Value of Immunohistochemistry in Diagnosing a Rare Case of Maxillofacial Plasma Cell Granuloma Masquerading as a Gingival Epulis

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Abstract

Background Plasma cell granuloma is a non-neoplastic lesion rather uncommonly seen in the maxillofacial region. Its etiology, biological behavior, ideal treatment and prognosis are still unclear and rather controversial.

Study A detailed histopathological examination and immunohistochemical study of the excised specimen was carried out, both for making a confirmatory diagnosis as well as to determine the etiopathology, biological behavior and prognosis of the lesion.

Results Light microscopy revealed a hyperplastic stratified squamous epithelial lining, overlying a densely fibrocellular granulation tissue containing a rich proliferation of mononuclear inflammatory cells, among which there was a predominance of plasma cells with their typical eccentric, cartwheel shaped, “clock-faced” nuclei. Strong immunohistochemical positivity was observed for CD-138 by numerous cells of the connective tissue of the lesion, thus confirming them to indeed be plasma cells. Further, immunohistochemistry (IH) analysis also demonstrated the expression of both, the lambda and kappa light chain immunoglobulins by the plasma cell population, thus confirming them to be polyclonal and of an inflammatory, non-neoplastic origin.

Summary and Conclusion As a plasma cell granuloma is rarely encountered in the oral and maxillofacial region, its diagnosis could have been very easily missed, had it not been for the detection of the large numbers of plasma cells by light microscopy, which was further confirmed by IH. IH also helped in establishing the likely etiopathology of the lesion and confirmed it to be of a non-neoplastic reactive/inflammatory origin.

Keywords Plasma cell granuloma · CD-138 · Plasma cells · Kappa and lambda light chain immunoglobulins · Immunohistochemistry (IH)

Introduction

Plasma cell granuloma is an uncommon non-neoplastic lesion that was first described in 1973 by Bahadori and Liebow. This lesion’s incidence, etiology, biologic behavior and most appropriate treatments are unclear, and little is known about the prognosis. A rare case of this lesion affecting the gingiva is presented here, which could easily have been mistaken for a pyogenic granuloma, a peripheral giant cell reparative granuloma or a fibrous gingival epulis, had it not been for a detailed histological and immunohistochemical study conducted on this lesion.

Histologically, the plasma cell granuloma consists of a proliferation of inflammatory cells, with a predominance of plasma cells, in a fibrovascular background. It has been called by different terms, i.e. inflammatory myofibroblastic tumour, inflammatory pseudotumour, inflammatory myofibrohistiocytic proliferation and xanthomatous pseudotumour [1]. It primarily occurs in the lungs [2]. It is also seen to occur in the brain [3], kidney [4], stomach [5] and heart [6].

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Fig. 1 **A** A localized extraoral swelling visible in the region of the upper lip just below the ala of the nose on the *right side*. **B, C** Introrally, an irregular *pinkish red*, firm, lobulated, pedunculated, gingival growth was seen in the upper anterior gingiva in 12, 13, 14 and 15 region. **D** The gingival lesion being excised. **E, F** The

excised mass. **G, H** The raw bleeding surface was given a palliative Coe-pak periodontal dressing, which led to a smooth, uneventful and quick postoperative healing. **I** Appearance 5 days following surgical excision of the lesion

Rarely seen in the oral cavity the lesions are usually single, seen primarily on the periodontal tissue, mainly the gingiva, followed by tongue, lips, buccal mucosa and palate [7–10].

A 56 year old male patient presented with a localized, non-tender swelling over the right side of his upper lip, measuring 3 cm × 2 cm, just below the right ala of the nose, causing obliteration of the nasolabial sulcus (Fig. 1A). It was related to an intraoral gingival growth in the upper anterior gingiva in 13, 14 and 15 region (Fig. 1B, C). The intraoral mass was oval in shape and measured around 2 cm × 1 cm.

It was irregular pinkish red in colour, lobulated, cauliflower shaped, non-tender and pedunculated, attached to the gingiva by a narrow stalk (Fig. 1B, C). The surface exhibited no evidence of secondary changes such as ulceration or any secondary discharge of pus. It was firm in consistency and bled readily on probing. The patient also complained of inability to maintain oral hygiene as the intraoral enlargement interfered with and bled on brushing. The patient's medical history was not contributory and he was on no long standing medications for any other medical condition. Routine blood and urine examination of the patient was

Fig. 2 A–C Haematoxylin and eosin stained sections of the lesion at $\times 30$ magnification, showing a hyperplastic parakeratinized stratified squamous epithelial lining, with an underlying richly fibrocellular connective tissue stroma densely infiltrated with fibroblasts and chronic inflammatory cells. D–F $\times 60$ Magnification, showing the hyperplastic, parakeratinized stratified squamous epithelium with

elongated rete pegs projecting into the richly cellular, relatively avascular and densely collagenous lamina propria beneath. G–I Connective tissue of the lesion, showing numerous collagen fibers sprinkled with spindle-shaped fibroblasts and a number of plasma cells

carried out and all the values were within normal limits. A differential diagnosis of pyogenic granuloma, peripheral giant cell reparative granuloma, fibrous epulis, giant cell epulis and fibroma were considered.

