Case Report

Archives of Infectious Diseases & Therapy

Concurrent Disseminated Cryptococcus neoformans and Abdominal Tuberculosis in a Renal Transplant Recipient – Paradoxical Reaction or IRIS?

Laila AL Dabal* MD, Fakhriya AL Alawi MD and Omar Farooq

Infectious Diseases Unit, Rashid Hospital, Dubai Health Authority, UAE

Nephrology Unit, Dubai Hospital, Dubai Health Authority, UAE

***Corresponding author**
Dr. Laila AL Dabal, Infectious Diseases Unit, Rashid Hospital, Dubai Health Authority, UAE, E-mail: lmdabal@dha.gov.ae.

Submitted: 22 Nov 2017; **Accepted**: 09 Dec 2017; **Published**: 15 Dec 2017

Abstract

A 36 year old-man diagnosed with ESRD on hemodialysis, presented with fever, moderate abdominal pain with frequent non-bloody loose stools, headache, blurring of vision and molloscum-contagiousum like skin lesions. HIV test was negative and CT brain was normal. Blood culture grew Cryptococcus neoformans with high titer antigenemia. Amphotericin B and fluconazole were started and the patient was discharged on oral fluconazole therapy. Four weeks later, he was readmitted with persistent high spikes of temperature, profuse sweating and severe frontal headache. CT brain revealed a faint hypodense lesion at right frontal lobe with ill-defined margin and lumbar puncture was deferred. Pan-sensitive mycobacterium tuberculosis was grown from stool sample. Blood cryptococcalantigenemia was reported again and he was started on a new IV amphotericin intensive cycle and high dose fluconazole. Quadruple anti-tuberculosis treatment was initiated. The patient made a full clinical recovery including total resolution of skin lesions; laboratory and radiological recovery.

Background

Cryptococcus neoformans is a ubiquitous yeast-like encapsulated basidiomycetous fungus that is widely distributed in soil and found in pigeon droppings. It usually presents as sub-acute or chronic meningitisin patients with advanced AIDS, however, it has been described with lower frequency in non AIDS immune compromised hosts and as case reports in relatively immune competent subjects [1-6].

This case describes initial diagnosis of disseminated C.neoformans which was followed few weeks later with abdominal mtb diagnosis. It highlights the risk of having two serious and potentially fatal infections occurring simultaneously in a dialysis patient and reviews management plan for both infections.

Case presentation

A 36 year old- UAE national man, diagnosed to have end stage renal disease secondary to focal segmental glomerulosclerosis, underwent renal transplantation in November 2010 from live unrelated donor, and was maintained on triple immunosuppressant therapy; steroids, Mycophenolate and Tacrolimus. The patient was following up in another hospital and he reported a gradual decline in allograft function. In October 2014, he presented to our hospital with a Creatinine of 5.6mg/dl (estimated GFR of 14ml/min) and a diffuse nodular facial skin lesions that were diagnosed by a dermatologist as warty lesions and he underwent several cryotherapy sessions. In view of a failing graft and suspicious skin lesions; his immunosuppressant drugs were tapered down and he was prepared for renal replacement therapy.

Two weeks later, he presented to the Accident and Emergency with few days history of high-grade fever, moderate abdominal pain with frequent non-bloody loose stools, headache and blurring of vision in both eyes without altered sensorium. Broad-spectrum antimicrobial cover was initiated after collecting appropriate samples and immunosuppressant medication were stopped. All cultures (blood, urine, stool, sputum) and virology work up were negative. CT brain revealed a faint hypodense lesion at right frontal lobe with ill-defined margin without hydrocephalus and Lumbar puncture was deferred as the patient refused the procedure. High Resolution CT scan of the chest revealed bilateral lower lobe ground glass opacities with dense consolidative infiltrates noted in the right lower lobe with mild pleural effusion and multiple small mediastinal lymphnodes. The patient remained febrile on braod spectrum antibiotic and IV Andidulafungin was added on day 7 of admission. On day 16 of admission, blood culture report was positive for Cryptococcus neoformans with Cryptococcal antigen level in blood of 1: 16384. IV amphotericin plus IV fluconazole were immediately started after stopping Anidulafungin.The patient showed significant symptomatic improvement with total resolution of headache and visual complaints; however, he was still having non-bloody loose motions. Follow up chest imaging showed radiological resolution as well and his follow up blood culture was negative. The patient was discharged home on oral fluconazole therapy with follow up appointment in

outpatient clinic. He did not show up for clinic appointment and four weeks later he presented to Accident and Emergency reporting high spikes of temperature, profuse sweating and severe frontal headache. He admitted not being compliant with oral fluconazole therapy post discharge. Empirical IV conventional Amphotericin B in addition to high dose IV fluconazole were started. MRI brain was performed and revealed multiple subcortical and to lesser extent periventricular white matter hyperintensities. Blood culture was positive for Cryptococcus neoformans with high titer antigenemia (>1:16384). The patient refused again having lumbar puncture. Within few days of second admission, stool samples that were collected in his first admission were positive for mycobacterium tuberculosis on culture and pansensitive strain was grown. Accordingly, quadruple anti-tuberculosis regimen was started and doses were modified to his dialysis status.

