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Sequelae of Cryptococcal-Immune Reconstitution Inflammatory Syndrome in a Kidney Transplant Recipient: A Case Report

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Abstract

Rationale: Cryptococcal-immune reconstitution inflammatory syndrome (C-IRIS) is a rare but recognized clinical entity in solid organ transplant recipients, though its clinical course and sequelae remain largely poorly described.

Presenting Concerns of the Patient: We present the case of a kidney transplant recipient who presented with headache and fever. A cerebrospinal fluid analysis was performed and found to be compatible with cryptococcal meningitis. After down titration of immunosuppression and antifungal initiation, the patient initially improved. Weeks later, they experienced a sudden deterioration in mental status, prompting admission to the intensive care unit (ICU).

Diagnosis: This deterioration was attributed to C-IRIS, which developed following rapid de-escalation of immunosuppression in response to the diagnosis of cryptococcal meningitis.

Interventions: The initial episode of C-IRIS responded well to high-dose steroids; however, maintenance immunosuppression was not increased.

Outcomes: Within 2 months, the patient presented again to the hospital with a pulmonary infiltrate and multifocal ischemic strokes.

Novel Findings: We argue this to be a case of relapsing multisystem C-IRIS, thus expanding the known spectrum of manifestations of C-IRIS in renal transplant recipients. We propose that following the diagnosis of C-IRIS, maintenance immunosuppression be escalated to avoid the risk of relapse and inflammatory-mediated organ dysfunction.

Abrégé

Justification: Le syndrome inflammatoire de reconstitution immunitaire dû au cryptocoque (C-IRIS) est une entité clinique rare, mais reconnue chez les receveurs d'une greffe d'organe solide. Son évolution clinique et les séquelles qu'il engendre demeurent cependant largement mal décrites.

Présentation du cas: Nous présentons le cas d'un receveur d'une greffe rénale qui souffrait de céphalées et de fièvre. L'analyze du liquide céphalo-rachidien du patient était compatible avec une méningite cryptococcique. La réduction de la dose du traitement immunosuppresseur et l'initiation d'un traitement antifongique ont d'abord permis d'améliorer l'état général du patient. Son état mental s'est toutefois détérioré quelques semaines plus tard, ce qui a nécessité son admission à l'unité de soins intensifs (USI).

Diagnostic: Cette détérioration a été attribuée au C-IRIS, lequel s'est développé à la suite de la désescalade rapide de l'immunosuppression en réponse au diagnostic de méningite cryptococcique.

Intervention: L'épisode initial de C-IRIS a bien répondu à une dose élevée de stéroïdes; l'immunosuppression d'entretien n'a cependant pas été augmentée.

Résultats: Le patient s'est de nouveau présenté à l'hôpital dans les deux mois suivants avec un infiltrat pulmonaire et des accidents vasculaires cérébraux ischémiques multifocaux.

Principales observations: Nous soutenons qu'il s'agit d'un cas de C-IRIS récidivant affectant plusieurs systèmes, ce qui élargit le specter des manifestations connues du C-IRIS chez les transplantés rénaux. Nous suggérons que le traitement immunosuppresseur d'entretien soit intensifié après un diagnostic de C-IRIS afin d'éviter les risques de rechute et de dysfonctionnement des organes à médiation inflammatoire.

Keywords
Cryptococcus, meningitis, C-IRIS, ischemic stroke, kidney transplantation

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Introduction

Cryptococcal-immune reconstitution inflammatory syndrome (C-IRIS) is a rare but recognized entity in solid organ transplant recipients (SOTRs).[1] Cryptococcal infections carry a lifetime incidence of 12% among SOTRs, comprising 7% of invasive fungal infections in this population. It most commonly manifests as meningitis, pulmonary or pleural infection, and cellulitis.[2] Following the diagnosis of cryptococcal disease, the estimated incidence of C-IRIS is 4.8%.[1] In HIV literature, 2 distinct entities have been described; unmasking and paradoxical C-IRIS.[3] In SOTRs, nearly all cases are paradoxical and triggered during recovery of immunity to *Cryptococcus* spp. following a decrease in immunosuppression and effective antifungal therapy. This results in an exaggerated host inflammatory responses.[3] Presentation of C-IRIS includes a range of central nervous system (CNS) symptoms such as raised intracranial pressure, seizures, neuropathies, and intracranial cryptococcomas and non-CNS symptoms including fever, lymphadenopathy, sterile abscesses, soft tissue lesions, and pneumonitis.[3]

Guidelines on the management of C-IRIS are largely informed by observational case series. In SOTRs, supportive management and immune-modulating therapies have been used, but there is no solid evidence of therapeutic benefit.[1,4-6] The most common treatment regimen is a trial of high-dose corticosteroids.[5-7] However, the resolution of neurologic symptoms in an HIV patient with C-IRIS without steroids has been reported.[8] The duration of therapy is not well established and cases of recurrent C-IRIS after cessation or tapering of corticosteroids have been described in HIV literature.[9,10] We present a case of a SOTR who was diagnosed with C-IRIS and then presented with a multisystem relapse weeks later.

