

Peer Review File

Article information: <https://dx.doi.org/10.21037/acr-23-159>

Reviewer A

This case report discusses the development of pyogenic granuloma in the hand of a 32-year-old T-cell acute lymphoblastic leukemia maintenance phase patient who is currently on immunosuppressive therapy. The authors successfully treated the patient for a *Pseudomonas aeruginosa* infection with oral antibiotics, without the need for additional therapies.

While the content of this report is relevant, the most significant issue lies in the complete disregard for the "Guidelines for Authors" in terms of its structure. Starting from the 17th line, it appears as though this might have been a resubmission of a previously submitted manuscript without proper reformatting.

In my personal opinion, the word limit of 2500 words seems sufficient for considering this case. However, the main body of the report is only around 620 words, which appears considerably short and lacks the necessary depth of analysis. It is recommended that the authors make the necessary revisions and resubmit to "Letters" after addressing these concerns, or reconsider the discussion section more comprehensively.

A text has been added to introduction see lines (58 - 60) & (62-67)

A text has been added to discussion see lines (120-136)

Reviewer B

The authors report two striking Lobular Capillary Hemangioma (LCH) in a patient treated with Chemotherapy for T-cell Leukemia. After shave biopsy followed by cauterizing the floor, positive culture for *pseudomonas aeruginosa* was tested with recurrence of lesions. The authors hypothesize that gram negative infection may be a primary trigger inducing the angiomatous proliferation and therefore specific antibiotic treatment can be result successful.

However, we consider that prior to acceptance of the manuscript, some considerations must be made.

1. Available evidence show that the pathogenesis of LCH pathogenesis is not fully understood . Genetic studies suggested that PG is the result of tissue injury, followed by an altered wound healing response, during which vascular growth is driven by gene mutations . Thus, this favors the idea that PG is a reactive lesion resulting from chronic tissue injury and not a true tumor.

Reply 1: A text has been added, see lines (62 – 67) A previous study where 11 PGs have been analyzed, identified embryonic stem cells markers in the endothelial cells, while more differentiated forms were recognized in the interstitial cells suggesting de novo vasculogenesis originating from the primitive stem cells.

Trauma has been described as a potential trigger, although history of trauma at the site of PG was reported in only 7 to 23 percent of patient.

Godfraind, C.; Calicchio, M.L.; Kozakewich, H. Pyogenic granuloma, an impaired wound healing process, linked to vascular growth driven by FLT4 and the nitric oxide pathway. *Mod. Pathol.* 2013, 26, 247–255.

2. Several causes as Chronic inflammation (onychocriptosis), immunosuppressive medication and retinoids treatment has been described as cause of PG.

Reply:

We are aware that the above-mentioned causes have been described in the literature. *de novo vasculogenesis originating from the primitive stem cells* has also been suggested, see lines (114-118)

Córdoba-Fernández, Antonio, María Dolores Jiménez-Cristino, and Victoria Eugenia Córdoba-Jiménez. "Large Lobular Capillary Hemangioma Associated with Ingrown Toenail: Histopathological Features and Case Report." *Dermatopathology* 9.3 (2022): 271-276.

Paronychia and pseudopyogenic granuloma are common adverse drug reactions associated with the use of epidermal growth factor receptor tyrosine kinase inhibitors. Although while local infection is currently ruled out as an etiologic factor for PG.

3. Multiple local antibiotics management approaches have been tested in PG with unsatisfactory results, however combination of available topical beta-blockers and antibiotic ointment for paronychia and pseudopyogenic granulomas have been useful .

Reply: see line (129 – 131)

Besides its anti-microbial action, Ciprofloxacin poses a well-known anti-inflammatory effect, which can potentially exert synergistic effect in treating PG, however treatment response cannot be explained solely by anti-inflammatory action since an organism has been isolated from PG lesion.

Liu, Hui-Lin, et al. "Combination of available topical beta-blockers and antibiotic ointment for epidermal growth factor receptor tyrosine kinase inhibitor-induced paronychia and pseudopyogenic granulomas in Taiwan." *Journal of Oncology Pharmacy Practice* (2022)

4. Some studies indicate that PG shows a lower rate of apoptosis and a more frequent expression of regulatory apoptosis proteins than typical granulation tissue of pseudopyogenic granulomas.

Reply: A text has been added, see lines (114-118)

A previous study where 11 PGs have been analyzed, identified embryonic stem cells markers in the endothelial cells, while more differentiated forms were recognized in the interstitial cells suggesting de novo vasculogenesis originating from the primitive stem

Our case describes a PG with an organism identified, a targeted treatment to this

bacterial infection has been used. Following that a spontaneous resolution of PG occurred. A programmed cell death does not explain such sequence of events

Nakamura, T. Apoptosis and expression of Bax/Bcl-2 proteins in pyogenic granuloma: A comparative study with granulation tissue and capillary hemangioma. *J. Cutan. Pathol.* 2000, 27, 400–405

We believe that the shave biopsy was key in resolving of this case along with the antibiotic treatment that could improve the inflammatory response and favor the activation of apoptosis mechanisms.

Reply: A text has been added, see lines (114-117)

A previous study where 11 PGs have been analyzed, identified embryonic stem cells markers in the endothelial cells, while more differentiated forms were recognized in the interstitial cells suggesting de novo vasculogenesis originating from the primitive stem cells.

Besides its anti-microbial action, Ciprofloxacin poses a well-known anti-inflammatory effect, which can potentially exert synergistic effect in treating PG, however treatment response cannot be explained solely by anti-inflammatory action since an organism has been isolated from PG lesion.

Reply: see line (167– 170)

We consider that the introduction and discussion of the case presented should be expanded and improved. We recommend reviewing and including the suggested bibliography

The discussion has been already expanded in the previous revision (text underlined)