REVISTA DA FACULDADE PAULO PICANÇO
revista.facpp.edu.br
ISSN 2764-6289

PLASMA CELL-RICH LESIONS IN THE ORAL CAVITY: AN OVERVIEW AND CASE PRESENTATION

Ana Paula Negreiros Nunes Alves[a], Mário Rogério Lima Mota[b], Fabrício Bitu Sousa[b], Karuza Maria Alves Pereira[c], Guilherme Costa Soares[d], Erick Helton Lima Fontenele[e], Dalgimar Beserra de Menezes[f].

[a]Full Professor of Oral Pathology of the Dentistry Course at the Faculty of Pharmacy, Dentistry and Nursing, Federal University of Ceará, ananegreirosnunes@gmail.com; [b]Associate Professor of Oral Pathology and Stomalogy of the Dentistry Course at the Faculty of Pharmacy, Dentistry and Nursing, Federal University of Ceará, mariolmota@yahoo.com.br; fbitu@hotmail.com; [c]Associate Professor of Histology at the Medicine Course, Federal University of Ceará, karuzaalves@yahoo.com.br; [d]Master by the Posgraduate Program in Dentistry, Faculty of Pharmacy, Dentistry and Nursing, Federal University of Ceará, gcsodontoufc@gmail.com; [e]Master Student of the Dentstry Posgraduate Program in Unichristus, Fortaleza, Ceará, erickfontenele@gmail.com; [f]Lecturer in Pathological Anatomy at the Medicine Course, State University of Ceará. Emeritus Professor at the Medicine Course, Federal University of Ceará, dalgimar@biopse.com.br.

ABSTRACT

The oral mucosa and gnathic bones can be targets of different types of diseases, however, some of them have plasma cell infiltrate as the main histopathological feature including reactive lesions, oral infectious disease, or a true neoplasm. It is important to examine the clonality of these conditions to demonstrate a polyclonal or monoclonal proliferation, being the last a finding that is more consistent with a neoplastic process. Here, we present four cases reports of oral plasma cell lesions, including Plasma cell mucositis (reactional inflammatory origin), Syphilis (infectious lesion) and two cases of Solitary Plasmacytoma/Multiple Myeloma (neoplastic lesion). Results from the microscopic characteristics associated with immunohistochemical analyses supported the final diagnosis each of them. The patients with Plasm cell mucositis and Syphilis were treated sucessfully. The two female patients with Plasmocytoma extramedullary were referred for chemotherapy treatment.

Keywords: Plasma cells. Oral syphilis. Plasma cell mucositis. Plasmacytoma.

INTRODUCTION

Plasma cells are differentiated cells that constitute the final stage of maturation of B lymphocytes. They are present mainly in the bone marrow and lymph nodes, being specialized in the production of antibodies (immunoglobulins) (1). These cells display plasma cell-specific markers (CD38 and CD138) in addition to other markers expressed at various stages of B cell differentiation, such as multiple myeloma antigen 1 (MUM-1) (2).

The oral mucosa and gnathic bones can be targets of different types of diseases, however, some of them have plasma cell infiltrate as the main histopathological feature. Three main types of oral plasma cell lesions are Plasma cell mucositis (reactional inflammatory origin), Solitary Plasmacytoma/Multiple Myeloma (neoplastic lesion) and Syphilis (infectious lesion).

Plasma cell mucositis, also known as orofacial plasma cell mucositis, idiopathic plasmacytosis, plasmacytosis of the mucous membranes of the upper aerodigestive tract or oral papillary plasmacytosis (3), is a non-neoplastic plasma cell proliferative disorder of the mucous membranes. It is a benign condition of unknown etiology, characterized by the infiltration of polyclonal plasma cells in mucosal tissues, which may affect the upper aerodigestive tract or genital mucosa. Clinically, an intensely erythematous, papillomatous, nodular, or velvety mucosa is observed. The most common symptoms are pain, dysphagia, persistent hoarseness, and sore throat. The diagnosis requires a correlation between clinical and histopathological findings. Squamous epithelium displays hyperplasia and spongiosis with narrow and elongated rete ridges under which there is a lamina propria consisting of fibrous tissue with an intense inflammatory component of polyclonal plasma cells without cytological and nuclear changes (4-11).

Plasmacytoma consists of a monoclonal neoplastic proliferation of plasma cells, which can occur in bone medullary area as solitary bone plasmacytoma, in extramedullary area as an extramedullary plasmacytoma, or involving several areas as multiple myeloma (13,14). Cases of solitary bone plasmacytoma usually

affect the axial skeleton and pelvic bones, being rare in the gnathic bones. Enlargement, bone pain, and pathological fractures are common clinical signs in this condition. They usually present two radiographic patterns: a well-defined radiolucent area or a lytic bone mass. For the diagnosis of these lesions, it is necessary to correlate the clinical, radiographic, and histopathological features, which reveal an atypical diffuse proliferation of plasma cells, usually monoclonal, with basophilic cytoplasm, hypodense chromatin, and eccentric nuclei with multiple nucleoli (1,12-17).

