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AGGRESSIVE ORAL PYOGENIC GRANULOMAS MIMICKING MALIGNANT TUMOUR: REPORT OF TWO CASES AND A SYSTEMATIC REVIEW

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Abstract

Oral Pyogenic Granuloma (PG) is inflammatory hyperplasia, that mostly affects the gingiva. It usually affects young adults and is seldom seen in the elderly population. While in most cases, PG rarely attains a size larger than 3 cm, in certain cases rapidly growing extensive lesions may be confused with malignancy. In the present article, the authors report two cases of an unusually large oral pyogenic granuloma clinically mimicking oral carcinoma. A review of the literature was also performed to identify similar cases and also those in which a malignant lesion resembled PG. The present article emphasizes the importance of a timely biopsy of all the oral pathological lesions and a thorough histopathological study preceding and deciding the final treatment plan.

Keywords: pyogenic granuloma, focal fibrous hyperplasia, lobular capillary haemangioma, mimicking malignancy

Introduction:

Pyogenic granuloma (PG) is a frequently encountered reactive growth seen in the oral cavity. While PG is a clinical term, histopathologically a myriad of changes in the mucosa such as fibroepithelial hyperplasia, the proliferation of blood vessels, engorgement of blood vessels and the presence of inflammatory cell infiltrate of varying intensity in the connective tissue may be noted.[1] The lesion is, however, benign and rarely attains a size greater than two centimetres.[2]

On the other hand, various primary and secondary malignancies occurring in the oral cavity are known for their rapid proliferation that can quickly attain a size greater than 5 cm.[2] Though the aetiologies of PG and primary oral cavity malignancies may be quite similar, they rarely have similar clinical presentations.[3]

Even so, in some cases, the PG may become extensive within a short span of time such that it mimics a malignancy. Likewise, a malignant lesion may be slow-growing or limited in size and may resemble a PG. This leads to occasional misdiagnosis on the part of clinicians which is problematic because the treatments for both lesions differ drastically. PG is a reactive entity that requires only excision of the lesion whereas malignant tumours require surgical resection along with adjunctive chemotherapy or radiotherapy.[4] It is, therefore, important to identify the likelihood of either entity resembling the other and also to differentiate them from each other.

Herein, we report two cases of PG that mimicked malignancy followed by a review of the literature of similar cases and also those in which a malignant lesion resembled PG.

Case Report:

Case 1

A 60-year-old female complained of difficulty in eating due to a painless, rapidly enlarging intra-oral growth in the left maxillary posterior region that rapidly enlarged in size over the past three months. The growth bled occasionally while eating or due to trauma from the opposing teeth and the patient also experienced pain at times. Her medical history was unremarkable except a few days prior, the patient was treated with tranexamic acid and diluted epinephrine intralesional injections to control the haemorrhage that occurred during a sudden profuse bleeding from the lesion. Blood investigations revealed microcytic hypochromic anaemia (Hemoglobin: 9 gm/dl) and mild thrombocytopenia (140000 /mm^3).

The intraoral examination revealed a large, dumbbell-shaped, firm, non-tender, pedunculated pinkish-white growth in the edentulous left maxillary molar region (Figure 1A). The dimensions of the growth were roughly 4x2.5x2cm. The growth occupied the space of the missing second premolar and covered the occlusal surfaces of the first premolar and molar teeth, which exhibited severe mobility. The buccal surface of the lesion was pale red, while on the occlusal aspect, it exhibited a whitish-cream colour. The occlusal surface was ulcerated and covered with a white fibrinopurulent slough. Indentations resulting from chronic contact by the opposing teeth with areas of pinpoint bleeding were noted.

The patient's oral hygiene was poor with severe halitosis, moderately advanced generalized periodontitis, and several carious and missing teeth. The submandibular lymph nodes were palpable and tender on the ipsilateral side. Based on the patient's history, age, and clinical presentation, the lesion was suspected to be malignant. Orthopantomogram (OPG) revealed a well-defined radiolucent sot tissue shadow in the affected area with

severe bone loss up to the apical third of the first premolar and molar teeth lesion (Figure 1B). The contrast computed tomography scan showed an alarming picture of an extensive, well-defined soft tissue lesion (Figure 1C).