Materials and Methods

An excisional biopsy and gingivoplasty was performed under local anesthesia (Fig. 1D) and the excised specimen (Fig. 1E, F) was sent for histopathological examination. A Coe-Pak dressing (Fig. 1G, H) was given to cover the raw surface and the gingival healing was quick and uneventful (Fig. 1I). Coe-Pak is a palliative surgical dressing and a periodontal pack, that protects raw areas and promotes their cleanliness and healing post operatively.

Light microscopy of hematoxylin and eosin stained sections (Figs. 2, 3) was carried out at $30\times$, $60\times$ and $80\times$ magnifications. Oil emulsion high power magnification provided valuable information as to the identity of constituent cells of the lesion.

In the immunohistochemical study conducted, the antibodies employed were from the biogenics company and were not diluted prior to use as they were available “ready to use (RTU)”. Antigen retrieval of the paraffin embedded tissue sections was performed using the “heat induced epitope retrieval (HIER)” technique. This was performed in an induction-based “decloaking chamber”. After incubation with the antibody, visualization was accomplished using di-amino benzidine (DAB) as the chromogen, which produced a typical brown staining of the cytoplasm of the positively reacting plasma cells (Fig. 4).

Fig. 3 A higher magnification ($\times 80$ under oil emulsion) of the plasma cells seen in the lesion. These cells are basically large lymphocytes with a considerable nucleus-to-cytoplasm ratio and a

characteristic appearance on light microscopy. They have basophilic cytoplasm and an eccentric nucleus with heterochromatin in a characteristic cartwheel or clock face arrangement

Fig. 4 A, B $\times 30$ and $\times 80$ Magnification. An immunohistochemical study of the lesion using DAB as the chromogen. C, D $\times 30$ and $\times 80$ Magnification. Immunohistochemical positivity for CD-138 expressed by numerous cells, confirming them to be plasma cells. E, F $\times 30$ and $\times 80$ Magnification. Immunohistochemical staining showing strong positivity for the kappa light chain seen in the

polyclonal plasma cell population. G, H $\times 30$ and $\times 80$ Magnification. A distinctly positive but relatively weak immunohistochemical expression noted for the lambda light chain by the polyclonal plasma cells. Immunohistochemical evaluation showed the kappa to lambda light chain ratio to be 2:1, confirming the diagnosis of plasma cell granuloma and its inflammatory/reactive origin

Immunohistochemical staining was first performed for a specific immunohistochemical marker for plasma cells, namely “CD-138” (Fig. 4C, D). Further, an immunohistochemical analysis for expression of kappa and lambda light chain immunoglobulins was also carried out (Fig. 4E–H), for confirmatory diagnosis of the plasma cell granuloma as well as to gather valuable information as to the lesion’s etiopathogenesis.

Results

Light microscopy revealed a parakeratinized stratified squamous parakeratinized hyperplastic epithelium (Fig. 2A, D–F). The sub epithelial tissue showed granulation tissue comprising of a few thin walled capillaries, numerous fibroblasts and a chronic mononuclear inflammatory infiltrate, consisting of a few lymphocytes, and abundant plasma cells (Figs. 2B, C, G–I, 3A–D). The plasma cells could be readily identified by their high nucleus to cytoplasmic ratio, basophilic cytoplasm and their typical eccentrically placed hyperchromatic, cart-wheel-shaped nucleus resembling the “face of a clock” (Fig. 3A–D) under high magnifications under oil emulsion. The histopathological appearance, when correlated with the clinical features, was suggestive of plasma cell granuloma of the gingiva.

On immunohistochemical analysis, there was a strong positivity expressed by a vast number of cells of the connective tissue of the lesion (Fig. 4A–D), confirming beyond all doubt that they were indeed plasma cells and the lesion a plasma cell granuloma.

It was also found that both, the kappa (Fig. 4E, F) as well as the lambda light chain immunoglobulins (Fig. 4G, H) were expressed by the plasma cells in the lesion as detected by the brown staining of their cytoplasm by the DAB chromogen. A strong positivity for the kappa light chain immunoglobulins was seen in the cytoplasm of the polyclonal plasma cell population (Fig. 4E, F), whereas, a weak but definitely positive expression was noted for the lambda light chain immunoglobulins (Fig. 4G, H), with a ratio of approximately 2:1, thus confirming the inflammatory/reactive etiology of the lesion by demonstrating the polyclonality of the plasma cells, thus helping to rule out graver pathologies such as myeloma or plasmacytoma (in which the proliferating plasma cells are monoclonal) and confirming the diagnosis to be plasma cell granuloma.