Figure 1: Rash in the face

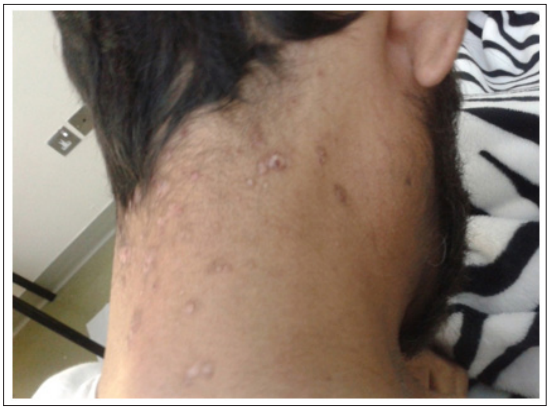

Figure 2: fading rash at the back of the neck

Differential diagnosis

Skin lesions were initially misdiagnosed to be warty lesions and had received several cryotherapy sessions though he reported some improvement, however, upon his hospital presentation with fever, headache and visual complaints; bacterial meningitis was the initial impression for which he was started on broad spectrum antibiotics and the facial lesions were thought to be a mulloscum contagiousum. The patient's refusal to do Lumbar puncture contributed to delay in initiating appropriate antifungal therapy for few weeks. Cutaneous histoplasmosis can have a similar appearance as well but this infection is not endemic in the region. Disseminated tuberculosis can explain the neurological, abdominal and respiratory findings; however, it does not explain the cutaneous lesions.

Treatment

The patient was started on new intensive cycle of IV conventional amphotericin combined with oral 400mg fluconazole therapy due to lack of flucytocine in our center as per treatment recommendations for cryptococcal meningitis in AIDS patients. In continuation phase, oral fluconazole at 400 mg daily was continued which was tapered to 200mg daily after six months. Upon the isolation of mycobacterium tuberculosis instool,quadrupleantituberculosis therapy using Rifampicin, Isoniazide, Pyrazinamide and moxilfloxacin instead of Ethambutol was started. Rifampicin was later changed to rifabutin at 150mg daily dose and he completed a total of 12 months of anti-tuberculosis therapy in view of initial neurological complaints and lack of CNS symptoms and radiological findings and lack of confirmatory CSF samples.

Outcome and follow up

The patient made full clinical, radiological and laboratory evidenced recovery and control of both infection. Skin lesions have totally disappeared and his visual acuity retuned back to his normal baseline, in addition, repeated stool cultures for AFB were all sterile and blood cryptococcal antigen level dropped to a nadir of 1:16 on follow up. The patient was last seen in Infectious Diseases Clinic in October 2017 doing very well and totally asymptomatic onhemodialysis 3 times per week. He was advised to continue low dose oral fluconazole therapy as secondary prophylaxis pending renal re-transplantation in the near future.

Discussion

This case represents a rare presentation of two serious infectionsin non-AIDS hemodialysis patient post-rejected renal transplantation within 4 weeks of discontinuation of immunosuppressant therapy. Isolated disseminated cryptococcosishas been sporadically described in patients with renal failure, nephrotic syndrome and in renal allograft recipients [7-9]. Concomitant infections, however, have been described as care reports in fewAIDS patients and on rare occasions in apparently immunocompetent adults [10-13]. Jarvis et al suggested that in AIDS patients, a history of tuberculosis can be a predisposing factor leading to reactivation of cryptococcosis and described several plausible mechanisms for concomitant infections [14]. In our patient, we were not able to confirm with confidence which infection came first as both infections were diagnosed within close time frame with subacute to chronic symptoms that could be explained by both. Deferral to perform appropriate invasive diagnostic work up like bronchoscopy for bronchoalvelar lavage and lung biopsy as well as lumbar puncture for full CSF analysis including cryptococcal antigen, India ink, TB PCR test and full fungal and mycobacterial culture had delayed the diagnosis. Tuberculosis is much more common among our cohorts of patients with ESRD or post-renal transplantation recipients and it the commonest infection among HIV/AIDS patients. We lack accurate data on the prevalence of cryptococcal disease in the UAE as it is mostly described as in patients with advanced AIDS who present with subacute or chronic meningitis.

