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Case Report

Granulomatosis with Polyangiitis Presenting with Bilateral Orbital Apex Syndrome

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Granulomatosis with polyangiitis · Orbital apex syndrome · Myeloperoxidase-anti-neutrophil cytoplasmic antibody

Abstract
We report a rare case of granulomatosis with polyangiitis (GPA) presenting with bilateral orbital apex syndrome (OAS). A 73-year-old woman with a history of endoscopic sinus surgery for ethmoidal sinusitis experienced a sudden decrease in visual acuity (VA) of both eyes. At the initial examination, her VA had decreased to 0.01 in the right eye and 0.03 in the left eye, and eye movement in both eyes was mildly limited in all directions. Visual field tests of both eyes showed a large central scotoma. Laboratory tests revealed an elevation of myeloperoxidase-anti-neutrophil cytoplasmic antibody. Facial computed tomography demonstrated a thickened mucosal membrane in the entire ethmoidal sinus, and the posterosuperior walls of Onodi cells filled with infiltrative lesions had thinned. Orbital magnetic resonance imaging showed severe inflammation in the orbital apex. From these clinical findings, the patient was diagnosed with GPA presenting with OAS associated with ethmoid sinusitis. Emergent endoscopic sinus surgery was performed for biopsy and debridement of the ethmoidal and sphenoid sinusitis to decompress the optic nerve. One day after endoscopic sinus surgery, the patient's VA and visual field were improved, and steroid pulse therapy was commenced postoperatively. Four

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days later, VA had recovered to 1.0 in both eyes, and eye movement and visual field had were improved. Although OAS is a rare manifestation, early surgical treatment should be considered when the orbital lesion presents as risk of rapid deterioration of visual function in patients with GPA.

Introduction

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a rare systemic autoimmune disease of unknown etiology that commonly affects the organ systems of the upper respiratory tract, lungs, and kidneys [1, 2]. The pathological alterations are characterized by granulomatous inflammation, tissue necrosis, and variable degrees of vasculitis in small and medium-sized blood vessels. Ocular manifestations are common and are present in 50% of cases [3]. Among these, orbital involvement is the most frequent manifestation, occurring in 22–45% of cases with ocular manifestations [3–5]. As a rare ocular manifestation, orbital apex syndrome (OAS) associated with GPA has been demonstrated in several reports [6–9]. OAS is characterized by optic neuropathy and total ophthalmoplegia caused by the damage of II, III, IV, V1, and VI cranial nerves due to the lesion of the orbital apex. The differential diseases broadly include infection, noninfectious inflammation such as sarcoidosis, idiopathic intraorbital inflammation, hypertrophic pachymeningitis, rheumatic polyarthritis, tumor invasion, vasculitis, and trauma [10]. Here, we report a case of GPA presenting with bilateral OAS caused by the spread of inflammation from extensive ethmoid sinusitis, in which visual function was completely recovered using a combination of early optic nerve decompression and treatment with oral prednisolone and cyclophosphamide.

Case Presentation

A 73-year-old woman noticed a loss of visual acuity (VA) in both eyes. One month later, her best-corrected VA (BCVA) decreased to 0.6 in the right eye and 0.4 in the left eye, and 10 days later, the BCVA of both eyes decreased to 0.1. She was referred to our hospital for further examination. The patient had a history of paranasal sinus surgery 2 years prior to presentation and hypertension with an unknown onset period. At the initial examination, her BCVA had further decreased to 0.01 in the right eye and 0.03 in the left eye. Intraocular pressure was 15 mm Hg in both eyes. Direct light reflex of both eyes was sluggish and incomplete, and the right eye had a relatively afferent pupillary defect. The eye movement of both eyes showed a mild limitation in all directions (Fig. 1a). Slit-lamp biomicroscopy showed a slight injection of bulbar conjunctiva and slight senile cataracts in both eyes. Fundus examination revealed slight hyperemia of the optic disc in both eyes. Goldmann kinetic perimetry revealed large central scotomas in both eyes (Fig. 2a, b). Optical coherence tomography did not show any abnormalities of the optic disc or retinal architecture in either eye.