In some infectious lesions, the detection of an inflammatory infiltrate, predominantly of plasma cells, can help us in the differential diagnoses. Syphilis, a sexually transmitted infection, is produced by Treponema pallidum and arises from direct contact with the site of injury. It has different stages: primary, secondary, latent, and tertiary. Some patients can present focal or diffuse lesions in the oral mucosa in the primary or secondary or tertiary stage with different clinical presentations. The histopathologic picture of the oral lesions in the syphilitic patient is not specific. Generally, the surface epithelium is ulcerated in primary lesions and may be ulcerated or hyperplastic with an extensive exocytosis of neutrophils in the secondary stage. A chronic inflammatory infiltrate, constituted predominantly by plasma cells in the connective tissue is noted primarily in the subepithelial region, around vascular channels and as perineural infiltrate (18-26).

The aim of the present article is to report four cases of oral plasma cell-rich lesions, highlighting the microscopic characteristics associated with the plasma cell infiltrate and the peculiarities in each of them, for the differential diagnoses.

CASE REPORTS

CASE 1

A 40-year-old male patient presented at the dental clinic with ulceration, pain and burning in the oral mucosa. During clinical examination, macules erythroleukoplastic macules were observed in oral mucosa, including upper and lower buccal gingiva, bilateral buccal mucosa, and bilateral tongue border.

According to the patient, these lesions started more than two years ago, having received a previous ineffective treatment with topical Nystatin and Corticosteroids, without resolution of the lesions. Clinical differential diagnosis of Oral Lichen Planus or Benign Mucosal Pemphigoid was performed.

The incisional biopsy of the tongue showed a dense and diffuse infiltration of mononuclear inflammatory cells, consistent with plasma cells and lymphocytes, besides numerous Russell bodies in the lamina propria. Sometimes, a chronic perivascular inflammatory infiltrate was observed. Immunoperoxidase reaction through BenchMark Ultra IHC/ISH Ventana Roche® processing, demonstrated membrane and/or cytoplasmic diffuse positivity for anti-CD138, anti-Kappa and anti-Lambda antibodies in plasma cell, without chain restriction. For the other hand, immunohistochemistry reaction directed against Treponema pallidum was negative for spirochetes within the surface epithelium and at the interface between the epithelium and the superficial connective tissue. So, the diagnosis of Plasma Cell Mucositis was made. (Figure 1).

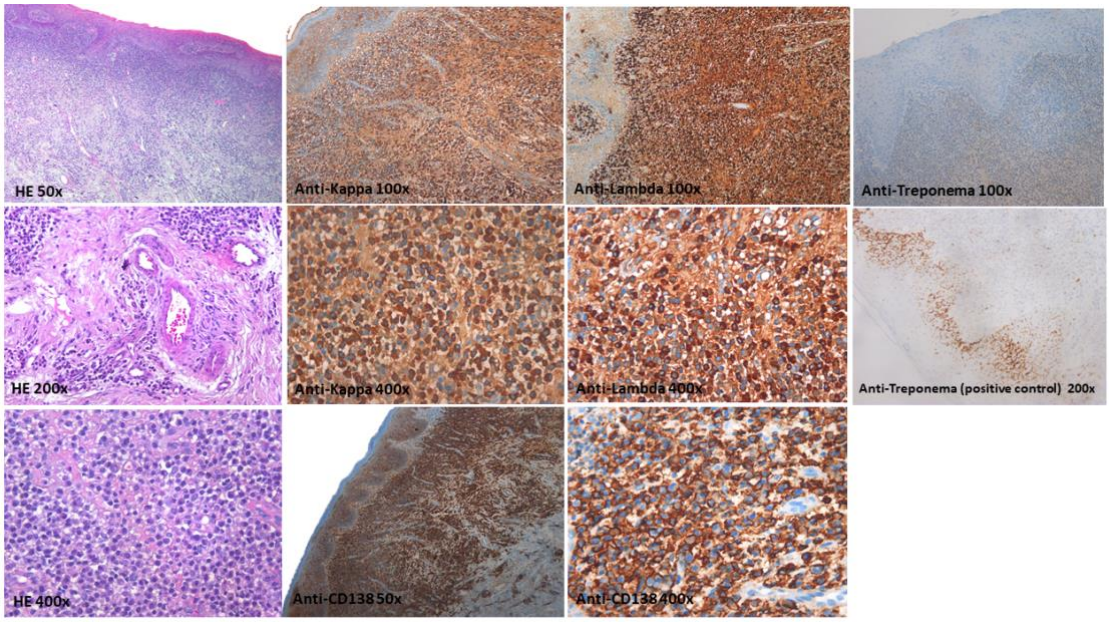


Figure 1: Plasma Cell Mucositis. Dense and diffuse infiltration of mononuclear inflammatory cells (50x and 400x) and a chronic perivascular inflammatory infiltrate (200x) were observed (H&E). Immunoperoxidase reaction demonstrated membrane and/or cytoplasmic diffuse positivity for anti-CD138,

anti-Kappa and anti-Lambda antibodies in plasma cell, without chain restriction. Treponema pallidum was negative for spirochetes.

