CASE REPORT

Solitary Extramedullary Plasmacytoma of the Maxillary Sinus, Progressing to Smoldering Multiple Myeloma with Multifocal Skeletal Involvement, which Resolved Completely Following Chemotherapy Alone

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Abstract Plasmacytoma is an uncommon malignant tumor originating either from plasma cells located in the bone marrow also known as the solitary bone plasmacytoma, or from plasma cells located outside the bone, for e.g. in mucosal surfaces, referred to as the extramedullary plasmacytoma also called the solitary extramedullary plasmacytoma. Both, solitary as well as extramedullary bone plasmacytomas may, particularly in later stages, be accompanied by other osteolytic bone lesions (multifocal bone involvement) and features such as anemia, hypercalcemia, or renal impairment attributable to and indicative of progression to multiple myeloma. These three distinct disorders together comprise the plasma cell neoplasms and essentially represent a continuum of related disease processes. Extramedullary and solitary bone plasmacytomas of the head and neck region are extremely uncommon, and amongst them plasmacytoma of the maxilla is extremely rare. Such a case is being reported here for its rarity. Also, it was associated with multifocal skeletal involvement, making a correct categorization difficult as well as imperative in order to institute the correct treatment. Radiotherapy is considered to be the treatment of choice of plasmacytoma, with adjuvant chemotherapy for multifocal involvement. Surgery is usually limited to biopsy and

excision of any residual disease following radiotherapy. The case presented responded extremely well to chemotherapy alone, with a complete resolution of the maxillary tumor, obviating the need for radiotherapy.

Keywords Multiple myeloma (MM) · Solitary bone plasmacytoma (SBP) · Extramedullary plasmacytoma (EP)

Introduction

A solitary plasmacytoma is a localized build-up of abnormal plasma cells that occurs either inside or outside the bone. Plasma cells are a variety of white blood cells, normally found in the bone marrow whose main function is to produce antibodies to fight infection. The plasma cells associated with solitary plasmacytomas are malignant, which means that solitary plasmacytomas are considered cancerous [1].

A plasmacytoma is a discrete, solitary mass of proliferating neoplastic monoclonal plasma cells in either bone (myelomatous type) or soft tissue (extramedullary type). The variants of plasmacytomas are as follows: soft-tissue or non-osseous extramedullary plasmacytoma (EMP), solitary bone plasmacytoma (SBP) or multifocal form of multiple myeloma [1–3]. These three variants essentially represent distinct manifestations of a disease continuum. Clinical findings and diagnostic criteria are critical to making the correct distinction of one disorder from the other, which has significant implications to treatment and prognosis [3].

A SBP arises from the plasma cells located in the bone marrow at a single focus, whereas EMP is thought to arise from plasma cells located in mucosal surfaces. Both represent a different group of neoplasms in terms of location,

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tumor progression, and overall survival rate. Some authors suggest that a SBP represents marginal cell lymphomas with extensive plasmacytic differentiation. Both SBP and EMP do, however, share many of the biologic features of other plasma cell disorders [3, 4].

Solitary bone plasmacytoma is relatively rare in the head and neck region and comprise approximately 3 % of all plasma cell tumors [4]. The SBP lesion of the maxillofacial skeleton is a unifocal, monoclonal, neoplastic proliferation of plasma cells arising within the bone as a single focus of myelomatous tissue with no dissemination to other parts of the skeleton [3, 4]. The plasmacytoma is usually detected in adult males, with an average age at diagnosis of 55 years. The male-to-female ratio is 3:1. It is most commonly seen within the age range of 50–80 years,

cases under the age of 40 being rare [3–5]. The mandible is involved far more frequently than the maxilla, especially the most active hematopoietic areas—the ramus, angle and molar region of the mandible. Concurrent multiple myeloma should be ruled out by appropriate laboratory and radiologic examinations. Local recurrence or dissemination can occur many years after the original lesion has been treated so that long term follow-up is mandatory [3].

Infrequently, plasmacytoma is observed in soft tissue, in which case, the term EMP is used [5–7]. Approximately 80–90 % of EMP involve the mucous-associated-lymphoid tissue of the upper airways with 75 % of these involving the nasopharynx and paranasal sinuses [2, 8, 9]. Other sites include salivary glands, the thyroid gland, tonsils, cervical lymph nodes, larynx and skin [8, 9]. The presenting

Fig. 1 A–C A 72 year old male patient. D, E A large, smooth surfaced, ellipsoidal, expansile lesion of the Lt maxillary alveolar region with obliteration of the gingivobuccal/vestibular sulcus and a

fluctuant swelling of the adjoining palatal region. F Extracted teeth 24 and 26. G, H Appearance immediately and 3 days following the extraction. I Appearance after a month of chemotherapy

symptoms in the sinonasal region are nasal obstruction, nasal mass, palatal or maxillary mass if bony erosion of palate of anterolateral wall of antrum has occurred, epistaxis, and facial pain mimicking sinusitis. Extraosseous lesions may also result in paresthesia of soft tissue and gingival enlargement with bleeding tendency [9].

