Case Report
Sino-Orbital Aspergillosis in a Kidney Transplant Recipient

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Sino-orbital aspergillosis is a rare and severe infection mostly seen in immunocompromised individuals in which diagnosis may be challenging with potentially life-threatening consequences. Infection usually starts in the paranasal sinuses with secondary spreading to the adjacent orbits. Here, we report the case of a kidney transplant recipient who presented with proven invasive sino-orbital aspergillosis resulting in irreversible loss of vision despite surgical management and antifungal therapy. We review the literature with a focus on clinical presentation, diagnostic tools, and recommended treatment in the context of kidney transplantation.

1. Introduction

Orbital aspergillosis is a rare orbital infection, mainly seen in immunocompromised individuals. It usually occurs as a complication of adjacent sphenoid or ethmoid sinusitis. Because of unspecific symptoms, diagnosis can be delayed with life-threatening consequences [1, 2]. Here, we describe a kidney transplant recipient (KTR) who suffered from a localized invasive sino-orbital aspergillosis with irreversible vision loss.

2. Case Presentation

A 55-year-old man on hemodialysis for diabetic nephropathy received a kidney transplant from a living donor in March 2018. His past medical history was relevant for malaria, pulmonary tuberculosis, and chronic pancreatitis. His treatment included tacrolimus (8 mg q.d), methylprednisolone (4 mg q.d), mycophenolate mofetil (500 mg b.i.d), aspirin (100 mg q.d), pantoprazole (40 mg q.d), pancrelipase delayed-release capsule (20000 units t.i.d), and insulin. In June 2019, he was admitted for fatigue, photophobia, right hemicranial headache, and progressive vision loss of the right eye. Clinical examination revealed a normal left eye with normal vision (10/10). On the right side, there was a ptosis with unreactive pupil, a complete afferent pupillary defect and a total paralysis. The vision was “no perception of light,” and the slit lamp examination was within normal limits except for a moderate cataract which did not explain the complete vision loss and the unreactive pupil. The fundus did not reveal any optic nerve oedema or atrophy, and vessels occlusions were ruled out. A diabetic retinopathy with panretinal photoagulations was described in both eyes. Intraocular tension was 14 mmHg in both eyes. Head computed tomography (CT) scanner demonstrated pansinusitis with diffuse mucosal thickening embedding punctate calcifications, chronic bone thickening, and focal osteolysis of the floor of the right optic canal (Figure 1). Orbital
magnetic resonance imaging (MRI) confirmed the massive inflammatory extension to the sphenoid fissure and the encasement of the intracanal segment of the right optic nerve by the process (Figures 2(a)-2(c)). Intrinsic tissue damage to the optic nerve was present (Figure 2(d)). No sign of intracranial extension was observed. Empirical antibacterial therapy with piperacillin-tazobactam and antifungal therapy with intravenous liposomal amphotericin B (LAmB) at the dosage of 3 mg/kg were empirically started. Surgical bilateral maxillectomy, ethmoidectomy, and sphenoidotomy were performed. Pathological examination of surgically resected specimens showed the presence of fungal hyphae (Figure 3). Voriconazole was therefore added (at the dosage of 6 mg/kg b.i.d. intravenously on day 1 followed by 4 mg/kg b.i.d. during 14 days and then oral 200 mg b.i.d.). Microbiological culture of the surgical samples showed Aspergillus flavus, which was confirmed by polymerase chain reaction (PCR), consistent with a proven sino-orbital aspergillosis. LAmB and mycophenolate mofetil were stopped. Voriconazole was pursued, and dosage of tacrolimus was tapered to reach a trough level of 3 to 4 ng/ml. In the meantime, culture of the surgical samples showed coinfection with Pseudomonas aeruginosa and Staphylococcus epidermidis, which was treated by ceftazidime and cefazolin. The patient was discharged six weeks later, with improved general status and relief of pain. While the eye motility recovered completely, the vision did not. Follow-up MR examination nine months later showed regression of the pansinusitis together with a right optic atrophy. At one year, the lesions on MRI were stable without signs of active inflammation, thereby allowing discontinuation of voriconazole. Three months after interruption of antifungal treatment, the patient is still doing well.

Figure 1: Head computed tomography scan. (a) Unenhanced axial transverse view in parenchymal reconstruction algorithm showing filling of the sphenoid sinus and of the right-sided posterior ethmoid cell by inflammatory material. Observe heterogeneous and amorphous calcium deposits within the right sphenoid cell (arrow). (b) Coronal reformatted view through the sphenoid in bone reconstruction algorithm showing disruption of the floor of the right optic canal (arrow). Observe calcium deposits within the sphenoid sinus (dotted arrow) and bone thickening of the sphenoid walls.
without neurological complaints except for right blindness. As expected, the last fundus exam confirmed major right optic nerve pallor. The slit lamp examination remains unchanged. Kidney graft function remains stable as well as MR features.

