Original Article

Plasma cells in oral lesion: A clue to diagnosis or a diagnostic dilemma

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Abstract

Objective: Plasma cells can just represent a part of host inflammatory response or form the cornerstone of diagnosis such as IgG4-related disease (IgG4RD) and plasma cell dyscrasias and sometimes create a diagnostic dilemma. The study aims to discuss a series of plasma cell lesions which we encountered in the oral cavity, discuss the diagnostic conundrum of plasma cell lesions. We also propose a working classification for their interpretation.

Materials and Methods: All plasma cell lesions affecting the oral and maxillofacial region were retrieved from the archives of the Department of Oral and Maxillofacial Pathology. The cases were analyzed on the basis of histomorphology and immunohistochemical markers along with clinical, imaging and laboratory findings.

Results: Thirteen (0.64%) of 2026 oral lesions were diagnosed with plasma cell lesions. Out of 13 cases, 9 were plasma cell gingivitis, 2 IgG4-RD, 1 plasma cell myeloma and 1 plasmablastic lymphoma. Representative case from each category is discussed along with one case of well-differentiated squamous cell carcinoma (WDSCC) masquerading as plasma cell dyscrasias.

Conclusion: We discuss the practical difficulties faced during the diagnosis of these oral plasma cell entities along with a working classification and propose an efficient diagnostic scheme for the correct characterization of these lesions.

Keywords: Diagnostic approach, oral cavity, plasma cell gingivitis, plasma cell lesions, plasma cell myeloma

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INTRODUCTION

Plasma cells are terminally differentiated B-cells produced subsequent to antigenic stimulation of B-cells. Understanding their origin is of utmost importance to comprehend the pathogenesis and immunoprofile of various lesions derived from them. Differentiation of plasma cells from B-cells through various intermediate stages marks the change in the expressions of their surface antigens. They lose one or more of Pan-B cell markers; express CD79a and plasma cell-specific antigens.[1-3] In addition, an exclusive expression of kappa or lambda light chain immunoglobulin components demonstrates their monoclonality and neoplastic nature [Figure 1].[4]

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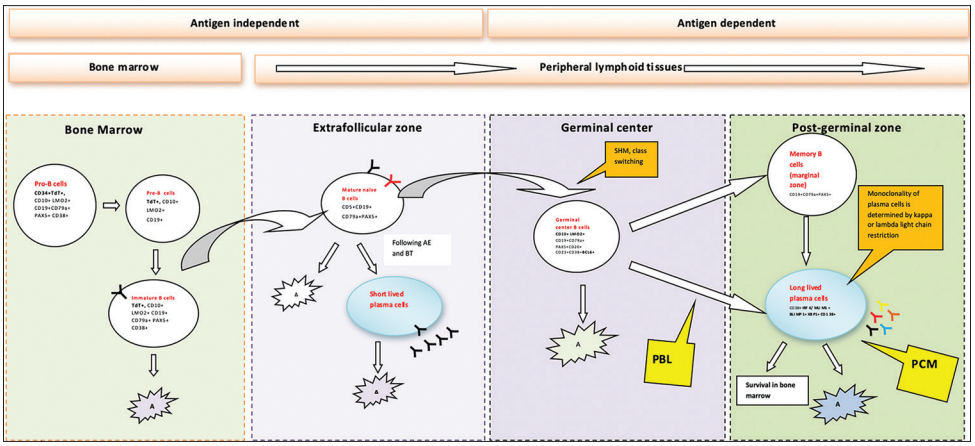

Figure 1: Origin of plasma cells through various stages of B cell development and change in expression of surface markers (immunoprofile). B-cells through various stages of development starting from Pre-B cells in bone marrow form naïve B cells in peripheral lymphoid organs, which undergo apoptosis. On antigenic stimulation, they get differentiated into short-lived plasma cells or migrate into germinal centers where they proliferate, undergo class switching and somatic hypermutations to form germinal center B cells. GCB cells can undergo apoptosis or migrate into the post germinal zone and differentiate (or through memory B-cells) into long-lived plasma cells which survive in bone marrow (survival niche). PBL arises from the stage of transition from immunoblasts to plasma cells, PCM originates from bone marrow homing plasma cells. Pan-B cell markers; CD19, CD20, PAX-5, CD79a, plasma cell-specific antigens; Syndecan-1 or CD138, CD38, IRF4 or MUM-1, BLIMP1 and XBP1 ⅄; surface IgM, A; apoptosis, ⅄; surface IgD, ⅄; surface IgE, ⅄; surface IgE, ⅄; surface IgM, surface IgA, AE; antigenic exposure, BT blastic transformation, SHM; somatic hypermutation, HGAL; human germinal center associated lymphoma gene also called GCET2, GCB; germinal center B cells, PBL; plasmablastic lymphoma, PCM; plasma cell myeloma