Case Report

A 72 year old male patient reported with complaints of pain and swelling in the left maxillary region in relation to the posterior teeth for the past 3 months (Fig. 1A). History revealed that the patient had developed a persistent headache at the left temporal and maxillary sinus regions for the past 5 months. Paranasal sinus (PNS) radiographic view of the skull (Fig. 1B) had revealed haziness of the left maxillary antrum, suggestive of acute maxillary sinusitis, for which he had received treatment elsewhere, with antibiotics and steam inhalation. The patient then developed acute pain in relation to the upper left second premolar tooth, which became mobile, and was extracted 4 months ago. Two months later, he developed a swelling in the region as well as a proliferative gingival enlargement at the extraction site. There was a rapid increase in size of the swelling over the next 2 months, with expansion of both the buccal and palatal cortical plates

of the alveolus in the region and first premolar and molar teeth developed mobility.

On examination, a large, smooth surfaced, ellipsoidal, expansile lesion of the Lt maxillary alveolar region was observed, measuring approximately 6×8 cm in size, extending from 24 to 27 region, with obliteration of the gingivobuccal/vestibular sulcus and causing a fluctuant swelling of the adjoining palatal region (Fig. 1D, E). There was Grade 3 mobility of teeth 24 and 26. The swelling was tender on palpation. There was no associated ulceration, bleeding or secondary discharge from the swelling. Orthopantomogram (Fig. 2A) revealed a well defined, unilocular radiolucency, with no sclerotic border, in relation to the maxillary alveolus of 24–27 region, extending into the maxillary antrum on that side. The radiolucency had smooth margins and there was resorption of roots of teeth 24 and 26 almost up to the levels of the cervical margins (Fig. 2A). Postero-anterior (PA) and PNS view skull radiographs (Fig. 1B, C) revealed a well defined radio-opacity filling the lower third of the left maxillary antrum and evidence of bony destruction of the floor of the sinus.

CT scan of the maxillofacial region was taken to know the extent of the soft tissue mass and the underlying bony destruction (Fig. 3). The soft tissue mass was seen involving the lower third of the interior of the left maxillary sinus and showed up as a dense opacity within the

Fig. 2 **A** Orthopantomogram revealing a well defined, unilocular radiolucency, with no sclerotic border, in relation to the maxillary alveolus of 24–27 region, extending into the maxillary antrum on that side. There was resorption of roots of teeth 24 and 26 almost up to the levels of the cervical margins. **B** Orthopantomogram following extraction of teeth 24 and 26

Fig. 3 A–C NCCT of maxillofacial region with 3-D reformatting showing evidence of destruction of the maxillary alveolus from 24 to 26 regions and erosion of the anterolateral wall of the left maxillary antrum. D–M Soft tissue mass seen involving the lower third of the

interior of the left maxillary sinus, revealed as a dense opacity within the sinus with destruction of its floor and lateral walls in the anterior region

sinus with destruction of its floor and lateral walls in the anterior region (Fig. 3D–M). Also there was evidence of destruction of the alveolus from 24 to 26 regions and erosion of the anterolateral wall of the left maxillary antrum. There was no evidence of expansion of the sinus cavity or remodeling of its osseous boundaries. There was

no evidence of erosion of its roof or medial wall and no extension of the mass into the nasal cavity or through the orbital floor into the orbit.

The fairly limited size and antral extension of the mass led to a differential diagnosis of a mitotic lesion other than carcinoma (e.g. lymphoma) or a benign process such as a

Fig. 4 **A, B** Section of soft tissue showing a diffuse infiltration by plasma cells. Broad sheets of plasma cells were found arranged in a delicate fibrovascular connective tissue stroma (Hematoxylin and Eosin 40 $\times$). **C, D** Cells demonstrated eccentrically placed nuclei and an increased Nuclear: Cytoplasmic ratio, with well-defined eosinophilic-staining cytoplasm. The nuclei displayed the characteristic “clock face” appearance. Many multinucleated cells were also seen

(Hematoxylin and Eosin 80 $\times$). **E–H** Immunohistochemical staining for Kappa and Lambda light chains, showing strong expression of only the Kappa light chain and Lambda light chain restriction. **E, F** Immunoperoxidase stain for Kappa light chain was strongly and diffusely positive. **G, H** Immunoperoxidase stain for Lambda light chain was negative

central giant cell reparative granuloma of bone, based on imaging grounds.

