

# The Challenges of Diagnosis and Management of Wegener's Granulomatosis with Negative ANCA

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## ABSTRACT

*Wegener's granulomatosis is an autoimmune disease that affects the walls of small and medium-sized blood vessels due to an immune complex reaction. Meanwhile, at present, the etiology of the disease is unknown with certainty. One of the diagnoses is the detection of cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA), but a negative ANCA examination is very rare. Therefore, this is a case report of a 33-year-old man that complained of sores on both legs, which were difficult to heal. The patient also experienced joint pain, fever at night, weight loss, hair loss as well as recurrent nosebleeds with an unknown cause. Furthermore, the physical examination found a saddle nose and black spots from the right and left groin to the back of the legs. Multiple irregular ulcers with different sizes were also discovered in the region cruris and dorsum pedis. The laboratory examination results showed Hb of 8.7 g/dl, 130 mm/hour ESR. Based on peripheral blood smear, the patient was suspected to have hypochromic-microcytic anemia, which caused chronic process along with bleeding. The IF pattern was also speckled with a titer of 1:320, and the ANCA test was negative (-). Meanwhile, the results of routine urine examination found blood +4 macroscopically and observed leukocyturia 2-10 LPB and 8-21 LPB erythrocyturia microscopically. The Doppler ultrasound of the left inferior extremity revealed the swelling of the left pedis soft tissue with peripheral arteritis in the cutis lesion area. The Anatomical Pathology examination showed non-specific chronic inflammation in the cruris and pedis region. Subsequently, the patient was administered with wound debridement by a surgeon, packed red cell (PRC) transfusion, metyprednisolone mg, azathioprine, and cefixime. After the treatment, the nosebleed was no longer felt, the joint pain reduced, and the fever improved.*

**Keywords:** *Wegener's granulomatosis, Autoimmune vasculitis, negative ANCA.*

## INTRODUCTION

Wegener's granulomatosis is a vasculitis that affects small and medium-sized blood vessels, thereby leading to changes in their walls. Furthermore, it is often found in patients within the age range of 40-50 years, especially in men, and the main symptoms include vasculitis, glomerulonephritis, and respiratory tract involvement.<sup>1-2</sup> Moreover, Wegener's granulomatosis can be classified into 2 forms, namely the general and rare/limited

forms. The general form is characterized by a triad of symptoms, including vasculitis, glomerulonephritis, and respiratory tract involvement, while the rare/limited form only affects the respiratory tract and does not involve the kidneys.<sup>2,3</sup>

At present, its etiology is not known with certainty, and some hypotheses stated that it is an autoimmune disease caused by an immune complex reaction on the walls of blood vessels, which leads to damage.<sup>4,5</sup> The

disease can be diagnosed through the detection of cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA). However, a negative ANCA examination is very rare because it is often caused by a localized form of the disease. There are also few studies or case reports on the Wegener's granulomatosis with ANCA-negative, hence, it is necessary to carry out a study to add information on its diagnosis.

### CASE ILLUSTRATION

A 33-year-old man complained of sores on both legs that were difficult to heal. The wound had occurred since December 1, 2020, and has been treated by a surgical specialist, but it reappeared again. At first, it was a red spot that gradually turned black with pain when pressed. The wound then started to peel off, ooze fluid/pus, and bleeds easily. Furthermore, the patient also complained of high fever and sweating, especially at night, which did not improve despite being given fever-reducing medication, and in April 2021, a large number of nosebleeds occurred. The complaints that were felt came in waves and were accompanied by headaches and pain throughout the body, especially from the waist to the soles of the feet. An ENT specialist was then consulted, and bone damage was observed in the nasal cavity. The patient also experienced a significant weight loss in the last 1 year as well as hair loss, watery eyes, and forgetfulness.

The conjunctiva was pale, the nose was snub, which appeared as a saddle nose, and there were black spots from the right and left groin to the back of the legs. In the cruris and dorsum pedis regions, multiple irregular ulcers were also found, which varied in size, well-demarcated, accompanied by livedo reticularis, pus (+), and crust (+). Otolaryngological examination using nasendoscopy showed perforation of the nasal septum, which was then diagnosed as suspected Lethal Midline Granuloma (LMG). Physical examinations are shown in **Figure 1** and **Figure 2**.

