CASE REPORT

DIFFUSE GRANULOMATOUS CONJUNCTIVITIS AS AN OCULAR MANIFESTATION OF ANCA-NEGATIVE LIMITED WEGENER'S GRANULOMATOSIS

Cindy Hartono[1], Andi Pratiwi[1], Ni Ketut Sungowati[2], Bahrul Fikri[3], Hasnah Eka[1]
[1]Department of Ophthalmology, Faculty of Medicine Hasanuddin University
[2]Department of Anatomical Pathology, Faculty of Medicine Hasanuddin University
[3]Department of Pediatric, Faculty of Medicine Hasanuddin University
Email : cindyhartonoo@gmail.com

ABSTRACT

Introduction: *Necrotizing granulomatous vasculitis, which is commonly known as Wegener's Granulomatosis (WG), frequently affects small to medium-sized blood vessels and is associated with anti-neutrophil cytoplasmic antibodies (ANCA). Despite ocular manifestations being prevalent in the disease, initial symptoms involving the eyelid and conjunctiva are infrequent. While most of WG cases shows ANCA positivity, this study report an unusual case of ANCA-negative, but biopsy-proven WG presenting only localized in conjunctiva*

Case Report: *An 11-year-old girl presented a red membrane covering the entire ocular surface and diminished vision in the left eye seven months before admission. At presentation, hand motion in the left eye was the best corrected visual acuity. There were granuloma formations in the palpebral and bulbar conjunctival, covering the entire ocular surface in the left eye. An incisional biopsy was performed in the conjunctiva, which revealed an ulcerative mucous membrane, prominent vasculitis, and necrotizing granulomas with giant cells and massive leukocyte infiltrate consistent with WG diagnosis.*

Discussion: *There is a need to consider the clinical manifestations suggesting the presence of vasculitis, ANCA determination, and histopathological evidence of the compromised organ to confirm the diagnosis. Overall, 82-94% of patients with WG were ANCA positive, leaving approximately 10% who tested negative, particularly those with limited WG. Moreover, a biopsy can confirm the diagnosis, specifically in ANCA-negative cases.*

Conclusion: *This case illustrated the consideration for WG diagnosis in limited form and negative ANCA-test. The clinical suspicion of WG based on symptoms and signs and alternative diagnostic criteria using tissue biopsy might be helpful in such cases for starting the treatment.*

Keywords: *Wegener's Granulomatosis, ANCA-negative, granulomatous conjunctivitis*

INTRODUCTION

Wegener's Granulomatosis (WG), which is also known as Granulomatosis Polyangiitis (GPA), is a type of pauci-immune necrotizing granulomatous vasculitis that typically affects small to medium-sized blood vessels, and often associated with anti-neutrophil cytoplasmic antibodies (ANCA). The disease primarily affects the kidneys and upper and lower airways. Although the condition frequently presents with symptoms in the eyes, incidences with eyelid and conjunctival involvement as the earliest symptoms of the disease are rare.[4] While the exact cause of WG remains unknown, previous studies have suggested the pathogenic role of

ANCA in the disease's progression.[1-3] Positive ANCA results are observed in 82-94% of WG patients, while approximately 10% of individuals tested negative, leading to the potential for misdiagnosis and delayed treatment. The absence of ANCA can obscure the clinical presentation, particularly in atypical cases, making histopathological confirmation through biopsy become crucial for accurate diagnosis. This case report highlights a case of an eleven-year-old girl diagnosed with localized WG in the conjunctiva, a rare site of involvement, with a negative ANCA test and biopsy strongly suggesting WG. We would like to emphasize the importance of considering WG as differential diagnosis of granulomatous conjunctival lesion, even in the absence of ANCA, and demonstrates the critical role of biopsy in confirming the diagnosis.

CASE ILUSTRATION

In June 2021, an 11-year-old girl was referred to the Rumah Sakit Umum Pusat Dr. Wahidin Sudirohusodo due to a conjunctival mass in her left eye. The patient had experienced a red membrane covering the entire ocular surface and diminished vision for seven months before admission. Two years prior to admission, the left eye had been red with excessive tearing, eye discharge, and itchiness, but no pain was reported. Despite being initially treated with antibiotic eye ointment, there was no improvement, and there was no previous history of any systemic autoimmune diseases. Six months later, the patient noticed a mass-like lesion in the upper region of the conjunctiva that progressively spread to the entire ocular surface.