Plasma cells, apart from being a part of inflammatory lesions, can sometimes present in oral malignancies (commonly in oral squamous cell carcinoma) due to host inflammatory response creating a diagnostic perplexity. Besides, infiltration by IgG4-positive plasma cells form an important distinguishing feature of IgG4-related disease (IgG4RD), while monoclonal plasma cells give rise to rare subset of malignancies called plasma cell dyscrasias (PCD).[5] These lesions show considerable degree of overlap in histology and immunophenotype.[6]

Thus, the aim of this study is to discuss a series of plasma cell lesions which we encountered in the oral cavity. In this report, we emphasize the integration of conventional histomorphology with ancillary techniques such as immunohistochemistry and clinico-imaging profile for conclusive diagnosis. The objectives are to discuss diagnostic peculiarities of plasma cell lesions. We have also proposed a working classification [Table 1] and an efficient diagnostic scheme for their correct interpretation [Figure 2].

Table 1: Proposed working classification of plasma cell lesions

Reactive lesions and immune-mediated lesions
Plasma cell gingivitis
IgG4 related disease
Neoplastic lesions or plasma cell dyscrasias
Non-IgM - MGUS
Plasmacytoma
Solitary plasmacytoma of bone
Extramedullary plasmacytoma
Plasma cell myeloma
Asymptomatic myeloma
Secretory and nonsecretory myeloma
Plasma cell leukemia
Monoclonal immunoglobulin deposition diseases
Primary amyloidosis
Systemic light and heavy chain deposition diseases
Plasma cells neoplasms associated with paraneoplastic syndrome
POEMS syndrome
TEMPI syndrome
NHL subtype with overlapping features with plasma cell dyscrasias
Plasmablastic lymphoma
A part of host inflammatory response
Oral squamous cell carcinoma

MGUS: Monoclonal gammopathy of undetermined significance, IgG: Immunoglobulin G, IgM: Immunoglobulin M, POEMS: Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormalities, TEMPI: Telangiectasias, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collections, intrapulmonary shunting, NHL: Non-Hodgkin lymphoma

MATERIALS AND METHODS

In accordance with the Helsinki Declaration, institutional ethical approval and following the guidelines in this study, formalin-fixed, paraffin-embedded sections of all plasma cell lesions were retrieved from the archives of the Department of Oral and maxillofacial Pathology of a tertiary referral Institute from January 2018 to June 2020. All lesions affecting the oral and maxillofacial region where plasma cells played a crucial role in diagnosis and applicable clinical, radiological and other details are available were included in the study irrespective of age, sex, site of involvement and final diagnosis. The cases lacking significant information regarding clinical details, radiology and other relevant investigations were