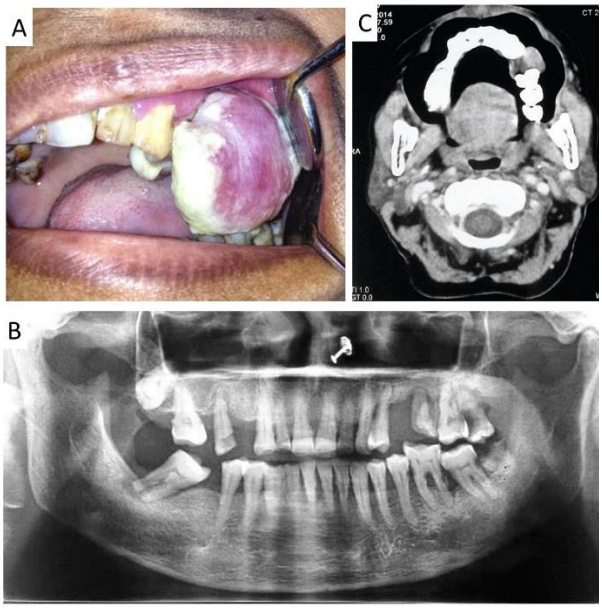

Figure 1: A) Growth in the left posterior maxillary region; **B)** Orthopantomogram showing a soft tissue shadow on the left maxillary posterior region with severe bone loss; **C)** Contrast computer tomography scan exhibiting the extensiveness of the lesion

Under local anaesthesia (2% lidocaine with 1:200000 adrenaline), the lesion was excised from its base in toto up to the periosteum of the bone with a surgical blade. Because of their severe mobility, the first premolar and molar were extracted. An initial profuse haemorrhage at the site was controlled with electrocautery, a hemostatic agent (feracrylum) and gauze pressure. A thorough curettage of the underlying bone and gingiva was performed to remove the remnants of granulation tissue. Haemostasis was achieved as soon as all the granulation tissue remnants were removed. Primary closure was achieved with 3-0 vicryl sutures.

Microscopic examination revealed the presence of hyperplastic parakeratinized stratified squamous epithelium. The underlying connective tissue stroma consisted of numerous small to large dilated blood vessels and thick-walled endothelial-lined capillaries arranged in a lobular pattern separated by fibrocellular septae. Mild chronic inflammatory cell infiltrate chiefly comprising lymphocytes and plasma cells was noted. The histopathological findings were suggestive of 'lobular capillary hemangioma'. The patient was followed up for 3 years and showed no evidence of disease.

Case 2:

A 64-year-old male complained of a rapidly enlarging growth in the right posterior mandibular region since two months. The growth caused discomfort during mastication due to its size but was not associated with pain or any functional impairment. He also experienced occasional bleeding from the growth with activities like brushing and chewing. The patient's medical history was unremarkable. A habit history of tobacco chewing three times a day since the past 15 years was elicited from the patient.

On extraoral examination, the submandibular and upper cervical lymph nodes were palpable, non-tender and mobile. Intraorally, the lesion presented as an exophytic pedunculated growth of size 4.5cms x 4cmx 3.5cm in the right posterior mandibular region engulfing the second premolar and second molar teeth. The right mandibular first molar was missing and the teeth adjacent to the lesion exhibited severe mobility. The growth was reddish pink and had a lobulated surface covered with greyish fibrinopurulent slough. The lesion was firm and non-tender on palpation and obliteration of the buccal vestibule was noted (Figure 2A). The oral hygiene of the patient was poor with significant halitosis and the periodontium was in a generalized compromised state.

OPG showed a well-defined, radiolytic punched-out lesion with smooth corticated border of 3 cm extending from distal surface of the second premolar to the mesial surface of the second molar (Figure 2B). There was an extensive mandibular bone destruction in the associated area extending close to the right inferior alveolar nerve.

The clinical and radiographic findings, although suggestive of a soft tissue malignancy, were difficult to correlate and hence an incisional biopsy was planned. Pre-operative blood investigations revealed a low Hb of 8g/dL. The patient was treated with a course of iron sucrose injection and preoperative blood transfusion to raise the Hb to 10g/dl. During the biopsy procedure, excessive bleeding was experienced which was controlled with cautery and gauze pressure pack.

The histopathology revealed an inflammatory lesion. The patient then underwent excision of the lesion under general anaesthesia. A local anaesthetic (2%lidocainewith 1:200000 adrenaline) was infiltrated pre-emptively to control hemorrhage. The lesion was excised in toto from the base along with the extraction of involved teeth. Excessive bleeding was encountered as anticipated. The brisk haemorrhage was controlled with gauze packs and adrenaline infiltration and the basal bone was curetted. Approximately 3 cm of bony cavity was observed below the lesion which was then curetted (Figure 7). The surgical site was closed with 3-0 vicryl.

