Aspergillus species is a ubiquitous fungus present in soil and decaying vegetation. The primary sites of infection in humans are lungs and paranasal sinuses. CNS aspergillosis rarely occurs without an extracranial source [1]. The mortality rate associated with CNS aspergillosis is reported to be as high as 90%, especially in the immunocompromised patients [2]. Its pathology includes infective vasculopathy, septic infarcts, infectious cerebritis and abscesses. Voriconazole is the drug of choice for systemic therapy [3]. Indications for surgical intervention are usually decompression of symptomatic lesions causing focal neurological deficits and for tissue diagnosis [4].

2. Case

Our patient is a 35-year-old lady who presented with fever and paraparesis of one week duration. The day of admission was considered as Day 0. She had backache without radicular symptoms, cough and occasional hemoptysis for five months prior to admission (Day-150). A tissue biopsy five years prior confirmed pulmonary sarcoidosis for which she has been on chronic oral steroids. On examination, she was febrile with normal vital signs. Systemic examination revealed cushingoid habitus and mid-thoracic spine tenderness. Neurological exam revealed MRC grade 3 paraparesis and a sensory level corresponding to T6 spinal level. Acid fast bacilli were detected in sputum examination and chest X-ray was normal. X-ray of the thoracolumbar spine showed loss of T8 vertebral height and no evidence of disc space collapse or other bony destruction (Fig. 1a and b). MRI of thoracolumbar spine showed abnormal marrow signals in the mid-thoracic vertebrae with a partial collapse of T8 and a large epidural abscess from T5-T9, all suggestive of spinal tuberculosis (Fig. 1c and d).

A diagnosis of pulmonary tuberculosis with probable associated tuberculous spondylitis was made and the patient was started on the 4-drug antitubercular regimen (INH 300 mg, Rifampicin 600 mg, Ethambutol 800 mg, Pyrazinamide 1500 mg) that was later modified, in view of drug-induced hepatotoxicity to Streptomycin(750 mg), Ethambutol(800 mg) & Ofloxacin(400 mg). However, in spite of the antitubercular treatment, her weakness worsened to complete paraplegia by the fourth week (Day+28). She then underwent T5-T8 laminectomy, debridement of epidural granulation tissue and posterior stabilization from T2-T12. Spinal tuberculosis was ruled out by negative multiplex PCR evaluation confirmed cerebral aspergillosis. Voriconazole was changed to intravenous lipid complex Amphotericin B to achieve sustained clinical and radiological response after six months of therapy.

3. Discussion

The patient had a history of chronic oral steroids and decaying vegetation. The imaging findings were suggestive of spinal tuberculosis. However, the histopathological examination revealed a granuloma with septate hyphae indicative of Aspergillus species [Fig. 2a and b]. Multiplex PCR and fungal culture [Fig. 2c and d] also confirmed Aspergillus fumigatus. Treatment with intravenous voriconazole, loading dose of 400 mgs twice daily followed by 200 mgs twice daily was initiated (Day+30). Her steroid was tapered to the lowest possible dose.
possible maintenance dose to avoid clinical symptoms of adrenal insufficiency.

After initial defervescence, the fever recurred after three weeks (Day +51) of intravenous voriconazole. By the fourth postoperative week, she developed seizures, altered sensorium and persistent fever. She was electively intubated for airway protection and nonenhanced head CT brain showed well defined hypodense lesions in the left parietal and bilateral frontal lobes [Fig. 3a and b]. CSF analysis showed glucose of 31.6 mg/dl (corresponding blood glucose 120 mg/dl), 12 cells per high power field with 30% polymorphonuclear and 70% mononuclear. MRI brain showed multiple T2FLAIR hyperintense, well-defined focal lesions with dense diffusion restriction and ring enhancement pattern on contrast administration located at the grey-white junction of the left parietal region, left frontal and right frontal lobes (Fig. 3c–g). CSF

![Fig. 1. X-ray of the thoracolumbar spine showing showing prevertebral and paravertebral opacity.](image1)

![Fig. 2. 2a H & E staining, 400× showing granuloma, 2b PAS staining, 400× showing fungal hyphae 2c Bluish grey colonies of A.fumigatus, 2d Lactophenol cotton blue preparation from the colonies, 40× showing flask shaped vesicle with philades arising from the upper half of the vesicle.](image2)
bacterial and AFB cultures were negative; whereas, CSF Multiplex PCR was positive for *Aspergillus fumigatus* and negative for tuberculosis and bacterial panel.