An incisional biopsy was carried out under LA. Histopathological examination of sections of the specimen revealed fibrocollagenous tissue (Fig. 4) infiltrated by a dense monomorphic population of atypical cells. There was noted diffuse and sheet like proliferation of plasma cells (Fig. 4A–D) with varying degrees of maturity and atypia. Many of the cells had abundant cytoplasm with eccentrically placed nuclei, which were oval to round. The large nuclei had irregular condensed chromatin towards the periphery (“clock-face” nuclear chromatin pattern) and many prominent nucleoli (Fig. 4C, D). Numerous cells showing mitosis were seen. Multinucleated cells were seen too. No areas of necrosis were noted.

An immunohistochemical analysis was carried out which revealed the atypical cells positive for Kappa light chain (Fig. 4E, F) and CD 38 and negative for Lambda light chain (Fig. 4G, H), CD3 and CD20. These features were indicative of plasmacytoma involving the left maxilla and maxillary antrum.

In order to rule out the possibility of smoldering or asymptomatic multiple myeloma or other foci of soft tissue or EMP, the following investigations were carried out as per the National Comprehensive Cancer Network (NCCN) Guidelines Version 2 of 2014:

1. Whole body bone scan—FDG PET/CT/MRI as clinically indicated

2. Quantitative immunoglobulins and quantization of M protein (serum and urine)
3. M band protein electrophoresis
4. Urine examination for Bence-Jones proteins
5. Complete and differential blood count, platelet count
6. Blood urea nitrogen (BUN), creatinine, corrected calcium
7. B2 Microglobulin
8. Bone marrow aspirate and karyotyping
9. Bone marrow biopsy—myeloma panel.

Urine tested negative for Bence Jones proteins, the liver and renal function tests revealed no abnormality. Blood counts were all within normal limits. Patient was negative for HIV, HBs Ag and Anti HCV. Blood sugar was within normal limits. Routine blood investigations were done, Hb was 14.6 gm %, TLC 4500, DLC (N-52, Lym-36, Mono-06 and Eosin-06), urea 26 mg/dL and creatinine 1.0 mg/dL. Serum electrophoresis was done and it showed alb 25-4.10 gm/dL, α 1-0.27 gm/dL, α 2-0.88 gm/dL, β -0.87 gm/dL and γ -1.29 gm/dL. Myeloma band was not detected.

F18-FDG whole body PET CT scan was carried out to look for multifocal involvement (Figs. 5, 6). Whole body CT scan was performed following oral contrast administration. 10 mCi-F18-FDG (fluorodeoxyglucose) was administered intravenously and whole body images were acquired at 45 min using discovery 610 system. Images were reconstructed in the axial, coronal and sagittal planes. The findings observed were FDG avid soft tissue mass

Fig. 5 **A** F18-FDG whole body PET CT scan carried out to look for multifocal involvement. D7 Vertebra and the left 6th Rib showed lytic skeletal lesions suggestive of a multifocal involvement. **B** The

myocardium, liver, kidneys, renal pelvis, ureters and gut showed physiologic distribution. **C, D** FDG avid lytic lesion was seen involving the left ischium and left posterior superior iliac spine

involving the left maxillary sinus (Fig. 6A, B) with underlying destruction of the upper alveolus, measuring 21×30 mm with SUV max 8.13. FDG avid lytic lesion was seen involving the left ischium (Fig. 5C) with SUV max of 8.44, body of D7 with SUV max 4.98, left 6th rib laterally with SUV max 3.84 and left posterior superior iliac spine (Fig. 5D) with SUV max 4.76. FDG avid left axillary lymph node was seen measuring 10 mm with SUV max 5.61—tracer pooling due to extravasation at the time of tracer administration. There was no evidence of FDG avid lesion in the neck or mediastinum. Tiny nodules were seen in the apical segment of right lower lobe and oblique fissure of the left lung likely to be inflammatory (Fig. 6C, D). No FDG avid lesions were seen in the liver, spleen or adrenals. No FDG avid retroperitoneal lymphadenopathy was noted. The myocardium, liver, kidneys, renal pelvis, ureters and gut showed physiologic distribution (Fig. 5B).

