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Cases of disseminated cryptococcosis in intravenous drug abusers without HIV infection: A new risk factor?

Mahmoud Shorman[a,b,*], Derek Evans[c], Christy Gibson[a], John Perfect[d]

[a] Department of Medicine/Division of Infectious Diseases, Marshall University, Huntington, WV, USA
[b] Department of Medicine/Division of Infectious Diseases, University of Tennessee Graduate School of Medicine, Knoxville, TN, USA
[c] Cabell Huntington Hospital, Huntington, WV, USA
[d] Department of Medicine/Division of Infectious Diseases, Duke University, Durham, NC, USA

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ABSTRACT

Cryptococcosis is a fungal disease which has been characterized by its identified risk groups. There are many risk factors identified. We present a surprising four cases of disseminated cryptococcosis in intravenous drug abuse (IVDA) patients in a short period of time and in one geographical area, this observation suggest that there may be a new association with IVDA and cryptococosis.

1. Introduction

Cryptococcosis is a fungal disease which has been characterized by its identified risk groups. The “awakening giant” of invasive mycoses has been ushered to a front-seat of attention in medical mycology by the appearance of the HIV pandemic, transplantation growth and the use of corticosteroids for specific underlying diseases. With these risk factors the incidence of Cryptococcosis has been estimated at over 500,000 cases per year. There are other niche risk factors such as hematological malignancies, sarcoidosis, liver disease, biological immune modulators such as anti-TNF therapies and other T-cell antibodies, and possibly even diabetes/COPD. However, Cryptococcus can even produce disease in apparently normal hosts although this group is shrinking with the risk identification of CD4 lymphocytopenia and anti-GM-CSF antibodies in these hosts without apparent underlying diseases. On the other hand, generally the normal host may be exposed to cryptococcus and develops infection but not disease. Thus, clinicians are always attempting to identify and/or understand the underlying host disease or condition when disseminated cryptococcosis is diagnosed.

In this report, we present a surprising four cases of disseminated cryptococcosis in intravenous drug abuse (IVDA) patients in a short period of time and in one geographical area. IVDA as a risk factor for cryptococcosis has been previously linked to infection with HIV but only rarely has a IVDA patient who is HIV- negative been reported to have disseminated cryptococcosis [1] but the following are cases of a small outbreak of cryptococcosis in patients linked by their IVDA and this observation suggest that there may be a new association with IVDA and cryptococosis not linked to HIV infection.

2. Case reports (Synopsis in Table)

2.1. Case #1

A 45year old male with past medical history of HCV, nicotine abuse, alcohol abuse, and IV heroin abuse for 15 years presented to our hospital via Emergency Medical Services (EMS) in June 2016 (at day 0) with a suspected drug overdose. Patient was given naloxone in the ER. A CT of head without contrast showed no acute findings and his chest X-ray showed no acute findings. AN EEG was unrevealing for seizures. Initially, he had a temperature as high as 100.8, blood cultures x2 were negative. He continued with altered mental status and an MRI of the brain with contrast showed extensive flair and enhancement with patchy areas of diffuse and leptomeningeal enhancement of left parietal lobe. He next underwent lumbar puncture (LP). Fluid was clear non-xanthochronic. WBC 138 mm^{-3}, neutrophils 3%, monocytes 13%, lymphocytes 84%, RBC 20 mm^{-3}, glucose 30 mg/dl, protein 66 mg/dl. Gram stain showed no organisms all on day zero. A Meningitis PCR Panel was positive for *Cryptococcus neoformans/gattii* and the yeast also grew on the aerobic bacterial culture on day +2. A serum cryptococcal antigen was positive and he was started on ambisome 450 mg intravenous (IV) daily and flucytosine 1500 mg per mouth (PO) every 6 h, he improved and was transferred to another facility for the remainder of his care (Table 1).

2.2. Case #2

A 54 year old male with past medical history of chronic low back pain, osteoarthritis, nicotine dependence, polysubstance abuse and

* Corresponding author at: Department of Medicine/Division of Infectious Diseases,University of Tennessee Graduate School of Medicine, Knoxville, TN, USA.

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Table 1
synopsis of the four cases of disseminated cryptococcal infection.