CASE 2

A 27-year-old male patient was admitted to a Dental Clinic with multiple intraoral lesions located on the hard palate, and bilateral tongue border. Clinical examination revealed circumscribed white maculopapular areas and elevated mucous patches involving the oral cavity showing irregular thickness. The patient informed that these lesions had appeared five weeks previously. (Figure 2).

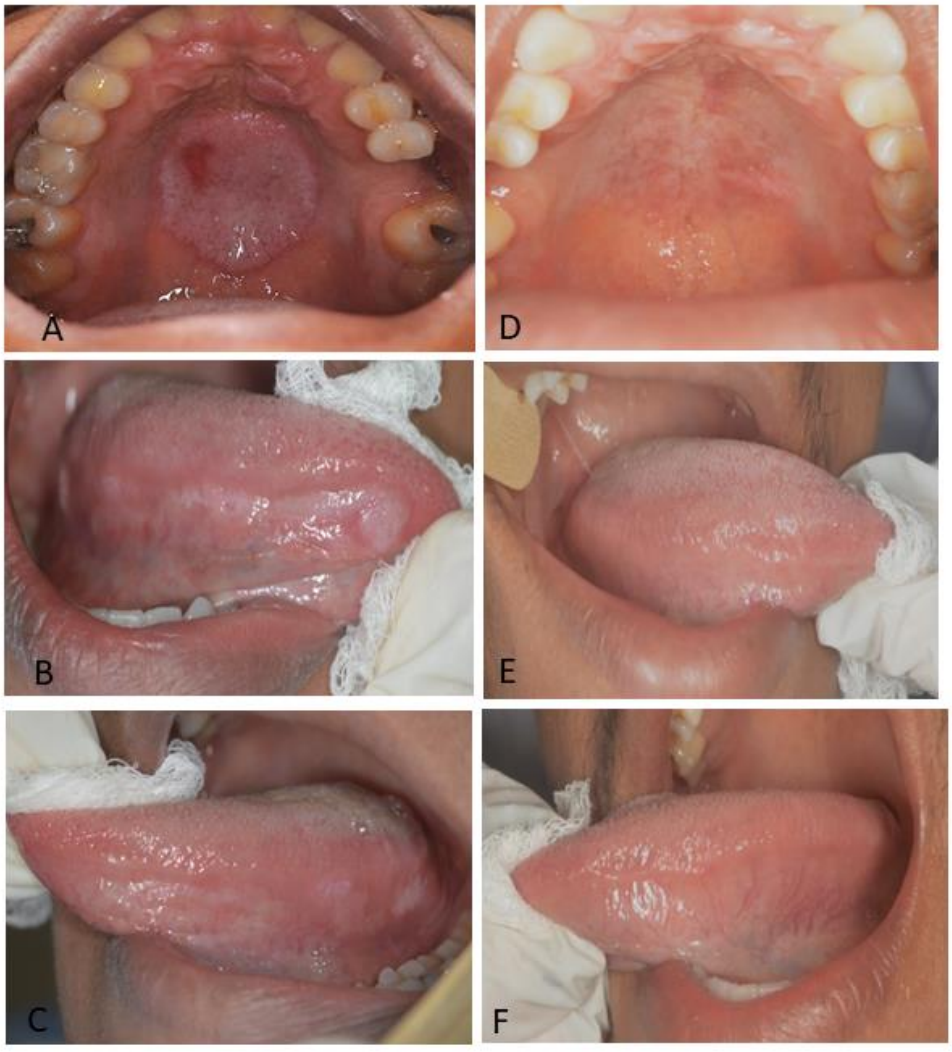


Figure 2: (A, B, C) Oral secondary syphilis - Circumscribed white plaque on hard palate and irregular thickened white plaque on tongue. (D, E, F) Total involution

of oral lesions of oral secondary syphilis on palate and tongue after treatment with penicillin.

Our clinical diagnostic hypothese was Secondary syphilis. A whole blood count, serology for Syphilis, HIV and Hepatitis B and C were requested. In addition, an incisional biopsy was carried out from the lesions of hard palate and buccal mucosa.

The histopathological analysis revealed the presence of a hyperplastic epithelium exhibiting intense exocytosis of neutrophils, with formation of microabscesses and spongiosis. The underlying lamina propria showed an intense chronic inflammatory infiltrate, predominantly plasma cells in subepithelial and perivascular regions. Immunohistochemical reaction for Treponema pallidum demonstrated numerous spirochetes in the epithelium. (Figure 3).