Laboratory tests showed an increase in the number of white blood cells (118,000/μL), erythrocyte sedimentation (124 mm/h), and C-reactive protein (10.42 mg/dL). Furthermore, the complement titer, myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA), and s-IL-2 increased to 83.7 U/mL (normal 30–450 U/mL), 235.1 U/mL (normal 0–3.5 IU/mL), and 854 U/mL (normal 122–496 U/mL), respectively. Anti-herpes simplex IgG

antibody, anti-varicella-zoster virus IgG antibody, and anti-cytomegalovirus IgG antibody were 79.4 (normal 0–2.0 antibody titer), 6.0 (normal 0–2.0 antibody titer), and 5.9 AU/mL (normal 0–11 AU/mL), respectively, indicating prior infections. Serum creatinine was within the normal range. The beta-D-glucan level was less than the reference value. Urinary examination showed an increase in urinary beta-2 microglobulin (345 μg/L, normal 0–290 μg/L). Cerebrospinal fluid examination showed no elevation in cell count (<1) or protein level (26 mg/dL).

Facial computed tomography (CT) revealed a thickened mucosal membrane in the entire ethmoidal sinus and an opening of the bone in the left Onodi cell, which seemed to have been created intentionally during the previous operation (Fig. 3a). The right Onodi cell was filled with infiltrative lesions, and the posterosuperior wall of the Onodi cell was obscure bilaterally (Fig. 3a, b). Orbital T1-weighted magnetic resonance imaging (MRI) with Gd-DTPA showed enhanced infiltrative lesions around the bilateral orbital apex (Fig. 3c). The imaging findings also showed extensive posterior ethmoid sinusitis that seemed to invade or compress the medial wall of the optic canal and orbital apex bilaterally. On day 2 after admission, endoscopic sinus surgery was performed to remove the thickened mucosal membrane and decompress the optic canal. Pathological examination of the extracted nasal membrane revealed a number of inflammatory cells but no granulomatous changes (i.e., negative for infection). From these clinical findings, the patient was diagnosed as having bilateral OAS caused by extensive inflammation associated with ANCA-associated vasculitis, likely via paranasal sinusitis. According to the algorithm of Watts's classification, this case was classified as GPA based on the presence of paranasal sinusitis that lasted for >3 months and a positive result of MPO-ANCA. On day 3 after admission, steroid pulse therapy was commenced, and the patient's VA and visual field rapidly recovered by the next day after surgery (Fig. 2c, d). At that time, the BCVA of both eyes had increased to 0.2 in the right eye and 0.7 in the left eye. On day 7 after admission, her BCVA had increased to 0.9 in the right eye and 1.2 in the left eye, and the large central scotomas had nearly disappeared (Fig. 2e, f). On day 14 after admission, her BCVA had further increased to 1.0 in the right eye and 1.5 in the left eye. After a course of steroid pulse therapy, combined therapy of oral prednisolone 45 mg and methotrexate was initiated. On day 21 after admission, the patient's eye movement disturbance had disappeared (Fig. 1b). To date (3 years after treatment), no recurrence of paranasal sinusitis or deterioration of her systemic condition has developed.

Discussion and Conclusion

Combined therapy of steroids with either cyclophosphamide or methotrexate is established as the standard treatment for GPA. GPA is recognized as a treatable disease with survival rates as high as 80% after 10 years of follow-up [2, 11]. Nevertheless, early diagnosis and an appropriate interdisciplinary approach are critical for managing GPA. Occasionally, specific surgical options may be chosen for diagnostic purposes or when the disease involves the orbits, optic canal, and nasolacrimal drainage system. Jiang et al. [12] revealed that among 19 cases of GPA with ocular and nasal manifestations, 14 cases had been misdiagnosed for 2–36 months, resulting in a delay in the initiation of treatment. Eventually, the diagnosis of 17 cases was determined by nasal biopsy.