Age	45	54	29	39
Drug Use	IV heroin, alcohol abuse	polysubstance abuse, IVDA	IVDA with suboxone and opiates	IVDA with heroin
MRI/CT findings	CT Head without contrast showed no acute. MRI with contrast showed extensive flair and enhancement with patchy areas of diffuse and leptomeningeal enhancement of left parietal lobe	CT Head without showed no acute findings.	MRI of brain showed atypical PRES pattern of edema. CT head showed worsening hydrocephalus, cerebellar tonsillar protrusion through foramen magnum and compression of 4th ventricle	Cervical spine MRI showed extensive lesion from C2-T3 that was intramedullary and did not enhance.
Cell Count on presentation	WBC 6500 RBC 20 Neutrophils 3 Monocytes 13 Lymphocytes 84 Glucose 30 Protein 66	WBC 33 RBC 18 Neutrophils 15 Monocytes 5 Lymphocytes 80 Glucose 24 Protein 45	No LP as concern for herniation	WBC 556 RBC 117 Neutophils 14 Monocytes 64 Lymphocytes 82 Macrophages 12 Glucose 12 Protein 1582
Serum *Cryptococcus* Ag	positive	positive	positive	n/a
Serum *Cryptococcus* Ag Titer	1:160	1:20	1:5	n/a
Cryptococcus Ag CSF	positive	positive	negative	positive
Cryptococcus Ag Titer CSF	1:2560	1:280	n/a	> 1:5120
HIV result	negative	negative	negative	negative
HCV result	positive	positive	positive	positive
Timing of onset of sx prior to hospital	unknown, presented as overdose	ataxia 6–8 months	headache over 1 week	headache over 3 weeks

IVDA, osteoarthritis, diabetes with neuropathy, presented to our hospital in March 2015 (day 0) with a 6–8 week history of worsening ataxia, recent falls, confusion and lethargy at home. He was evaluated initially by neurosurgery who recommended anterior cervical decompression and fusion at a later date due to his sleep apnea. He was afebrile on day zero. CT of his head without contrast showed no acute findings. Two blood cultures obtained from his right hand and arm grew coagulase-negative staphylococcus and one grew *Cryptococcus neoformans* at +3 day. Initially, he was placed on intravenous fluconazole then changed to ambisome and flucytosine. LP tried but could not be performed due to body habitus initially. Blood cultures were consistently positive for *Cryptococcus neoformans* on +2, +3, +4 days. He then underwent CT-guided LP on +5 d. No opening pressure recorded, cell counts: WBC 33 mm^{-3}, neutrophils 15%, monocytes 5%, lymphocytes 80%, RBC 18 mm^{-3}, glucose 24 mg/dl, protein 45 mg/dl. CSF culture grew *Cryptococcus neoformans*. HIV and HCV antibody were negative. CD4 count was 1028 mm^{-3}. ANA and ANCA panel were both negative. Serum cryptococcus antigen was positive on day +2. He had a prolonged hospital course that was complicated by septic shock and acute respiratory failure due to acute cholecystitis on day +14. He completed 6 weeks of ambisome 450 mg IV daily, as could not tolerate flucytosine due to side effects, followed by high dose consolidation with fluconazole 800 mg po orally for 8 weeks then lower dose fluconazole 200 mg daily as a maintenance dose. He was last seen at month + eight of his treatment doing well.

2.3. Case #3

A 29 year- old male with past medical history of HCV, IVDA presented with altered mental status in July 2015 (day 0). His day zero MRI of the brain showed an atypical PRES pattern of edema. CT findings showed worsening hydrocephalus, cerebellar- tonsillar protrusion through the foramen magnum and compression of the fourth ventricle. Day +1 CTA of head and neck showed vasculitis and findings in posterior temporal lobe suggestive of encephalitis. He did not have a LP due to concern for herniation. He was seen by neurosurgery team who performed a biopsy of the brain on day +5 which showed yeasts consistent with cryptococcus. His biopsy cultures were negative. However, the serum cryptococcal antigen was positive. He was started initially on ambisome 400 mg iv daily for 2 weeks then changed to fluconazole 1000 mg po daily for 2 months with improvement. He was HIV negative, and CD4 cell count was 486 mm^{-3}. He was then lost to follow up.