Histopathological features of the excised tissue showed a hyperplastic parakeratinised stratified squamous surface epithelium covering a fibrocellular connective tissue. The epithelium was ulcerated in some areas wherein the connective tissue stroma was covered by a fibrinopurulent exudate. Underlying connective tissue consists of abundant small to large, engorged endothelium lined blood vessels filled with red blood cells many of which also exhibited extravasation of the blood elements. The connective tissue stroma was tissue was oedematous consisting of loose bundles of collagen fibers and had an acute inflammatory infiltrate chiefly comprising neutrophils. Deeper areas showed muscle tissue and adipocytes. The overall histopathological findings were suggestive of telangiectatic granuloma. Evidence of good bone formation was noted six months after the surgery and no evidence of disease was noted after a follow-up of one year (Figure 2C).

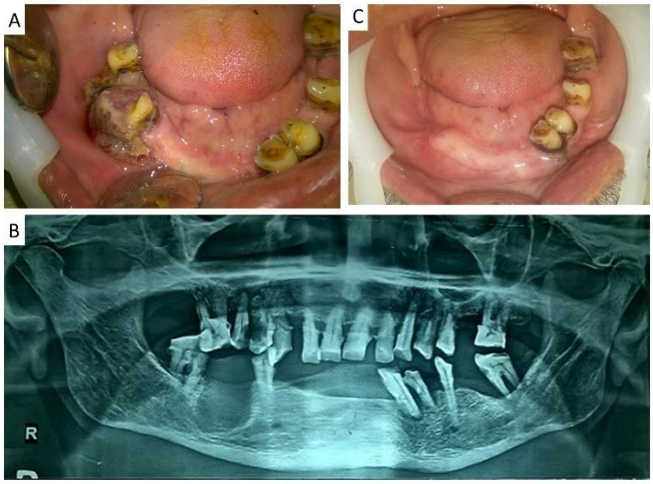

Figure 2: A) Growth in the right mandibular posterior region; **B)** Orthopantomogram showing a well-defined lytic lesion of about 3 cm with smooth corticated border; **C)** Post-operative follow-up after 6 months

Systematic Review of Literature:

The features of our cases as well as the above studies, piqued our interest to identify if there were more cases of pyogenic granuloma mimicking malignancies in the oral cavity, and if there were reports of incidental findings of malignancies in an unsuspected clinically diagnosed pyogenic granuloma in the oral cavity. The search was performed to identify similar case reports published in the English language from 01/01/1990 to 12/01/2022 with key terms: pyogenic granuloma[MeSH Terms] AND mimicking[All Fields], pyogenic granuloma[MeSH Terms] AND Oral AND

mimicking, pyogenic granuloma[MeSH Terms] AND Oral AND malignancy, pyogenic granuloma[MeSH Terms] AND tumor[MeSH Terms] AND masquerading, Lobular capillary hemangioma[MeSH Terms]AND Malignancy[MeSH Terms], Pregnancy Tumor[MeSH Terms] AND Malignancy[MeSH Terms]. A manual search was also performed to identify possible additional studies by reviewing the reference list of included articles to further identify similar cases. The selection process of the articles included in the present review is depicted in Figure 3.

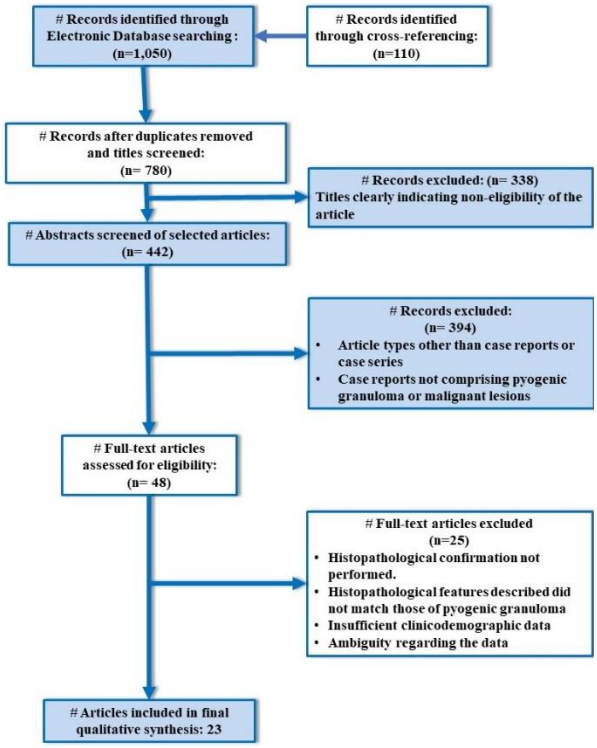

Figure 3: PRISMA flow diagram depicting the selection process of the articles in the review of literature.

