

## Recurrent Oral Pyogenic Granuloma in Port-Wine Stain

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**Abstract:** Pyogenic granuloma (PG) is a benign inflammatory lesion, nonneoplastic in nature, which occurs in the oral cavity and skin. This lesion arises in response to various stimuli such as low-grade local irritations, traumatic injury, or hormonal factors. Recently, in some cases, the occurrence of recurrent PGs in skin associated with vascular lesions, such as port-wine stains, has been described. It has been postulated that this association is promoted by arteriovenous anastomoses in the vascular lesions, leading to the development of PG. The authors discuss 2 cases of recurrent PG in patients with a port-wine stain, and the treatment options adopted.

**Key Words:** Port-wine stain, pyogenic granuloma, recurrent, treatment

Pyogenic granuloma (PG) is a benign inflammatory lesion that occurs in the oral cavity or skin and is considered to be of a nonneoplastic nature. This term *pyogenic granuloma* is a misnomer, because the lesions consist of neither granulomatous inflammation nor pyogenic infection, unless they become ulcerated and secondarily infected.<sup>1,2</sup>

The clinical presentation is generally of a red, sessile, or pedunculated, smooth-surfaced nodule that may easily bleed. The surface is characteristically ulcerated and friable, depending on the lesion age. The mucosal lesions are up to twice as common in women than in men, and they appear in young adults and children and usually grow rapidly. Mucosal lesions are especially common in pregnancy, possibly due to hormonal factors.<sup>3,4</sup>

The common intraoral site is the gingiva, but lesions have been described on the lips, tongue, buccal mucosa, and palate. Extraoral sites involve the skin of the face, neck, or upper and lower extremities and the mucous membrane of the nose and eyelids.<sup>2,3</sup>

Although some authors have postulated that infection may participate in recurrent PG as a promoting factor, it is usually considered to be a reactive tumor-like lesion in response to various stimuli such as low-grade local irritation, traumatic injury, or hormonal factors, and it is now believed to be unrelated to infection.<sup>4,5</sup>

The development of multiple recurrent PGs may occur as a complication of tumor removal. The authors have reported that these

lesions can develop around the site of a recently treated PG within weeks or months. The lesions tend to be asymptomatic and are characterized as being similar to the original ones. The pathogenesis of this phenomenon is unclear, and exogenous factors such as trauma and endogenous factors, such as angiogenesis enhancers (vascular endothelial growth factor, basic fibroblast growth factor, angiopoietin 1, angiopoietin 2, and Tie-2), can be associated as promoters of PG development.<sup>6-8</sup>

Sturge-Weber is a sporadic neurocutaneous disorder characterized by a facial capillary malformation, ipsilateral leptomeningeal angioma, and vascular eye abnormalities. However, many incomplete forms, lacking 1 feature of this triad, exist. The facial capillary malformation in Sturge-Weber has often been referred to as facial port-wine stain (PWS), due to the characteristic dark red color similar to the Portuguese liquor.<sup>9-11</sup>

Recent reports have demonstrated the rare association between skin PG and PWS, which are either de novo or following trauma, such as laser therapy and cryotherapy. It is not certain whether PG pathogenesis is associated with PWS.<sup>12</sup>

The PWS is a congenital facial capillary malformation that occurs in 3 per 1000 live births. The facial port-wine typically involves the forehead and upper eyelid, in a distribution that resembles the area innervated by the first branch (ophthalmic branch) of the trigeminal nerve (V1). The pathogenesis of PWS remains controversial.<sup>12,13</sup>

The PG has been reported to be associated with PWS particularly in association with pregnancy, trauma, or laser treatment. The pathogenesis of these PGs is unclear.<sup>14,15</sup>

Histopathologic findings of the recurrent PG are similar to that of PG, showing a highly vascular proliferation that resembles granulation tissue. Numerous small and large channels are formed, which are engorged with blood cells and lined by flat or plump endothelial cells. The blood vessels often show a clustered or medullary pattern separated by less vascular fibrotic septa.<sup>2,3</sup>