As there was evidence of progression of infection to the brain on systemic voriconazole therapy, our patient was started on lipid complex amphotericin B (Day+58). She was initially started at 5 mg/kg/day, subsequently increased to 10 mg/kg/day as fever and altered sensorium persisted. In the interim, she developed signs of adrenal insufficiency requiring escalation of her steroid dosage. She defervesced within a week’s time of starting amphotericin. After defervescence her amphotericin B dose was reduced to 5 mg/kg/day. The modified antitubercular regimen, started for her sputum AFB culture positivity, was continued. Following defervescence and control of seizures, she improved neurologically and was transitioned to long-term rehabilitation. Intravenous lipid complex amphotericin was continued for a total of six months with close monitoring. Meanwhile her sputum became AFB-negative and antitubercular treatment was continued to complete a nine month course. In the interim, steroids were gradually tapered and discontinued.

MRI Brain and spine at 1 year showed complete resolution of her lesions (Fig. 4). At two year follow-up, she remains afebrile with a normal sensorium and is seizure-free. The spinal infection has resolved radiologically and her myelopathy is clinically improving to the extent that she has MRC grade 3 power in the lower limbs, and is able to stand with support.

3. Discussion

Invasive aspergillosis is a disseminated fungal infection associated with a high mortality despite treatment [5]. A systematic review of the literature of 1223 cases of invasive aspergillosis reported case fatality rates of 99% for cerebral aspergillosis, 86% for pulmonary, and 66% for paranasal sinus infection. Mortality rates remained high despite
remains the gold standard for diagnosis [7]. Given the limitations of serum has been reported using galactomannan (GM) [1,3], beta-D-glucan (BDG) and mannan enzyme immune assays [11]. The polymerase chain reaction (PCR) assay serves as a powerful non-conventional methods of diagnosis for invasive fungal infections, a perforating arteries [6].

Galactomannan is relatively specific for Aspergillus spp. Moreover, it is the most sensitive test for the diagnosis of invasive aspergillosis; with a favourable outcome of up to 35% when coupled with surgery [3].

Spinal Aspergillosis may occur by hematogenous spread or direct extension from the lung. As this case depicts, differentiation between spinal aspergillosis and tuberculosis may be impossible on clinical and radiological grounds alone [7,8], especially in an immunocompromised individual. However, the distinction between the two is important, as delay in diagnosis contributes to the high morbidity and mortality of invasive aspergillosis [9]. In our case, the clinical presentation and MRI findings in the setting of sputum AFB positivity was highly suggestive of spinal tuberculosis. Radiologically, it is difficult to differentiate spinal aspergillosis and tuberculous spondylitis. Spinal tuberculosis most commonly leads to disc space collapse and paradiscal involvement of the vertebral body [8]; whereas in invasive aspergillosis, the lesion expands circumferentially and destroys all the surrounding spinal structures, including vertebral bodies, discs, and neural arches, as well as all the contiguous structures, like ribs, thoracic wall, lungs, etc [9].

The pathophysiology of the cerebral aspergillus infection implicates an infective vasculopathy-mediated septic infarction or hemorrhage, causing infectious cerebritis that evolves into an abscess. Its anatomic distribution is mainly in the corticomedullary junction, thalami, basal nuclei or the corpus callosum. The apparent affinity of CNS aspergillosis for perforating artery distributions is most likely due to the invasive character of Aspergillus spp. compromising the origins of the perforating arteries [6].