3. Discussion

Aspergillus are ubiquitous saprophytic dichotomously branching fungi mainly present in hot, dry, and dusty climates. Infection occurs via inhalation of fungal spores [3]. Invasive aspergillosis (IA) is the most common fungal infection in solid organ transplant (SOT) recipients after candidiasis. It has been reported in 1 to 15% of SOT recipients and in 0.5 to 4% of KTR [1, 4–6]. IA most frequently affects lungs and sinuses. Orbital involvement is uncommon [7]. Only few case reports and small case series of Aspergillus optic neuritis have been reported up to now [1, 2, 7–12]. In most cases, orbital aspergillosis occurs mainly through the paranasal sinuses spreading by bony erosion or through vessel walls. Invasive aspergillosis can remain localized or become fulminant with multiple organ involvement [1, 8, 9].

Although it has improved over the past two decades, the diagnosis of Aspergillus infections remains difficult and is highly dependent on appropriate clinical suspicion [2, 10]. In 2019, an expert consensus group revised the definitions of invasive fungal disease [13]. The diagnosis of a proven invasive fungal disease requires the histologic demonstration of fungal elements in tissue or fluid samples.
of fungal elements within associated tissue damage, irrespec-
tively of host factors or clinical features. More specifi-
cally, the diagnosis of a proven invasive aspergillosis as in our
patient requires the identification of Aspergillus by culture
or PCR in the affected tissue [13]. If the histological proof
of fungal elements within tissue is lacking, the diagnosis of
probable invasive fungal disease is made by the combina-
tion of host, clinical, and mycological evidences (Table 1) [13].
A possible invasive fungal disease is defined by the combina-
tion of host and clinical features without mycological sup-
port [13].

Symptoms of invasive aspergillosis depend on the
affected organ. In orbital aspergillosis, the patient presents
with unspecific initial symptoms such as persistent unilateral
headache or retrobulbar pain, eye redness, and proptosis.
Over time, symptoms may worsen to acute pain, cranial
nerve palsies, amaurosis, and orbital apex syndrome [2, 11].
Symptoms of the eyes often precede those of the sinuses
[11]. Orbital aspergillosis mimics other common optic neu-
ritis. A key feature is the intensity of the pain described as
unbearable. Misdiagnosing leads to inappropriate treatment
and dire consequences [11].

Performing orientated neuroimaging is mandatory as
illustrated by our patient. CT scanner is usually the most
available imaging modality. Dense intraluminal calcifica-
tions in the sinuses are highly suggestive of fungal infection
but their absence does not rule out the diagnosis. Bone ero-
sions allowing sino-orbital way of spreading are commonly
seen but at late stage of the disease course and not systema-
tically because the agent may spread through vessel walls.
The benefit of MRI relies in enhanced soft tissue contrast
allowing better delineation of the extent of the inflamma-
tion towards orbits together with sensitive detection of tissue
damage to the optic nerve [8, 9, 12].

Every effort should be made to obtain adequate amounts
of tissues for microbiological and pathologic examination.
Fine-needle aspiration or biopsy of the sinus or the orbit is
required. As in our patient, pathological examination may
show the characteristic dichotomously branching septate
hyphae. The most helpful stains for visualizing fungi are
the methenamine silver stain and the periodic acid-Schiff
(PAS) stain [12]. Repeated biopsies are often necessary due
to frequent inconclusive results. Antigen-based diagnosis
relies on detection of either galactomannan or bêta-D-glucan,
two constituents of fungal-cell walls. The first can be
performed on plasma, serum, bronchoalveolar, or cerebro-
spinal fluid, while the latter is mainly limited to serum.
The galactomannan test is more specific than beta-D-
Glucan. A meta-analysis of studies about serum galactomannan
test for early diagnosis of invasive aspergillosis in SOT
recipients reported sensitivity and specificity of 22% and
84%, respectively (cutoff value not mentioned) [6]. Lately,
the expert group recognized the usefulness of PCR methods
for confirming the diagnosis of Aspergillus disease [13].
Moreover, PCR is able to detect both genus, species, and cer-
tain mutations associated with triazole resistance.

