



Management of Orbital Granulomatous Polyangiitis Presenting with Lacrimal Gland Involvement: Treatment of Subsequent Peripheral Ulcerative Keratitis, Anterior Uveitis, and Exudative Retinal Detachment in a Challenging Case

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Abstract

This case report discusses a case of granulomatosis with polyangiitis (GPA) initially presenting with lacrimal gland involvement and subsequently developing additional features. GPA is a disease known for inflammation in the respiratory tract and kidneys. A 63-year-old male patient presented with a mass, swelling, and ptosis in the right upper eyelid. The patient was referred to us when his symptoms had persisted and worsened despite topical and oral antibiotic therapy administered at another center. Based on clinical and laboratory findings from evaluation and consultations, GPA was diagnosed and confirmed by biopsy. The patient initially presented with necrotizing scleritis and later developed peripheral ulcerative keratitis and anterior uveitis, which regressed under cyclophosphamide treatment but progressed to exudative retinal detachment due to orbital involvement. Clinical remission was achieved after adding rituximab therapy. Presentation with lacrimal gland involvement may serve as an initial manifestation of locally aggressive orbital and adnexal GPA, which can exhibit variable clinical features. Rapid diagnosis and aggressive treatment are critical for preserving vision and preventing complications in patients with GPA.

Keywords: Granulomatosis with polyangiitis, lacrimal gland, peripheral ulcerative keratitis, retinal detachment, necrotizing scleritis, uveitis

Introduction

Granulomatosis with polyangiitis (GPA) is a rare autoimmune condition characterized by vasculitis primarily affecting the respiratory tracts and kidneys.¹ Predominantly observed in Caucasians, GPA shows a peak incidence in the fifth decade of life and is less common in individuals under 19 years old.² Both sexes are equally affected, although in Europe the incidence is relatively higher among men.³ Diagnostic markers such as serum cytoplasmic antineutrophil cytoplasm antibodies (c-ANCA) are crucial, and up to 80% of ANCA-positive GPA patients present with antibodies against proteinase 3 (PR3). Ophthalmic involvement is common, with over half of patients experiencing related symptoms, including vision loss in 8% of cases.⁴ Orbital GPA occurs in 45% of patients and may be the initial symptom in 16% of cases.⁵ In the present case, we report initial involvement of the lacrimal gland that subsequently progressed to an orbital mass and led to significant ocular complications.

Case Report

In this case study, we present a 63-year-old male diagnosed with GPA initially affecting the lacrimal gland and adjacent sclera. Despite treatment, the condition rapidly progressed to peripheral ulcerative keratitis (PUK), leading to widespread orbital masses and exudative retinal detachment. This report offers an overview of the disease progression and medical management of ocular manifestations in this case. The study adhered to the principles of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act. The patient consented to the publication of his anterior segment photographs.

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A 63-year-old Caucasian male who was initially seen at the neurosurgery clinic presented to the Ophthalmology Department of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital with complaints of right upper eyelid swelling, ptosis, and eye redness. He reported that his symptoms had worsened despite three months of treatment with topical Maxidex eye drops (dexamethasone 0.1%, Alcon Laboratories, Inc., Fort Worth, TX, USA) and oral Monodoks antibiotic (doxycycline 100 mg, Deva Holding Co., İstanbul, Türkiye). Examination revealed a Snellen best-corrected visual acuity of 20/30 in the right eye (OD) and 20/20 in the left eye (OS), with intraocular pressures of 23 mmHg OD and 15 mmHg OS. The right upper eyelid exhibited ptosis and proptosis, with a palpable mass in the superotemporal quadrant of the orbit. Extraocular muscle movements were normal. Anterior segment examination showed ciliary injection, marked erosion, and necrosis in the superotemporal quadrant of the bulbar and forniceal conjunctiva (Figure 1a, b), along with necrotizing scleritis in the adjacent sclera (Figure 1c). The area of necrotizing scleritis measured approximately 2x4 mm. Fundoscopic examination revealed retinal pigment epithelium (RPE) changes in the bilateral macula consistent with age-related macular degeneration. A computed tomography (CT) scan revealed an intraorbital mass without bony destruction (Figure 1d) and magnetic resonance imaging (MRI) indicated a heterogeneously enhancing mass in the superotemporal orbit (Figure 1e). By joint decision with the neurosurgery department, excisional biopsy (Figure 1f) involving a superotemporal orbitotomy and right dacryoadenectomy was performed as a collaborative effort between the neurosurgery and ophthalmology departments. Three days after surgery, we noted persistent conjunctival necrosis and necrotizing scleritis, with the new development of PUK (Figure 2a). Additionally, +2 cells

were observed in the anterior chamber, along with iris pigments on the anterior lens capsule (Figure 2b).