Clinical Case

Presenting Concerns

A 58-year-old male who had received a deceased donor kidney transplantation 3 years prior presented with a 4-day history of headache, malaise, and chills. He was known for type 2 diabetes, hypertension, and coronary artery disease. Figure 1 and Table 1 presents a detailed clinical and laboratory timeline. His initial immunosuppression consisted of tacrolimus targeted to a trough of 6 to 8 ng/mL and mycophenolic acid 720 mg twice daily. Four months prior to current presentation, he had a biopsy proven diagnosis of borderline T-cell mediated rejection that was treated with pulse steroids and the addition of and prednisone 5 mg once daily to his maintenance immunosuppressive regimen. His baseline creatinine was between 132 and 150 umol/L.

Clinical Findings

Initially, an extensive workup was pursued and a diagnosis of cryptococcal meningitis was established following cerebrospinal fluid (CSF) analysis (positive cryptococcal polymerase chain reaction [PCR], antigen titer of 1:2048, white blood cells (WBCs) 49 c/uL, opening pressure (OP) 10.5 cmH_2O). Magnetic resonance imaging (MRI) of head showed small foci of contrast update in the subarachnoid space, in keeping with infection. Liposomal amphotericin B (270 mg intravenously daily, corresponding to 4 mg/kg/day) and flucytosine (1500 mg orally every 6 hours, 25 mg/kg/dose) were started, mycophenolic acid was discontinued, and the tacrolimus dose was decreased so as to target a trough of 4 to 6 ng/mL. This led to a significant improvement in symptoms, decline in cryptococcal titers (1:256 from 1:2048), and CSF sterilization. After 3 weeks of dual antifungal therapy, fluconazole (400 mg orally daily) monotherapy was initiated. Antifungal therapy was well tolerated, and although the patient's creatinine increased to 256 umol/L, with supportive care, it returned to his baseline value.

Diagnostic Focus and Assessment

However, 41 days into his hospitalization, the patient experienced a sudden deterioration in his mental status, prompting ICU admission. His Glasgow Coma Score was 7, and he required vasopressors and mechanical ventilation. Computed tomography (CT) imaging detected no acute intracranial abnormalities, however MRI showed small areas of diffusion restriction in left pons and internal capsule, thought to represent lacunar infarcts. A repeat lumbar puncture showed an inflammatory profile (cryptococcal antigen titer of 1:128, WBC 118 c/uL, OP 23 cmH_2O), but cryptococcal PCR and cultures were negative. His serum C-reactive protein (CRP) was 268. Given the inflammatory response, this neurological deterioration was attributed to C-IRIS. This was further confirmed with repeatedly negative septic profiles, and a rapid clinical response to steroids.

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Figure 1. Timeline of events, investigations, and clinical decisions in a kidney transplant recipient who developed cryptococcal-immune reconstitution inflammatory syndrome.

Note. CT = computed tomography; PCR = polymerase chain reaction; WBC = white blood cells; MRI = magnetic resonance imaging; ICU = intensive care unit; C-IRIS = cryptococcal-immune reconstitution inflammatory syndrome; EBV = Epstein–Barr virus.

Table 1. Cerebrospinal Fluid Analyses Throughout the Clinical Course.

Date	Organism identified (culture and PCR)	Cryptococcal antigen titer CSF	WBC (c/uL), (%lymphocytes) [normal 0-10]	RBC (c/uL) [normal = 0]	Protein (g/L) [normal = 0.15-0.45]	Glucose (mM/L) [normal = 2.5-4.4]	Opening pressure (cm H2O)
Day 20	*Cryptococcus neoformans*	1:2048 (serum: 1:256)	49 (60%)	132	2.9	1.4	10.5
Day 32	Negative	1:256	44 (93%)	34	1.92	2.1	13
Day 47	Negative	1:128 (serum: 1:128)	118 (75%)	18	2.25	0.4	23
Day 65	Negative	1:128	66 (94%)	20	1.62	12.1	14
Day 132	Negative	Negative	39 (92%)	2	3.40	3.7	12

Note. PCR = polymerase chain reaction; CSF = cerebrospinal fluid; WBC = white blood cells; RBC = red blood cells.