A review of the existing literature identified 5 cases were identified similar to the present cases wherein an aggressive PG was provisionally suspected as a malignancy (Table 1).[5-9] The mean age of these cases was 37 + 17.88 years. With the exception of one case, all the other (n=7) patients were females. Clinically, three cases involved the posterior mandibular region, two occurred in the anterior mandible, and one case each in the posterior and anterior maxillary regions respectively

On the other hand, a total of 18 cases of malignant tumors diagnosed as PG were identified,[10-27] of which 12 were males and 6 were females (Table 2). The mean age of all the cases is 54.72 + 14.43 years. Clinically, 9 cases occurred in the mandible and 7 in the maxilla. The posterior region was involved in 11 cases, while 7 cases involved the anterior region.

Discussion:

Oral PG accounts for 3.81% to 7% of all biopsy findings from oral cavity and represents an exaggerated soft tissue and vascular response resulting from chronic low-grade irritation.[28] It is well known that PG exhibits a strong female predilection. This corroborates findings from our review which found a male-to-female ratio of 1:6.

While PG can occur at any age, it commonly presents in young adults and its incidence in the elderly is only 0.7%. The present review found that all the cases reported in the literature occurred in patients younger than 30 years of age. These statements, however, are in contrast with the present cases wherein both cases occurred in the elderly above 60 years of age. PGs in the elderly appear to be more collagenized and pink whereas in young patients they are highly vascular, composed of hyperplastic granulation tissue.[3,29]

Malignancies, on the other hand, occur more frequently in the elderly.[30] The findings from the present review corroborate this statement wherein the mean age of patients with malignancy diagnosed as PG was found to be about 55 years. Therefore, although a rapidly enlarging growth in the elderly may resemble PG and the clinician may also diagnose it so, a differential diagnosis of a malignant lesion cannot be overlooked.

Oral PG shows a predilection for the gingiva accounting for 75% of all cases followed by buccal mucosa, tongue and

lips.[6] In support of this statement, the present review found that with the exception of two cases occurring in the floor of mouth and hard palate respectively, all the other cases of PG occurred in the gingiva. There was a propensity for the lesions to occur in the posterior region of both the jaws (1.3 to 1.5 times). When concerned with the specific jaws, the mandible was more commonly involved and the propensity to occur in the mandible was more pronounced in cases of PG (2.5 times) as compared to the malignant lesions (1.29 times).

The pathogenesis of PG is not well understood. It is now largely agreed upon that pyogenic granuloma arises as a result of various stimuli such as trauma, low-grade chronic irritation, hormonal imbalances and drugs, resulting in an overzealous proliferation of vascular connective tissue.[31,32] Discussion pts It was obvious that both the patients in the present report neglected oral hygiene practices. The presence of extensive lesions further added hindrance to hygiene maintenance.

Many lesions resemble pyogenic granuloma clinically as well as radiographically. These include fibroma, peripheral ossifying fibroma, peripheral giant cell granuloma or squamous cell carcinoma which may involve the gingiva. However, other rare presentations mimicking pyogenic granuloma can be lymphangioma, hemangioma, Kaposi's sarcoma, angiosarcoma, and non-Hodgkin's lymphoma.[3,32,33]

Given the short history of the rapid growth, the lesions are generally considered as ‘aggressive’, as was also noted in the present cases. Although the radiographic images were helpful, the benign nature of both cases were still unconfirmed due to severe destructive bone loss or a cupping type of bone loss in the associated region. It is also to be highlighted that pyogenic granuloma is seldom seen in an aged population and rarely reaches a size over 2 centimetres, both of these findings were seen in our cases, confounding clinical judgement and warranting biopsy. Studies have found that localized gingival enlargements of sizes approaching 2 cm are more likely to be malignant.[34] The short clinical history, the age of presentation, and clinical findings of both the lesions, raised suspicion of a malignant lesion, however, the histopathology deemed it benign.

While the treatment of pyogenic granuloma is simple excision to the periosteum and curettage, and it has a low recurrence (3-16%), the treatment of malignancies can be very challenging with high incidence of recurrence and metastasis even after chemotherapy, radiotherapy, surgery, depending on the type and stage of cancer at the time of diagnosis. [1, 32-35] Hence, we reiterate the importance of timely biopsy of all benign and malignant looking lesions and a thorough histopathological study.