Laboratory test results suggested hemoglobin level of 8.7 g/dl, MCV 73.5 fl, MCH 22.4 pg, and erythrocyte sedimentation rate of 130 mm/hour. The results of the peripheral blood smear showed the appearance of erythrocytes,

namely hypochromic, microcytic, anisocytosis, normocytes, ovalocytes, anulocytes, the appearance of teardrop cells and the presence of erythroblast cells. The leukocyte population was within normal limits and no blast cells were found. The picture of platelets found in normal numbers and evenly distributed, found the existence of giant platelets. Based on the result of the tests, the patient was suspected to have hypochromic-microcytic anemia, which caused chronic process along with the bleeding process.

The ANA-IF pattern was speckled with a titer of 1:320,1 and negative ANCA test result. Routine urine examination macroscopically found positive blood 4, while microscopic observation found leukocyturia 2-10 LP.40X and erythrocyturia 8-21 LP.40X.

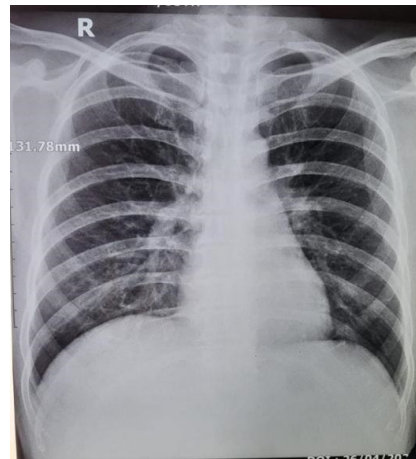
The Thorax PA examination results were within normal limits (**Figure 3**), while the Doppler ultrasound examination in the left lower extremity showed swelling of the left pedis soft tissue with peripheral arteritis in the cutis lesion area (**Figure 4**).

The histopathological examination of a skin biopsy revealed the presence of tissues that were partially lined with stratified squamous epithelium and keratin cell nuclei that are within normal limits (**A**). The Subepithelial had visible fibrocollagenous connective tissue with massive inflammation of lymphocytes, PMNs, histiocytes, and dilated blood vessels (**B-D**). Furthermore, no malignant tumor cells were found, hence, the patient was diagnosed with a non-specific chronic inflammation of the cruris and pedis region (**Figure 5**).

Based on the aforementioned findings, the patient was diagnosed with a suspected autoimmune disease caused by Wegener's granulomatosis. The patient also had microcytic hypochromic anemia, epistaxis, and hematuria. Subsequently, wound debridement by a surgeon, packed red cell (PRC) transfusion, methylprednisolone 16 mg t.i.d., azathioprine 50 mg b.i.d., and cefixime 200 mg b.i.d. were administered. After treatment for approximately 2 weeks, the complaints improved, the fever was gone, the joint pain was reduced, the nosebleeding ceased, and the wounds on the legs were healing gradually.



**Figure 1.** The nasal bone shows a saddle nose, and eyebrow hair loss.



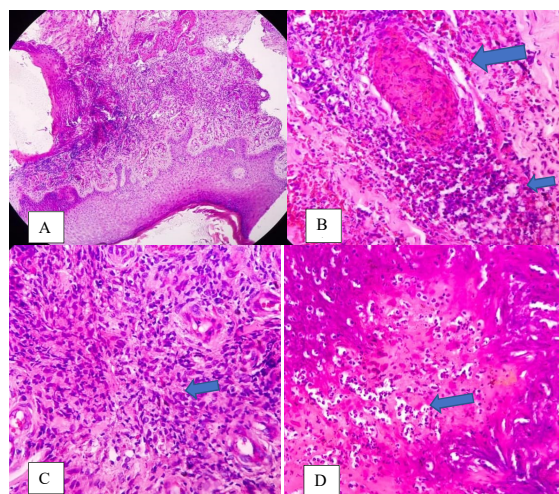
**Figure 3.** Thorax Postero Anterior showing the heart and lungs within normal limits.



**Figure 2.** Black spots, varied shapes, multiple ulcers of varying sizes, pus (+), irregular, livedo reticularis (+), crustae (+)



**Figure 4.** Doppler ultrasound showing left pedis soft tissue swelling with peripheral arteritis in the cutaneous lesion area



**Figure 5.** The histopathological examination of a skin biopsy

Microscopic skin biopsy showed tissue fragments that are partially lined with stratified squamous epithelium, keratinized with normal cell nuclei (10X magnification);

Subepithelial visible fibrocollagenous connective tissue massively strewn with inflammatory cells of lymphocytes, PMNs, histiocytes, and dilated blood vessels (100X magnification);

Fibrocollagenous tissue with lymphocyte and PMN inflammatory cells (100X magnification); PMN and histiocyte infiltration with granulomatous inflammation (100X magnification).