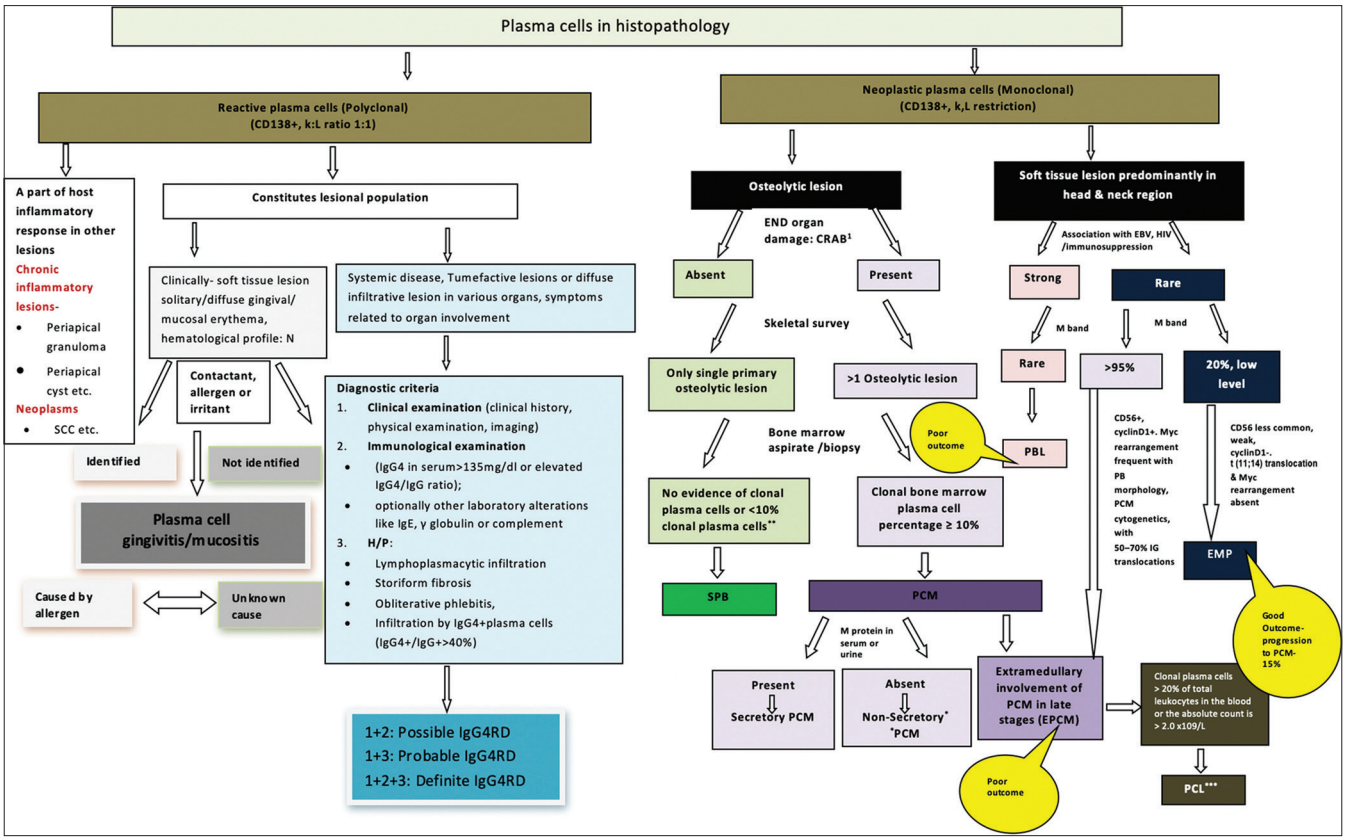

Figure 2: Plasma cell lesions in the head and neck region-A diagnostic approach. Abbreviations: K: L; kappa, lambda light chain ratio, N; Normal,[1]; also called myeloma defining events -CRAB; hypercalcemia, renal insufficiency, anemia, bony lesions, SPB; solitary plasmacytoma of bone, PCM; plasma cell myeloma, EPCM; extramedullary involvement by PCM, PCL; plasma cell leukemia, PBL; plasmablastic lymphoma, EMP; extramedullary plasmacytoma, PB; plasmablastic morphology, MGUS; monoclonal gamapathy of undetermined significance. *Plasma cell myeloma variants are secretory, nonsecretory and asymptomatic/smoldering myeloma. Approximately 1% of plasma cell myeloma are nonsecretory, clinical features are similar to secretary plasma cell myeloma except lower incidence of renal insufficiency and hypercalcemia and less depression of normal Ig, immunophenotype. ** Non—IgM (plasma cell) Monoclonal gammopathy of undetermined significance also shows Clonal bone marrow plasma cells <10% along with presence in the serum of an IgG, IgA or (rarely) IgD M protein at a concentration <30 g/ Land absence of CRAB and amyloidosis. ***Primary plasma cell leukemia presentation in plasma cell myeloma is seen in 2%–4% of myelomas, secondary plasma cell leukemia is a leukemic transformation that occurs in approximately 1% of previously diagnosed plasma cell myeloma. About 60%–70% of all plasma cell leukemia s are primary, plasma cell leukemia are usually CD56-ve

excluded from the study. The selected cases were analyzed by three pathologists independently on the basis of hematoxylin- and eosin-stained sections; and re-evaluation of immunohistochemical markers. Information about the clinical history and other pertinent details were retrieved from the case files of patients. The final diagnosis was rendered on the basis of histomorphology supplemented by array of immunohistochemical markers along with the integration of available clinical, imaging, laboratory findings. Further, treatment profile and follow-up status were also analyzed.