Currently, treatment of invasive sino-orbital aspergillosis
is based on the guidelines established for the treatment of
general invasive aspergillosis [1, 2, 12]. Former therapy
included the use of systemic amphotericin B (deoxycholate),
but this treatment has a number of toxicities (including renal
dysfunction), and the mortality once intracranial spread has
occurred is 80%. If fungal infection is initially suspected,
broad empirical antifungal therapy like LAmB should be
quickly started to cover other fungal infections like mucor-
mycosis. After identification of Aspergillus, antifungal ther-
apy should be switched to voriconazole. The latter is
recommended as the first treatment for IA by the guidelines
of the Infectious Diseases Society of America (IDSA), the
American Thoracic Society (ATS), and the European Society
for Clinical Microbiology and Infectious Diseases (ESC-
MID), after demonstrating a 22% survival benefit with better
tolerance and lower toxicity over amphotericin B deoxycho-
late [14–17]. It is recommended as the drug of choice for

Figure 3: Histopathologic examination of the sinus material stained with periodic acid Schiff stain (PAS) showing fungal hyphae morphologically consistent with Aspergillus.
treatment of invasive aspergillosis including in SOT recipients [6, 14]. Voriconazole trough level should be monitored [18]. Lately, isavuconazole has been shown as noninferior to voriconazole with fewer adverse events [19]. There is a paucity of data to guide the administration of antifungal therapy in patients with IA resistant or refractory to voriconazole: lipid amphotericin B formulation is recommended; posaconazole, itraconazole and echinocandins may be other alternatives [1–3, 6, 17]. While in immunocompetent hosts the recommended duration of therapy is 6 to 12 weeks minimum, it should be prolonged in immunocompromised hosts and depends on the clinical evolution. Aggressive surgical debridement of the affected sinonasal and orbit tissue with clean margins is strongly recommended but is often complicated by difficulty in determining the precise extent of the lesion and needs to be considered on an individual basis [1, 11, 12, 17]. Special aspects must be considered in the context of transplantation. Drug interactions between antifungal agents and immunosuppressive drugs must be carefully evaluated. The triazole agents are potent inhibitors of the CYP3A4 isoenzymes and have the potential to increase the levels of calcineurin-inhibitor agents (CNI) and sirolimus. A 50–60% reduction in the dose of CNI agents may be necessary [4]. The triazole agents are potent inhibitors of the CYP3A4 isoenzymes and have the potential to increase the levels of calcineurin-inhibitor agents (CNI) and sirolimus. A 50–60% reduction in the dose of CNI agents may be necessary [4]. The triazole agents are potent inhibitors of the CYP3A4 isoenzymes and have the potential to increase the levels of calcineurin-inhibitor agents (CNI) and sirolimus. A 50–60% reduction in the dose of CNI agents may be necessary [4]. The triazole agents are potent inhibitors of the CYP3A4 isoenzymes and have the potential to increase the levels of calcineurin-inhibitor agents (CNI) and sirolimus. A 50–60% reduction in the dose of CNI agents may be necessary [4]. The triazole agents are potent inhibitors of the CYP3A4 isoenzymes and have the potential to increase the levels of calcineurin-inhibitor agents (CNI) and sirolimus. A 50–60% reduction in the dose of CNI agents may be necessary [4]. The triazole agents are potent inhibitors of the CYP3A4 isoenzymes and have the potential to increase the levels of calcineurin-inhibitor agents (CNI) and sirolimus. A 50–60% reduction in the dose of CNI agents may be necessary [4]. The triazole agents are potent inhibitors of the CYP3A4 isoenzymes and have the potential to increase the levels of calcineurin-inhibitor agents (CNI) and sirolimus. A 50–60% reduction in the dose of CNI agents may be necessary [4].

The prognosis of invasive sino-orbital aspergillosis remains poor. Despite appropriate treatment, many patients definitely lose vision and even die few days or months after the initial symptoms [9, 11]. In overall cases of invasive aspergillosis, the mortality rate decreased to 25% since the use of voriconazole [6, 16]. Poor outcome may be attributed to delay in diagnosis, cerebral extension, and recurrence of Aspergillus within involved tissues, in spite of extensive debridement and long duration antifungal treatment, particularly in the immunocompromised hosts [11]. In conclusion, sino-orbital invasive aspergillosis is an uncommon fungal infection mostly seen in immunocompromised hosts who present with acute and painful visual loss. A high index of suspicion is required for adequate diagnosis. Pathological and microbiological analysis of multiple surgical samples may be necessary for diagnosis and prompt start of appropriate therapy. Surgical debridement and prolonged course of antifungal therapy as well as reduction of immunosuppression are currently the cornerstones of IA management. Overall outcome is poor and depends on the host factors and the extension of aspergillosis.