## DISCUSSION

Wegener's granulomatosis is an autoimmune disease that attacks small and medium-sized blood vessels. The manifestations of the disease include symptoms in the respiratory tract, kidneys, and lungs.<sup>6-9</sup> The disease can also be classified into 2 groups, namely the generalized and limited form. The generalized form is characterized by 3 classic granulomatosis symptoms, including glomerulonephritis, vasculitis, and airway involvement, while the limited form only affects the respiratory tract without the involvement of the kidneys.<sup>3,10</sup>

Furthermore, constitutional symptoms in the early stages of the disease include weight loss, fever, and weakness. The patient can also experience manifestations in the upper respiratory tract, such as nasal congestion, rhinitis, pain in the nose, epistaxis, brown crusts mixed with blood, and septal perforation, which causes a saddle-shaped nose.<sup>11</sup> Until now, the etiology of Wegener's granulomatosis is not known with certainty. The diagnosis of the disease can be established with the criteria issued by the American College of Rheumatology in 1990 along with further examinations, namely cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies (cANCA), complete blood count, chest X-ray examination, urinalysis, presence of mouth ulcers or nasal secretions, and histological observation to check for the presence of granulomatous inflammation.<sup>12</sup>

In this case report, the patient experienced constitutional symptoms of fever, weakness, and

weight loss. Manifestations in the respiratory tract were in the form of nose pain, recurrent epistaxis, which occurred sometimes in large quantities. Meanwhile, the results of the ENT-KL specialist examination using nasendoscopy showed a perforation of the nasal septum, which was diagnosed as a suspected lethal midline granuloma (LMG). The ENT-KL doctor did not perform a biopsy on this patient because of the limited examinations that could be carried out at our hospital, and also the patient at that time refused to be referred for further examination due to cost constraints and the referral hospital was far away.

The histopathological ulcers biopsy in the cruris region revealed the presence of tissues that were partially lined with stratified squamous epithelium and keratinized cells within normal limits. The Subepithelial examination showed fibrocollagenous connective tissue with massive inflammation of lymphocytes, PMNs, and histiocytes as well as dilated blood vessels. Furthermore, no malignant tumor cells were found along with the granulomatous inflammation. Based on the tests and examinations, the patient was concluded to have a non-specific chronic inflammation in the cruris and pedis region as well as a granulomatous inflammation.

Subsequently, the diagnosis was made based on the criteria of the American College of Rheumatology in 1990, namely abnormalities in urine sediment, the presence of nasal secretions, and histopathological results showing a granulomatous inflammation. The diagnosis of the disease can also be made when 2 or more ACR criteria are met.<sup>13,14</sup> This case belongs to the general form because the patient had glomerulonephritis, vasculitis with airway involvement. The disease can still be confirmed even though the cANCA test results was negative. However, the diagnosis cannot be made quickly because the patient should be referred to a hospital for a more complete investigation and the initial symptoms shown were not typical of Wegener's Granulomatosis. cANCA is one of the tests that support the diagnosis of the disease, but in 10-20% of cases, ANCA is negative.<sup>15-17</sup>

Other criteria that can be used to establish Wegener's diagnosis Granulomatosis can be

Iran's criteria, and the latest criteria were the 2017 ACR/EMA criteria. The Iran's criteria consist of manifestations in the ear, nose and throat (ENT) (3 points), pulmonary (2 points), kidney (1 point), ANCA (2 points), and biopsy (3 points).<sup>18</sup> Iran's criteria are met if there are 4 out of 11 points. In this patient, ENT and kidney criteria were met, namely 4 points. ACR/EMA 2017 criteria, these criteria are used when no biopsy is performed. The parameters consist of manifestations in the lower respiratory tract based on chest X ray, ear, nose and throat (ENT) manifestations, glomerulonephritis, and positive ANCA.<sup>18</sup> Based on the 2017 ACR/EMA criteria, this patient was found to have manifestations in nose area. Glomerulonephritis is still possible because it is found presence of hematuria +4. In this patient, no renal biopsy was performed to support the manifestation of glomerulonephritis because the patient still does not agree and also Renal biopsy examination at our hospital cannot be done.