With regard to early intervention, Fishman et al. [13] reported two cases of GPA with orbital involvement whose visual function deteriorated rapidly with resistance to medical

management. One case presented with a left diffuse intraorbital lesion and received emergent orbital decompression surgery. The patient's VA increased postoperatively from finger counting to 6/24. In the present case, imaging tests revealed contiguous invasion of the optic canal and the orbital apex from the extensive ethmoid sinusitis. Furthermore, the rapid improvement in VA observed the day after surgery suggests that early intervention to relieve mechanical compression or remove the infiltration might be an effective treatment choice.

Overall, in the differential diagnosis of GPA, it is necessary to consider not only ophthalmic diseases but also various systemic diseases. Regarding the systemic approach, the diseases occurring due to upper or lower respiratory inflammation, glomerulonephritis, and paranasal sinusitis should be included as differential diseases. In case of ophthalmic diseases, GPA has diverse ophthalmic manifestations involving the orbital, conjunctiva, sclera, retina, choroid, and optic nerve [14]. Being the most frequent ocular manifestation, orbital involvement of GPA is broadly associated with various pathological conditions such as infectious, inflammatory, and neoplastic diseases. Thus, the differential diseases are broad-ranging orbital diseases such as dysthyroid ophthalmopathy, idiopathic orbital inflammation, Churg-Strauss syndrome, Erdheim-Chester syndrome, Tolosa-Hunt syndrome, sarcoidosis, and orbital tumor metastasis. Next, scleritis and episcleritis are also frequent involvements of GPA, whose differential diseases may include rheumatoid arthritis and relapsing polychondritis. Therefore, when patients present with these symptoms, comprehensive examinations, including a blood test, imaging test, and radionuclide scanning, must be performed to establish a diagnosis of GPA. In particular, a blood test for ANCA, an imaging test with CT or MRI to detect orbital and pulmonary inflammatory lesion, and histological examination are critical for establishing the definitive diagnosis of GPA. To establish the diagnosis using the Watts's classification algorithm, it is necessary to ensure that the cases fulfill the entry criteria before implementing the classification [15]. When the criteria are met with, along with the classification algorithm, the cases can be classified and consequently categorized into eosinophilic GPA, GPA, microscopic polyangiitis, or polyarteritis nodosa. According to the algorithm of Watts's classification, this case was classified as GPA based on the presence of paranasal sinusitis that lasted for >3 months and seropositivity for MPO-ANCA as a surrogate marker.

To date, there have been several case reports of GPA presenting with OAS, and these cases can be divided into those with good and bad visual prognosis. Hisahara et al. [9] documented a case of GPA presenting with OAS caused by recurrent pachymeningitis. Other than OAS, this case presented with facial numbness, facial palsy, and hearing difficulty. Steroid pulse therapy followed by oral medication of prednisolone and cyclophosphamide resulted in an improvement in diplopia, facial palsy, meningeal thickening, and orbital abnormalities. Siddiqui et al. [8] also reported a case of GPA presenting with OAS who achieved good recovery. Laboratory data showed an elevation in inflammatory markers. Facial CT showed proptosis of the left orbit and encapsulated inflammatory soft tissue in the left orbital apex. OAS caused by infection was suspected in this case, and urgent surgery was performed to drain the abscess. This case was diagnosed postoperatively as having GPA based on the pathological examination of intraoperative tissue and positive findings of MPO-ANCA. Intravenous administration of steroids and antibiotics was initiated after surgery, followed by additional oral cyclophosphamide. Consequently, VA and ophthalmoplegia promptly recovered in this case within 1 week after surgery. Foster et al. [6] demonstrated a case of GPA presenting with OAS. CT revealed destruction of the lateral nasal walls and posterior septum with sclerosis of the remaining bony paranasal sinuses. Soft tissue densities occupied the ethmoid, left sphenoid, and frontal sinuses. Repeated biopsy from the mucosal membrane of the nose led to the diagnosis of GPA

within 7 days of the initial examination. Intravenous administration of methylprednisolone and cyclophosphamide was effective, and complete remission of ophthalmic manifestations was achieved. Thus, the prompt diagnosis of GPA might lead to marked recovery of visual function.