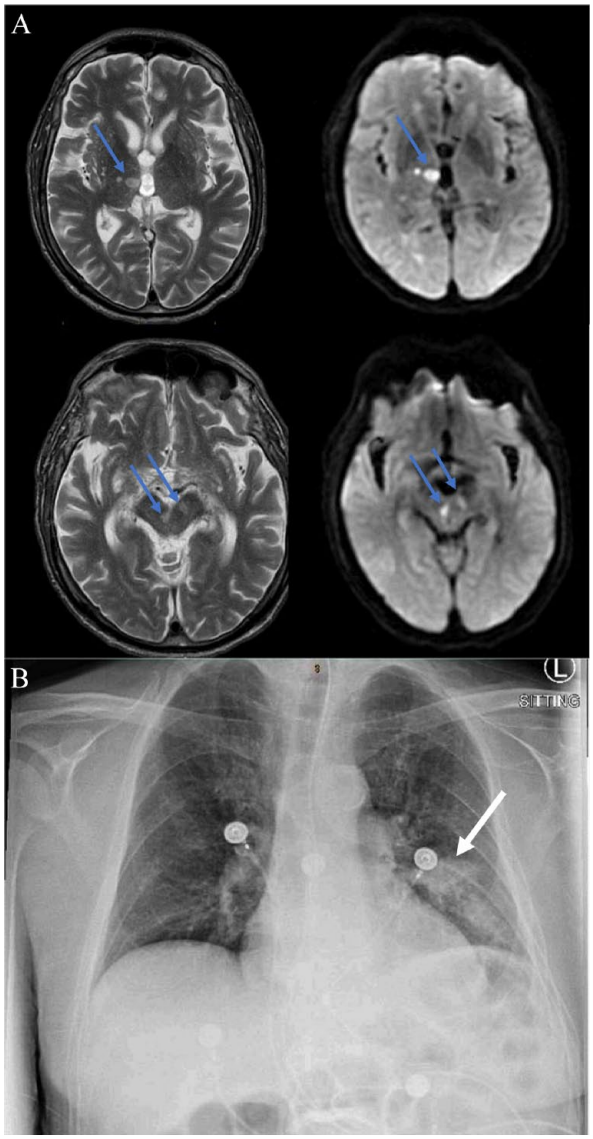

Figure 2. (A) Selected axial MRI head T2 (top left) and equivalent diffusion-weighted images (top right) showing acute posterior circulation infarcts affecting the thalamus and brainstem. (B) Chest X-ray showing a left lower lobe infiltrate (bottom).

Therapeutic Focus and Assessment

After a 10-day course of dexamethasone (10 mg/d), his clinical status improved, and he returned to his neurocognitive baseline. As there are no consensus guidelines on the optimal treatment of C-IRIS, the dose and duration were chosen based on case reports and series with favorable outcomes found in the literature.[6,11] During this treatment, he continued fluconazole 400 mg daily as consolidation therapy. CSF analysis post treatment showed a stable cryptococcal antigen titer (1:128), and a decreasing WBC count (66 c/uL from 118 c/uL). He was eventually discharged on fluconazole 400 mg daily, prednisone 5 mg daily (which was resumed after the course of dexamethasone), and tacrolimus 1 mg daily targeted to a trough of 4 to 6 ng/mL. The patient went to a rehabilitation facility and was scheduled to see the infectious disease and transplant nephrology team to reassess the dosing of immunosuppression based on his clinical status. Given his clinical stability and stable renal function, no outpatient changes were made to his therapy.

Follow-up and Outcomes

Less than 2 months after discharge, he returned to the hospital with fever. His maintenance immunosuppression consisted of 1 mg of tacrolimus and 5 mg of prednisone. A septic workup was non-diagnostic except for an opacity in the left lower lobe (Figure 2), concerning for pneumonia. He was treated with amoxicillin/clavulanic acid and treated as an outpatient. However, 4 days later, he presented again; this time febrile and confused. Neurologic abnormalities were noted, including somnolence, dysarthria, and left hemibody weakness. MRI revealed multiple acute end-vessel infarcts involving both thalami (Figure 2, top), pons (Figure 2, middle), midbrain, and left temporal uncus. However, no cardiac or large vessel atheroembolic etiologies were found to explain the strokes: the computed tomography angiography showed no neurovascular abnormalities, and the transthoracic echocardiogram and 48-hour Holter monitor did now detect any evidence of arrhythmia or cardioembolic nidus. The repeated CSF analysis was inflammatory (WBC 39 c/uL, protein 3.4 g/L), yet sterile (negative cryptococcal PCR