RESULTS

A total 13 (0.64%) of 2026 cases were diagnosed with plasma cell lesions where plasma cells played crucial role. Out of 13 cases, 9 were plasma cell gingivitis (PCG), 2 IgG4-RD, 1 plasma cell myeloma (PCM) and 1 plasmablastic lymphoma (PBL). Representative case from each category is discussed along with one case of well-differentiated squamous cell carcinoma (WDSCC) masquerading as plasma cell dyscrasias.

Cases

Case 1

A 82-year-old female patient complained of swelling in the right lower gingiva for 1 month. On examination, there was a sessile, firm growth with erythematous surface associated with mandibular right canine and premolar region measuring approximately 1.0 cm × 1.0 cm × 0.3 cm. The patient had a history of implant placement with fixed partial denture prosthesis in the same region two years back. Contrast-enhanced computed tomography (CECT) showed smooth thickening along the right buccal space adjacent to the lower premolars without any abnormal enhancement. Biopsy revealed intense stromal inflammation abutting

the epithelium and showing hyperplastic parakeratinized stratified squamous surface epithelium in a focal region with plasma pooling and neutrophilic exocytosis. Stroma showed intense plasmalymphocytic infiltrate comprising predominantly of CD138 immunopositive plasma cells (>70%) and engorged blood vessels. Kappa and lambda positivity revealed polyclonal nature of plasma cells. Hematological investigations did not reveal any abnormality [Figure 3]. The final diagnosis of PCG was suggested. The prosthesis was removed followed by oral prophylaxis and the lesion was excised. Follow-up at 1 year showed no recurrence.

Case 2

A 74-year-old female presented with diffuse bony hard swelling in the left mandible approximately 4 cm × 4 cm × 4 cm in size, which had been noticeably enlarging over a period of a month. Orthopantomography (OPG) and CECT revealed an osteolytic lesion involving the entire ramus of the left mandible, including condyle, coronoid and pterygoid muscles. Biopsy revealed diffuse monotonous sheets of plasmacytoid cells exhibiting abnormal morphology with large blast-like nuclei, condensed chromatin, marked nuclear pleomorphism, minimal eosinophilic cytoplasm and increased mitosis (10/10 HPF). Histological differentials of plasmablastic plasmacytoma and PBL were considered. Tumors cells showed immunopositivity for CD138 and immunonegativity for PanCK and leukocyte common antigen (LCA) with 90% of Ki67 proliferative index [Figure 3]. In view of osseous involvement and seronegativity for HIV, plasma cell dyscrasias were considered. The serum calcium levels were normal and the skeletal survey revealed no other bony lesions. Anemia, sharp M spike in gamma region and 70% clonal plasma cells in bone marrow led to the final diagnosis of PCM (plasmablastic type). The elevated serum β_2 microglobulin levels (6.08 mg/L) indicated Stage III as per the international staging system (ISS).[1] The patient was referred to the medical oncology department for treatment, where he underwent chemotherapy followed by palliative radiotherapy [Table 2].

Case 3

A 65-year-old HIV seropositive male presented with diffuse swelling affecting the right side of the face for 1 month. OPG showed irregular destruction in the right quadrant with thinning of cortex. Biopsy revealed the diffuse monotonous distribution of large round tumor cells exhibiting open-faced nuclei intermixed with tingible body macrophages (starry sky appearance) and a few cells showed plasmacytoid differentiation. Histomorphological differentials of PBL, diffuse large

