic features	Immunohistochemistry findings	Treatment	Follow-up details
Matsumura *et al*., 2000[5]	83/male	Right maxilla	Swelling of buccal gingiva and pain on percussion of involved teeth	IOPA-multilocular honeycomb appearance OPG-radiopaque lesion	Positive staining for IgG and λ light chain	60 Gy RT delivered in 20 fractions by 4-mV x-rays combined with CHT- intravenous cyclophosph-amide 100 mL and prednisolone (15 mg×3 per day) 3 times a week given during RT	Follow-up for 6 months and decrease in size of lesion
Muzio *et al*., 2001[6]	53/male	Right mandible	Pain and paraesthesia	OPG-bone resorption with vacuolar images CAT-osteolytic area with erosion of buccal and lingual cortical plates	Monaclonal restriction for lambda chain	Refused to surgery. RT of 4000 rads over 20 day's period. CHT for 12 months- Cyclophosphamide 100 mg, prednisonum 100 mg; scaling down prednisonu-m 25 mg after 5th day with melphalan orally 10 mg daily every 4 weeks for 12 months	6 years follow-up with no recurrence
Lae *et al*., 2002[7], 21 cases	14 cases- males 7 cases- females Mean age -57.7 years	15 cases-maxilla, 6 cases-mandible	17 cases-swelling, 5 cases-infected teeth, 5 cases-nasal obstruction, 2 cases-headache, 1 case-pathologic fracture	Multilocular soap-bubble appearance, unilocular radiolucency with cystic appearance, and ill-defined, destructive bony lesion	Details not available	8 cases- RT, 8 cases- surgery+RT, 3 cases-surgery+RT+CHT, 1 case- surgery+CHT, 1 case- surgery	9 cases progressed to MM in median of 20.7 months 12 patients died after median disease-free survival of 6.75 years
Yoon *et al*., 2003[8]	15/male	Right mandible	Severe gingival enlargement, size-3 cm×2 cm	Displaced second molar, PDL widening	Positivity for kappa chain and IgG. *In situ* hybridization with EBV encoded RNA- positive signals in tumour cells	RT 4000 rads daily for 3 weeks	7 years follow-up with no recurrence
Anil, 2006[9]	52/male	Right maxilla	Pain and swelling, size-4.5 cm×2.5 cm	Diffuse radiolucency apical to 15, 16. Paranasal sinus view-radiopacity filling sinus	Details not available	Details not available	Follow-up for 5 years with no recurrence
Canger *et al*., 2006[10]	76/female	Anterior mandible	Slowly developed indurated and nontender swelling of size 5.5 cm	OPG-multilocular radiolucent lesion of size-6 cm×3.5 cm with ill- defined borders	Details not available	Details not available	Deceased before finishing the treatment
Poggio, 2007[11]	75/female	Left mandible	History of SPB spine 12 years back. Presented as swelling and pain in chin	Panoramic radiograph showed a large transparency	Details not available	RT	Details not available
Rao K *et al*., 2011[12]	31/male	Right maxillarytuberosit-y	Nontender, ulcerated swelling following extraction of 16, covered with slough	Radiolucency with slight bony erosion	Positivity for κ light chain	Details not available	Details not available

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Table 1: Contd....