By contrast, Chua et al. [16] documented a case of systemic GPA presenting with OAS, severe necrotizing anterior scleritis, and bilateral pansinusitis during the administration of prednisolone. Although a combination therapy of prednisolone and cyclophosphamide was administered, the patient's visual prognosis remained poor, which was probably due to irreversible ischemic optic neuropathy, extensive corneoscleral melt, and corneal neovascularization. Shunmugam et al. [7] also demonstrated an unusual case of GPA presenting with OAS attributed to localized intraorbital inflammation at the apex. This case had received oral administration of both prednisolone and methotrexate for 4 years. Nevertheless, this case suddenly lost light perception and began to feel severe orbital pain and was resistant to intravenous administration of 500 mg methylprednisolone for 5 days. Concurrent MRI showed an enhanced lesion in the orbital apex, which was suspicious for a tumorous lesion induced by methotrexate. To exclude tumorous lesions, a biopsy was performed via the transcaruncular approach. The pathological findings of the optic nerve sheath specimens were consistent with GPA. The patient received intravenous administration of cyclophosphamide and rituximab followed by oral prednisolone, but VA and eye movement disturbance did not recover, although orbital pain was clinically relieved. From these case reports, the visual function of most patients recovered with the use of the combined therapy of immunosuppressants and steroids. However, some cases continued to experience worsened visual function with resistance to treatment. Although more cases need to be examined, the visual prognosis might depend on the severity of GPA or the length of time between the diagnosis and initiation of therapy.

Regarding the management of GPA, at the induction of remission, treatment with a combination of glucocorticoids and either cyclophosphamide or rituximab is recommended. In severe cases, pulse therapy of methylprednisolone and plasma exchange is also considered. Regardless of the beneficial effects of the combination of glucocorticoids and immunosuppressants, the relapse rate will be high unless the combined therapy of glucocorticoids and immunosuppressants is continued. Therefore, to reduce the relapse, it is recommended that the combined treatment of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate, or mycophenolate mofetil be continued for at least 24 months following the induction of sustained remission [17, 18]. In the present case, it was possible to maintain the remission using a long-term combined therapy of low-dose prednisolone and methotrexate.

In conclusion, although OAS is a rare manifestation, early surgical intervention should be considered as a treatment option in patients with GPA when rapid visual impairment is easily predicted because of the inflammatory invasion to the orbital apex.

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Statement of Ethics

This report was published with the permission and written informed consent of the patient.

Conflict of Interest Statement

None of the authors have any conflicts of interest.

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Author Contributions

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References

1 Srouji IA, Andrews P, Edwards C, Lund VJ. Patterns of presentation and diagnosis of patients with Wegener's granulomatosis: ENT aspects. J Laryngol Otol. 2007 Jul;121(7):653–8.
2 Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992 Mar;116(6):488–98.
3 Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med. 1983 Jan;98(1):76–85.
4 Haynes BF, Fishman ML, Fauci AS, Wolff SM. The ocular manifestations of Wegener's granulomatosis. Fifteen years experience and review of the literature. Am J Med. 1977 Jul;63(1):131–41.
5 Bullen CL, Liesegang TJ, McDonald TJ, DeRemee RA. Ocular complications of Wegener's granulomatosis. Ophthalmology. 1983 Mar;90(3):279–90.
6 Foster WP, Greene JS, Millman B. Wegener's granulomatosis presenting as ophthalmoplegia and optic neuropathy. Otolaryngol Head Neck Surg. 1995 Jun;112(6):758–62.
7 Shunmugam M, Morley AM, Graham E, D'Cruz D, O'Sullivan E, Malhotra R. Primary Wegener's granulomatosis of the orbital apex with initial optic nerve infiltration. Orbit. 2011 Jan;30(1):24–6.
8 Siddiqui S, Kinshuck AJ, Srinivasan VR. Orbital apex syndrome secondary to granulomatosis with polyangiitis. BMJ Case Rep. 2013 Dec;2013:bcr2013009519.
9 Hisahara S, Yamada M, Matsuura Y, Tsuda E, Akiyama Y, Saitoh M, et al. ANCA-negative granulomatosis with polyangiitis presenting with orbital apex syndrome and recurrent pachymeningitis: A case report. J Neurol Sci. 2016 Sep;368:175–7.
10 Badakere A, Patil-Chhablani P. Orbital Apex Syndrome: A Review. Eye Brain. 2019 Dec;11:63–72.
11 Villa-Forte A, Clark TM, Gomes M, Carey J, Mascha E, Karafa MT, et al. Substitution of methotrexate for cyclophosphamide in Wegener granulomatosis: a 12-year single-practice experience. Medicine (Baltimore). 2007 Sep;86(5):269–77.
12 Jiang B, Zhao YY, Wei SH. Granulomatosis with polyangiitis: the relationship between ocular and nasal disease. Ocul Immunol Inflamm. 2013 Apr;21(2):115–8.