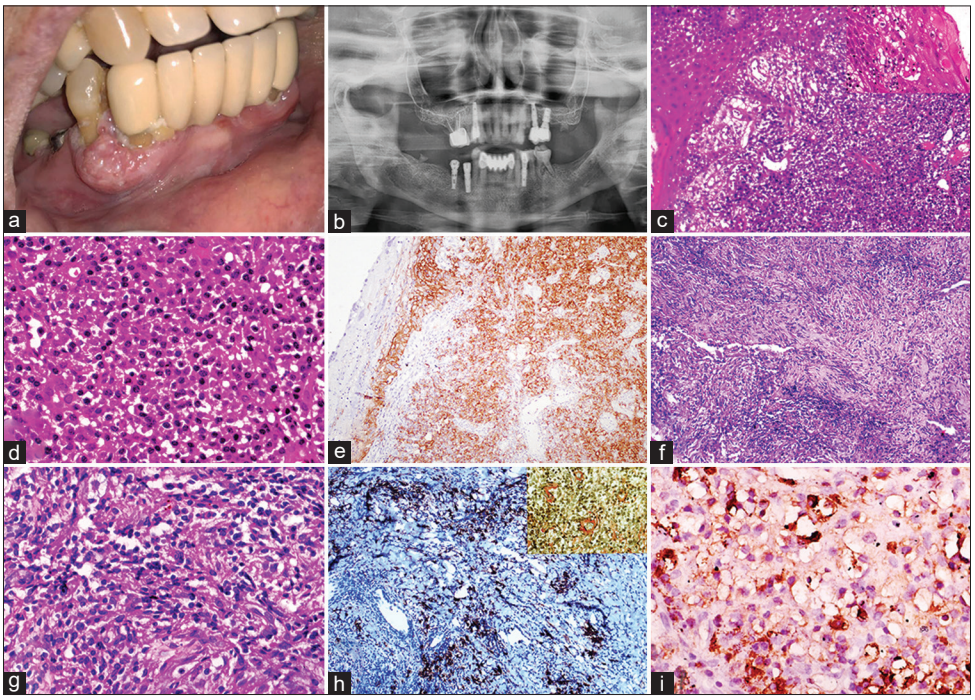

Figure 3: Case depicting reactive and immune-mediated lesions. Patient presenting with gingival swelling with the associated fixed prosthesis in the right mandible (a) and Orthopantomography showing implants in the same quadrant (b). Histology shows intense inflammation abutting epithelium (c; H and E, ×4; inset showing plasma pooling and neutrophilic exocytosis in epithelium) with the predominance of plasma cells. (d and e) Plasma cells showed CD138 diffuse membranous positivity. (f and g) Histology of IgG4-RD showing storiform fibrosis with intense plasma lymphocytic infiltrate, CD138 positivity in plasma cells (h, inset showing obliterative phlebitis in VVG stain) and IgG4 stain showing >10 IgG4 + plasma cells (i)

Table 2: Summary of cases included in the study

Case	Age	Gender	Clinical site	Radiology	Other parameters	IHC	Final diagnosis	Treatment	Follow up
1	82	Female	Gingiva	Smooth thickening in right buccal space	-	CD 138+	PCG	Removal of prosthesis followed by oral prophylaxis and excision of the lesion	No complains presently (after 1 year)
2	74	Female	Mandible	Radiolucent lesion in the mandibular molar region	Anemia, sharp M spike in gamma region and 70% clonal plasma cells in bone marrow, increased serum β2 microglobulin, serum globulin, albumin globulin ratio, and serum phosphate. decreased serum albumin	CD 138+PanCK - LCA Ki67-90%	PCM	Bortezomib 2 mg, lenalidomide 15 mg, dexamethasone 20 mg weekly, Zolendronic acid 3.5 mg once in a month along with calcitriol 0.25 mg acyclovir* 400 mg and antibiotics	2 cycles of chemotherapy completed and is stable (after 4 months)
3	65	Male	Mandible	Irregular destruction in the right quadrant with thinning of cortex	HIV +	Immunopositive LCA Focal patchy positive CD 138, EMA and CD 10 Ki67: 100% Immunonegative PanCK, CK7, PAX-5, CD3, CD 15, CD30, BCL-2 and chromogranin	PBL	Returned to home town for treatment	Lost to follow-up
4	67	Male	Gingivobuccal complex	Ill-defined radiolucency		CD 138+, Kappa: Lambda-1:1	WDSCC	Surgical excision with radical neck dissection	No recurrence at follow-up at 1 year

*Prophylactic antiviral drug was added to prevent herpes zoster infection universal protocol in myeloma patients who are on bortezomib or bortezomib-containing regimens. IHC: Immunohistochemistry, PCG: Plasma cell gingivitis, WDSCC: Well-differentiated squamous cell carcinoma, LCA: Leukocyte common antigen, PCM: Plasma cell myeloma, EMA: Epithelial membrane antigen

B-cell lymphoma, Burkitt's lymphoma (immunodeficiency associated), anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma, T-cell lymphomas and poorly differentiated carcinoma were considered. Tumor cells showed immunopositivity for LCA, focal patchy positivity for CD138, EMA and CD10; and immunonegativity for PanCK, CK7, PAX-5, CD3, CD15, CD30, BCL-2 and chromogranin. Ki67 proliferation index was approximately 100% [Figure 4]. Considering histomorphology and immunoprofile, we narrowed down to the final diagnosis of PBL (most common in HIV positive). The patient returned to his regional hospital for further treatment.

