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Citation
Woude, D. van der, Bajema, I. M., & Specks, U. (2025). Granulomatosis with polyangiitis presenting as strawberry gingivitis: methodologic aspects: comment on the article by Liu et al. *Arthritis &Amp; Rheumatology*, *77*(10), 1454-1454. doi:10.1002/art.43177

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Note: To cite this publication please use the final published version (if applicable).

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American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis & Rheumatology
Vol. 77, No. 10, October 2025, pp 1454–1459
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LETTER

DOI 10.1002/art.43177

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To the Editor:

With interest, we read the report by Liu et al[1] describing a patient with strawberry gingivitis, attributed to granulomatosis with polyangiitis (GPA). The authors state "…co-localization staining for proteinase 3 (PR3) and IgG revealed specific PR3-ANCA [anti-neutrophil cytoplasmic antibody] positivity… (Figure C, D)" and "This case underscores the diagnostic challenge of GPA, especially in ANCA-negative presentations by [indirect immunofluorescence] IIF, necessitating reliance on histopathology and targeted immunologic testing to establish a diagnosis." Unfortunately, the presented histopathology and immunologic testing results have substantial inadequacies. Central to their argument is their interpretation of stainings of PR3 and IgG in approximately the same location as conclusive evidence of specific presence of PR3-ANCA. We respectfully disagree with this conclusion because it is not proven by the evidence provided.

PR3, the target of PR3-ANCA, is expressed mainly by neutrophils. Upon neutrophil priming by inflammatory cytokines, PR3 expression on the cell surface is up-regulated by binding to NB1 (also known as CD177), and it can also be released by activated neutrophils into the extracellular environment during the process of NETosis or other forms of inflammatory neutrophil cell death.[2,3] Detection of PR3 in inflamed tissue is therefore not specific for GPA. Furthermore, colocalization with IgG in immunohistochemistry does not demonstrate that IgG is bound to a colocalized protein in a specific antibody–antigen binding manner. Thus, the statement that colocalization staining for PR3 and IgG would reveal specific PR3-ANCA positivity appears to be a misconception. Furthermore, Figure 1C and 1D are uninterpretable because the underlying anatomic structures cannot be identified, the images do not seem to represent serial sections, and Figure 1C seems to show only stained PR3 and 1D shows only stained IgG, without clear red-green overlap anywhere.

The serologic diagnosis of GPA could also be challenged. The patient first tested negative for ANCA by IIF but was nonetheless classified as having GPA after a low-positive PR3-ANCA enzyme-linked immunosorbent assay (ELISA) result. This testing sequence is not consistent with the latest ANCA-testing consensus guidelines, which recommend the use of a high-quality antigen-specific immunoassay as the preferred first screening method. If this test reveals low antibody levels (as in this case), a second, different immunoassay or IIF is advised for confirmation.[4] Therefore, the PR3-ANCA test result reported here (weakly positive ELISA with negative IIF) is not conclusively supportive of GPA.

In summary, although strawberry gingivitis is considered pathognomonic for GPA, and the follow-up with persistently elevated cytoplasmic ANCA and PR3-ANCA levels makes the diagnosis of GPA plausible, we would like to add a word of caution regarding the diagnostic methods employed here. GPA can be difficult to diagnose, and it is important to only embrace diagnostic methods with validated sensitivity and specificity to avoid overdiagnosis and possibly overtreatment.

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/art.43177.

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