Author, year	Age/sex	Site	Clinical features	Radiographic features	Immunohistochemistry findings	Treatment	Follow-up details
Rodríguez-Caballero *et al*., 2011[13]	64/male	Left preauricu-lar region in maxilla	Painless swelling of size 5 cm, bulging on the mandibular angle	Ill-defined, multilocular, radiolucency, MRI-6.5 cm×5 cm×6.7 cm	CD 138 positivity with kappa light chain restriction	Local RT of 45 Gy	1 year follow-up with no recurrence
Sekar *et al*., 2011,[14] 2 cases	60/female 58/male	Both cases- left mandible	Case 1-swelling- nontender and bony hard in consistency, difficulty in eating Case 2-fungating mass covering the edentulous alveolus, tender with profuse bleeding	Case 1-OPG- lytic lesion without sclerotic border, pathologic fracture and impacted 38 present Case 2-large lytic lesion extending from 35 to 48 giving moth-eaten appearance	In both the cases positivity for light chain kappa and negativity for lambda was found	Both cases underwent RT	No recurrence, follow-up duration not mentioned
Meziane *et al*., 2012[15]	42/male	Right maxillary sinus	Headache and permanent right nasal obstruction	CT scan-radiopacity in right maxillary sinus and nasal cavity	CD38 positivity and expression of the lambda restricted light chain	Surgery followed by RT	1 year follow-up with no recurrence
Singh *et al*., 2012[16]	38/female	Left posterior mandible	Gradually increased nontender, bony hard swelling of size 2.5 cm×2 cm×2 cm, deviation of chin towards left	OPG-solitary, ovoid, unilocular radiolucent lesion extending along the entire angle- ramus region without sclerotic borders	Details not available	Surgery	No recurrence. Follow-up years not mentioned
Ashraf *et al*., 2013[17]	48/male	Left mandible	Pain and numb chin syndrome	CBCT-large destructive lesion of left mandible involving body of mandible and condylar processes	Positivity for kappa light chain and CD38 and MyoD1, desmin, SMA, LCA and cytokeratin negative	Local RT with no significant improvement, later underwent surgery	9 months follow-up with no recurrence
Baad *et al*., 2013[18]	56/male	Posterior mandible	Loose and mobile teeth, pain and swelling of size 6 cm×5 cm	Punched out radiolucency with ill-defined borders	Positivity for Kappa light chain, CD138, CD117 and EMA	Local RT	Details not available
Kaur *et al*., 2013[19]	60/male	Left mandible	Swelling with buccolingual cortical plate expansion	OPG- ill-defined, multilocular radiolucent lesion in body of mandible	Positivity for kappa light chain, CD117, and EMA and negative for λ light chain, pan-cytokeratin, vimentin, S-100, CD1a, tryptase, and SMA	Left hemimandib-ulectomy with bone plating	6 months with no recurrence
Obimakinde *et al*., 2014[20]	70/female	Right zygoma	Painless right zygomatic swelling of size 8 cm× 10 cm	Plain radiograph -an area of patchy opacity with diffuse opacification of upper half of right maxillary sinus	Lambda light chain positivity	Surgery (modified Al-Kayat access incision) followed by RT	6 monthly follow-up for 2 years with laboratory analyses of urine and blood. No recurrence reported

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Table 1: Contd....

Author, year	Age/sex	Site	Clinical features	Radiographic features	Immunohistochemistry findings	Treatment	Follow-up details
Kamal *et al.*, 2014[21]	60/male	Right mandible	Pedunculated growth of size 3 cm×4 cm present since 3-4 months, associated with dull pain and mobility of teeth	Generalized bone loss	CD138 positivity	Details not available	Details not available
Sharma *et al.*, 2015[22]	54/female	Left mandible	Swelling of size 3 cm×2 cm associated with pain, bluish discoloration of the overlying mucosa	CT-expansion along with loss of trabeculae and slight perforation of the lingual cortical plate	Positive for CD45, EMA, and CD138, negative for CD20	Surgery+RT	Patient lost for follow-up due to post radiation complications
Alrashedi *et al.*, 2015[23]	60/male	Left posterior mandible	Asymptomatic	OPG- well- defined unilocular radiolucency of size 3 cm×2 cm	Details not available	Recommended RT with dose of at least 40 Gy in 4 weeks	Recommended follow-up at 6-week intervals for 2 years. Details not available
Dayisoylu *et al.*, 2015[24]	70/male	Right mandibular premolar region	Mobility, pain and numbness	Poorly defined destructive radiolucent lesion with expansion of bony cortices	CD138 positivity and monoclonal restriction for Kappa chain	Surgery	Follow-up for 2 years with no recurrence
Rajkumar *et al.*, 2015[25]	55/female	Right palate	Swelling of size 4 cm×6 cm associated with pain	Paranasal sinuses radiograph-opacity of right maxillary sinus Paranasal sinus CT- heterogeneou-s mass involving right half of hard palate with destruction of posterolateral wall of right maxilla	Positivity for CD 138 and LCA	Details not available	Details not available
Rezaei *et al.*, 2016[26]	46/male	Posterior mandible	Painless swelling since 2 months	Panoramic radiograph-well-defined, multilocular radiolucent lesion MRI- expansile destructive lesion	CD138, vimentin, Ki-67, EMA-positive; LCA, CK, CD3, CD20, CD1, NSE negative	RT- 40 Gy in 20 fractions and CHT-cyclophosphamide, hydroxydaun-orubicin and prednisone	Follow-up for 5 years with no recurrence
Beegum *et al.*, 2017[27]	59/female	Right posterior mandible	Gradually increased painless swelling since 1 year	OPG-multilocular lytic lesion CT-expansile lytic lesion with central sclerosis, cortical discontinuity and scalloping	Lambda light chain and CD138, membrane positivity	RT	6 monthly follow-up for 1 year with no recurrence

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Table 1: Contd....