The patient, now medically stable, was transferred to an ophthalmology inpatient clinic for further evaluation and intervention. Potential infectious etiologies such as tuberculosis, syphilis, fungal infections, and viral causes were thoroughly considered and excluded through comprehensive laboratory tests. Blood tests revealed anti-PR3 antibodies at levels >200 RU/mL (relative units per milliliter) and positive c-ANCA. Anti-myeloperoxidase (anti-MPO) antibody levels were negative (<2 U/mL, with C3 and C4 levels within normal range (1.44 and 0.21 g/L, respectively). Inflammatory markers such as C-reactive protein (95.58 mg/L) and erythrocyte sedimentation rate (55 mm/h) were elevated. Due to the rapid progression of inflammatory signs such as PUK, anterior uveitis, and necrotizing scleritis, as well as consistent laboratory tests including positive c-ANCA, we suspected GPA and promptly initiated high-dose intravenous methylprednisolone (500 mg for 3 days; Prednol, Mustafa Nevzat Pharmaceutical Industry Co., İstanbul, Türkiye) followed by oral tapering to prevent vision loss and further tissue damage without waiting for the definitive pathology report.

The pathology report later confirmed geographic necrosis, granuloma formation, fibrosis, vasculitis, and giant cell formation (Figure 2c, d), suggesting necrotizing granulomatous disease consistent with GPA. Following clinical, serological, and radiological assessments confirming GPA, consultations with the rheumatology, pulmonary medicine, and otorhinolaryngology departments were initiated for systemic evaluation. Incidentally, two pulmonary nodules were detected on thoracic CT and were monitored. No renal impairment or upper respiratory tract manifestations were observed. As recommended by

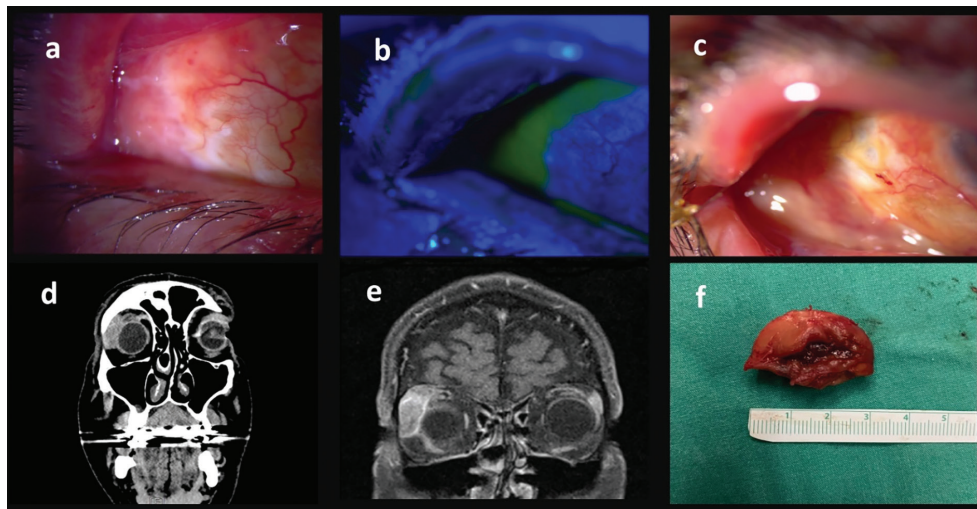


Figure 1. a) Slit-lamp anterior segment examination at presentation showed ciliary injection, marked erosion, and necrosis in the superotemporal quadrant of the bulbar and forniceal conjunctiva. b) After applying 1% fluorescein dye, the cobalt blue filter indicates necrosis in the superotemporal quadrant of the bulbar and forniceal conjunctiva. c) Hemorrhage, conjunctival necrosis, and scleral thinning in the region corresponding to the area where the enlarged palpebral lobe of the lacrimal gland makes contact, consistent with necrotizing scleritis. d) Coronal computed tomography scan of the orbit revealed an intraorbital mass located superotemporally, in the area corresponding to the lacrimal fossa, without any bony erosion. e) A coronal T1-weighted magnetic resonance image of the orbit showed a hyperintense orbital lesion in the lacrimal fossa. f) Excisional biopsy material measuring 30x20 mm was removed from the lacrimal fossa intraoperatively

