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Pyogenic Granuloma – A Common Benign Vascular Tumor with Variable Clinical Presentation: New Findings and Treatment Options

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Abstract

Pyogenic granuloma is a common benign vascular tumour occurring in all ages. Both skin and mucous membranes can be affected. Of pathogenetic importance are trauma, BRAF mutations and probably herpes virus type 1, Orf virus and/or human papilloma virus type 2. The tumour consists of capillary proliferations, venules and fibromyxoid stroma. The development of a lesion occurs in three stages and bleeding is a common symptom. The tumour can mimic various other vascular lesions, solid tumours, and soft tissue infections. In recent years, targeted tumour therapies have become the most common cause of drug-induced pyogenic granulomas. The backbone of treatment is surgical procedures including laser therapy. New developments in medical drug therapy include topical and systemic beta-adrenergic receptor antagonists timolol and propranolol. Drug therapy is an alternative for young children, ocular and periungual pyogenic granuloma.

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Introduction

Pyogenic granuloma (PG) – also known as lobular capillary hemangioma - is a benign vascular tumour that occurs on the skin and mucous membranes, occasional it can be found subcutaneously or intravascularly. PG can arise spontaneously, in sites of injury, or within capillary malformations [1].

PG has been associated with certain medications such as oral contraceptives, retinoids, gefitinib, cabecitabine, and afatinib [2-5]. Most tumours occur as solitary lesions, but multiple grouped or disseminated tumours have been

described. Multiple disseminated tumours are an adverse cutaneous effect of melanoma treatment with selective BRAF inhibitors like vemurafenib or encorafenib [6]. Multiple periungual PGs occur with targeted oncological therapies using epidermal growth-factor receptor inhibitors or mitogen-activated protein kinase (MEK) inhibitors [7], and rituximab [8].

Histology and Pathogenesis

Histologically, PG is composed of capillaries and venules with plump endothelial cells separated

into lobules by fibromyxoid stroma. The development can be classified into (i) cellular phase, (ii) capillary phase or vascular phase, and (iii) involutionary phase. Slow fibromatous regression is seen in untreated lesions after longer time [9]. The endothelial cells in PG express CD34, ICAM-1, VCAM-1 associated with an increased microvascular density [10].

Recently, BRAF c.1799T>A mutation had been identified in endothelial cells as a major driver mutation in the pathogenesis of PG [11]. This explains the occurrence of multiple PGs in patients treated with BRAF inhibitors.

The participation of viral particles in PG pathogenesis has been discussed. Alpha-herpes viridiae type 1 is considered as a possible indirect factor stimulating angiogenesis in PG. In some patients, dermatotropic parapoxvirus (Orf) could be identified by polymerase-chain reaction (PCR). Human papilloma virus DNA could be identified in 44% of these lesions with HPV type 2 as the most common [12-15].

Clinical Presentation

PG occurs in all age groups. There is no clear predominance of a gender. PG appear as small or large, smooth or lobulated, reddish exophytic vascular nodules that can grow rapidly (Fig. 1). Larger lesions become lobulated and sometimes develop into mushroom-like, pediculated tumours (Fig. 2). PGs have a tendency to bleed profusely. Bleeding is the leading symptom for a visit to the doctor's office.

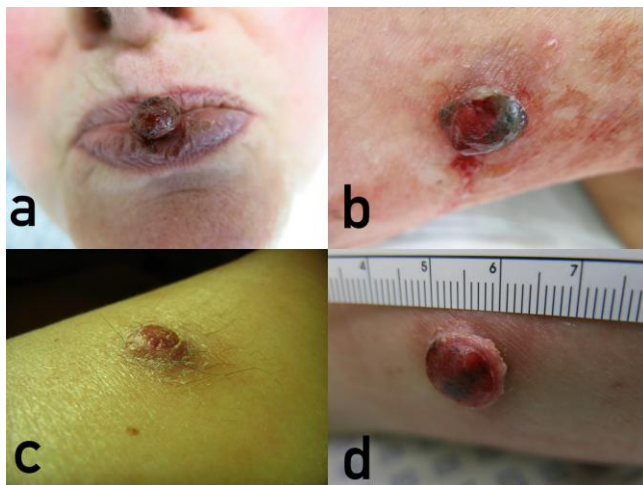


Figure 1: Pyogenic granuloma (PG) – common clinical presentations. (a) Nodular PG of the lower lip; (b) Collerette-like demarcation of a PG on the knee; (c) Flat, keratotic PG on the lower leg. (d) Marked collerette with a flat nodule on the lower arm

Hands, lower lips and gingiva are most frequently affected [1]. In one study, PG was the most

common benign lesion of the lips responsible for 48% of all cases [16]. Another study from Brazil investigated gingival lesions in children and adolescents. PGs accounted for 42% of all gingival lesions [17]. Considering the nail organ, most lesions occur on the nail folds, but subungual tumours have also been observed [18].