Author, year	Age/sex	Site	Clinical features	Radiographic features	Immunohistochemistry findings	Treatment	Follow-up details
Balreddy *et al*., 2017[28]	31/male	Right posterior mandible	Gradually increased swelling for 7 years with history of SPB of left mandible	CECT- ill- defined, expansile, osteolytic, sclerotic lesion of size 7.1 cm×4.6 cm×7.2 cm with complete destruction of ascending ramus, partial destruction of body of right side of mandible	Lambda light chain restriction with negative kappa	40 Gy RT in 20 fractions	Follow-up for 3 years with no recurrence
Dos Santosa *et al*., 2018[29]	57/male	Anterior mandible	Pain and spontaneous drainage of purulent secretion	Unilocular radiolucent lesion with loss of cortical bone plate and resorption involving inferior anterior teeth		Surgery	6 monthly follow-up for 2 years with no recurrence
Ibikunle *et al*., 2018[30]	60/female	Right posterior mandible	Toothache of 2 weeks duration. Postextraction hemorrhage on extraction	Periapical radiograph- periradicular radiolucency in association with 47 PA skull view-unilocular radiolucency involving right mandibular angle-ramus region with poorly defined borders	Negative for keratin and CD45	RT	Details not available
Chittemsett-i *et al*., 2019[31]	46/female	Right mandible	Pain and swelling of size 5 cm×6 cm	OPG-ill-defined radiolucency	Strong positivity for CD138 and MUM1, variable membrane positivity for CD45 and negativity for CD20. Elevated serum free lambda light chains	Details not available	Details not available
Basavaiah *et al*., 2019,[32], 2 cases	Case 1-58/ female Case 2-60/ female	Case 1-Hard palate Case 2-Right zygomati-c arch	Not available	Not available	Details not available	Details not available	Details not available

IOPA: Intra oral periapical, RT: Radiotherapy, CHT: Chemotherapy, CAT: Computed Tomography, OPG: Ortho Pantomogram, MM: Multiple myeloma, PDL: Periodontal ligament, EBV: Epstein-Barr virus, SPB: Solitary plasmacytoma of bone, MRI: Magnetic resonance imaging, CT: Computed tomography, CBCT: Cone-beam computed tomography systems, LCA: Leukocyte common antigen, SMA: Smooth muscle actin, EMA: Epithelial membrane antigen, CK: Cytokeratin, NSE: Neuron-specific enolase, CECT: Contrast-enhanced computed tomography, PA: Posterio-anterior

and MUM1 were suggestive of terminally differentiated plasma cells. In SPB, Ki-67 labeling index is usually reported as 10%.[9] In our case, it was 20%–25%, which suggested high tumor aggressiveness. According to the Durie and Salmon staging system,[42] SPB can be regarded as Stage I MM. Stage I MM is where hemoglobin is >10 g/dL, serum calcium level is normal, bone structure is normal or there is solitary plasmacytoma only and M-component is low (IgG <5 g/dL and IgA <3 g/dL) and urine light chains are <4 g/24 h.[43]

SPB requires a meticulous overview of the patient by the specialist to rule out MM, a fact that would mark a dramatic change in the treatment and prognosis of the patient. To diagnose SPB, there should be absence of clonal plasma cells or presence of <10% clonal plasma cells on a random marrow sample, no other lesions on bone survey, absence of M-protein in both serum and urine and no evidence of systemic myeloma (bone pain, anemia, hypercalcemia, thrombocytopenia, neutropenia and renal failure).[3] MRI, PET/CT can help to determine bone marrow disease.[44] 18F-fluorodeoxyglucose PET (FDG PET) can aid in diagnosing relapse or progression to MM in clinically suspicious SPB cases. Upon positivity on 18F- FDG PET or on presence of bone marrow disease, patients having been suspected of SPB should be upstaged for MM.[44,45]