the rheumatology department, the patient received 500 mg pulse cyclophosphamide (Endoxan, Baxter Oncology GmbH, Halle/Westfalen, Germany) intravenously every two weeks for induction therapy. During treatment, ciliary injection decreased, reconjunctivalization of necrotic areas occurred, scleral thinning improved, necrotizing scleritis regressed, and the PUK stabilized (Figure 2e, f). However, in the 8th week of treatment, the patient reported vision loss. Fundoscopic examination revealed a large exudative retinal detachment in the inferotemporal quadrant of the OD, extending to the macula with associated serous macular detachment (Figure 3a). Optical coherence tomography (OCT) also showed serous retinal detachment and choroidal thickening (Figure 4a). MRI

revealed significant infiltration of granulomatous lesions in the right orbit (Figure 5a, b, c, d), indicating a relapse. Treatment involved 1 g pulse methylprednisolone (Prednol) for 3 days and increased intravenous cyclophosphamide (750 mg; Endoxan), with additional 1000 mg rituximab induction every 2 weeks, followed by maintenance therapy every 6 months (MabThera®, Roche Müstahzarları Sanayi A.Ş., İstanbul, Türkiye).

Five months after rituximab initiation, significant regression of the exudative detachment was observed (Figure 4b), and the serous detachment on OCT gradually resolved over time (Figure 4c). The exudative detachment affecting the inferotemporal quadrant of the retina regressed (Figure 3b) into formations resembling chorioretinal scars, with areas of RPE hyperplasia,

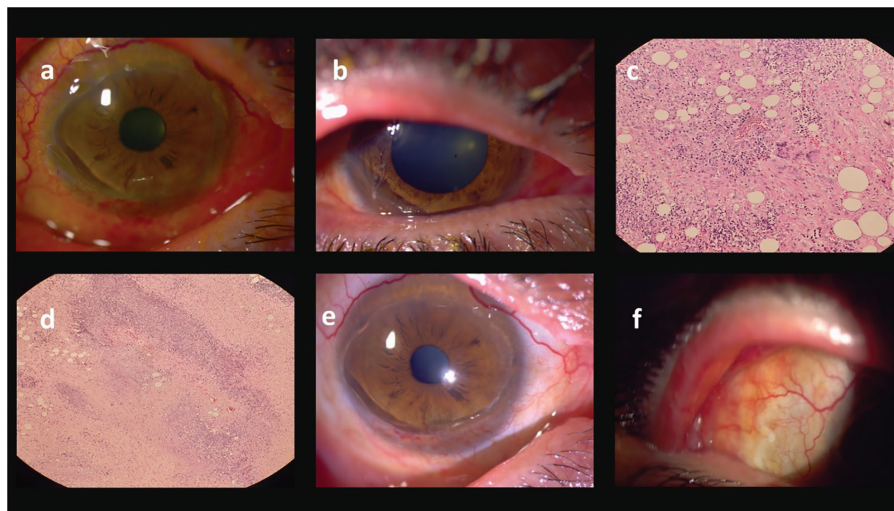


Figure 2. Anterior segment photographs showing (a) onset of peripheral ulcerative keratitis (PUK) and (b) anterior uveitis and iris pigments on the anterior lens capsule. c) On histopathological examination of the mass, high-magnification photomicrograph revealed an area characterized by vasculitis and the presence of giant cells (hematoxylin & eosin [H&E] staining). d) Medium magnification photomicrograph showed an area of geographic necrosis, granuloma formation, and fibrosis (H&E staining). e) Observations during treatment indicated that the PUK area had become demarcated, conjunctival hyperemia had decreased, and vascularization had begun. Healing with lipid degeneration was observed in the superior corneolimbal region. f) Post-treatment images showed the scleral thinning had regressed and the necrotic conjunctival area had reconjunctivalized