During pregnancy, large intraoral PGs may develop [19]. Uncommon sites are vulva and penis, oesophagus, gut, and tracheobronchial tree [20-24]. Gastrointestinal PG can cause severe anaemia [25]. Extremely rare are intravascular tumours which bear the risk of thrombosis [26].

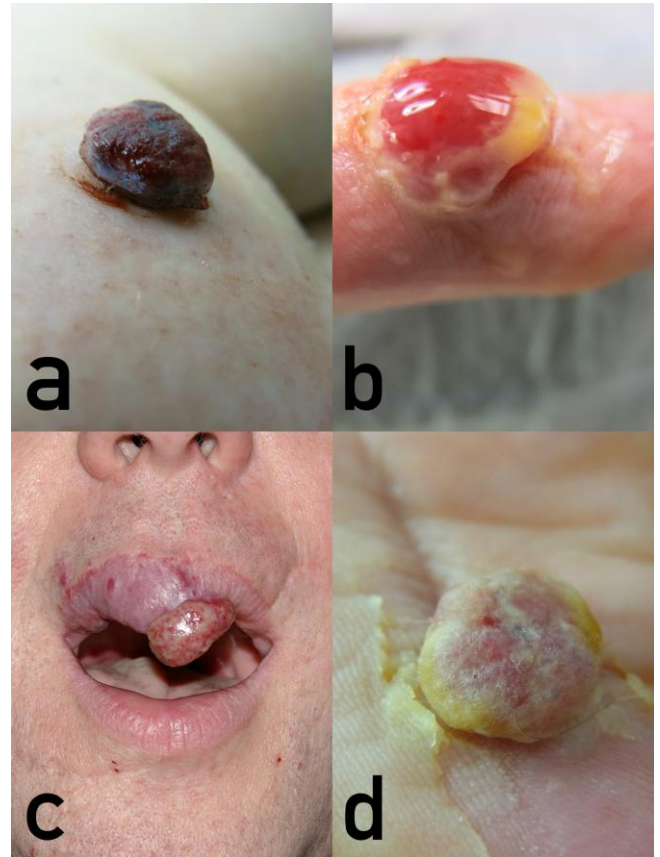


Figure 2: Pyogenic granuloma (PG) – less common clinical findings. (a) Larger mushroom-like, thrombosed PG – melanoma-like; (b) Mushroom-like PG on the finger bow with a wet surface and maceration of the surrounding skin – pyoderma-like; (c) Large pedunculated PG of the upper lip – hemangioma like; (d) Large, firm nodular PG of the palm – non-melanoma skin cancer-like

Portwine stains are at risk for secondary PG [27]. Their treatment with vascular lasers may induce PG as well [28].

Satellitosis is a very uncommon phenomenon in benign tumours. Nevertheless, satellitosis has been observed in paediatric PG [29, 30]. Deep-seated PG is a rare entity with 3.8% of all PGs diagnosed in childhood [31].

Differential diagnoses

PG can mimic other vascular tumours, including Kaposi form hemangioendothelioma, infantile hemangiomas, vascular malformations, and Kaposi sarcoma. In so-called “Kaposi-like PG” human herpes virus type 8 could be identified. These lesions are true Kaposi sarcomas, not PG [32]. Other malignancies that can mimic PC are malignant lymphomas, basal cell carcinoma, or malignant melanoma [33-35]. In immunocompromised patients, deep soft tissue infections like phaeohyphomycosis or bartonellosis should be considered [36, 37].

Treatment

The usual treatment for PG consists of excision, the treatment with the lowest rate of recurrence [1]. Depending on the area, size and patient wishes, curettage, electrocautery, radiosurgery, cryosurgery, sclerotherapy, or laser treatment are alternative options. Among lasers, diode lasers of wave-length between 808 to 980 nm [38-40] or solid-state neodymium - yttrium aluminium garnet (Nd:YAG) lasers [41, 42], erbium-YAG and CO₂ lasers [43, 44] have all been used successfully. Erbium-YAG laser lacks coagulation, what may become a disadvantage in larger lesions. Successful photodynamic therapy (PDT) with 5-aminolevulinic acid has been reported for a single PG on a finger [45]. A possible advantage of PDT compared to laser removal has yet not proved.

In small children, topical or oral medical therapy with beta-adrenergic receptor antagonists timolol or propranolol seems to be effective [46]. Periungual PGs have been treated off-label with topical 1% propranolol cream [47]. For PG on ocular surfaces medical treatment with topical 0.5 % timolol eye drops twice daily for a minimum of 21 days, is an option [48]. The treatment, either oral or topical, warrants monitoring. Since systemic absorption can occur even after timolol eye drops, patients should be monitored for bradycardia, hypotension, hypoglycemia, and bronchoconstriction. In elderly patients, syncope and falls have been observed [49, 50].

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