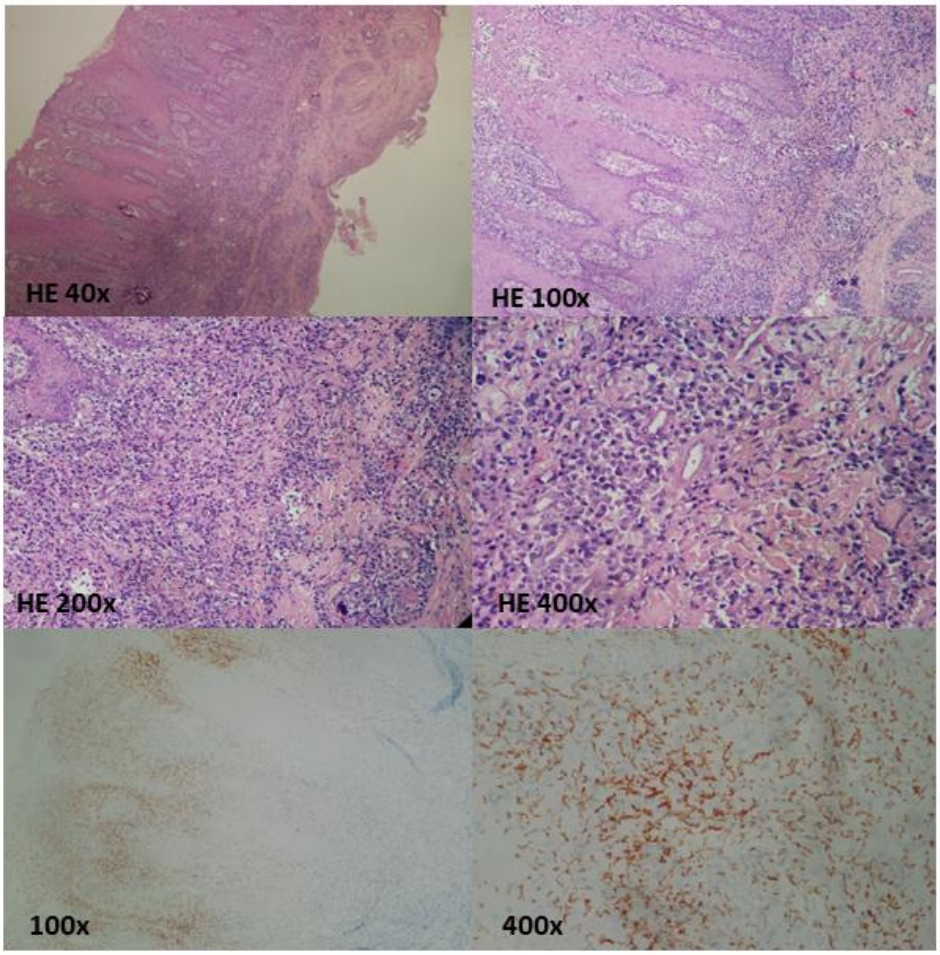
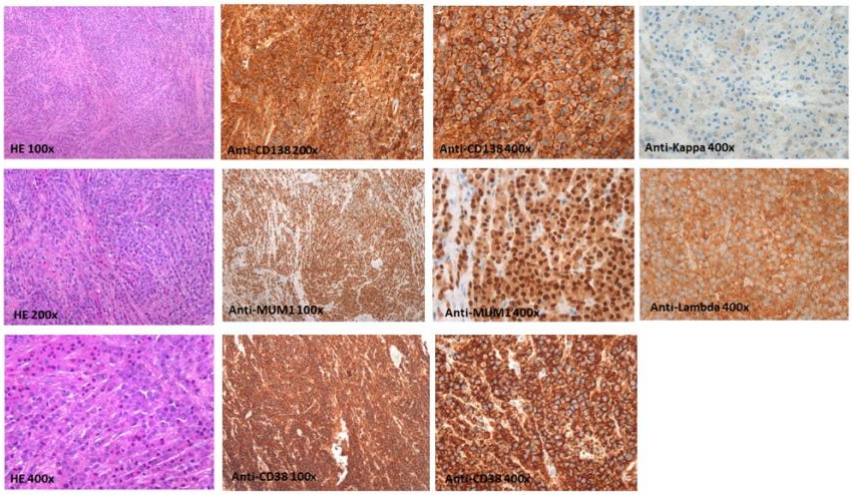


Figure 3: Photomicrograph of palate biopsy showing epitelial hyperplasia and a heavy plasmacytic infiltrate in the connective tissue. In high-power view, chronic perivascular inflammatory cells (H&E). Immunoperoxidase reaction for *Treponema pallidum* demonstrating numerous spirochetes in the epithelium.