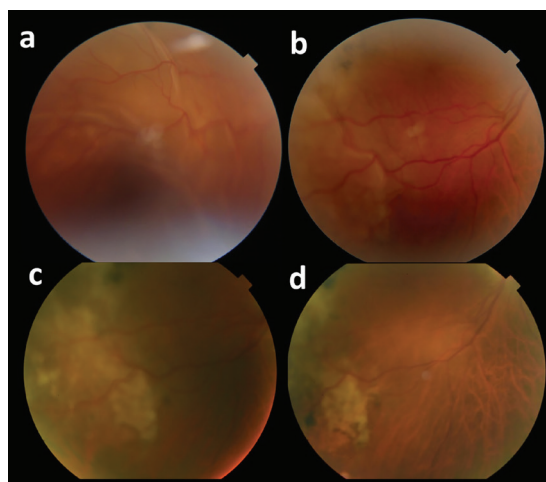


Figure 3. Digital color fundus photographs of the exudative retinal detachment. a) A large exudative retinal detachment was seen in the inferotemporal region of the right eye. b) The exudative retinal detachment appeared to be limited. c) Improvement in the exudative retinal detachment with residual exudation and retinal pigment epithelium (RPE) changes was noted. d) Regression of posterior segment findings with RPE hyperplasia, RPE atrophy, and choroidal alterations was observed

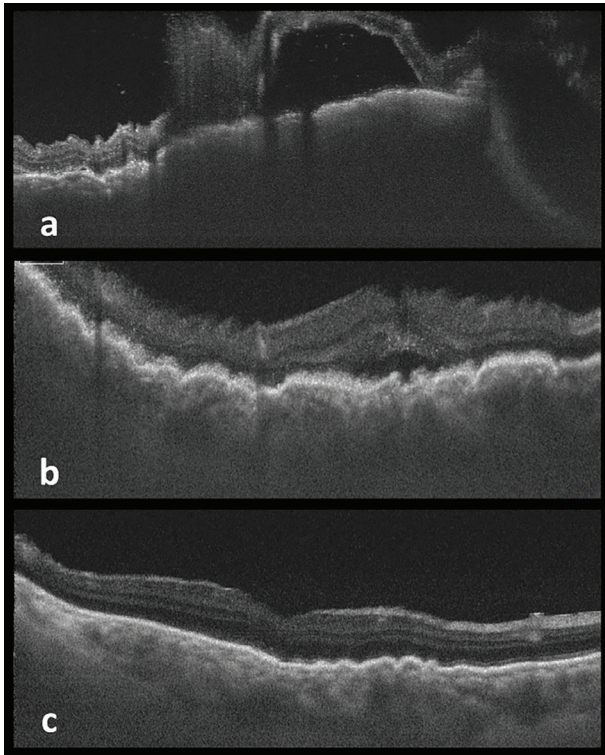


Figure 4. Optical coherence tomography (OCT) sections of the right eye. a) The OCT section passing through the area of exudative retinal detachment. b) The macular OCT section showed diffuse, bumpy choroidal thickening with serous macular detachment. c) The serous detachment on OCT gradually resolved over time

RPE atrophy, and choroidal alterations (Figure 3c). Maintenance corticosteroids were gradually tapered to 8 mg/day and were supplemented by methotrexate (15 mg/week; Metoart®, Deva Holding Co., İstanbul, Türkiye) around the 7th month of treatment. Rituximab effectively controlled the recurrent orbital GPA episode, resulting in regression of posterior segment findings (Figure 3d). The final BCVA was 70/100 OD.

Discussion

This case report describes a patient with GPA presenting with a lacrimal gland mass and necrotizing scleritis without systemic symptoms. GPA can affect various organs, and up to sixty percent of patients experience ocular symptoms.⁶ Eye involvement can occur at any stage of the disease, either as a limited or systemic condition. However, Tan et al.⁷ found that none of their patients with lacrimal gland involvement developed systemic symptoms, suggesting possible long-term localization. Despite this, they noted significant progression of orbital disease necessitating systemic immunosuppressive therapy in all cases, with high ocular morbidity. Similarly, our patient's orbital disease advanced without systemic involvement despite effective therapy.