During the patient's presentation, her best-corrected visual acuity for the right eye was 1.0, while for the left eye, it was limited to hand motions. The results of the slit-lamp test indicated that the anterior segment of the right eye was within normal limits. However, in the left eye, ectropion was observed in the lower eyelid, and granuloma formations were present in the palpebral and bulbar conjunctiva, which covered the entire ocular surface as shown in Figure 1. The conjunctiva was observed to bleed easily with friction, and there was a presence of white mucopurulent eye discharge. However, evaluation of other structures of the anterior segment was not conducted.

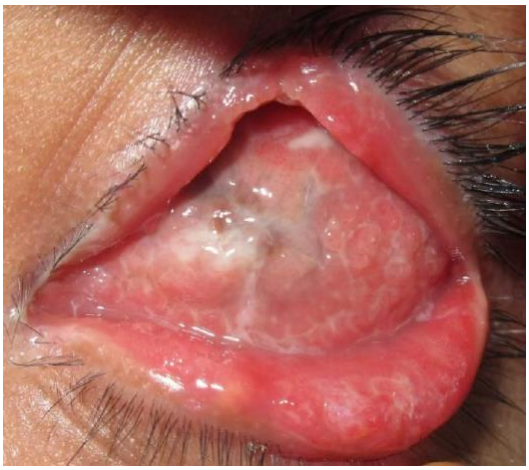

Figure 1. Granuloma formation in palpebral and bulbar conjunctival that covers the entire ocular surface

Blood testing revealed normal renal as well as liver function tests and unremarkable complete blood count. Furthermore, the urinalysis was negative, except for bacteria and mucus. Chest X-Ray examination was within the normal limit. Brain MRI without contrast showed a conjunctival mass in the left eye that infiltrated the cornea, suggestive of basal cell carcinoma or squamous cell carcinoma, bilateral ethmoidal and maxillary sinusitis, atrophicans rhinitis, and nasal septum deviation to the right side, as presented in Figure 2.

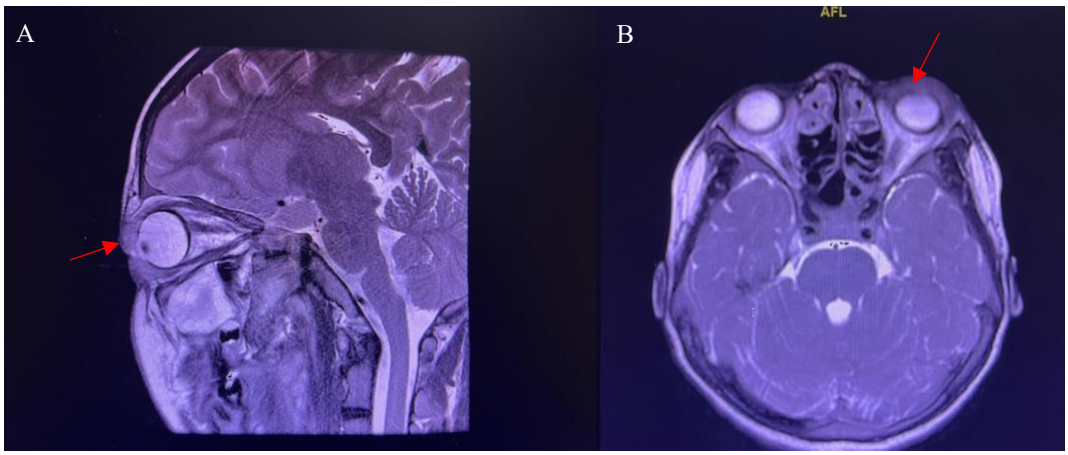

Figure 2. MRI brain without contrast. Red arrow shows conjunctival mass in the left eye infiltrated the cornea, (a) sagittal view ; (b) axial view

An incisional biopsy was carried out on the conjunctiva to collect specimens for anatomic pathology examination. The report showed an ulcerative mucous membrane, prominent vasculitis, and necrotizing granulomas with giant cells and massive leukocyte infiltrate consistent with a Wegener's Granulomatosis diagnosis. ANCA Test was performed to support the WG diagnosis, however, the result was negative.