CASE 3

A 69-year-old female patient came to the Dentistry Service with swelling in the posterior region of the mandible. According to the patient, the lesion had appeared two months ago previously with no symptoms. Panoramic radiography showed an ill-defined margin radiolucency with radiopaque areas in a pattern like “sunburst”. The clinical hypothesis of Osteosarcoma was considered.

An incisional biopsy was done, and the specimen was sent for histopathological examination, which revealed diffuse and monotonous sheets of malignant plasmacytoid cells with eccentric nuclei and stippled nuclear chromatin. Immunohistochemical reaction displayed a uniform positivity of the plasma cells for antibodies against Lambda light chains. A clonal population of 75% or more of the total population of plasma cells indicating a monoclonal neoplastic proliferation. Furthermore, the tumors cells were positive for anti-CD138 e CD MUM-1 and negative for anti-CD20 and anti-CD45, results that are consistent with a diagnosis of Intraosseous Plasmacytoma. (Figure 4). The patient was referred for chemotherapy treatment.



DOI: https://doi.org/10.59483/rfpp.v3n4.97

Figure 4: Plasmacytoma. Monotonous proliferation of plasmacytoid cells showing eccentric nuclei (H&E). An intense expression for anti-CD138, anti-CD38, anti-MUM-1 and anti-Lambda in neoplastic cells besides a negativity for anti-Kappa were visualized.

CASE 4

A 62-year-old female patient sought out a Dental Clinic complaining of swelling in the posterior region of the left mandible. On clinical examination, the dentist observed mucosa with normal color and local swelling on the buccal, lingual, and basilar areas. The lower left third molar tooth showed significant mobility and the patient reported sporadic and painful symptoms on palpation.

The radiographic analyses (periapical and orthopantomography) demonstrated unilocular radiolucent lesion in the region of teeth 37 and 38 with poorly defined limits, apparently causing thinning of the alveolar and basilar cortical, and projecting over the mandibular canal (Figure 5). The patient was submitted for an incisional biopsy to clarify if it was a neoplastic or an inflammatory lesion. During the surgical procedure, it was observed negative puncture and destruction of the alveolar and vestibular cortex.

Histopathologic examination of the lesional tissue showed an atypical neoplasm composed for a monotonous proliferation of plasmacytoid cells showing eccentric nuclei replacing the normal tissue.

The monoclonality of the plasma cell population could be demonstrated through a positive and uniform reaction of the cells for antibodies against Kappa light chain exhibiting kappa-lambda ratio greater than 3:1. An intense expression for CD138 and MUM-1 in neoplastic cells besides a weak and focal expression of CD56 and CD45 and negativity for CD79a and CD20 were visualized. So, these findings were compatible with Intraosseous Plasmacytoma. The patient was referred to the oncohematology sector to investigate the possible occurrence of Multiple Myeloma and it was confirmed. The patient began chemotherapy treatment with partial involution of the lytic lesion in the jaw, but she died of COVID-19 before the bone marrow transplant.

DOI: https://doi.org/10.59483/rfpp.v3n4.97

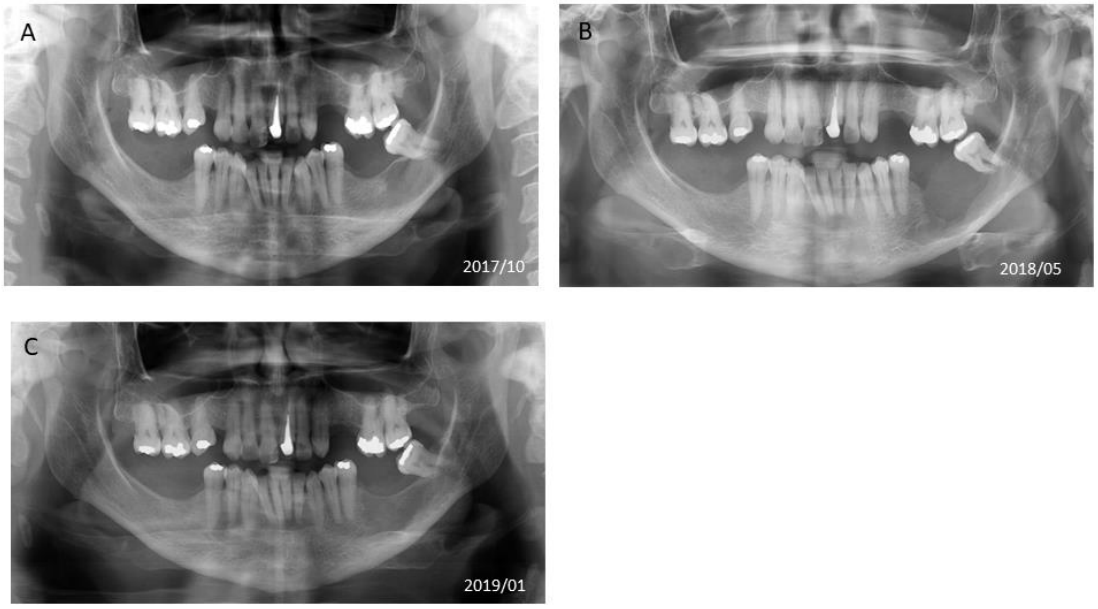


Figure 5: (A) Radiolucent area in the region of teeth 37 and 38), unilocular, with poorly defined limits, apparently causing thinning of the alveolar and basilar cortices, and projected over the mandibular canal. (B) Intense bone destruction in the left mandibular body region seven months after histopathological diagnosis. (C) Follow up of eight months after outset of chemotherapy treatment.