In the differential diagnosis of a patient presenting with lacrimal gland enlargement, PUK, and necrotizing scleritis, it is

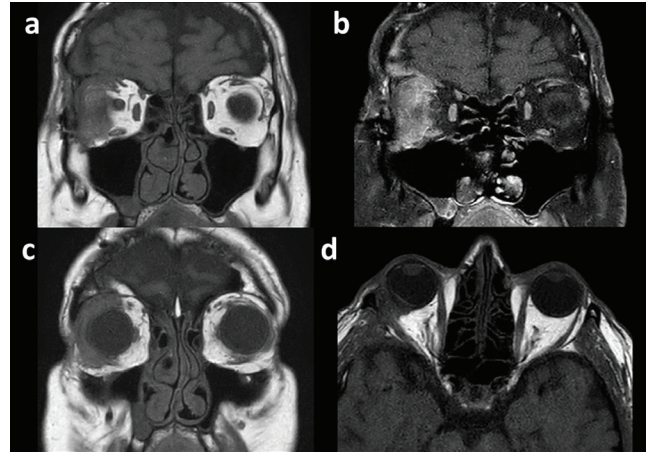


Figure 5. Imaging of the orbital structures using different magnetic resonance imaging (MRI) sequences. a) A coronal T1-weighted orbital MRI scan showed that the granuloma extended to the apex of the orbit, in proximity to the optic nerve. b) A coronal T1-weighted orbital MRI scan with contrast and fat suppression revealed contrast enhancement (hyperintensity) in the region corresponding to the orbital granuloma. c) A coronal T1-weighted orbital MRI scan revealed a presentation consistent with an intraorbital granuloma surrounding the globe circumferentially and involving the superior, inferior, and temporal aspects. d) An axial T1-weighted orbital MRI scan indicated relapse, with intraorbital infiltration and exudative retinal detachment in the right eye

crucial to consider a variety of conditions that mimic the clinical features of GPA. Sarcoidosis is a key consideration, as it can present with lacrimal gland masses and ocular inflammation.⁸ However, it typically lacks the necrotizing vasculitis seen in GPA and is characterized by non-caseating granulomas. Infectious etiologies, such as tuberculosis or syphilis, should also be ruled out, particularly in the presence of orbital granulomas or necrotizing scleritis, as these infections require specific antimicrobial treatments.^{9,10} Idiopathic orbital inflammation is another important differential diagnosis. It presents with orbital masses but lacks systemic vasculitis and is ANCA-negative.¹¹ Another neoplastic condition to consider is lymphoma, especially in cases involving lacrimal gland masses.¹² However, biopsy findings in lymphoma show monoclonal lymphoid proliferation rather than granulomatous inflammation and necrosis.

Immune cells and substances that cause inflammation often move to the peripheral cornea through chemotaxis from the nearby sclera and episcleral tissues. This process can result in the formation of PUK.¹³ The patient in our case report developed conjunctival necrosis, scleral thinning, and PUK with anterior uveitis. Corneal involvement can be a primary manifestation of GPA as well as a secondary manifestation of orbital and conjunctival disease resulting in cicatrization, tear film deficiency, poor eyelid closure, and trichiasis.¹⁴ Previous research has demonstrated that the existence of PUK and necrotizing scleritis are indicative of an unfavorable prognosis regarding the severity of systemic GPA.¹⁵

Orbital involvement has been identified as the first or second most prevalent ocular finding after conjunctivitis/episcleritis, accounting for 15% of all cases and 45% of all

ocular manifestations. In a retrospective study including 74 patients with orbital GPA, it was observed that 35.1% of patients presented with isolated lacrimal gland involvement, while orbital mass involvement (without primary lacrimal gland involvement) was seen in 60.8%. The group with orbital mass involvement was noted to have a more severe disease course compared to the group with isolated lacrimal gland involvement. Additionally, the orbital mass group exhibited significantly more anterior segment findings (e.g., necrotizing scleritis, PUK), ANCA-positivity, and visual loss, a higher incidence of systemic disease, and a greater association with relapses in comparison to the group with isolated lacrimal gland involvement.¹⁶