13 Fishman JM, Slovick A, East CA. Wegener's granulomatosis of the orbit: two cases requiring endoscopic surgical decompression. J Laryngol Otol. 2008 Nov;122(11):1257–9.
14 Sfiniadaki E, Tsiara I, Theodossiadis P, Chatziralli I. Ocular Manifestations of Granulomatosis with Polyangiitis: A Review of the Literature. Ophthalmol Ther. 2019 Jun;8(2):227–34.
15 Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis. 2007 Feb;66(2):222–7.
16 Chua J, Lim L. Systemic Wegener's granulomatosis with severe orbito-ocular involvement. Singapore Med J. 2008 Oct;49(10):e259–62.
17 Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016 Sep;75(9):1583–94.
18 Shi L. Anti-neutrophil cytoplasmic antibody-associated vasculitis: prevalence, treatment, and outcomes. Rheumatol Int. 2017 Nov;37(11):1779–88.

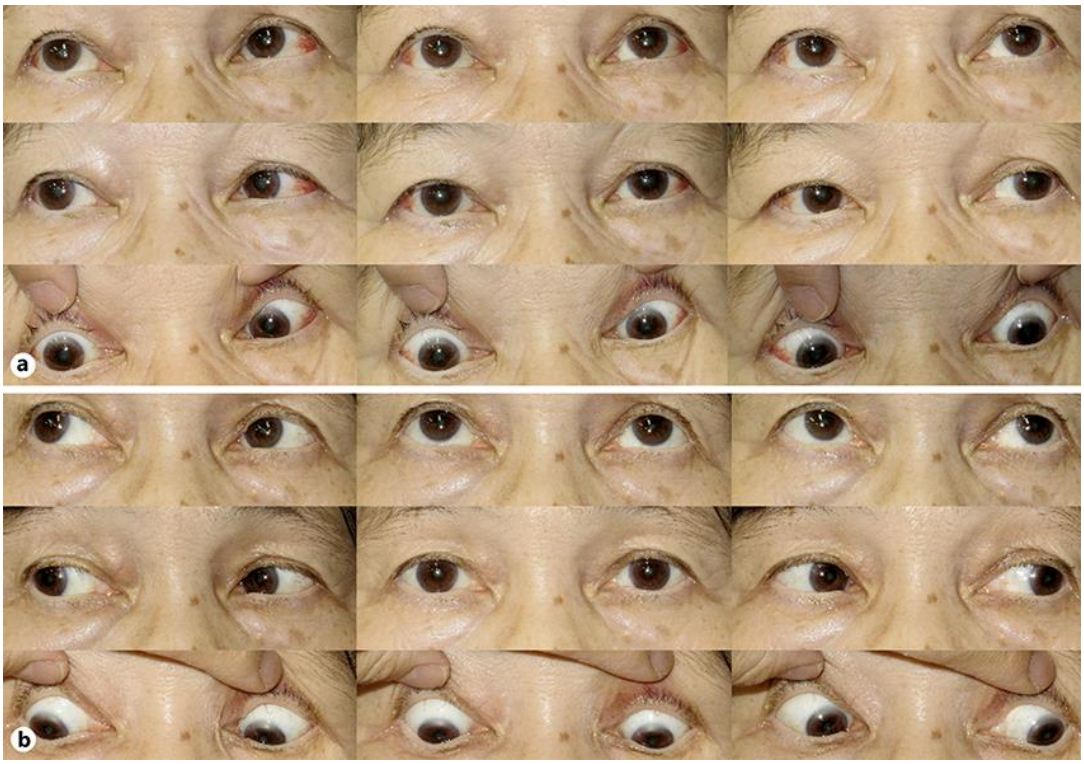

Fig. 1. Photographs of the nine directions of gaze at initial examination (**a**) and on day 21 after admission (**b**). The eye movement disturbance in all directions disappeared.