DISCUSSION

Plasma cells show distinct characteristics in different lesions, and may have a benign behavior, as in reactional or infectious cases, or malignant. Such lesions are rare in the maxillomandibular complex and represent a challenging diagnosis, requiring a meticulous evaluation of clinical and complementary exams (27). In the head and neck region, plasmacytoma and multiple myeloma are the most common diseases.

Immunohistochemistry is a fundamental tool to analyze the phenotype and clonality of these cells, allowing the differentiation between neoplastic and non-neoplastic proliferations (4,12). Mainly because different tumors can exhibit cells with plasmacytoid morphology, making the histopathological diagnosis challenging, such as myoepithelial tumors, carcinomas and melanomas (5-7).

First described in 1970, plasma cell mucositis is the main example of benign infiltration of plasma cells in soft tissues, with a polyclonal characteristic. This process takes place in a wide variety of locations, including larynx, epiglottis, vulva, and conjunctiva (9). Specifically, in oral cavity, it commonly affects the lips and tongue (10), but it can involve other sites such as the gingiva and buccal mucosa, as evidenced in the case number one (3).

The diagnosis of plasma cell mucositis requires a thorough correlation between history and clinical aspects with histopathological and immunohistochemical analysis. The clinical differential diagnosis of this lesion includes several other conditions, such as lichen planus, secondary syphilis, candidiasis, contact dermatitis, drug reactions, herpes simplex, vascular malformations, necrotizing sialometaplasia and extramedullary plasmacytoma (10).

The chief histological findings include epithelial hyperplasia and spongiosis with dense polyclonal plasma cells infiltrate in the lamina propria. In addition, the presence of Russell bodies, a feature found in our case, can also be observed, but less frequently (8). A polyclonal proliferation exhibits a mixture of Kappa and Lambda light chains, and, consequently, the benign nature of the lesion, and can be identified using the immunohistochemical reaction. Moreover, positivity for CD138 antibody confirms the plasma cell population (4,10).

Treatment for plasma cell mucositis includes therapy with topical, intralesional or systemic corticosteroids, antibiotics, immunosuppressive agents such as Tacrolimus®, cryotherapy, and surgical excision in some cases. It is reported that the most used treatment modality is the use of corticosteroids, but the results are still not reliable (4).

Another example of a benign lesion that has plasma cell infiltration is syphilis. It is a sexually transmitted infection caused by the bacterium Treponema pallidum, which can have oral repercussions, whose manifestations depend on the clinical stage of the disease (primary, secondary, latent, and tertiary) (18-26).

Primary Syphilis is characterized by a "chancre", a solitary painless papular lesion with a central ulceration, which develops at the site of the bacteria inoculation, in

about 3 weeks. Regional lymphadenopathy is seen in most patients (22). These initial lesions tend to heal naturally, followed by the spread of the microorganism systemically. The secondary stage appears at about 3 to 12 weeks after the initial infection, but the lesions can arise before chancre has resolved completely. It is usually the stage at which oral syphilis is diagnosed, as occurred in the case presented (case 2). Syphilitic oral lesions develop in a varied way and may appear as mucous plaques, macules, papules, nodules, or ulcers, in addition to papillary lesions known as condyloma lata, together with maculopapular changes in the skin. This diversity of clinical features can simulate other conditions, such as lichen planus, eosinophilic ulcers, traumatic ulcers, lymphomas, leukoplakia, gonorrhea, squamous cell carcinoma and necrotizing sialometaplasia. It is important to establish a clinical differential diagnosis with these. The latent phase is considered the inactive form of the disease, with serological evidence of infection, but without symptoms, developing about 1 year after secondary syphilis. The tertiary phase is systemically established and causes severe changes in various parts of the body, appearing within 15 years after the initial infection. It is characterized by the presence of syphilitic gums (granulomatous inflammation) in several places, including the oral mucosa, appearing mainly on the palate and tongue (atrophic luetic glossitis) (22,24).

Histological features are nonspecific and mimic many other conditions. In the case described, we observed the presence of a hyperplastic epithelium exhibiting extensive neutrophil exocytosis and microabscesses besides fibrous lamina propria with marked inflammatory cell infiltrate, predominantly plasmocytic. Such characteristics are considered highly suspicious and guide the diagnosis of this condition (24). The immunohistochemical reaction to identify Treponema pallidum can also facilitate this process and was one of the diagnostic resources used in this case. However, serological tests are essential for the final diagnostic of syphilis (23-25).