Case 4

A 67-year-old male presented with proliferative growth on the right lower gingivobuccal complex extending from right mandibular canine to second premolar and Grade III mobility of both premolars. OPG showed an ill-defined radiolucency with floating teeth appearance of premolars. Histopathology revealed hyperplastic epithelium and underlying diffuse intense chronic inflammatory cell infiltrate comprising predominantly of CD138+ plasma cells. However, kappa and lambda were expressed in 1:1 ratio indicating reactive etiology. In view of aggressive lesion on imaging, deeper biopsy was undertaken which revealed features of WDSCC [Figure 4]. It indicated that the plasma cells in this lesion were part of a host inflammatory response.

DISCUSSION

Plasma cell lesions encompass a wide spectrum ranging from reactive to immune-mediated and neoplastic lesions with varying etiopathogenesis. Their correct characterization is of utmost importance because of therapeutic and prognostic implications. Reactive plasma cell lesions include PCG; a rare disease characterized by diffuse infiltration of plasma cells in gingival connective tissue. This lesion is thought to be a hypersensitivity reaction to allergens and some authors consider three varieties of PCG; caused by allergen, neoplasms or from uncertain cause.[7-10] Infrequently, they clinically mimic lethal conditions such as leukemia (excluded through hematological screening) and look similar to plasma cell dyscrasias histopathologically (excluded by studying