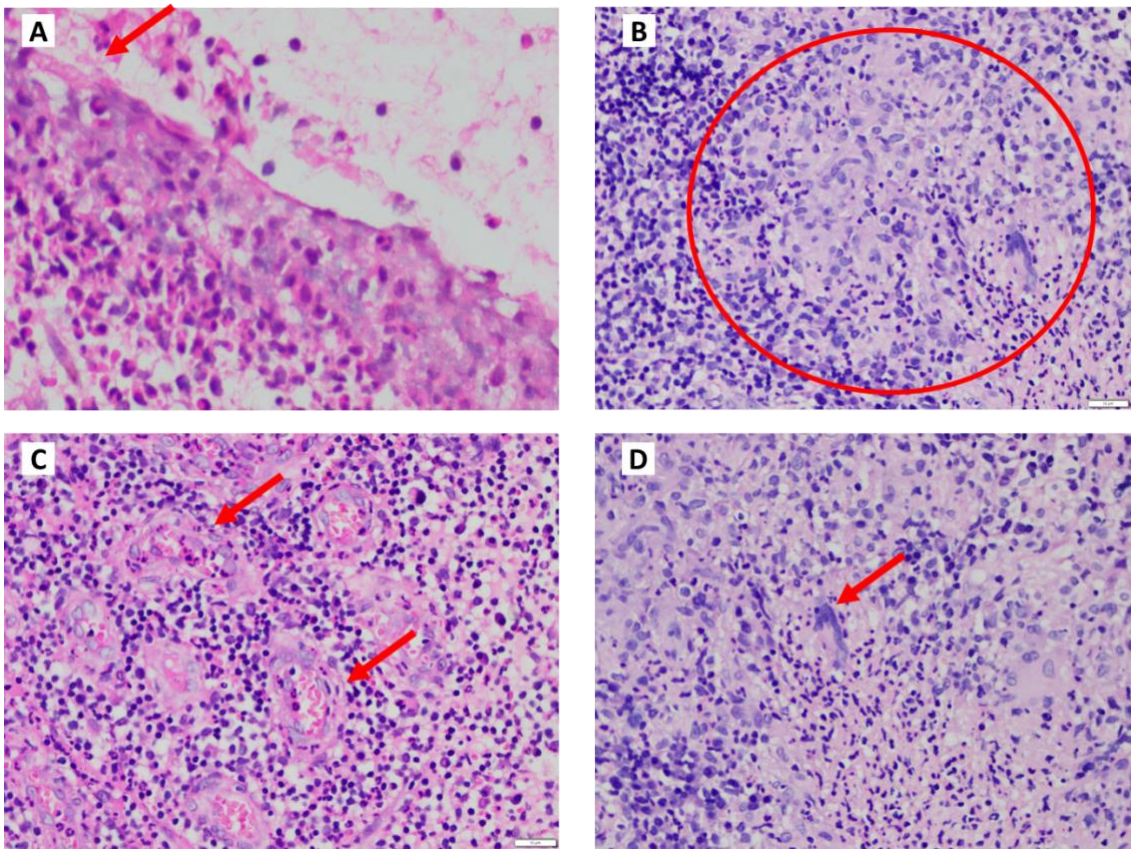

Figure 3. The conjunctival biopsy histopathology showed A) Ulcerated mucous membrane; B) Necrotizing with granuloma area; C) Vasculitis suggestive of a Wegener's Granulomatosis; D) Multinucleated giant cells

DISCUSSION

Wegener Granulomatosis is a necrotizing granulomatous inflammation of small to medium-sized vessels associated with ANCA. This disease is often presented in the classic form, which involves the kidney and the respiratory tract. It can also affect one or two organ systems and typically spares the kidneys. In this study, we found interesting that Wegener's Granulomatosis in children can present as a solitary, localized form, as in this case, which only affected the conjunctiva. Moreover, the most prevalent clinical manifestations of WG included necrotizing glomerulonephritis, sinusitis, and pulmonary infiltrates. Sinusitis that was identified through MRI was one typical manifestation found in the patient presented in this study. However, the Ear, Nose, and Throat Department found no anomaly during their consultations.[5, 6]

Almost half of the patients experienced ocular and orbital involvement, which may be the first signs of WG. These symptoms include inflammatory conditions of the orbit, episcleritis, scleritis, uveitis, nasolacrimal duct obstruction, peripheral ulcerative keratitis, dacryoadenitis, and optic nerve illness, as well as retinal vasculitis. Moreover, conjunctival

involvement also occurred in approximately 16% of WG patients and the early sign often manifested as conjunctival hyperemia. Further cicatrizing conjunctivitis may result from granuloma necrosis and ulceration. Progressive conjunctival cicatrization may also lead to symblepharon, which is the formation of fibrovascular tissue that covers the ocular surface. Symptoms of conjunctival involvement include eye redness, blurred vision, foreign body sensation, as well as bloody tears in some cases. As we found in our case, there was granuloma formations in the palpebral and bulbar conjunctiva which bleed easily with friction along with white mucopurulent eye discharge. Ectropion was also observed in the lower eyelid.[7, 8]