The treatment modalities available for SPB are RT, surgery and CHT. For SPB of other bones, authors have advised combination therapies such as surgery followed by RT, RT followed by surgery or RT followed by CHT. According to our review of jaw cases, 17 (34.69%) cases were treated by RT alone, 13 (26.5%) cases by RT in combination with surgery, surgery alone in 6 (12.24%) cases, RT with CHT in 4 (8.16%) cases, 3 (6.12%) cases were treated with combination of surgery, RT and CHT and one (2.04%) case was treated with combination of surgery and CHT. In four case reports, authors have not mentioned treatment details but have suggested RT as an ideal treatment modality for SPB. According to our review, RT followed by surgery or surgery followed by RT has been reported as the most common treatment modality. Surgery has been suggested as the treatment of choice in those jaw cases where tumors can be removed with minimal cosmetic or functional deficit or to prevent or stabilize a pathologic mandibular fracture and for rapidly progressive neurological symptoms.[46] However, it has been found that treatment outcome with surgery alone can carry high rates of local recurrence.[47] Jawad *et al.* found that there is no advantage of surgery alone or RT combined with surgery over RT alone in treatment of SPB of jaw bone.[48] SBP is a highly radiosensitive disease. It has been found that there is an excellent local control rate (>80%) achieved with RT alone.[49] Li *et al.* have considered RT alone as a more effective treatment modality for SPB over surgery.[50] Majority of data in literature has suggested that higher dose is required during the intend-curative treatment, especially for the bulky or large SPB (of size >5 cm). Lae *et al.*[7] in his case series of 21 SPB cases reported that seven patients who had surgery followed by adjuvant RT had better survival. As per present review, 11 cases which have been treated by surgery followed by RT had no recurrence. However, to confirm the same, follow-up of longer duration is required. Matsumura *et al.*[5] had found decrease in tumor size in 6 months when SPB was treated with RT of dose 60 Gy combined with CHT (intravenous cyclophosphamide and prednisolone). Radical RT comprising 40–50 Gy has shown 80% of local disease control in SPB.[7] Some authors have suggested using doses of 40–50 Gy for lesions smaller than 5 cm and >50 Gy for lesions >5 cm. Radiation dose of 45–50 Gy within 4.5–5 weeks, if tolerable by normal tissue, is recommended in clinical practice for SPB. As per the present review of SPB of jaw bone, eight cases which were treated with RT of 40 Gy did not show recurrence or progression into MM. RT should be advised after gross excision of the lesion to eradicate microscopic residual disease in SBP of jaw. A dose-response relationship needs to be established for SPB of jaw bone.

Management of SPB of jaw bone with CHT is questionable. For patients with tumors larger than 5 cm and high-grade histology, adjuvant CHT may be considered. Melphalan and prednisone-based CHT has been reported to give favorable effects. CHT delays the progression time of plasmacytoma to MM. However, its use does not decrease the conversion rate.[51] Authors have suggested that CHT can be kept as a reserved treatment option in cases which progress to MM.[52] Application of CHT to prevent or halt the progression of SPB to MM needs further evaluation. Vascular endothelial growth factor (VEGF) level and increased vascularity are correlated with clinical outcome in SPB. Grade of angiogenesis has been found to be directly associated with the plasma-cell labeling index and inversely with patient survival.[51] According to Kumar *et al.*,[52] increased angiogenesis may help to detect the possibility of progression of SPB to MM. Therefore, targeting angiogenic compounds such as VEGF or proteasome inhibitors may represent a promising new therapeutic approach to improve prognosis in SPB. Use and quantification of dose of radiation and CHT to prevent conversion of SPB to MM needs to be explored. Clinical trials should focus on the use of adjuvant CHT and/or novel therapeutic agents.