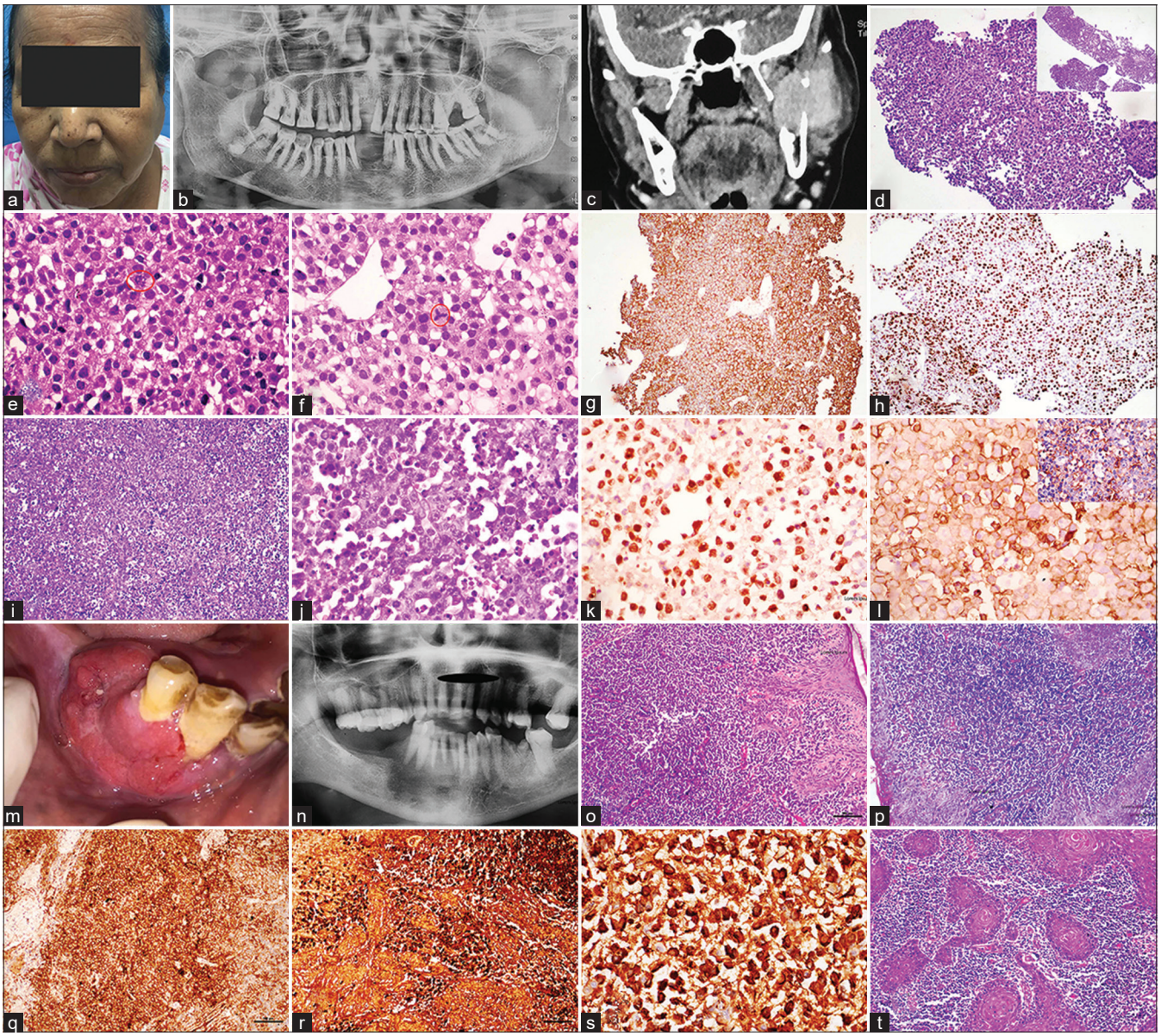

Figure 4: Case depicting plasma cell dyscrasias and their mimickers. Case of plasmacytoma (a-h) showing diffuse swelling on the left side of the face (a) and radiologically osteolytic lesion in the right mandible (b and c). Sheets of plasmacytoid cells (d; inset showing scanner view). (e and f) Higher magnification showed plasma cells with blastic morphology and increased mitosis (red circle). Tumor cells showed immunopositivity for CD138 (g) and high Ki67 proliferative index (h). Case of PBL (i-l) showing diffuse infiltration by atypical lymphoid cells with interspersed tingible body macrophages (starry sky appearance) (i). Higher magnification showed atypical lymphoid cells with few cells showing plasmablastic morphology (j; inset- showing crushing of cells in other areas). Tumor cells showed high Ki67 proliferative index (k) and diffuse CD45 positivity (l, inset-showing CD138 positivity in few cells). Case of well-differentiated squamous cell carcinoma (m-t) clinically showing proliferative growth in right mandibular gingiva (m) and ill-defined bone loss in radiology (n). Histology showed intense inflammation covering epithelium (o) with predominantly plasma cells with clock face nuclei (p). Plasma cells showed CD138 immunopositivity (q) and expression of both kappa (r) and lambda light chains (s). Deeper biopsy revealed atypical epithelial proliferation within intense lymphoplasmacytic infiltrate suggesting of well differentiated squamous cell carcinoma (t)

clonality of plasma cells). Case 1 was diagnosed with PCG based on normal hematological profiles and polyclonal plasma cells histologically in response to associated contactant.

Various case reports mention plasma cell granuloma as a solitary lesion with similar etiology, or a localized subtype of PCG. However, the World Health Organization recommendations and recent literature reveal plasma cell granuloma as a synonym for inflammatory myofibroblastic tumor (IMT) which typically arises in the lungs, unusually involves the head-and-neck region and shows myofibroblastic spindle cells and inflammatory cells.[11] ALK positivity is an important hallmark to differentiate

IMT from histological mimickers and may be a favorable prognostic indicator.[12] Since the first description of IMT, several names have been used for this lesion like "inflammatory pseudotumor (IPT)," "pseudosarcoma," etc., and these heterogeneous terminologies reflect the uncertain biological nature of this entity.[11,13] Some of the IPTs have been found to be associated with IgG4RD, a fibroinflammatory disease affecting virtually every organ. It mimics malignancy and histologically exhibits IgG4 positive plasma cells.[14] The accurate and early characterization of this disease are important as it is treated with steroids and irreversible injury to organs may occur if effective treatment is not initiated.[5] A comprehensive diagnostic criterion established to diagnose IgG4RD is given in Figure 2.[15] Initial literature supports >50 IgG4 immunopositive plasma cells per high-power field as diagnostic criteria, but recent evidence suggests that IgG4/IgG + cells ratio of >40% is a better indicator [Figure 3]. However, none of these criteria is exclusive for IgG4RD and blood or bone marrow biomarker (plasmablasts) levels by flow cytometry has some potential to improve diagnostic accuracy in future.[5,16]