MRI is more effective than CT in detecting orbital granulomas and mucosal changes. On the other hand, CT is more useful for assessing the destruction of bones and the hardening of sinus walls in orbital GPA with sinonasal involvement. Orbital granulomas appear hypointense on T2 images and may show varying levels of contrast enhancement.¹⁷ Orbital GPA can be difficult to distinguish from other orbital inflammatory conditions based solely on clinical features. However, the presence of sinonasal involvement and bony changes on imaging strongly indicate orbital GPA. Nevertheless, during our initial presentation, there were no signs of bone erosion or sinonasal manifestations. In suspected cases of GPA, biopsy of the orbital lesion is performed to obtain a definitive pathological diagnosis due to the unusual presentations and non-specific clinical findings. The biopsy often demonstrates the typical histological characteristics of GPA, including vasculitis, necrosis, and granulomatous inflammation. However, Kalina et al.¹⁸ discovered that the traditional pathological triad was observed in only 54% of orbital biopsies, whereas it was identified in 91% of open lung biopsies. Thus, the lack of the typical histopathological findings does not exclude the diagnosis of orbital GPA.

Retinal and choroidal involvement in GPA is uncommon. Ismailova et al.¹⁶ reported that retinal involvement was detected in 4.4% of all ophthalmic manifestations. Retinal disease manifestations may include retinal vasculitis, retinal vein occlusion, and rarely, exudative retinal detachment.¹⁹ Posterior scleritis or chorioretinal granulomas can also lead to exudative retinal detachment. Furthermore, in patients presenting with widespread exudative detachment, Sugisawa et al.¹⁹ suggested that GPA-associated necrotizing scleritis and inflammation spread may contribute to the development of exudative retinal detachment. In our case, the exudative detachment area was more limited, and it was postulated that the orbital granuloma caused choroidal compression, resulting in choriocapillaris ischemia and RPE pump dysfunction. Following rituximab therapy, as the granulomas diminished and compression symptoms improved, the exudative detachment regressed, leading to healing with the formation of chorioretinal scars. Similar to the case reported by Sugisawa et al.¹⁹, the noteworthy development of exudative detachment under cyclophosphamide treatment in our case suggests that GPA presenting with exudative detachment may indicate resistance to initial treatment.

The primary goal of treating GPA is to induce and maintain remission of the disease. Cyclophosphamide and glucocorticoids form the cornerstone of GPA treatment, providing remission in 70-90% of patients. However, due to the potential side effects of cyclophosphamide, such as cytopenia and the risk of cancer, and the fact that 50% of those who achieve remission may experience relapse within 2 years, there is a clear necessity for alternative treatment options.²⁰ Rituximab, an anti-CD20 monoclonal antibody, recently emerged as an alternative to traditional treatments. A multicenter study on ANCA-associated vasculitis showed that rituximab was as effective as cyclophosphamide in treating the disease without significant adverse effects. Moreover, rituximab was found to be superior to cyclophosphamide in the treatment of relapsed disease.²¹ There are also some studies in the literature showing the effectiveness of rituximab in treating orbital GPA.²² In our case, rituximab therapy was chosen due to the recurrence of orbital disease under cyclophosphamide and maintenance corticosteroid treatment. Additionally, in GPA, there is a higher likelihood of orbital masses showing a refractory course. In one series, complete remission in orbital masses was observed in only 8.1% of 37 patients, with disease progression seen in 40% despite initial treatment.²³ These findings indicate the need for alternative treatment options in this group. Given that rituximab is a well-known systemic treatment for GPA, its intralesional or intraorbital application in refractory orbital masses could be similarly effective.²⁴ This emphasizes the need for further research in this area to explore the potential efficacy of intralesional rituximab in treating refractory orbital masses.

In conclusion, presenting with lacrimal gland involvement may be an initial manifestation of locally aggressive orbital and adnexal GPA, which displays variable clinical features. Despite the common belief in the literature that lacrimal gland involvement is associated with a favorable prognosis, our case highlights the potential coexistence of multiple ophthalmic conditions in the same individual but at different times, such as lacrimal gland enlargement, PUK, anterior uveitis, necrotizing scleritis, orbital mass, and exudative retinal detachment. Our aim was to contribute this perspective to the literature.

Ethics

Informed Consent: Obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: M.O., H.S.K., H.S., T.Ç., M.E.T., Concept: M.O., M.E.T., Design: M.O., H.S.K., T.Ç., Data Collection or Processing: M.O., E.S., T.Ç., Analysis or Interpretation: M.O., H.S., Literature Search: M.O., E.S., H.S., M.E.T., Writing: M.O., E.S., H.S.K.

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