



Research Article



Study the Correlation Between Pyogenic Granuloma and the Expression of FOXP1 Marker

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Abstract:

A typical inflammatory proliferation of the skin and oral mucosa is called a pyrogenic granuloma. Contrary to what its name would imply, in terms of histology, it is more similar to angiomatous lesions than granulomatous ones since it lacks pus. Granuloma pyogenicum, granuloma pediculatum benignum, Crocker and Hartzell's illness and when it appears during pregnancy, granuloma gravidarum are further names for the condition. This development, which resembles a tumor and can manifest in the oral cavity in a variety of clinical and histological ways, is thought to have a non-neoplastic origin. The study is discussed in this article and it is said that the term pyogenic granuloma is incorrect and provides a case report of a large pyogenic gingival granuloma and its treatment due to its frequent occurrence in the oral cavity, specifically the gingiva. The pyrogenic granuloma is a common benign vascular tumor that can affect anyone. Skin as well as mucous membranes might be affected. Trauma, BRAF mutations and maybe herpes virus type 1, orf virus, or human papilloma virus type 2 are all important pathogenetic factors. Venules, fibromyxoid stroma and capillary proliferations make up the tumor. A lesion develops in three phases and bleeding is a typical sign. The tumor might resemble a number of different vascular abnormalities, solid tumors and infections of the soft tissues. Targeted tumor therapy have emerged as the leading contributor to drug-induced pyogenic granulomas in recent years. Surgery, including laser therapy, is the mainstay of treatment. The topical and systemic beta-adrenergic receptor antagonists timolol and propranolol are recent advancements in medical medication treatment. For young children, ocular pyogenic granuloma and periungual pyogenic granuloma, drug treatment is an alternative.

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INTRODUCTION

Granuloma pyogenicum, sometimes referred to as a pyogenic granuloma, is a typical benign vascular tumor that can develop in tissues including the skin and mucous membranes. The lobular capillary hemangioma is the correct scientific name for this condition. The words pyogenic granuloma and granuloma pyogenicum were sometimes used to describe pyogenic granulomas, which were assumed to represent an excessive granulomatous reaction to an infectious or pyogenic stimulus. However, the misnomer pyogenic granuloma may initially lead to misunderstanding. Grossly, the lesion looks like a single, very friable, red, pedunculated papule. A sessile plaque may occasionally be the only symptom. It rapidly takes on an exophytic appearance and frequently ulcerates its surface^[1-3]. It generally shows up on mucosal or cutaneous surfaces. The oral cavity of the latter group is where it is typically observed. Rarely, it may occur at various locations all along the digestive tract. Granuloma gravidarum, granuloma of pregnancy, or epulis gravidarum are all terms used to describe a condition that affects the intraoral mucosa during pregnancy, notably on the gingiva, typically in the second or third trimester. Two cases have been described in the literature: one is a patient who used an oral contraceptive pill and suffered a significant number of disseminated lesions and the other involves a patient who developed lesions following a kidney transplant. Any patient can develop a pyrogenic granuloma. On the epidemiologic pattern of disease, there are conflicting reports^[4-6]. The lesion exhibited a modest majority in certain studies and one analysis found that the incidence peaked in the second decade of life. In this review, mucosal lesions were more frequent in women than in men, and they mostly affected this cohort's fourth decade of life. Another assessment found a male to female ratio of 1-1.2. Male patients in this review tend to present earlier than female patients, who typically present later in life, between the ages of thirty and forty, when taking into account both cutaneous and mucosal forms, typically from childhood to the late twenties. When taken on its own, mucosal pyogenic granuloma seems to happen to males at any time. Contrarily, the majority of instances in women happen before the age of 40.

A pyogenic granuloma was first described in English literature by Hüllihen in 1844. Botryomycosis hominis was the name given to pyrogenic granulomas in humans for the first time in 1897. In 1904, Hartzellin coined the terms pyogenic granuloma and granuloma pyogenicum for the first time. Crocker and Hartzell's illness was another name for it. Because the lesion has many blood

vessels and is inflamed, Angelopouloshistologically referred to it as a hemangiomatic granuloma. Due to the many blood vessels that may be observed in histological sections, it has been referred to as granuloma telangiectacticum in dermatological literature. They spoke about two varieties of pyogenic granulomas: lobular capillary hemangioma (LCH) and non-lobular capillary hemangioma (non-LCH). Pyogenic granulomas seldom develop in the gastrointestinal system but frequently appear on the skin or in the mouth^[7,8].