Discussion

Plasma cells are terminally differentiated B lymphocytes which are typically found in the red pulp of the spleen,

medulla of the lymph nodes, tonsils, lamina propria of the entire gastrointestinal tract, mucosa of the nose and upper airway, and sites of inflammation. They are characterized by a basophilic cytoplasm with an eccentrically placed nucleus. They range in size from 14 to 20 μm . A plasma cell’s main function is to produce immunoglobulins or antibodies [1].

The phenomenon of plasma cell infiltrate was first described by Zoon in 1952 when he described balanitis plasma cellularis. Plasma cell infiltrates have also been found on the vulva, buccal mucosa, palate, nasal aperture, gingiva, lips, tongue, epiglottis, larynx and other orificial surfaces [1].

During the late 1960s and early 1970s, cases of plasma cell infiltrates of the lips, gums, and tongue were described primarily in the dental literature under the names of atypical gingivostomatitis, idiopathic gingivostomatitis, and allergic gingivostomatitis [11]. The lesions were thought to be a result of a reaction to chewing gum, dentrifices, and other foreign substances, although extensive allergy testing had been inconclusive [11].

Tumors that are mainly composed of plasma cells may be multiple myeloma, solitary myeloma, soft tissue myeloma (plasmacytoma), or plasma cell granuloma. Multiple myeloma and solitary myeloma are tumors of the bone, whereas, plasmacytoma and plasma cell granuloma are soft tissue tumors. Differentiating the type of soft tissue tumor is mandatory, as plasma cell granulomas may be benign, but plasmacytomas may show early stages of multiple myeloma [11].

The pathogenesis of the plasma cell granuloma remains unclear. The large number of plasma cells may represent an autoimmune reaction or an alteration of blood flow imposing congestive vasodilatation. Lesions occurring due to parasitic infiltration can also not be ruled out [11]. The presence of polyclonal plasma cells, lymphocytes, and histiocytes suggests an infectious or autoimmune origin [12]. This lesion has no sex predilection and may occur at any age. Plasma cell granuloma is thought to result from inflammation following minor trauma or surgery or to be associated with malignancy [13–15], however, this was not so in the present case and our patient was free of any history of trauma or malignancy. However his oral hygiene was extremely poor with generalized chronic destructive periodontitis, which could have contributed to the genesis of this lesion, which was present on the gingival and was solitary.

The immunohistochemistry determines the clonality of the lesion, wherein in a reactive lesion, the plasma cells are polyclonal with the kappa to lambda light chain ratio around 2:1, and in the case of malignancy the ratio may be greater than 10:1 [11] indicating monoclonal proliferation of the plasma cells. In the present case, ratio was

approximately 2:1, suggestive of an inflammatory etiology. A polyclonal population of plasma cells (that is, positive immunohistochemical staining exhibited by these cells for both kappa as well as lambda light chain immunoglobulins), as was demonstrated by this lesion, is suggestive of a reactive etiopathology, that is, a lesion of inflammatory origin. On the other hand, a monoclonal population, that is, all plasma cells staining positive for either the kappa or the lambda light chain immunoglobulin, suggests a neoplastic etiology, for e.g. a myeloma or a plasmacytoma, which have a significantly graver prognosis than a reactive lesion.

Thus immunohistochemical analysis and study of the specimen helped not only in making a challenging confirmatory diagnosis of a plasma cell granuloma of the maxillofacial complex, but also provided valuable information regarding its etiopathology, biological behavior and likely prognosis; ruling out graver neoplastic lesions, thus helping in dictating the ideal treatment modality to be employed. As the lesion was now confirmed to be non-neoplastic, and it already had been excised in toto, no further surgical intervention was contemplated and the patient was followed up for a period of 4 months with no evidence of any recurrence.

A Coe-Pak palliative surgical dressing and a periodontal pack, was used to protect the raw area after excision of the lesion, which promoted a very quick, comfortable and uneventful healing of the wound post operatively.

Conclusion

Plasma cell granuloma can sometimes be mistaken for a malignant lesion due to its aggressive clinical appearance. In this case, cauliflower-shaped, pedunculated appearance also raised the suspicion of a verrucous carcinoma. Excisional biopsy followed by histopathological examination using haematoxylin and eosin stains exhibited the characteristic plasma cells in a richly fibrocellular connective tissue stroma. Plasma cells are large lymphocytes with a considerable nucleus to cytoplasm ratio and a characteristic appearance on light microscopy. They have basophilic cytoplasm and an eccentric nucleus with heterochromatin in a characteristic cartwheel or clock face arrangement. Numerous plasma cells were observed in the connective tissue stroma of the lesion. Immunohistochemistry greatly aided in making a confirmatory diagnosis, by positively

identifying the plasma cells and their origin. Further immunohistochemistry was also employed for establishing the likely etiopathology of the lesion, confirming it to be of a non-neoplastic, reactive/inflammatory origin. In this way we see that an appropriate identification of any lesion is important to avoid needless extensive and radical surgical procedures and immunohistochemistry plays a very useful, sometimes crucial role in making a difficult and challenging diagnosis and provides vital information regarding the origin, biological behavior and likely prognosis of any pathology, thus guiding the further treatment plan.

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