It is noteworthy that the patient in case 2 was positive for FTA-Abs test. It is a specific treponemal test for detection of the microorganism, in addition it can identify the infection at any stage. However, it is more expensive than the other

tests. Unlike VDRL, which is a faster and cheaper test, but not specific and less sensitive in the early stages. This test is reactive in secondary and latent stages, and also in Systemic Lupus Erythematosus, Ulcerative Colitis, and Rickettsiae Disease (26).

Several studies demonstrate an important association between Syphilis and HIV infection (18-26). Syphilis can enhance the transmission of HIV, and patients with HIV may not respond effectively to antibiotic regimens (18). This co-infection is of worldwide interest and several cases are reported in the literature, and it is extremely important to investigate a possible HIV infection in patients with suspected syphilis. Furthermore, syphilis/hepatitis B or C co-infection also occurs quite frequently, and HBS-Ag and anti-HCV tests are often required in these cases (20-21). The patient in our case was negative for HIV, Hepatitis B and Hepatitis C.

Plasma cell dyscrasias are diseases caused by the proliferation of malignant B cells. Solitary plasmacytomas represent less than 5% of plasma cell dyscrasias and are classified as osseous or extramedullary. Such lesions are more common in men and occur in median age of 55 years, differing from cases 3 and 4, in which they affected women over 60 years of age. The extramedullary variant is rare and the solitary bone plasmacytomas in the craniomaxillofacial region is extremely unusual. In the gnathic bones, the mandible is the most common location, similarly to the two cases reported. Bone pain is a frequent symptom of patients affected by this condition besides paresthesia, mobility and migration of teeth and increase in volume in hard and soft tissues (12-17).

The most frequent radiographic characteristics in Solitary Bone Plasmacytomas and Multiple Myeloma are osteolytic lesions with a “soap bubble” appearance but in the case 3 presented it was observed osteosarcomas “sun burst” pattern. For the other hand, the neoplastic aspect, clonality and phenotype of the plasmocytoid cells in the cases 3 and 4 was compatible with that described in the literature (14).

The diagnosis of Solitary Plasmocytoma must be careful. It is important to analyze clinical examinations, patient history, histopathological features, and laboratory tests. Biopsy and histopathologic examination are mandatory since the definition of diagnosis determines a systemic investigation to rule out the possibility of Multiple Myeloma. It is necessary to assess whether there is only a single site of bone involvement through imaging examinations. In addition, the absence of anemia, hypercalcemia, or renal failure, low concentrations of serum or urinary monoclonal protein, and preserved levels of immunoglobulins are essential diagnostic criteria to exclude the possibility of other plasma cell dyscrasias (12-17). In our two cases, a single site of involvement together with the histopathological and immunohistochemical profile were decisive for the diagnosis.

Knowledge of the maxillofacial manifestations of Solitary Bone Plasmacytomas and Multiple Myeloma on the part of the dentist is important for early diagnosis of the disease, especially when it occurs in its primary form in the maxillary bones.

FINAL CONSIDERATIONS

We concluded that in the event of marked infiltration of plasma cells in oral lesions, the diagnosis of plasma cell mucositis, syphilis and plasmacytoma/multiple myeloma should be considered. Aspects related to the architecture and distribution of cells, cytological alterations and imaging aspects are essential to build the diagnosis. Immunohistochemical analysis of plasma cells is used to confirm its phenotype and determine if there is a monoclonal or polyclonal proliferation. Finally, in some cases, serological tests are fundamental to conclude the diagnosis.

REFERENCES

1. Hilgert R, Fonseca LAM, Ribeiro FF, Soares LY. Plasmocitoma solitário em mandíbula: relato de caso. Revista de Cirurgia e Traumatologia Buco-maxilo-facial, 2012; 12(3):67-72.

2. Cicinelli E, Haimovich S, De Ziegler D, Raz N, Ben-Tzur D, Andrisani A, et al. MUM-1 immunohistochemistry has high accuracy and reliability in the diagnosis of chronic endometritis: a multi-centre comparative study with CD-138 immunostaining. J Assist Reprod Genet. 2021; 39(1):219-226.

3. Solomon LW, Wein RO, Rosenwald I, Laver N. Plasma cell mucositis of the oral cavity: report of a case and review of the literature. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 2008; 106(6), 853-860.

4. Puvanendran M, Lieder A, Issing W. Plasma cell mucositis of oro-and hypopharynx: a case report. Case Reports in Otolaryngology. 2012

5. Jo VY. Soft Tissue Special Issue: Myoepithelial Neoplasms of Soft Tissue: An Updated Review with Emphasis on Diagnostic Considerations in the Head and Neck. Head Neck Pathol. 2020; 14(1):121-131.