Different researchers have put forth different etiologic explanations for the development of pyogenic granulomas of the skin and oral cavity. Pyogenic granulomas have been associated with a number of events, including physical trauma, hormonal factors, bacteria, viruses and certain drugs. The gingiva is involved in 75% of cases with oral pyogenic granulomas, indicating this is their preferred location. The triggering variables are local irritants such as calculus, foreign objects in the gingiva and poor dental hygiene.

The term pyogenic granuloma is a misnomer, as we have underlined after reviewing the literature and discussing the current case in light of it. The benign vascular tumor known as a pyrogenic granuloma (PG), also known as a lobular capillary hemangioma, most commonly affects the skin and mucous membranes but can also occasionally be discovered subcutaneously or intra vascularly. PG can develop on its own, at injury sites, or inside of capillary abnormalities.

PG has been linked to a number of drugs, including afatinib, cabecitabine, gefitinib, retinoids and oral contraceptives. The majority of tumors are solitary lesions, although there have also been reports of several clustered or disseminated tumors. Multiple disseminated tumors are a cutaneous side effect of selective BRAF inhibitor therapy for melanoma, such as vemurafenib or encorafenib. With targeted oncological therapy using rituximab, mitogen-activated protein kinase (MEK) inhibitors, or epidermal growth factor receptor inhibitors, multiple periungual PGs can develop.

A wide family of transcription factors, FOX proteins perform a key function both during ontogenesis and in adulthood. The forkhead domain (FHD), often referred to as the winged helix domain, allows FOX proteins to connect to DNA. Three N-terminal-helix sections, three-strands and two loops (referred to as wings or wing domains) toward its C-terminal area make up the structure of FHD. A single nomenclature was created in 2000 with the goal of streamlining the nomenclature, categorization and identification of the FOX proteins. FOX transcription factors were separated into

letter-designated subfamilies. Each member of a subfamily received a unique Arabic number. 19 FOX subfamilies (A-S) have been discovered by studies to yet. In contrast to other FOX subfamilies, the FOXP group (one of the subfamilies) varies structurally and exhibits a wider range of activities. The deletions in the wing regions of the FHD are found near the C-terminus. In addition, FOXP transcription factors have a zinc finger and leucine zipper motif in common, which allows them to assemble into heterodimers. FOXP proteins primarily function as transcriptional repressors at the molecular level. The FOX protein P1 (FOXP1) plays a significant role in the growth of neurons. Its gene, FOXP1, which is found on chromosome 3p14.1, can cause mutations that cause intellectual disability, speech and language impairment, motor development delay and autism spectrum disorder. Along with B-cell development, FOXP1 is involved in the morphogenesis of the lung and esophagus. Despite some lingering questions, the widely studied role of FOXP1 in carcinogenesis is of paramount importance^[9,10].

The purpose of this study is to determine if the expression of the FOXP1 marker correlates with pyogenic granuloma.

MATERIALS AND METHODS

The Oral and Maxillofacial Pathology Department's files contained information on each of the cases. All biopsies were processed into tissue blocks using paraffin and fixed in 10% formalin. We looked at representative Hematoxylin and Eosin sections to confirm the diagnosis.

Immunohistochemistry: Streptavidin-biotin-peroxidase Using immunohistochemical staining, the expression of FOXP1 was evaluated. Tissue samples were preserved in formalin and immersed in paraffin before being sliced into 4 mm thick slices. Prior to being rinsed in distilled water, Microwave slides were subjected to a 15-minute treatment with 0.01 mol/L citrate buffer (PH=6.2) at 95 oC. Colorectal cancer samples used as positive controls (based on the linked data sheet) to compare antibody expression. The slides were exposed to the main antibody for 60 minutes whereas no primary antibody was utilized for the negative control.