Histological examination of PG readily distinguishes it from nonvascular lesions, such as squamous cell carcinoma, basal cell carcinoma, and melanotic melanoma, but does not distinguish PG from other vascular lesions, such as Kaposi sarcoma, hemangioma, hemangioendothelioma, and angiosarcoma; therefore, the morphologic aspect may help with the differential diagnoses between PG and other vascular lesions.<sup>1,2</sup>

Immunohistochemical markers, such as CD31 or factor VIII, may be useful to confirm that the lesion is vascular in nature. Smooth muscle actin and type IV collagen may also be useful in this regard. Moreover, angiogenic factors, including vascular endothelial growth factor, basic fibroblast growth factor, angiopoietin 1, angiopoietin 2, and Tie-2, are detected in significantly greater amounts in PG.<sup>1,7,8</sup>

Pyogenic granulomas in patients with PWS are treated by various methods, most commonly by complete excision. Other possible treatment options include curettage, cryotherapy, chemical and electric cauterization, and the use of lasers.<sup>16</sup> However, some cases of recurrent PG treated successfully with intralesion corticosteroids have been reported.

The following are 2 clinical reports of recurrent intraoral PG in patients with PWS.

### Patient 1

A 57-year-old woman presented to the Oral Diseases Treatment Center of the São Leopoldo Mandic Institute and Research Center, in Campinas, Brazil, with recurrent lesion localized gingival between lower right second premolar and lower right second molar of 3-month duration. This lesion was recurrent more than 7 times over the previous 3 years, and the lesions previously were all signed out as PG.

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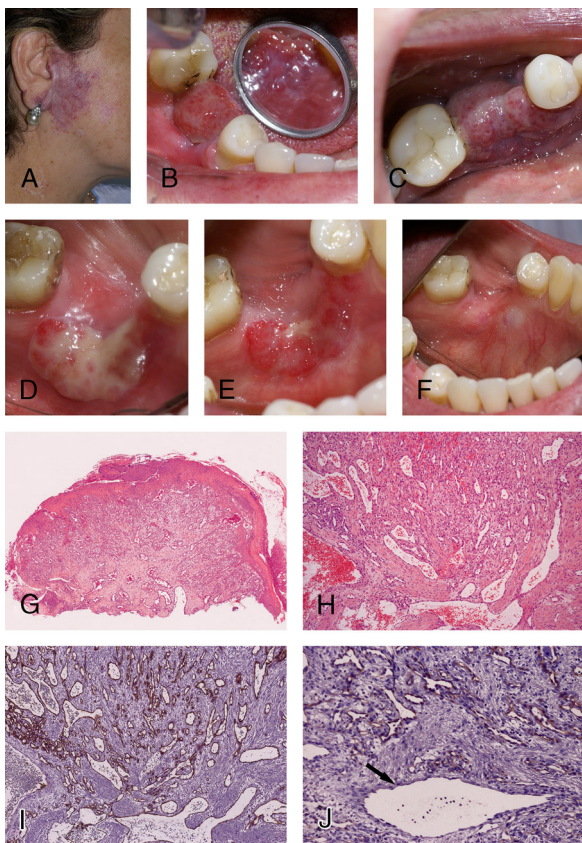
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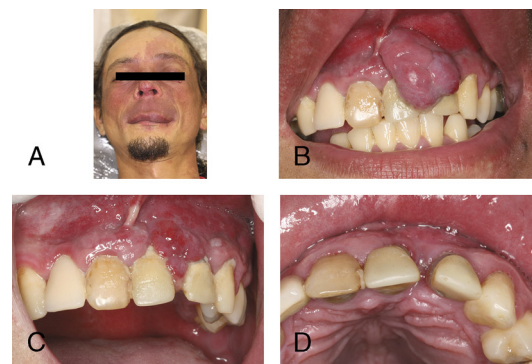
There was prior trauma history due to deep-scaling procedures in the gingiva of the mandibular right quadrant after exodontias in this site. The lesion was asymptomatic and has rapidly been increasing in size since it was first noticed.