The next subgroup of plasma cell lesions includes plasma cell dyscrasias. These neoplasms are derived from postgerminal center B-cells with somatic hypermutation and immunoglobulin heavy chain class switching [Figure 1], which secrete single monoclonal protein called as "M protein." PCD is the term used for heterogeneous plasma cell neoplasms [Table 1]. It includes plasmacytoma and PCM, which can affect the head-and-neck region (rare site). Solitary plasmacytoma (SP) is characterized by the presence of single lytic lesion, histologically showing sheets of monoclonal neoplastic plasma cells, negative bone marrow result (or <10% plasma cells) and no evidence of widely disseminated disease.[12,17] Two types of plasmacytoma are described: SP of bone (SPB) and extramedullary plasmacytoma (EMP). SPB arises within the bone; the spine being the most common site. On the contrary, EMP presents as soft-tissue mass, with 80%–90% cases occurring in the head-and-neck region.[4,12] EMP needs to be differentiated from PCM with extramedullary involvement as the latter has a relatively poor prognosis in contrast to the indolent course of EMP [Figure 2].[17]

PCD exhibiting multi-centric origin within the bone are called as PCM. PCM accounts for 1% of all malignant tumors and 10%–15% of hematopoietic neoplasms.[4] It typically involves bone marrow and sometimes shows secondary involvement of other organs. Diagnosis of PCM requires the presence of >10% clonal bone marrow plasma cells or biopsy-proven plasmacytoma and >1 of myeloma defining events (hyper calcemia, Renal insufficiently, Anemia, Bony lesions (CRAB)- hypercalcemia, renal failure, anemia and >1 osteolytic lesions in bone).[12] Serum or urine M protein is present in 97% of patients with the concentration of serum M protein >30g/L of IgG and >20g/L of IgA. Cytokine interleukin (IL-6) plays a significant role in the proliferation and survival of myeloma cells and bone marrow stromal cells. Myeloma-derived macrophage inflammatory proteins 1α augment the expression of receptor activator of NF-kB ligand, leading to bone resorption.[3] Cytological spectrum of PCM varies, ranging from small lymphoplasmacytic to mature plasma cells or plasmablasts. The terminal stage of PCM can further progress to plasma cell leukemia with altered hematological profile [Figure 2].[18]

Case 2 was diagnosed with plasmablastic PCM on the basis of microscopy showing monoclonal plasmablasts, high Ki67 index along with anemia, 70% clonal bone marrow plasma cells, M band on electrophoresis [fulfilling PCM diagnostic criteria- Figure 2] and exclusion of PCL through hematological screening. Although plasmablastic PCM is a high-grade variant conferring poor prognosis, risk stratification is considered primarily on the basis of clinical staging system (ISS for PCM) and recognition of high-risk cytogenetic profiles.[19] Treatment of PCM involves systemic chemotherapy. Radiotherapy is reserved for the palliative treatment of painful bony lesions.[4,19]

PCM with blastic morphology or with widespread extramedullary involvement shares virtually identical histology and immunophenotype with PBL. PCM presents with osteolytic involvement and infrequent association of HIV and EBV. However, PBL is a highly aggressive subtype of B-cell NHL; it usually shows frequent association with HIV infection (immunosuppression), EBV positivity and predominantly involves the oral cavity as soft-tissue mass.[6] These features are consistent with our case of PBL (case 3). PBL with unusual presentation (HIV negative, EBV negative and osseous involvement) should be advised workup for PCM. Further, myeloma-like treatment may be rendered as an alternative therapy in such cases.[19] PBL usually responds to aggressive chemotherapeutic agents and autologous stem cell transplantation instead of conventional CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) for lymphomas.[20] The neoplastic cells in PBL are derived from immunoblasts in transition to plasma cells, while PCM arises from plasma cells. This indicates an ontogenic relationship between the two and justifies the use of myeloma-like drugs for PBL treatment.[6,21] Despite various treatment regimens employed, the prognosis remains poor and median survival rate is 6–9 months.[22]

CONCLUSION

For accurate characterization of plasma cell lesions, it is critical to distinguish between plasma cells representing the lesional population, either reactive or neoplastic; and those associated with inflammatory response to a separate pathology. However, histomorphology is the gold standard, but correlation with clinico-imaging and sometimes ancillary techniques become critical for conclusive diagnosis. The diagnostic scheme proposed by us crystallizes the available information on these infrequently encountered lesions within the oral cavity. It will be helpful for the oral pathologists and clinicians encountering such entities.

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Conflicts of interest
There are no conflicts of interest.

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