Evaluation of Immunohistochemical Staining: Light microscopy was used to measure the FOXP1 cytoplasmic and/or nuclear immuno-histochemical expression, according to Danielss on^[11]. The percentage calculated in OLP-affected and surrounding normal tissue and the tissues were divided into four groups based on the number of stained epithelial cells in each categories based on the staining intensity (weak to severe): 0%, 1%,

2%, 26-50%, 3%, 5% and >75% are all shown with a magnification of 100.

Statistical Analyses: The Wilcoxon test and paired T-test were used to determine the statistical significance of the associations between pyogenic granuloma and the expression of FOXP1 marker was assessed, with a significance threshold of P0.05.

RESULTS AND DISCUSSIONS

A pleiotropic protein called FOXP1 is involved in the development of several organs, including the heart, lungs, and esophagus, as well as brain development and immunological responses (B-cell formation, regulation, and differentiation). FOXP1 not only controls most of normal human tissue development, but also promotes cancer growth. The relationship between FOXP1 expression and tumor prognosis is still unclear, though. To examine the connections between clinicopathological characteristics and FOXP1 expression, FOXP1 expression was assessed in the stromal cells (SCs) and tumor cells (TCs) of cutaneous melanomas. This study, in our perspective, is the first to examine the connections between the expression of FOXP1 and clinicopathological and histological features of melanoma.

sections, immunohistochemical staining was performed. peroxidase/DAB (brown) immunostaining, counterstained with hematoxyline (blue)

In table 2, the staging procedure comprises determining the extent of the cancer's presence and its location throughout the body. In our investigation, there

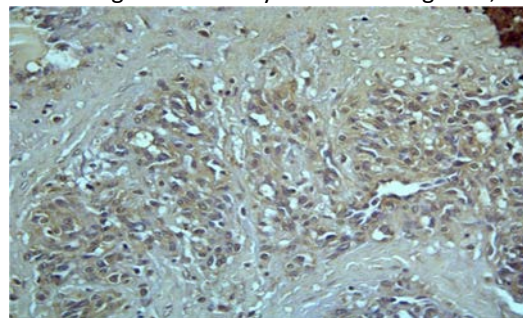


Fig. 1: In Pyogenic Granuloma

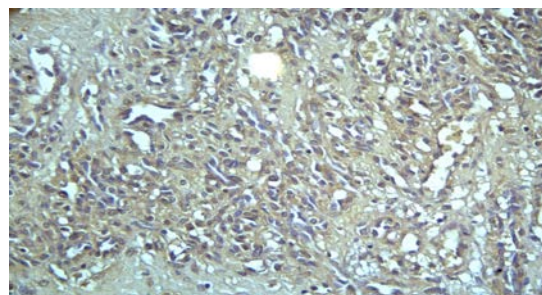


Fig. 2: (IHC) FOXP1 expression in pyogenic granuloma (40X)

Table 1: Immunohistochemical, FOXP1 b Expression in tissues

	Negative	Minimal	Moderate	Strong
Scoring Marker				
FOXP1	10(32.25%)A	5(16.12%)D	5(16.12%)D	5(16.12%)D
Control	Not expressed(0).			

**P <0.05

Table 2: the correlations between the expression of FOXP1 marker and stage of pyogenic granuloma

		I and	III	IV
Stage marker				
FOXP1	Pearson Correlation	0.413	0.079	0.113
	Sig. (2-tailed)	0.005	0.005	0.083
	No.	12	13	3

was a significant correlation between the three markers and the case's stage (P0.05). Most importantly, show in Vázquez-Martínez *et al.*, (2015) it was shown in this study that the lowest survival times occurred in cases with high FOXP1 expression and the difference was rather pronounced^[11-13].

VEGF has been identified as a supporter of tumor angiogenesis in pyogenic granuloma. There is a clear correlation between VEGF expression in tumor tissue and intumoral microvessel density show in Rana *et al.* (2015). It is used as a tumor marker or prognostic factor in the diagnosis of breast cancer. Show in Tobouti *et al.* (2017) An important indicator of metastasis and prognosis in pyogenic granuloma is angiogenic analysis^[14-17]. The bulk of the positive VegF staining was linked to tumor cells, which was consistent with the investigation's virtually exclusive emphasis on tumor cells.

who reported in 2010 that 70% of patients with pyogenic granuloma had VEGf. The study was based on research rather than the outcomes of the clinical trial itself, as the author desires to stress^[18].