2.4. Case #4

A 39 year old male with past medical history of IVDA, HCV, aseptic meningitis two years prior to presentation, and a cerebral aneurysm status/post clipping, presented to the ER in November 2015 (day 0) with complaints of a 3-week history of progressively worsening headaches, pain in his lower extremities and inability to move his lower extremities. Cervical spine MRI showed extensive vertebral lesions from C2-T3 that were intramedullary and did not enhance. Initial LP performed and showed: WBC 556 $mm^{-3,}$ neutrophils 3%, monocytes 64%, lymphocytes 21%, macrophages 12%, RBC 117 mm^{-3}, glucose 12 mg/dl, protein 1582 mg/dl. CSF culture was negative; Meningitis PCR Panel was negative; AFB smear was negative. He was started empirically on tuberculosis treatment for history of untreated latent tuberculosis. He was given corticosteroids per neurology and was undergoing plasmapheresis for transverse myelitis. Persistent ongoing weakness required another LP obtained on +8 day and cell count was WBC 97 mm^{-3}, neutrophils 14%, monocytes 4%, lymphocytes 82%, RBC 1 mm^{-3}glucose 1 mg/dl protein 544 mg/dl. CSF culture grew *Cryptococcus neoformans*. HIV test was negative. He was started on ambisome 370 mg IV daily and flucytosine 1500 mg po every 6 h for 4 weeks with improvement. Patient was lost to follow up after that.

3. Discussion

Infections due to *Cryptococcus* species occur worldwide with *Cryptococcus neoformans* being associated with the majority of the cases. *Cryptococcus* enters the host primarily through the respiratory tract, where it is usually contained by the host immune responses [2,3].

However, *Cryptococcus* is an encapsulated yeast that can mitigate antibody responsiveness and cell-mediated immunity allowing it to accumulate in tissue, especially in those who are immunocompromised [3,4]. This encapsulated yeast began to emerge as a significant opportunistic pathogen with the development of immunosuppressive agents used for organ transplantation and the treatment of malignancies [5]. The incidence of cryptococcal disease significantly rose with the HIV/AIDS pandemic and this viral infection has contributed to more than 80% of cryptococcosis cases globally [2].

Disseminated disease in immunocompetent patients is uncommon. However, in this case series, we have identified four cases of disseminated cryptococcosis in IVDA patients without HIV infection in the same geographical area within a 7 month time period. These cases occurred within a 60 mile range of each other in West Virginia. None of the patients in these cases were found to have any apparent underlying immunodeficiency condition or were receiving immunosuppressive therapy at presentation. The cases that we describe in this report are potentially linked to IVDA as a risk factor for disseminated cryptococcosis and might be considered an outbreak but this fungal infection is not a reportable CDC event so general prevalence of cryptococcosis in this area is not known. Interestingly and of uncertain importance all patients were HCV positive. Unfortunately, the identification of this small outbreak occurred after the ability to do detailed epidemiological studies. Thus, no specific link to a common source injectable material or practices could be obtained.

Cases of cryptococcal meningitis have been reported in immunocompetent non-HIV infected IVDA patients; however, the number of published individual cases is very limited [6,7]. It is uncertain how disseminated cryptococcal disease might develop in this patient population. However, methamphetamine has been shown to promote dissemination of cryptococcus from the respiratory tract into the brain parenchyma in animal models [3]. Methamphetamine facilitates this process by acting as an immunosuppressive agent through altering phagocytosis and antigen processing by inhibition of endosomal acidification [3,4,8]. Furthermore, methamphetamine accumulation in the lungs can results in defects in macrophages and neutrophils creating conditions more likely to result in disease [3,8]. For instance, adhesion of cryptococcus to lung tissue in the presence of methamphetamines stimulates the excessive release of glucuronoxylomannan (GXM) and biofilm formation thereby predicting the facilitation of dissemination to the central nervous system (CNS) [3].

On the other hand, given the time range, location of these case reports, and the amount of heroin abuse in this region, one must consider the potential for drug-related contamination. Outbreaks of disseminated candidiasis have been reported in IVDA who were using brown heroin. These outbreaks were attributed to contamination of the lemon juice used to dissolve the heroin. [1].

There has also been reports of the immune stimulant, levamisole, being used in heroin and possibly, it could have immune dysregulation potential. In our cases associated with heroin abuse, it is unknown what was used to dissolve the heroin or what it was cut with, or how it had been stored. As a result, the potential for contaminated drugs could not be excluded as a source of these cases of cryptococcal meningitis in this retrospective review [9].

In summary, this apparent small outbreak of cryptococcosis in IVDA should be noted and clinicians may consider it a potential risk factor for cryptococcosis even if patient is HIV-negative and allow for earlier work-ups for CNS fungal disease. Unfortunately, the retrospective nature of these cases did not allow for detailed epidemiologic enquires of each case as the microbiology laboratory did not save the isolated cryptococcus, but should provide stimulus for future cases in IVDA to consider what may have been injected to allow this fungus to grow and disseminate in the host.

Conflict of interest

Authors declare no conflict of interest.

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