Prognostic factors

Progression to MM, local recurrence and development of new bony lesion other than MM are the three patterns which worsen the prognosis of SPB. Dimopoulos MA *et al*.[53] have reported that SPB has a significantly higher risk of progression to MM at a rate of 65%–84% in 10 years and 65%–100% in 15 years. As per our review, out of fifty cases of SPB of jaw bone, 9 cases progressed to MM within 5 years with mean duration of 1 year and 9 months. Eight (89%) of these patients died of the disease after a median survival of 6 years 9 months, while one patient (11%) was alive with the disease 20 years after transformation to MM and 22 years after the diagnosis of SPB. Four patients died due to SPB within a mean duration of 2 years and 4 months, while three patients died of unknown cause in mean duration of 8 years. In 16 cases (32%), there was no recurrence of the disease when followed for 4 months to 7 years with mean duration of follow-up being 2 years 9 months after treatment. In 17 cases (35.9%), recurrence and follow-up data are not available. Once SPB gets converted to MM, the prognosis of the patients with secondary MM is similar to *de novo* MM patients. Prognosis of SPB to MM is found to be affected by several factors including the tumor size (≥5 cm), presence of bone marrow plasma cells, age of the patient (patients aged 40 years or above), serum immune globulin level (presence of light chains), cervical spondylitis/spine lesions, SPB-related neuropathology, the dose of RT and persistence of M protein after treatment. These factors influence the outcome in SPB patients and may be indicative of progression to MM. Tsang *et al*.[54] in their study reported that lesions of size <5 cm resulted in 100% local disease control as compared to SPB cases with tumors >5 cm in size. The presence of M protein in SPB is considered to be an important prognosticator and is helpful in disease monitoring.[31] Persistence of M-protein detected following RT or a suppression of the normal immunoglobulin classes may indicate poor prognosis in SPB.[31,55] In our review, one case of SPB which progressed to MM had positive M band. In such cases, adjuvant systemic therapy should be considered. There should be regular checks for the possible presence of M-protein for detecting recurrence or conversion of SPB to myelomatosis. Anaplasia and Ki-67 labeling index can be considered as an important factor deciding the prognosis of SPB. New bone lesions, detected as either generalized osteopenia or new abnormalities on MRI studies, may indicate progression to symptomatic MM. Progression of SPB into MM occurs in two peaks. The first peak is found to occur within 3 years of treatment which can be attributed to undetected existing disease and the second peak is observed after 6–7 years. However, it is difficult to predict which case of SPB will transform to MM. Therefore, after treatment, SPB cases must be closely followed up with routine laboratory monitoring of immunoglobulins and monoclonal proteins in serum using kappa and lambda markers and Bence-Jones proteins in urine for minimum of 5 years. In addition, in case of recurrence or occurrence of new bony lesion, if bone tissue biopsy shows monoclonal plasma cell proliferation, the patient should undergo a repeat bone marrow evaluation to rule out progression to MM.

Future direction for clinical research

Clear guidelines to establish and refine diagnosis as well as treatment modalities in SPB of jaw bone are required. Different imaging techniques should be compared for SPB diagnosis and follow-up. Techniques should be developed to identify prognostic subgroups in SPB. RT or CHT as valid treatment modalities with quantification of their doses to prevent transformation of SPB to MM requires an evaluation. Large prospective clinical trials should be carried out to evaluate addition of systemic treatment (including novel agents) and to define the optimal treatment approach for patients presenting with poor prognostic factors.

CONCLUSION

Plasma cell neoplasms of jaw bones are rare. Distinguishing one from the other has significant implications for treatment and survival. SPB of jaw manifests as a single osteolytic lesion and has better prognosis compared to MM. As found through our review, the most common clinical presentation of SPB of jaw is of a painless swelling, and radiographically, it manifests as multilocular radiolucency with well-defined borders. Diagnosis of the SPB depends on the microscopic evidence of plasma cell proliferation and absence of any other bone involvement. Ancillary techniques such as immunohistochemistry play an important role in distinguishing SPB from other hematological diseases. After treatment, SPB patients must be closely followed up with routine laboratory monitoring of immunoglobulins and monoclonal proteins in serum and Bence-Jones proteins in urine to check the transformation to MM. As SPB can progress to MM, treatment modalities are required to halt or prolong the progression of SPB to MM. Furthermore, there is a need to look for the prognostic factors for SPB of jaw bone-like size of the lesion, anaplasia, vascularity, Ki-67 labeling index and presence or persistence of M band. Large prospective studies to establish the factors which can confirmatively predict the progression of SPB to MM and mechanisms playing role in this transformation are required

to be explored. Further, RT or CHT as valid treatment modalities with quantification of their doses to prevent transformation of SPB to MM requires an evaluation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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