One of the inflammatory hyperplasias that can appear in the oral cavity is the pyrogenic granuloma. Because the lesion actually develops in response to a variety of stimuli, such as low-grade local irritation, trauma, or hormonal factors, the term infection-related lesion is misleading. Most affected are young females in their second decade of life, show in Zhao *et al.*, (2017) most likely as a result of the vascular effects of female hormones^[19-22]. In terms of medicine, an oral pyogenic granuloma is a small, smooth or lobulated exophytic lesion, erythematous papules with hemorrhagic bases that are usually pedunculated or sessile. The lesion's surface color might range As it ages, its color changes from pink to red to purple^[23,24]. Additional therapeutic options to excisional surgery, the primary treatment method, include the Nd:YAG laser, flash lamp pulsed dye laser, cryosurgery, intralesional injection of ethanol or corticosteroid and sodium tetradecyl sulfate sclerotherapy. show in Rana *et al.* (2015) A thorough assessment of the literature on this lesion is provided, along with details on cutting-edge treatment options,

due to the high prevalence of pyogenic granuloma in the oral cavity, particularly during pregnancy and the need for an accurate diagnosis and treatment^[25-27].

CONCLUSION

A frequent lesion of the skin and oral cavity, particularly the gingiva, is a pyrogenic granuloma. This case study of a patient with a large gingival pyogenic granuloma provides insight into the condition's several etiologies, clinical characteristics, histologic signs, accessible therapies, recurrence rates, and diagnostic strategy. Despite being frequently used, the term pyogenic granuloma is incorrect, according to the article, because it lacks pus Histologically, it resembles an angiomatous lesion more than a granulomatous lesion.

REFERENCES

1. Simmons, B.J., L. Chen and S. Hu, 2016. Pyogenic granuloma association with isotretinoin treatment for acne. *Austr J Derm.*, 57: 144-145.
2. Massa, A., A. Antunes and P. Varela, 2016. Pyogenic granuloma in a patient on gefitinib. *Acta Med Port.* Vol. 29, No. 6.
3. Fujiwara, C., S.I. Motegi, A. Sekiguchi, H. Amano and O. Ishikawa, 2016. Pyogenic granuloma possibly associated with capecitabine therapy. *J Dermatol.*, Vol. 0.
4. Inoue, A., Y. Sawada, D. Nishio and M. Nakamura, 2015. Pyogenic granuloma caused by afatinib: Case report and review of the literature. *Austra J. Derm.*, 58: 61-62.
5. Henning, B., P. Stieger, J. Kamarachev, R. Dummer and S.M. Goldinger, 2016. Pyogenic granuloma in patients treated with selective braf inhibitors: Another manifestation of paradoxical pathway activation. *Melanoma Res.*, 26: 304-307.
6. Robert, C., V. Sibaud, C. Mateus, M. Verschoore, C. Charles, E. Lanoy and R. Baran, 2015. Nail toxicities induced by systemic anticancer treatments. *Lancet Oncol.*, 16: 181-189.
7. Marla, V., A. Shrestha, K. Goel and S. Shrestha, 2016.