6. Agaimy A, Hartmann A, Antonescu CR, Chiosea SI, El-Mofty SK, Geddert H, et al. SMARCB1 (INI-1)-deficient Sinonasal Carcinoma: A Series of 39 Cases Expanding the Morphological and Clinicopathological Spectrum of a Recently Described Entity. Am J Surg Pathol. 2017; 41(4):458–471.

7. Kocovski L, Bane A, Tang S, Salama S, Alowami S. Amelanotic Melanoma Presenting with Plasmacytoid Morphology and BRAF V600 Mutation. Rare tumors. 2015; 7(2):5698.

8. Smith JGF, Smith CP, Leyden PJ. Plasma cell mucositis of the larynx. Clinical case reports. 2018; 6(9):1761.

9. Triplett J, Hee G, McLean-Tooke A, Lucas M. Long-term control of laryngeal plasma cell mucositis with systemic immunosuppression. Case Reports. 2018; 2018:bcr-2017-221333.

10. Gasparro R, Adamo D, Masucci M, Sammartino G, Mignogna MD. Use of injectable platelet-rich fibrin in the treatment of plasma cell mucositis of the oral cavity refractory to corticosteroid therapy: A case report. Dermatologic therapy. 2019; 32(5):e13062.

11. Micucci SB, Zim SA, Hosfield EM. Plasma Cell Mucositis of the Hard Palate. Ear, Nose & Throat Journal. 2019; 0145561319872732.

12. Shanahan D, Shipley D, Staines K. Plasma cell mucositis. Ear, Nose & Throat Journal. 2020; 99(6):NP64-NP65.

13. Seoane J, Aguirre J, Esparza G, Suárez M, Campos J, Pomareda M. Espectro de las neoplasias de células plasmáticas en el ámbito de la patología maxilofacial. Med Oral. 2003; 8:269-80.

14. Marotta S, Di Micco P. Solitary plasmacytoma of the jaw. Journal of blood medicine. 2010; 1:33.

15. Kucukkurt S, Karan NB, Senguven B, Kahraman S. Solitary plasmacytoma of the mandible: report of two cases. Case Reports. 2016; 2016.

16. Lombardo EM, Maito FLDM, Heitz C. Solitary plasmacytoma of the jaws: therapeutical considerations and prognosis based on a case reports systematic survey. Brazilian Journal of Otorhinolaryngology. 2018; 84(6): 790-798.

17. Tsang RW, Campbell BA, Goda JS, Kelsey CR, Kirova YM, Parikh RR, et al. Radiation therapy for solitary plasmacytoma and multiple myeloma: Guidelines from the International Lymphoma Radiation Oncology Group. International Journal of Radiation Oncology* Biology* Physics. 2018; 101(4):794-808.

18. Pham A, Mahindra A. Solitary plasmacytoma: a review of diagnosis and management. Current hematologic malignancy reports. 2019; 14(2):63-69.

19. Leuci S, Martina S, Adamo D, Ruoppo E, Santarelli A, Sorrentino R, et al. Oral syphilis: a retrospective analysis of 12 cases and a review of the literature. Oral diseases. 2013; 19(8):738-746.

20. Hertel M, Matter D, Schmidt-Westhausen AM, Bornstein MM. Oral syphilis: a series of 5 cases. Journal of oral and maxillofacial surgery. 2014; 72(2):338-345.

21. Strieder LR, León JE, Carvalho YR, Kaminagakura E. Oral syphilis: report of three cases and characterization of the inflammatory cells. Annals of Diagnostic Pathology. 2015; 19(2):76-80.

22. Araujo JP, Jaguar GC, Alves FA. Syphilis related to atypical oral lesions affecting an elderly man. A case report. Gerodontology. 2015; 32(1):73-75.

23. Pires FR, Da Silva PJS, Natal RF, Alves FA, Pinto CAL, Rumayor A, et al. Clinicopathologic features, microvessel density, and immunohistochemical expression of ICAM-1 and VEGF in 15 cases of secondary syphilis with oral manifestations. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2016; 121(3):274-281.

24. Schuch LF, Da Silva KD, De Arruda JAA, Etges A, Gomes APN, Mesquita RA, et al. Forty cases of acquired oral syphilis and a review of the literature. International Journal of Oral and Maxillofacial Surgery. 2019; 48(5):635-643.

25. Thompson LDR. Oral Syphilis. Ear, Nose & Throat Journal. 2019: 0145561319890154.

26. Porterfield C, Brodell D, Dolohanty L, Scott G. Primary Syphilis Presenting As a Chronic Lip Ulcer. Cureus. 2020; 12(2).

27. Matias MDP, Jesus AO, Resende RG, Caldeira PC, Aguiar MCF. Diagnosing acquired syphilis through oral lesions: the 12 year experience of an Oral Medicine Center. Brazilian journal of otorhinolaryngology. 2020; 86(3):358-363.