To sum up, the study showed hypermetabolic areas, predominantly lytic skeleton lesions involving the left maxilla with associated soft tissue component, D7 vertebra, left 6th rib, left posterior superior iliac spine and left

ischium (Figs. 5, 6) suggestive of multifocal skeletal involvement.

Serum Beta 2 microglobulin test was carried out. Serum immunoturbidimetry results for Kappa and Lambda free light chains showed Kappa free light chain = 373.54 mg/L, Lambda free light chain = 5.85 mg/L; and a high Kappa/Lambda ratio of 63.85, which was suggestive of monoclonal gammopathy with bone marrow suppression.

Bone marrow aspirate was studied and bone marrow biopsy was conducted (Fig. 7). Numerous plasma cells including occasional plasmablasts were seen in the bone marrow aspirate (Fig. 7A, B). Bone marrow biopsy showed diffuse scarred plasma cells (9 %) (Fig. 7C, D). An immunohistochemical analysis of the bone marrow specimen showed the plasma cells strongly positive for and highlighted by CD38 (Fig. 7E, F). Immunoperoxidase stain for Kappa light chain was strongly and diffusely positive, while immunoperoxidase stain for Lambda light chain was negative (Fig. 7G, H).

Based on all of the above findings, a definitive diagnosis of sinonasal extramedullary plasmacytoma of the left

Fig. 6 **A, B** FDG avid soft tissue mass involving the left maxillary sinus with underlying destruction of the upper alveolus. **C, D** Tiny nodules were seen in the apical segment of right lower lobe and oblique fissure of the left lung likely to be inflammatory

maxillary antrum associated with multifocal bone involvement was made.

It was decided to extract the mobile teeth 24 and 26 (Fig. 1F–H) prior to initiation of radiation or Zoledronic acid chemotherapy. Although plasmacytoma is an extremely radiosensitive tumor, the multifocal involvement in this case warranted chemotherapy.

The patient was put on a chemotherapeutic regimen of Bortezomib, Thalidomide and Dexamethasone. He received Lanalidomide 10 mg daily, Tab Dexamethasone 40 mg weekly, Inj Zoledronic acid 4 mg in 100 mL NS over 30 min, weekly for a period of 3 months.

There was a rapid regression in size in a month's time following initiation of chemotherapy (Fig. 1I), and a complete resolution of the tumorous mass of the maxilla after 3 months of chemotherapy (Fig. 8A, B). Post treatment CT scans of the maxillofacial skeleton (Fig. 9) confirmed the same, with disappearance of the entire antral mass. The patient was provided with dentures to replace the missing teeth (Fig. 8C, D). He is presently under regular monthly follow up. F18-FDG whole body PET CT scan was carried out after 6 months to observe for any

changes in the multifocal involvement. There was no evidence of any FDG avid lesion anywhere, including the maxilla, confirming successful treatment of the patient with the use of chemotherapy as the sole management modality.

Discussion

A plasmacytoma can arise in any part of the body. A SBP arises from the plasma cells located in the bone marrow, whereas EMP is thought to arise from plasma cells located in mucosal surfaces [3]. With the use of magnetic resonance imaging, flow cytometry, and polymerase chain reaction, the currently accepted diagnostic criteria for SBP and EMP are as follows [6, 10].

Solitary bone plasmacytoma (SBP):

1. Single area of bone destruction due to clonal plasma cells,
2. Bone marrow plasma cell infiltration not exceeding 5 % of all nucleated cells,
3. Absence of osteolytic bone lesions or other tissue involvement (no evidence of myeloma),

Fig. 7 **A, B** Bone marrow aspirate showing numerous plasma cells including occasional plasmablasts. **C, D** Bone marrow biopsy showing diffuse scarred plasma cells (9 %). **E, F** Plasma cells

positive for and highlighted by CD38. **G** Immunoperoxidase stain for Kappa light chain was strongly and diffusely positive. **H** Immunoperoxidase stain for Lambda light chain was negative

Fig. 8 **A, B** A rapid regression in size and a complete resolution of the tumorous mass of the maxilla after 3 months of chemotherapy. **C, D** The patient was provided with dentures to replace the missing teeth

4. Absence of anemia, hypercalcemia, or renal impairment attributable to myeloma,
5. Low, if present, concentrations of serum or urine monoclonal protein.