Human cryptococcal infection is caused by c.neoformans which has a worldwide distribution and is considered as a serious opportunistic infection among AIDS patients mainly. The fungus enters the body via respiratory tract by inhalation of fungal spores and remains dormant for years to reactivate later upon defective cell mediated immunity occurring in the setting of long-term high dose steroid or immunosuppressant therapy or post transplantation. Reactivation

usually occurs in the CNS or respiratory tract leading to meningitis or less commonly as cerebral cryptococomas [15]. Respiratory illness presents as pulmonary consolidation, nodular, or cavitary infiltrates, miliarypattern or rarely as pleural effusion [16]. Cutaneous lesions are often described as nodular, waxy nodules with central umblication mimicking molluscum contagiosumlesions (cutaneous cryptococcosis). Indeed, cutaneous cryptococcosis is characteristic of HIV-infected patients, while amongst transplant recipients, cutaneous cryptococcal infection are frequently mimicked and is clinically indistinguishable from bacterial cellulitis, commonly affecting upper or lower extremities [17,18]. However, cutaneous cryptococcosis nodular lesions in the transplant sitting are indicative of hematogenous dissemination and should be treated with systemic antifungal agents.

Organ transplant recipients have become the group of immunocompromised patients at highest risk for cryptococcosis, though patients receiving calcineurin-inhibitor-based regimen such as Tacrolimus and cyclosporine arenoted to be less likely to have disseminated cryptococcaldisease or to have CNS involvement with lower mortality than patients who received non-tacrolimus-based regimen [19,20]. This could be partly related to the antifungal activity of these agents through inhibiting thecalcineurin. Renal failure as in our patient has been proposed to increase the risk for cryptococcosis and uremia is considered as independent predictor of death in transplant recipients with cryptococcosis [20]. Interestingly, few case reports have described renal transplants recipients who developed severe cryptococcosis upon immunosuppressant reduction post successful renal transplantation mimicking IRIS phenomenon in AIDS patients [21-23]. We speculate a similar process in our patient and we propose that he had latent infection with both c.neofromans and mtb which reactivated simultaneously or sequentially upon discontinuation of his immunosuppressant therapy.

Treatment recommendations are based on treating opportunistic infections in AIDS patients and no current guidelines address specifically non-AIDS patients [24,25]. Our patient received 2 weeks of IV conventional amphotericin B in combination with oral fluconazole therapy but in lower dose than recommendation both in intensive and continuation phase. Antituberculosis therapy was modified to both hemodialysis status and moxifloxacin was used instead of ethambutol in view of his visual complaints. Rifabutin then replaced rifampicin for continuation phase. The patient was monitored for clinical signs and symptoms as well as compliance and any drug-related side effects. He completed 12 months of antituberculosis treatment course keeping in mind possible disseminated TBas well and was advised to continue long-term oral fluconazole therapy for at least 6 months post-renal transplantation. Intravenous Dexamthasone was tested in HIV-associated cryptococcal meningitis and was associated with complications without mortality benefit and it was not used in our patient [26].

The incidence of disseminated cryptococcal infection is expected to rise in non-AIDS immune compromised hosts and managing physicians are in serious need for controlled studies in this field addressing optimal acute and long-term therapeutic options considering drug toxicity and drug-drug interaction profiles.

Learning points

- Opportunistic infections causing meningitis and disseminated infections are serious threat to immunecompromised host and should be rapidly diagnosed and correctly managed.
- Organ transplant recipients and hemodialysis patients are at risk of having serious dual infections mandating timely diagnosis and appropriate management.
- Nodular waxy skin lesions in immunecompromised hosts should raise suspicion for disseminated cryptococcal infection.
- Monitoring cryptococcalantigenemia level guides in clinical management and deciding on length of therapy.