In addition to using the three criteria above, the diagnosis of Wegener's granulomatosis can also be supplemented by using several supporting examinations such as histopathological biopsy examination, ANCA examination of proteinase 3 (PR3) and myeloperoxidase (MPO) and radiological examination.<sup>18</sup> The histopathologic features of Wegener's granulomatosis are varied and non-specific. Some of these features include acute and chronic inflammation, granulomatous foci, collagen deposition, necrosis, plasma cells and eosinophil infiltrates, lymphocytes and histiocytes that form a granulomatous reaction with multinucleated giant cells.<sup>19-21</sup> The patient in this case showed a histopathological picture from the skin biopsy according to the theory (**Figure 5**).

The cANCA results can also be used to describe the disease's activity, and in patients with limited clinical manifestations or mild symptoms, cANCA results were negative in more than 40% of cases.<sup>11,13</sup> due to early stages of the disease. A negative cANCA made it difficult for clinicians to make a diagnosis because the initial symptoms were atypical, hence, the therapy given was asymptomatic.<sup>13</sup>

Possibility, which occurs when the titer

is not sufficient or it does occur, Wegener's granulomatosis in this case is still in early onset. Wegener's patient granulomatosis with upper respiratory manifestations generally has ANCA negative, and 83% of negative ANCA cases involve disorders of the central nervous system brightly.<sup>11,17,22</sup>

A negative cANCA test result does not exclude Wegener's diagnosis of granulomatosis because the results of the cANCA examination did not meet one of the criteria diagnosis. However, the cANCA results are still used to support Wegener's diagnosis granulomatosis (ACR 1990 criteria) due to a positive cANCA result in 80-90% of Wegener's granulomatosis patients in the general form and 55-56% in patients with the limited form.<sup>11,23</sup> However, after the patient's condition was evaluated and reviewed through the history, physical examination, and positive ANA test results with negative cANCA, Wegener's granulomatosis was confirmed.

Wegener's granulomatosis therapy consists of 2 phases, namely an initial phase for 3-6 months to achieve remission and a maintenance phase for 12-24 months to prevent recurrence. The gold standard therapy for Wegener's granulomatosis is a combination of corticosteroids and immunosuppressants, but one can also be given. Administration of cyclophosphamide and corticosteroids is an effective therapy for active Wegener's granulomatosis.<sup>25</sup> Maintenance therapy of Wegener's granulomatosis is by combining oral corticosteroids with azathioprine or methotrexate.<sup>26</sup>

The patient then received wound debridement therapy, antibiotics, azathioprine, and methylprednisolone. The gold standard in the management of the disease is a combination of corticosteroids and immunosuppressants. Therapy can be given until remission occurs, and this can take up to 3-6 months.<sup>11</sup> Meanwhile, the administration of the immunosuppressant azathioprine was based on the availability of drugs at the hospital as well as the cost constraints and the distance of the patient's home.

The diagnosis in this report had limitations because the clinical symptoms that appeared were atypical and not all gold standard examinations

were carried out due to cost constraints as well as the long-distance to the hospital where supporting examinations can be carried out. These constraints affected the choice of therapy and the disease's prognosis.<sup>27</sup>

## CONCLUSION

Wegener's granulomatosis is a rare disease, and its diagnosis requires history taking, physical examination, ANCA, and cytology, but under certain conditions, a negative cANCA examination may be found. However, a negative cANCA test result does not rule out the diagnosis of the disease. Treatment can be carried out when the history, physical examination, and further examinations confirm the disease. Therefore, prompt diagnosis and appropriate treatment are needed to accelerate remission and prevent the worsening of the disease.