Extraoral examination of the skin showed a well-circumscribed, red to purple plaque over the right side of the face involving the ear (the nevus flammeus or PWS) presented at birth. There was no family history of similar lesions. She also reported having undergone surgery and laser therapy for the PWS and presented 2 scars on the ear and neck (Fig. 1A).

Intraoral examination revealed a firm, mobile, red to purple nodule with a pedunculated base, measuring approximately 3 cm in diameter, with an ulcerated surface covered by a yellow fibri-



**FIGURE 1.** A, Extraoral view presenting PWS and scars on the neck and ear. B and C, Intraoral characteristics of the lesion as a red to purple nodule extending from vestibular to lingual alveolar mucosa in the mandibular right first molar region. D, Recurrent lesion in lingual alveolar mucosa with similar aspects to that in the first one, which appeared after complete excision and cryotherapy. E, Decrease of the lesion after intralesional corticosteroid injection. F, Total resolution of the lesion after sclerotherapy. G and H, Microscopic aspects of the lesion consistent with PG. Note numerous, newly formed blood vessels in the superficial lamina propria and larger-caliber blood vessel in the deeper connective tissue (hematoxylin-eosin stain, original magnifications  $\times 40$  and  $\times 100$ , respectively). I and J, Immunohistochemical staining. I, CD34 showing positivity in the endothelial cell of all vessels (original magnification  $\times 100$ ). J, CD105 present only in the newly formed blood vessels in the superficial area of the lamina propria (original magnification  $\times 100$ ).



**FIGURE 2.** A and B, Clinical aspects. A, Diffuse PWS on the face and a swelling on the right side of the upper lip in the extraoral examination. B, Intraoral characteristics of the lesion showing an erythematous nodule, located on the vestibular gingival between the maxillary left central and lateral incisors. C, Recurrent lesion in the same site. D, Total remission of the lesion, after intralesional ethanoline.

nous membrane on the vestibular alveolar mucosa in the mandibular right first molar region. The lesion extended to the lingual alveolar mucosa presenting as a purple nodule with irregular shape and bleeding easily on manipulation, but was not painful (Fig. 1B, C).

An excisional biopsy was performed and revealed a fragment of mucosa exhibiting an extensive ulcer covered with purulent fibrin exudate; connective tissue consisting of cell-rich fibrous tissue with numerous, newly formed vessel blood of various sizes and shapes; and intense chronic inflammatory infiltrate under the ulcer and inside the lesion (Fig. 1G, H). In addition, immunohistochemical staining for CD105 was positive in the walls of the blood vessels located at the surface of the connective tissue and negative in the deeper region of the connective tissue (Fig. 1I, J). CD34 was positive both on the walls of the newly formed blood vessels at the surface and in the larger-caliber blood vessel in the deeper connective tissue.

Based on the clinical history and histologic features of the lesion, a diagnosis of recurrent PG associated with PWS was established. Sturge-Weber syndrome was ruled out, because the patient did not present other characteristics for the diagnosis of this syndrome.

The lesion was completely excised 3 times; nevertheless, recurrences of it were observed in the same anatomic site. After this, cryotherapy was performed, but the treatment was not successful (Fig. 1D).

Therefore, as an alternative to another surgical procedure, the lesion was injected with intralesional corticosteroids. A solution was prepared by diluting 0.1 mL of triamcinolone 40 mg/mL with 0.5 mL of 0.5 % bupivacaine. A total of 0.1 mL of the mixture was injected into the lesion. The applications were performed weekly in 4 sessions. At each visit, there was significant improvement of the lesion, but there was no complete resolution (Fig. 1E).

Thus, sclerotherapy with intralesional ethanoline was performed by injecting 0.05 mL of the solution into the lesion in 3 sessions. This treatment was successful with disappearance of the lesion (Fig. 1F). The patient continues to be clinically followed up.

## Patient 2

A 32-year-old man presented to the Clinic for Treatment of Oral Diseases at São Leopoldo Mandic Institute and Research Center, for evaluation of localized gingival enlargement between the maxillary left central and lateral incisors. The patient had been aware of the enlargement for nearly 4 months. Patient's medical history revealed

Sturge-Weber syndrome since birth, and there was nothing else noteworthy in his medical history.