Nejebat et al. noted a case of protracted conjunctivitis in a 37-year-old guy with Wegener's granulomatosis. After receiving treatment for conjunctivitis for a month, the patient unexpectedly started experiencing photophobia, ocular pain, as well as diminished visual acuity in the left eye. According to immunologic tests, the patient had cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA). Subsequently, the patient experienced worsening Peripheral Ulcerative Keratitis (PUK), scleritis, and scleromalacia, which was treated with oral cyclophosphamide, followed by pulse treatment of intravenous (IV) methylprednisolone. Although prolonged conjunctivitis in WG was thought to be uncommon, a delay in identification can lead to blindness and death.[9]

Conjunctivitis in Wagener's granulomatosis may become ulcerative and necrotic, leading to cicatricial alterations to the ocular surface. Tarsal conjunctivitis can also cause areas of necrosis, active fibrovascular alterations, and fibrovascular scarring. Subglottic stenosis and nasolacrimal duct obstruction may both cause tarsal conjunctivitis. Robinson et al. conducted a study examining all patients who were referred to the eye clinic with the diagnosis of WG. Among the 82 WG patients investigated for 6.5 years, 13 (16%) patients developed a tarsal-conjunctival illness. The median age of these patients at diagnosis of the illness was 47 years, and 11 patients were male. All the patients had at least one eyelid affected by tarsal-conjunctival illness, only two had a bulbar conjunctival disease, and 5 patients had a bilateral tarsal-conjunctival illness. Furthermore, among patients with upper eyelid involvement, 5 also had lower eyelid involvement. The most frequent locations for tarsal-conjunctival lesions were the superior border of the upper eyelid and the inferior border of the lower eyelid.[10]

A better understanding of the etiology of tarsal-conjunctival lesions can clarify the disease's predominant distribution in the superior and inferior borders of the upper as well as lower eyelids, respectively. The terminal branches of the marginal and peripheral arcade vessels provide the upper and lower eyelid tissues with their circulatory supplies. The mostly avascular superior part of the tarsus of the upper eyelid may, however, be a factor in the

occlusive vasculitis of the peripheral arcade arteries and branches. This may result in ischemia, and infarction, as well as ultimately provide an explanation for the pattern of horizontal tissue destruction in the area of the posterior eyelid. Due to a richer blood vessel supply, the lower eyelid may be less prone to tissue infarction.[10]

Conjunctival hyperemia with or without granuloma formation and areas of apparent necrosis were the disease's initial symptoms in patients with early disease at presentation who had long-term follow-up. Among six patients with active disease, four had entropion in one or both eyes due to contracture deformities of the tarsus. Moreover, two of these patients exhibited trichiasis symptoms in both eyes. The histopathologic results from eyelid biopsies found conjunctival and tarsal scarring, granulomatous inflammation, and necrosis, as well as occlusive vasculitis. Therefore, in order to fully analyze the palpebral area, it is advised to routinely eversion the upper and lower eyelids during the assessment of patients with WG. This is because the tarsal-conjunctival involvement was most commonly found on this location.[10]

A case of persistent cicatrizing conjunctivitis with negative antineutrophil cytoplasm antibodies was also described in the study by Miserocchi et al (ANCA). The patient had been experiencing redness, itchiness, and a foreign body sensation in both eyes for two years. Epilation as well as topical corticosteroids were used in the treatment, but there was no change. An external examination revealed trichiasis, diffuse conjunctival injection, mucous strands in the inferior fornix, bilateral fornix foreshortening, as well as symblepharon development. Histopathology analysis of a conjunctival sample revealed striking microangiopathy with vaso-occlusion and extensive inflammatory cell infiltration of the conjunctival stroma. The patient's Wegener granulomatosis caused catastrophic lung problems, which led to the death. Despite receiving methotrexate, the patient's ocular and extraocular mucosal inflammation persisted, leading to the development of peripheral ulcerative keratitis.[11]

Non-specific conjunctival inflammation is a possible conjunctival symptom of Wagener's granulomatosis with or without cicatricial changes. In a case study by Jordan et al., an enlarged left upper eyelid exhibited trichiasis and an eyelid notch affecting the medial 20% of the eyelid edge. The entire palpebral surface displayed pronounced conjunctival inflammation, cicatricial alterations, and surface abnormalities. During the follow-up care 7.5 months later, a spontaneous conjunctival adhesion was found to have formed in the lateral canthus and the patient tested positive for c-ANCA. The patient had cyclophosphamide and prednisone treatment. Eyelid biopsy results showed perivascular inflammation areas as well

as chronic granulomatous inflammation suggestive of WG. For the past years, the prognosis has improved due to the combined use of prednisone and cyclophosphamide.[12]