Data Availability
The datasets used during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest
The authors have no conflicts of interest to disclose.

References

[1] B. Mukherjee, N. Raichura, and S. Alam, “Fungal infections of the orbit,” Indian Journal of Ophthalmology, vol. 64, no. 5, pp. 337–345, 2016.
[2] D. Ohlstein, C. Hooten, J. Perez, C. L. Clark III, and H. Samy, “Orbital aspergillosis: voriconazole – the new standard treatment?,” Case Reports in Ophthalmology, vol. 3, no. 1, pp. 46–53, 2012.
[3] B. Segal, “Aspergillosis,” The New England Journal of Medicine, vol. 360, no. 18, pp. 1870–1884, 2009.
[4] N. Singh and D. Paterson, “Aspergillus infections in transplant recipients,” Clinical Microbiology Reviews, vol. 18, no. 1, pp. 44–69, 2005.
[5] S. Shoham and K. Marr, “Invasive fungal infections in solid organ transplant recipients,” Future Microbiology, vol. 7, no. 5, pp. 639–655, 2012.
[6] N. Singh, S. Husain, the AST Infectious Diseases Community of Practice, and the AST, “Aspergillosis in solid organ transplantation,” American Journal of Transplantation, vol. 13, no. 54, pp. 228–241, 2013.
[7] K. Mody, M. Ali, G. Vemuganti, S. Nalamada, M. N. Naik, and S. G. Honavar, “Orbital aspergillosis in immunocompetent patients,” The British Journal of Ophthalmology, vol. 98, no. 10, pp. 1379–1384, 2014.
[8] L. Lee and T. Sullivan, “Aspergillus sphenoid sinusitis-induced orbital apex syndrome in HIV infection,” Australian and New Zealand Journal of Ophthalmology, vol. 23, no. 4, pp. 327–331, 1995.
[9] J. Sivak-Callcott, N. Livesley, R. Nugent, S. L. Rasmussen, P. Saeed, and J. Rootman, “Localised invasive sino-orbital aspergillosis: characteristic features,” The British Journal of Ophthalmology, vol. 88, no. 5, pp. 681–687, 2004.
[10] L. Yuan and R. Prayson, "Optic nerve aspergillosis," *Journal of Clinical Neuroscience*, vol. 22, no. 7, pp. 1191–1193, 2015.
[11] H. Kawakami, K. Mochizuki, K. Ishida, and K. Ohkusu, "Seven cases of localized invasive sino-orbital aspergillosis," *Japanese Journal of Ophthalmology*, vol. 61, no. 2, pp. 179–188, 2017.
[12] L. Levin, R. Avery, J. Shore, J. J. Woog, and A. Sullivan Baker, "The spectrum of orbital aspergillosis: a clinicopathological review," *Survey of Ophthalmology*, vol. 41, no. 2, pp. 142–154, 1996.
[13] J. P. Donnelly, S. C. Chen, and C. A. Kauffman, "Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group education and research consortium," *Clinical Infectious Diseases*, 2019, ciz 1008.
[14] T. Patterson, G. Thompson, D. Denning et al., "Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America," *Clinical Infectious Diseases*, vol. 63, no. 4, pp. e1–e60, 2016.
[15] A. Limper, K. Knox, G. Sarosi et al., "An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients," *American journal of respiratory and critical care medicine*, vol. 183, no. 1, pp. 96–128, 2011.
[16] R. Herbrecht, D. Denning, T. Patterson et al., "Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis," *The New England Journal of Medicine*, vol. 347, no. 6, pp. 408–415, 2002.
[17] A. J. Ullmann, J. M. Aguado, S. Arikan-Akdagli et al., "Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline," *Clinical Microbiology and Infection*, vol. 24, no. 1, pp. e1–e38, 2018.
[18] A. Pascual, T. Calandra, S. Bolay, T. Buclin, J. Bille, and O. Marchetti, "Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes," *Clinical Infectious Diseases*, vol. 46, no. 2, pp. 201–211, 2008.
[19] J. A. Maertens, I. I. Raad, K. A. Marr et al., "Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (secure): a phase 3, randomised-controlled, non-inferiority trial," *Lancet*, vol. 387, no. 10020, pp. 760–769, 2016.
[20] J. W. Baddley, D. R. Andes, K. A. Marr et al., "Factors associated with mortality in transplant patients with invasive aspergillosis," *Clinical Infectious Diseases*, vol. 50, no. 12, pp. 1559–1567, 2010.