Extraoral examination showed diffuse PWS on of his face and a swelling on the right side of the upper lip (Fig. 2A). Intraorally, an asymptomatic firm erythematous nodule was observed, located on the vestibular gingiva of the maxillary left incisor area. The lesion had a lobulated surface and was measured 3 cm in diameter. The patient was not able to establish good oral hygiene, with dental plaque accumulation at the lesion site (Fig. 2B).

No radiographic changes were evident. Under local anesthesia, the lesion was completely excised. All soft tissue at this site, including the periosteum, was removed from the bone. Histological examination yielded findings similar to the first case, being the lesion diagnosed as a PG (Figs. 2C, D).

The lesion reportedly reappeared within 1 month (Fig. 2E), and sclerotherapy with intralesional ethanolamine was performed by injecting 0.02 mL of the solution into the lesion in 1 session. This treatment was successful with disappearance of the lesion. At 4 months of follow-up, no recurrence has been observed so far (Fig. 2F).

## DISCUSSION

The recurrent PG is a rare phenomenon that has been reported in the literature, and some documented cases describe its occurrence on the skin; however, in the oral mucosa, it has not been related. This recurrent lesion has similar aspects to the original one. Some of them showed multiple recurrences in distant areas from the original sites.<sup>6</sup>

The recurrent nature of these lesions could be related to their histologic appearance, because all lesions share similar features of lobules of capillaries. The differences are in the location of the vascular structures: dermal, subcutaneous, or intravenous. In the present case, the histopathologic features are similar to those mentioned in the literature.<sup>17</sup>

Recurrent PGs are characterized as a smooth or lobulated exophytic lesion manifesting as erythematous nodules or papules with pedunculated or sessile bases, variable diameter, asymptomatic, and usually hemorrhagic. They may grow rapidly, and their colors range from pink to red or purple, depending on the age of the lesion. There is predilection for the gingiva, accounting for 75% of the cases.<sup>6,17</sup> The same characteristics are seen in the present case, in which PG recurred 6 times. Moreover, it may occur at all ages, but is predominant in the second decade of life in young adult women.<sup>2,3</sup> Although the patient in this case was a 57-year-old woman, this is in agreement with other reports.

The PG has been reported in vascular lesions, but there are few reports about the association of recurrent PG and PWS. This association could be explained by PG, which is considered a lesion that tends to develop in highly vascularized areas such as hands, face, tongue, and PWS. These sites are associated with microscopic arteriovenous anastomoses, leading to the development of PG.<sup>12,13</sup>

In the present cases, the histopathology revealed numerous, newly formed (positive for CD105), proliferating blood vessels in the surface connective tissue, consistent with PG diagnosis. In the deeper tissue, some thick- and thin-walled vessels were anastomosed in accordance with literature on the histologic description of PWS, which could suggest the association of PG and PWS.

Based on the histologic features, except for the depth of the tumor, it is not possible to distinguish PG from the other vascular lesions such as Kaposi sarcoma, hemangioma, hemangioendothelioma, angiosarcoma, and spindle cell tumor.<sup>2,3</sup>

The treatment of recurrent PG associated with a PWS can most commonly be performed by complete excision of the lesion. Furthermore, methods such as curettage, cryotherapy, sclerotherapy, and

laser therapy can be used.<sup>16</sup> A recent clinical report presented the treatment of recurrent PG with intralesional corticosteroids. The authors believe the lesions respond to the anti-inflammatory and vasoconstrictive actions of the corticosteroids, which may prevent or suppress the release of angiogenic factors.<sup>6,16</sup>

Based on the literature, all treatment options for PG were performed, including excisional surgery with the removal of causative irritants, cryosurgery, intralesional corticosteroids, and sclerotherapy using ethanolamine oleate. In the present case, only after intralesional steroid injections and sclerotherapy was there significant improvement of the lesion until its total resolution. More cases are necessary to establish a treatment protocol for this association.

In conclusion, clinicians and dentists should be aware of this possible association (recurrent PG and PWS) to plan the patient's treatment.

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