Orbital inflammatory illness or pseudotumor is a typical WG ocular symptom. The rare presentation of painless bulbar-conjunctival ulcer without underlying episcleritis or scleritis described by Toh et al. showed the possibility of a dangerous underlying pathology, even in the presence of a painless ulcer. The patient also experienced a transient left visual loss that lasted for 15 minutes before full recovery. Upon examination, the patient was found to have a modest 2 mm right proptosis, engorged right eye, and twisted episcleral blood vessels. The patient also encountered a sudden and complete loss of vision in the left eye as well as a fundus examination showed a left central retinal artery occlusion (CRAO). Serum antineutrophil cytoplasmic antibodies (c-ANCA) were significantly elevated. For the first three days of treatment, the patient received 1000 mg/day of intravenous methylprednisolone. The vast clinical and pathological spectrum of WG was highlighted by this case, underscoring the need to maintain a high index of suspicion for this condition. This is due to the fact that the disease can advance quickly, as seen by the emergence of the left CRAO soon after the presentation.[13]

Considerations for diagnosis workups include the histological evidence of the damaged organ, the ANCA result, and the clinical signs that suggest the existence of vasculitis. In 1990, the American College of Rheumatology (ACR) defined 4 criteria, at least 2 of which should be met to diagnose WG, including 1) alterations in urine sediments like hematuria and hematic cylinders, 2) histology with perivascular granulomas presence 3) alterations in pulmonary radiology, and 4) sinus involvement. Approximately 82–94% of WG patients had positive ANCA results, leaving only 10% of individuals with negative results. Patients with specific disorders, as reflected in our study, were more frequently discovered to be ANCA-negative. Although it was recommended to repeat the ANCA test six months after the first test, there was no agreement on how often and according to what procedures ANCA testing should be repeated. According to Kemna et al., longitudinal ANCA measures are less valuable in individuals with the nonrenal disease but may be helpful in those with renal involvement. [5, 14, 15]

Tissue diagnosis of active sites plays a crucial role in confirming WG. In most cases of ANCA positivity, treatment may be initiated without a biopsy result. However, a biopsy is required to verify the diagnosis when the ANCA test is negative. Histological findings are comparable between ANCA-positive and ANCA-negative diseases.[5, 14]

A biopsy can confirm the diagnosis, particularly in cases of orbital WG and conjunctival involvement. When a granuloma is present, the conjunctiva is a potential site for biopsy. According to Ursea et al., a conjunctival biopsy is an easy and minimally invasive procedure to support granulomatosis with polyangiitis diagnosis. Isa et al. stated that vasculitis, necrosis, neutrophil, eosinophil, and macrophage infiltration of orbital tissue are all related to a clinical diagnosis of WG. Recommendations by EULAR has stated that positive biopsy is strongly supportive of diagnosis of vasculitis, therefore, biopsy can be used to support a new diagnosis and for further evaluation for patients suspected of having relapsing vasculitis. [8, 16, 17,18]

The treatment of Wegener's Granulomatosis consists of two phases, namely the induction phase, from 6 to 12 months to achieve remission. Secondly, the maintenance phase, which lasts from 24 to 48 months to consolidate the remission and avoids relapses. For induction of remission in patients with new-onset or relapsing WG with organ-threatening or life-threatening disease, EULAR recommends treatment with a combination of glucocorticoids (GCs) and either Rituximab (RTX) or Cyclophosphamide (CYC). RTX is more preferred in relapsing disease. The recommended starting dose of oral GCs is 50-75 mg prednisolone equivalent/day, depending on body weight. For the non-organ-threatening or non-life-threatening WG, treatment with a combination of GCs and RTX is recommended. Methotrexate (MTX) or Mycophenolate Mofetil (MMF) can be considered as alternatives to RTX. For the maintenance phase, EULAR recommends treatment with RTX. Azathioprine (ZA) or MTX can be considered as alternative. In patients with signs and/or symptoms raising suspicion of a WG diagnosis, supported by ANCA or tissue biopsy, the initiation of treatment should not be delayed. However, due to communication issues, the patient in this study has not received treatment until now.[18]

CONCLUSION

In conclusion, this study showed the consideration for Wegener's Granulomatosis diagnosis in limited form, despite the normal lung and kidney function and negative ANCA-test. The clinical suspicion of WG based on symptoms and signs and alternative diagnostic criteria using tissue biopsy might be helpful in such cases for starting the treatment.

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