References

1. Joseph N Jarvis,GraemeMeintjes ,Anthony Williams ,Yolande Brown (2010) Tom Crede. Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspectedcases. BMC Infectious Diseases 10: 67.
2. Zhu LP, Wu JQ, Xu B, Ou XT, Zhang QQ, Weng XH (2010) Cryptococcal meningitis in non-HIV-infected patients in a Chinese tertiary care hospital, 1997-2007. Med Mycol 48: 570-579.
3. Banks R, Williams A, Glover S, Burton P, Warnock D, Mackenzie C (1985) Disseminated cryptococcosis in a patient receiving chronic haemodialysis. Postgrad Med J. Aug 61: 745-747.
4. Ni W, Huang Q, Cui J (2013) Disseminated cryptococcosis initially presenting as cellulitis in a patient suffering from nephroticsyndrome. BMCNephrol 22: 14: 20.
5. Bichile LS, Gokhale YA, Sridhar V, Gill NH (2001) Disseminated cryptococcal infection in immune competent patients. JAssoc Physicians India 49: 377-378.
6. Ecevit IZ, Clancy CJ, Schmalfuss IM, Nguyen MH (2006) Clin Infect Dis.The poor prognosis of central nervous system cryptococcosis among nonimmunosuppressed patients: a call for better disease recognition and evaluation of adjuncts to antifungal therapy 42: 1443-1447.
7. Marques S, Carmo R, Ferreira I, Bustorff M, Sampaio S, Pestana M. (2016) Cryptococcosis in Renal Transplant Recipients: A Single-Center Experience. TransplantProc 48: 2289-2293.
8. Qadir F, Manzoor K, Ahmed E (2006) Disseminated cryptococcosis in a patient with Nephrotic syndrome. Indian Journal of Medical Microbiology 2: 141-143.
9. Nina Singh, Francoise Dromer, John R Perfect, Olivier Lortholary (2008) Cryptococcosis in Solid Organ Transplant Recipients: Current State-of-the-Science 47: 1321-1327.
10. Singh U, Aditi, Aneja P, Kapoor BK, Singh SP, Purewal SS. (2013) Cryptococcal meningitis associated with tuberculosis in HIV infected patients.Indian J Tuberc 60: 180-183.
11. Chandrashekar UK, Acharya V, Varghese GK, Rao L (2012) An unusual presentation of pulmonary cryptococcosis with co-existing disseminated tuberculosis in an AIDS patient. Trop Doct 42: 60-62.
12. Musabende M, Mukabatsinda C, Riviello ED, Ogbuagu O (2016) Concurrent cryptococcal meningitis and disseminated tuberculosis occurring in an immunocompetent male. BMJ Case Rep 25.
13. Chomicki J (1966) Coexistence of pulmonary tuberculosis with pulmonary and meningeal cryptococcosis. Report of a case.Dis Chest 50: 214-216.
14. Jarvis JN1, Harrison TS, Corbett EL, Wood R, Lawn SD (2010) Is HIV-associated tuberculosis a risk factor for the development of cryptococcaldisease? AIDS 24: 612-614.
15. Koshy JM, Mohan S, Deodhar D, John M, Oberoi A, Pannu A. Clinical Diversity of CNS Cryptococcosis.JAssoc Physicians India. 2016 Oct; 64(10): 15-19.

16. Liu K, Ding H, Xu B, et al. (2016) Clinical analysis of non-AIDS patients pathologically diagnosed with pulmonary cryptococcosis. J Thorac Dis 8: 2813-2821.
17. Chaya R, Padmanabhan S, Anandaswamy V, et al. (2013) Disseminated Cryptococcosis presenting as cellulitis in a renal transplant recipient.J Infect Dev Ctries 7: 60-63.
18. Orsini J, Nowakowski J, Delaney V, et al. (2009) Cryptococcal infection presenting as cellulitis in a renal transplant recipient. Transpl Infect Dis11: 68-71.
19. Singh N, Alexander BD, Lortholary O, et al. (2007) Cryptococcal Collaborative Transplant Study Group. J Infect Dis. Cryptococcus neoformans in organ transplant recipients: impact of calcineurin-inhibitor agents on mortality 195: 756-764.
20. Kontoyiannis DP1, Lewis RE, Alexander BD, et al. (2008) Calcineurin inhibitor agents interact synergistically with antifungal agents in vitro against Cryptococcus neoformans isolates: correlation with outcome in solid organ transplant recipients with cryptococcosis.Antimicrob Agents Chemother 52: 735-738.
21. Scemla A, Gerber S, Duquesne A, Parize P, Martinez F, et al. (2015) Dramatic improvement of severe cryptococcosis-induced immune reconstitution syndrome with adalimumab in a renal transplant recipient.Am J Transplant 15: 560-564.
22. Legris T, Massad M, Purgus R, Vacher-Coponat H, Ranque S, et al. (2011) Immune reconstitution inflammatory syndrome mimicking relapsing cryptococcal meningitis in a renal transplant recipient. Transpl Infect Dis 13: 303-308.
23. Panackal AA, Wuest SC, Lin YC,et al. (2015) Paradoxical Immune Responses in Non-HIV Cryptococcal Meningitis PLoSPathog 11: 004884.
24. Day JN, Chau TT, Wolbers M, Mai PP, Dung NT, Mai NH, et al. (2013) Combination antifungal therapy for cryptococcalmeningitis. NEngl J Med 368: 1291-1302.
25. Williamson PR, Jarvis JN, Panackal AA, et al. (2017) Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy.Nat Rev Neurol 13: 13-24.
26. Beardsley J, Wolbers M, Kibengo FM, et al. (2016) CryptoDex Investigators.Adjunctive Dexamethasone in HIV-Associated