Most of the published literature mentions bleeding related to pyogenic granuloma. However, there were two articles in literature which have reported profuse bleeding from an oral pyogenic granuloma similar to the present cases.[36,37] Many articles in the medical literature report anaemia secondary to pyogenic granuloma, similar to our cases. However, most of these cases were in the lower gastrointestinal tract, making it difficult to diagnose and treat.[38-42]

The diagnosis of a growth in the oral cavity such as a pyogenic granuloma is relatively easier, given the visual proximity. However, it is believed that anaemia secondary to bleeding associated with oral pyogenic granuloma may be quite under reported. Contrary to many dental literature where pyogenic granuloma is considered an inflammatory hyperplastic tissue in origin, the medical fraternity considers it to be a of vascular origin due to its bleeding tendencies, and hence the term ‘lobular capillary haemangioma’ is commonly used.[38-42]

Conclusion:

The presence of a rapid onset, large-sized growth in an older patient in the oral cavity should raise the index of suspicion of a malignant lesion. A prompt and thorough radiological and histopathological investigation is pertinent to either catch or rule out malignancies, for better treatment outcomes. In doing so, the patient may benefit in more ways than one.

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Ethical approval: This article does not contain any experimental studies with human participants.

Informed Consent: Informed consent of publication of scientific content and photographs have been obtained.

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Tables:

Table 1: Lesions mimicking Malignancy but diagnosed histologically as oral pyogenic granuloma

Sr. No.	Author (Year)	Age of the patient	Sex	Arch	Region
1.	Thada, S.R. et al. [5]	Early 20s	F	Mandible	Posterior
2.	Ababneh, K. and T. Al-Khateeb[6]	28	F	Mandible	Posterior
3.	Ye, C., et al.[7]	24	F	Mandible	Anterior
4.	Chopra, D.K.et al. [8]	26	F	Mandible	Anterior
5	Paulo, R. S. et al.[9]	20	F	Maxilla	Anterior
6	Present Case 1	60	F	Maxilla	Posterior
7	Present Case 2	64	M	Mandible	Posterior

Table 2: Lesions clinically diagnosed as pyogenic granuloma and then histopathologically confirmed as malignanacy in the oral cavity

Sr No.	Author	Age (in years)	Sex	Region	Location	Histopathological Diagnosis
1.	Moshe, M., et al.[10]	58	F	Posterior	Mandible	Amelanotic Melanoma
2.	Soares, C.D., et al.[11]	43	M	Posterior	Mandible	Metastatic Gastric adenocarcinoma
3.	Lima, C.F., et al.[12]	45	M	Posterior	Hard palate	Adenosquamous carcinoma
4.	Gallo, C.B., et al.[13]	71	M	Anterior	Floor of Mouth	Carcinosarcoma
5.	Ramon Ramirez, J., et al.[14]	65	M	Posterior	Maxilla	Metastatic Hepatocellular Carcinoma

6.	Greenstein, A., et al.[15]	68	M	Anterior	Maxilla	Metastatic Hepatocellular Carcinoma
7.	da Silva, L.C., et al.[16]	21	F	Posterior	Mandible	Kaposi's Sarcoma
8.	Taicher, S., et al.[17]*	45	F	Anterior	Maxilla	Metastatic Chondrosarcoma
9.	Elkhoury, J., et al.[18]*	44	F	Posterior	Mandible	Metastatic tumor of unknown origin
10.	Lopez-Jornet, et al.[19]*	76	M	Posterior	Mandible	Undifferentiated small cell lung carcinoma
11.	Curien, R.et al. [20]*	64	M	Posterior	Maxilla	Metastatic Bronchogenic adenocarcinoma
12.	Jaguar, G.C., et al.[21]*	52	M	Anterior	Maxilla	Metastatic Lung Non-small cell carcinoma
13.	Rim, J.H., et al.[22]*	70	F	Anterior	Mandible	Metastatic Hepatocellular Carcinoma
14.	Medina, B.R., et al.[23]	67	F	Anterior	Mandible	Metastatic Uterine Angiosarcoma
15.	Munoz, M., et al.[24]	68	M	Posterior	Mandible	Oral Angiosarcoma
16.	Dhawad MS, et al.[25]	46	M	Posterior	Mandible	Metastatic Lung carcinoma
17.	Scolozzi P, et al.[26]	36	M	Posterior	Maxilla	Testicular choriocarcinoma
18.	Buchner A, et al.[27]	46	M	Anterior	Maxilla	Renal cell carcinoma