and antigen titer, negative bacterial culture). A Chest X-ray showed an enlarging left lower lobe infiltrate, and a bronchoalveolar lavage, performed to investigate the pulmonary infiltrate, was also sterile. Dual antiplatelet therapy, broad-spectrum antibiotics (piperacillin-tazobactam and vancomycin), and stress dose steroids (hydrocortisone 100 mg intravenously every 8 hours) were immediately initiated. Despite these measures, his mental status continued to deteriorate over the next 48 hours. He was admitted to the neurological intensive care unit where he was intubated and sedated. He remained febrile and minimally conscious throughout his 2-week stay. The patient's family decided on palliative extubation. He passed away shortly after.

Discussion

C-IRIS is a rare clinical entity in SOTRs and is a diagnosis of exclusion. Considerations must be given to relapsed infection, newly acquired infections, or an adverse effect of therapy.[6] In our patient, C-IRIS was initially diagnosed within a month of cryptococcal meningitis treatment initiation based on the paradoxical worsening of neurological symptoms while on appropriate antifungal agents. Also, the CSF profile became more inflammatory despite negative fungal cultures and declining cryptococcal titers.

The underlying etiology of the second presentation was challenging. In SOTRs, cardiac and vascular diseases are the predominant causes of ischemic strokes. However, in our patient, we argue for an immunoinflammatory etiology of stroke given the bilateral involvement of end-vessels, a negative workup for any embolic or thrombotic sources, and an inflammatory yet sterile CSF. Ischemic stroke can present as an acute complication of cryptococcal meningitis thought to be mediated by an infectious vasculitis, or in the context of C-IRIS.[8,12,13] Multiple reports in the HIV population starting antiretroviral therapy have shown that ischemic strokes occur disproportionately in patients with C-IRIS, or other forms of neurological IRIS.[13-15] The proposed pathogenesis of ischemic stroke in neuro-IRIS is that of exaggerated CNS inflammation causing endothelial damage in cerebral microvasculature and multiple small-vessel occlusions.[14] Thus, strokes in this context are believed to be immunoinflammatory in etiology, rather than thromboembolic.

We hypothesize the stroke in our patient's case to be occurring as part of a multisystem C-IRIS relapse, affecting both CNS and lungs. The patient was diagnosed with pneumonia but failed to respond to antibiotics, making the pulmonary infiltrate more likely inflammatory than infectious. This is further cemented by a bronchoalveolar lavage culture that was negative and by the progression of the pulmonary infiltrate and ongoing fevers while on broad-spectrum antibiotics. Previously uninfected organs have been reported as the site of C-IRIS in both SOTRs and HIV patients,[1,3] and pneumonitis or pulmonary nodules is a described manifestation of C-IRIS.[3]

Other than supportive care, the optimal treatment for recurrent C-IRIS is unknown. In a case series of 3 HIV patients with relapsing or refractory C-IRIS, thalidomide treatment induced clinical remission and permitted corticosteroid withdrawal without clinical relapse.[10] In another patient with recurrent C-IRIS manifesting as lymphadenitis after cessation of corticosteroids, symptoms resolved without additional anti-inflammatory drugs.[9] We found 1 case of a SOTR who was deemed to have steroid-refractory C-IRIS, but responded well to tumor necrosis factor (TNF)-α blockade.[4] In our patient, unlike the first C-IRIS episodes, the second episode failed to respond to steroids, possibly due to the severity of presentation and the fragile neuroanatomy involved.

Overall, we report a case of relapsing multisystem C-IRIS in a SOTR, manifesting with immunologically mediated subcortical strokes and pneumonitis. This report thus expands on the literature highlighting that C-IRIS can relapse in SOTRs, despite effective initial therapy. We propose that following the diagnosis of C-IRIS, consideration be given to escalating maintenance immunosuppression to avoid the risk of C-IRIS relapse. While recurrent C-IRIS in HIV patients has been reported, to our knowledge, this is the first case report of an SOTR with relapsing multisystem C-IRIS.

List of Abbreviations

C-IRIS, cryptococcal-immune reconstitution inflammatory syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; SOTR, solid organ transplant recipient.

Ethics Approval and Consent to Participate

Ethics approval is not applicable. Consent to participate obtained from the next of kin.

Consent for Publication

Consent for publication obtained from the next of kin.

Availability of Data and Materials

Not applicable.

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