Extra medullary plasmacytoma (EMP):

1. Tissue biopsy showing monoclonal plasma cell histology
2. Bone marrow plasma cell infiltration exceeding 5 % of all nucleated cells
3. Absence of osteolytic bone lesions or other tissue involvement (no evidence of myeloma)

Fig. 9 A–D Post treatment CT scans of the maxillofacial skeleton confirmed complete resolution of the maxillary tumor, with disappearance of the entire antral mass

4. Absence of hypercalcemia or renal failure
5. Low serum M protein concentration, if present

Solitary bone plasmacytoma (SBP) develops into multiple myeloma in 50–60 % of patients [10]. Median overall survival time is 10 years [11]. EMP progresses to multiple myeloma in 11–30 % of patients at 10 years [10]. Overall survival rate at 10 years is 70 % [11]. High-grade angiogenesis in the SBP was associated with increased progression to multiple myeloma and shorter progression-free survival [9]. Some have postulated that SBP may be considered an intermediate step in the evolution from monoclonal gammopathy of undetermined significance to multiple myeloma [3].

The case presented here represented the category of EMP, along with multifocal skeletal involvement, suggestive of progression towards multiple myeloma (MM).

Serum Beta 2 microglobulin test is a prognostic indicator for multiple myeloma and other hematopoietic malignancies [11]. Serum concentration of free light chains depends upon the balance between production of plasma cells and their progenitors and renal clearance. When there is increased polyclonal immunoglobulin production, and/or

renal impairment, concentration of the Kappa and Lambda light chains can increase by 30–40 fold but the Kappa/Lambda ratio remains unchanged. In contrast, a tumor produces monoclonal excess of only one type of light chain, often with bone marrow suppression of alternate light chains resulting in an abnormal Kappa/Lambda ratio [11]. In this patient, serum immunoturbidimetry results for Kappa and Lambda free light chains showed Kappa free light chain = 373.54 mg/L, Lambda free light chain = 5.85 mg/L; and Kappa/Lambda ratio = 63.85 which was suggestive of monoclonal gammopathy with bone marrow suppression.

CD138 or syndecan-1 is a glycoprotein found in simple epithelial, stratified epithelia, mesenchymal cells and lymphocytes. It is a good marker for multiple myeloma and Reed-Sternberg cell identification. The monoclonal antibody CD138/B-B4 can be used on formalin-fixed, decalcified biopsies to localize normal and neoplastic plasma cells on routine bone marrow sections [12].

Plasma cell neoplasms are highly radiosensitive [13]. Radiation therapy is currently the treatment of choice for EMPs and SPBs. Plasmacytomas respond to radiation at doses of 4,500–6,000 cGy, delivered as daily fraction of

125–200 cGY 5 days a week [14, 15]. Excellent loco regional control has been demonstrated using radiation therapy as the primary modality of therapy. Hence, while these tumors may present as aggressive locally destructive lesions, their management should be conservative and organ sparing, because of the excellent control that can be achieved in majority of the cases by irradiation [16, 17]. The role of surgery is limited to biopsy and to excision of residual disease [18, 19]. However, for those cases with a high risk of evolution towards multiple myeloma, or which have progressed or converted to multiple myeloma; studies recommend a combined treatment modality which includes adjuvant chemotherapy along with radiotherapy or surgical excision for a complete and comprehensive disease control [20–23].

In the case presented, excellent loco-regional control of the maxillary tumor as well as complete resolution of multifocal skeletal involvement was achieved with the use of chemotherapy as the sole treatment modality.

Conclusion

It is important to distinguish multiple myeloma from SBP or EMP, because the treatment and prognosis are different. Evaluation for plasma cell neoplasms include total body skeletal survey, serum and urine electrophoresis or immunoelectrophoresis, complete blood count, calcium level and bone marrow biopsy. The diagnosis of EMP or SPB is made by three negative findings- no clinical, histologic or radiologic evidence of MM, in the presence of a single plasmacytoma in soft tissue or bone respectively. Having said that, either of the two may progress to MM (20–30 % of EMPs and 55–60 % of SPBs).

Radiation therapy is currently the treatment of choice for EMPs and SPBs. However, in the case presented, gratifying results were obtained using chemotherapy alone, with a rapid regression in size of the tumorous mass of the maxilla in a month's time following initiation of chemotherapy and a complete resolution after 3 months of chemotherapy. Post treatment CT scans of the maxillofacial skeleton taken 3 months following the treatment confirmed the same, with disappearance of the entire antral mass. F18-FDG whole body PET CT scan carried out after 6 months, showed no evidence of any FDG avid lesion anywhere, including the maxilla, confirming successful treatment of the multifocal skeletal involvement in the patient. In this way chemotherapy alone can be an efficacious sole treatment modality in patients with “solitary extramedullary plasmacytoma of the maxillary sinus, progressing to smoldering multiple myeloma with multifocal skeletal involvement”.

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