- The histopathological spectrum of pyogenic granuloma: A case series. *Case Rep. Dent.*, Vol. 2016 .10.1155/2016/1323798.
8. Seyedmajidi, M., S. Shafaei, G. Hashemipour, A. Bijani and H. Ehsani, 2015. Immunohistochemical evaluation of angiogenesis related markers in pyogenic granuloma of gingiva. *Asian Pac. J. Cancer Prev.*, 16: 7513-7516.
 9. Groesser, L., E. Peterhof, M. Evert, M. Landthaler, M. Berneburg and C. Hafner, 2016. Braf and ras mutations in sporadic and secondary pyogenic granuloma. *J. Invest. Dermatol.*, 136: 481-486.
 10. Hayderi, L.E., A. Rübber and A.F. Nikkels, 2017. Alpha-herpesviridae in der dermatologie. *Der Hautarzt*, 68: 181-186.
 11. Ozkaya, D.B., B. Taskin, B. Tas, Z.A. Serdar, C. Demirkesen, et al., 2014. Poxvirus-induced angiogenesis after a thermal burn. *J. Dermatol.*, 41: 830-833.
 12. Ran, M., M. Lee, J. Gong, Z. Lin and R. Li, 2015. Oral acyclovir and intralesional interferon injections for treatment of giant pyogenic granuloma-like lesions in an immunocompromised patient with human orf. *JAMA Dermatol.*, 151: 1032-1034.
 13. Vázquez-Martínez, O.T., B.A. González, C.M.C. Barboza, G.S.E. González and T.Á. Lugo, et al., 2015. Human papillomavirus type 2 associated with pyogenic granuloma in patients without clinical evidence of warts. *Int J Dermatol.*, 55: 745-750.
 14. Tobouti, P.L., I. Olegário and S.C.O.M. de Sousa, 2017. Benign vascular lesions of the lips: Diagnostic approach. *J. Cutan Pathol.*, 44: 451-455.
 15. Amenábar, J., F. daSilva, C. Piazzetta, C. Torres-Pereira and J. Schussel, 2016. Gingival proliferative lesions in children and adolescents in Brazil: A 15-year-period cross-sectional study. *J. Indian Soc. Periodo.*, 20: 63-66.
 16. Wollina, U., 2017. Subungual telangiectatic granuloma. *Deuts Ärzte intern.*, Vol. 114, No. 8 .10.3238/arztebl.2017.0136.
 17. Figueiredo, C.S.D., C.G.C. Rosalem, A.L.C. Cantanhede, É.B.A.F. Thomaz and M.C.F.N. da Cruz, 2017. Systemic alterations and their oral manifestations in pregnant women. *J. Obstet. Gyna. Res.*, 43: 16-22.
 18. Abreu-dos-Santos, F., S. Câmara, F. Reis, T. Freitas, H. Gaspar and M. Cordeiro, 2016. Vulvar lobular capillary hemangioma: A rare location for a frequent entity. *Case Rep. Obstet. Gynecol.*, 2016: 1-3.
 19. Katmeh, R.F., L. Johnson, E. Kempley, S. Kotecha, W. Hamarneh and S. Chitale, 2017. Pyogenic granuloma of the penis: An uncommon lesion with unusual presentation. *Curr. Urol.*, 9: 216-218.
 20. Zhao, J., Q. Feng and S. Shi, 2017. Pyogenic granuloma of the esophagus. *Clin. Gastro. Hepat.*, Vol. 15 .10.1016/j.cgh.2017.03.028.
 21. Mascarell, C.R., J.C.G. Pagán, I.K. Araujo, J. Llach and B. González-Suárez, 2017. Pyogenic granuloma in the jejunum successfully removed by single-balloon enteroscopy. *Rev. Esp Enfe Dige.*, 109: 152-154.
 22. Qiu, X., Z. Dong, J. Zhang and J. Yu, 2016. Lobular capillary hemangioma of the tracheobronchial tree. *Medicine*, Vol. 95 .10.1097/md.0000000000005499.
 23. Misawa, S.I., H. Sakamoto, A. Kuroguchi, Y. Kirii and S. Nakamura et al., 2015. Rare cause of severe anemia due to pyogenic granuloma in the jejunum. *BMC Gast.*, Vol. 15 .10.1186/s12876-015-0355-6.
 24. Matsuzaki, K., Y. Imamura, M. Ozawa, T. Nakajima, A. Ikeda, T. Konishi and T. Jikuya, 2016. Intravenous lobular capillary hemangioma in the subclavian vein. *Ann. Thor Surg.*, 102: 427-429.
 25. Brightman, L.A., R.G. Geronemus and K.K. Reddy, 2015. Laser treatment of port-wine stains. *Clin. Cosmet. Invest.al Derm.*, 8: 27-33.
 26. Rana, R., S.S. Ramachandra, U.C. Prasad, P. Aggarwal and J.K. Dayakara, 2015. Recurrent pyogenic granuloma with a satellite lesion. *Cutis*. 96: 27-30.
 27. Gupta, V., A.R. Mridha and V.K. Sharma, 2016. Pediatric dermatology photoquiz: Multiple erythematous papules on the back. *Pediatr. Dermatol.*, 33: 97-98.