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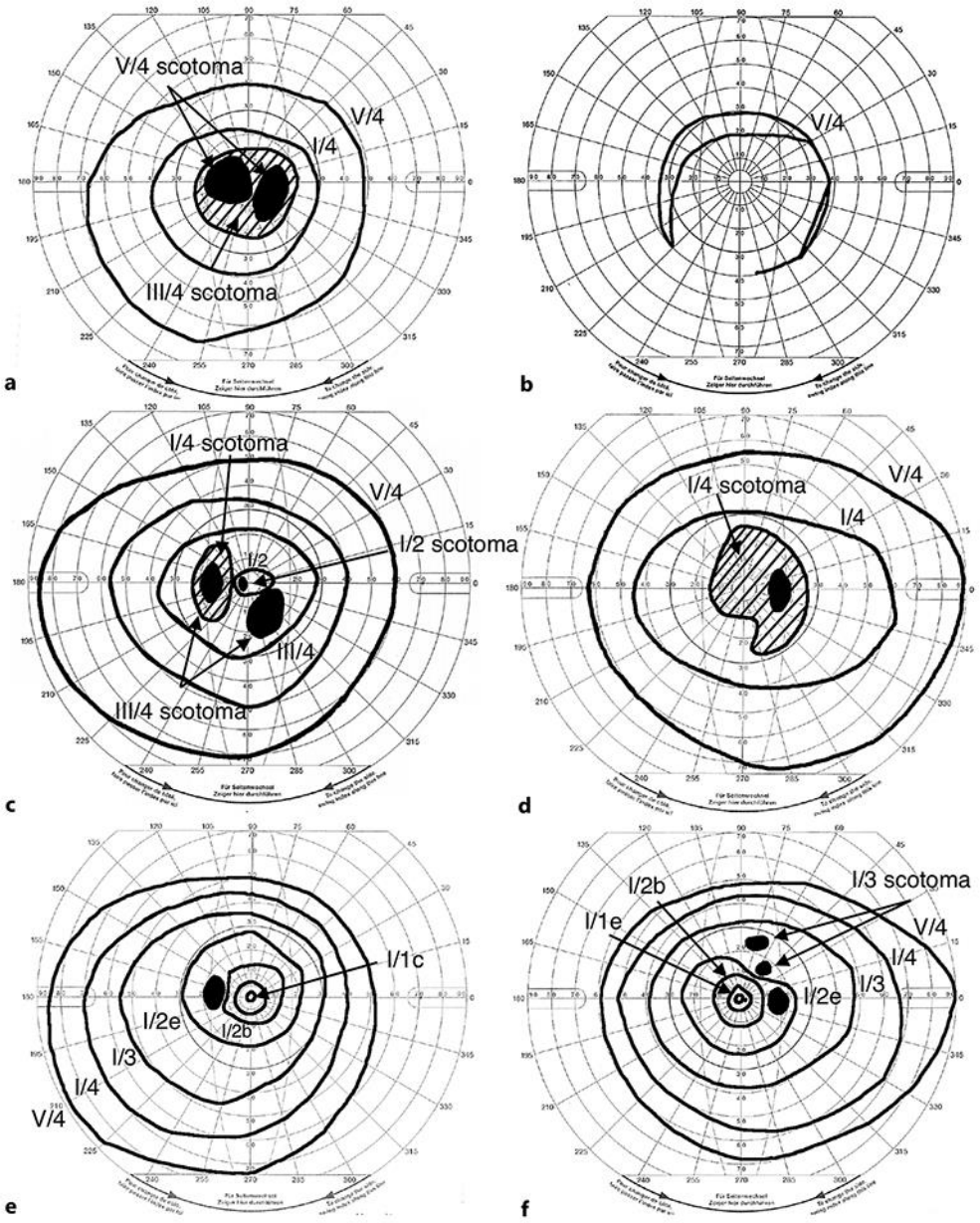