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## REFERENCES

- Rudita BAA, Werdiningsih Y, Nurudhin A, et al. 38 years old man with anca negatif Wegener's granulomatosis vasculitis with type 2 diabetes mellitus and electrolyte imbalance: A case report. *Ina J Rheum*. 2020;12(2):309-4.
- Almouhawis HA, Leao JC, Fedele S, Porter SR. Wegener's granulomatosis: a review of clinical features and an update in diagnosis and treatment. *J Oral Pathol Med*. 2013;42(7):507-16.
- Sudibyo TKAP, Mulya DP, Budiono E, et al. Meningoensefalitis manifestation in Wegener's granulomatosis with anca negative: Case report. *JPDI*. 2019;6(3):150-5.
- Erickson VR, Hwang PH. Wegener's granulomatosis: Current trends in diagnosis and management. *Curr Opin Otolaryngol Head Neck Surg*. 2007;15:170-17.
- Nolle B, Specks U, Ludemann J, Rohrbach MS, DeRemee RA, Gross WL. Autoantibodi antisitoplasma: nilai imunodiagnostiknya pada granulomatosis Wegener. *Ann Intern Med*. 1989;111:28-40.
- Petkovic TR, Radovic M, Pejic T, Rancic M, Borovac DN, Djordjevic I. Wegener's granulomatosis - case report. *Acta Medica Medianae*. 2008;47(3):78-81.
- Mubashir M, Eisha MD, Ahmed, et al. Granulomatosis Wegener: A case report and update. *South Med J*. 2006;99(9):977-988.
- Sharma P, Sharma S, Baltaro R, Hurley J. Systemic vasculitis. *Am Fam Physician*. 2011;83:556-65.
- Marisca S, Tanurahardja B. Aspek klinikopatologik vaskulitis. Departemen Patologi Anatomik Fakultas Kedokteran Universitas Indonesia. *Pratista Patologi*. 2015;4(1):1-10.
- Duggal L, Jain N. Limited Wegener's granulomatosis. *J Indian Acad of Clin Med*. 2004;5(2):186-7.
- McCarthy E, Mustafa M, Watts M. ANCA-negative granulomatosis with polyangiitis: a difficult diagnosis. *EJCRIM* 2017;4: doi:10.12890/2017\_000625
- Afsha K, Catherine AL, Mark AQ, et al. Case report: Successful treatment of ANCA-negative Wegener's granulomatosis with Rituximab. *Int J Rheumatol*. 2010;2: doi:10.1155/2010/84606
- Hiz F, Cinar M, Karagol T, Bozkurt D, Ozcan RK. Wegener's granulomatosis: Case report. *J Neurol*. 2007;6(1):1-5.
- Chaturvedi J, Shobha V, Rout P, Alexander B, Nayar RC. Diagnostic dilemma of a midline destructive disease - a case report. *Int J Oto Laryngol*. 2010;12(1).
- Greco P, Palmisano A, Vaglio A, et al. Meningeal involvement in apparently ANCA-negative Wegener's granulomatosis: a role for PR3 capture-ELISA? *Rheumatology*. 2007;46:1375-6.
- Salahi-Abari I. 2017 ACR/EMA revised criteria fot too early diagnosis of granulomatosis with polyangiitis (GPA). *Autoimmune Dis and Ther Approaches*. 2016;3(2):1-9.
- Thiel G, Shakeel M, Ah-See K.. ANCA-negative Wegener's granulomatosis with Wegener's granulomatosis presenting as meningitis. *J Laryngol Otol*. 2012;126(2):207-9.
- Muller K, Lin JH. Orbital granulomatosis with polyangiitis (Wegener granulomatosis): clinical and pathologic findings. *Arch Pathol Lab Med*. 2014;138(8):1110-4.
- Sarsat VW and Thieblemont N. Granulomatosis with polyangiitis (Wegener granulomatosis): a proteinase-3 driven disease? *Joint Bone Spine*. 2018;85(2):185-9.
- Guevara DL, Cerda F, Carreno MA, Piottante A, Bitar P. Update in the study of granulomatosis with polyangiitis (Wegener's granulomatosis). *Rev Chil Radiol*. 2019;25(1):26-34.
- Isa H, Lightman S, Luthert PJ, Rose GE, Verity DH, Taylor SRJ. Histopathological features predictive of a clinical diagnosis of ophthalmic granulomatosis with polyangiitis (GPA). *Int J Clin Exp Pathol*. 2012;5(7):684-9.
- Graves N. Wegener granulomatosis. *Proc (Bayl Univ Med Cent)*. 2006;19(4):342-4.
- LanguageF, Cinar M, Karagol T, Bozkurt D, Ozcan RK. Wegener's granulomatosis: case report. *J Neurol*. 2007;6(1):1-5.
- Jokar M, Amir Feizi Z. Granulomatosis with polyangiitis (Wegener's granulomatosis): An analysis

- of 59 patients. *Rheum Resc.* 2017;2(4):115-8.
25. Kesel N, Kohler D, Herich L, et al. Cartilage destruction in granulomatosis with polyangiitis (Wegener's granulomatosis) is mediated by human fibroblasts after transplantation into immunodeficient mice. *Am J Pathol.* 2012;180(5):2144-55.
  26. Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. *Autoimmun Rev.* 2014;13(11):1121-5.
  27. Sangle S, Karim MY, Hughes GRV, D'Cruz DP. Sulphamethoxazole-trimethoprim in the treatment of limited paranasal Wegener's granulomatosis. *Rheumatol.* 2002;41:589-90.