Fig. 2. Goldmann kinetic perimetry. At the initial examination, large central scotomas were seen in both eyes (**a** left eye, **b** right eye). On the day after surgery (day 3 after admission), the central scotomas of both eyes were reduced in size (**c** left eye, **d** right eye). Furthermore, 4 days later (on day 7 after admission), the central scotomas of both eyes had markedly disappeared (**e** left eye, **f** right eye).

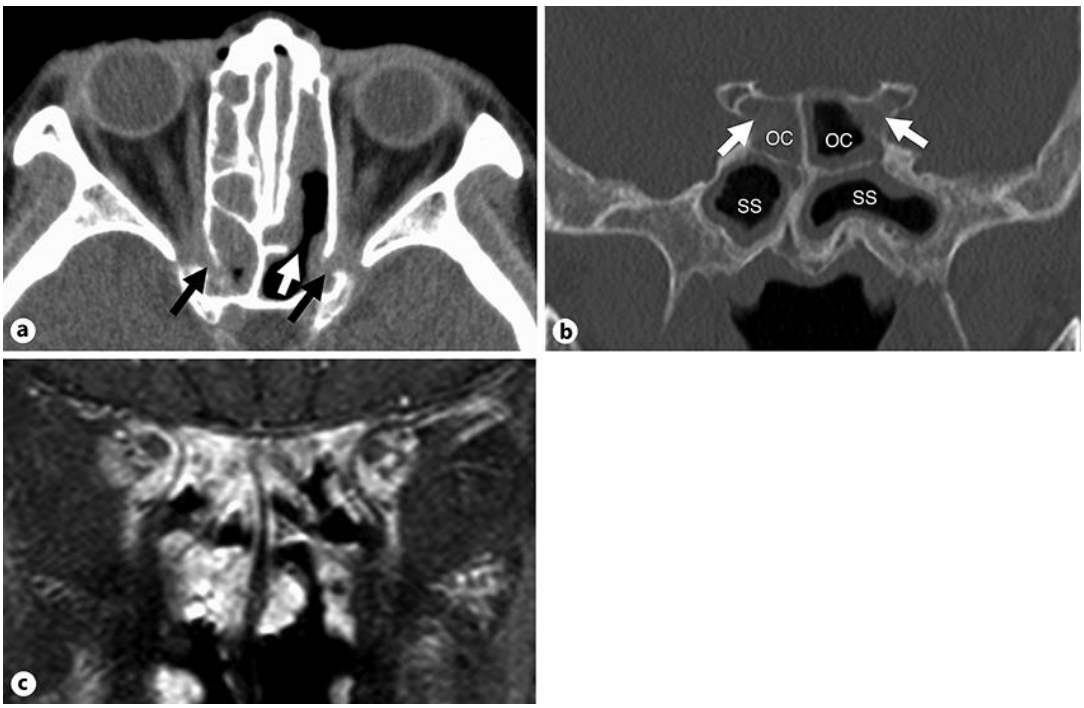

Fig. 3. Imaging test. **a**, **b** Axial (**a**) and coronal section (**b**) images of computed tomography. **c** Coronal section image of T1-weighted image enhanced by gadolinium. The black arrows indicate a bone defect of the lateral wall of the Onodi cell (**a**). The white arrow indicates the opening between the posterior ethmoid and the Onodi cell on the left side (**a**). The coronal section of CT depicted the posterosuperior walls of the Onodi cell, which became faint and were accompanied by infiltrative changes (white arrows in **b**). Magnetic resonance imaging revealed severe inflammatory changes in the bilateral orbital apex (**c**). OC, Onodi cell; SS, sphenoid sinus.