Culture of clinical specimens to isolate the etiologic fungal agent remains the gold standard for diagnosis [7]. Given the limitations of conventional methods of diagnosis for invasive fungal infections, a negative result on direct or pathologic smears and cultures does not rule out infection [10]. The detection of fungal cell wall markers in serum has been reported using galactomannan (GM) [1,3], beta-1-3-glucan (BDG) and mannan enzyme immune assays [11–13]. Galactomannan is relatively specific for Aspergillus species, and can be detected in body fluid specimens with enzyme immunoassay [11]. The polymerase chain reaction (PCR) assay serves as a powerful non-culture method for the diagnosis of systemic fungal infection in high-risk patients [12]. The sensitivity of CSF PCR in detecting CNS Aspergillosis is 100% as compared to galactomannan 80%. Molecular methods yielding results within 6 h have now revolutionized the diagnosis of fungal infections, allowing for diagnosis and therapy during the incubation period and early stage of infection [1]. Despite the increasing burden of opportunistic fungal infections, early accurate diagnosis of fungal infections remains a challenge.

Voriconazole is the recommended therapy for CNS aspergillosis, with favourable response of up to 35% when coupled with surgery [3]. Azole resistance in A. fumigatus has been associated with mutations in the Cyp51A gene, the target for antifungal azoles [14]. In our patient, though we were unable to monitor therapeutic drug levels of voriconazole, we believe that coadministration of rifampicin would have contributed to clinical voriconazole failure [15]. For patients intolerant of or refractory to voriconazole, a formulation of Amphotericin B is an appropriate alternative. Though Amphotericin B deoxycholate has historically been used in the treatment of invasive aspergillosis, the lesser nephrotoxicity makes Liposomal amphotericin B preferable [16]. Intrathecal administration of amphotericin B does not allow penetration beyond the pia-mater. Instead, high-dose systemic amphotericin B is recommended to achieve higher parenchymal concentration [17]. In our patient we used lipid emulsion amphotericin with great success [18].

Because of continued high rates of mortality despite the use of newer antifungals, surgical resection of large infective foci is an important adjunct to improve outcome [4]. Surgical debridement and stabilization of the spine was necessary in our patient once she developed acute compressive myelopathy. Once our patient developed multiple cerebral abscesses, stereotactic aspiration, though considered, was not required since she responded favorably to medical management alone.

Though duration of therapy for aspergillosis has not been optimally defined, amphotericin B or voriconazole for a total duration of 8 – 12 weeks is recommended [9]. To date, clear-cut guidelines are lacking due to the rarity of these infections. Infectious Diseases Society of America (IDSA) guidelines advise treatment of invasive aspergillosis until resolution or stabilization of all clinical and radiographic mani-

**Fig. 4.** MRI brain and spine after 1 year revealing complete resolution of lesions.
vestation. Hence we chose to continue antifungal regimen for six months till complete radiological resolution. Our case also highlights the possibility of voriconazole resistance, as she developed fever with new symptomatic cerebral lesions while on therapy for spinal aspergillosis requiring treatment with lipid complex amphotericin B. Azole resistance in A. fumigates is an emerging problem and may develop during azole therapy. Other alternative treatments include caspofungin, micafungin, posaconazole and itraconazole [19]. Withdrawal of corticosteroids or reduction of dosage is often critical for successful outcome in invasive aspergillosis. Failure to reduce an immunosuppressive dosage of systemic corticosteroids usually results in relentless invasive fungal infection [20]. For patients with successfully treated invasive aspergillosis who require continued immunosuppression, antifungal prophylaxis may prevent recurrent infection from residual foci of infection [21].

4. Conclusion

This case highlights the efficacy of aggressive medical and surgical co-management for invasive fungal disease of the CNS. Invasive aspergillosis poses a serious challenge for physicians and tissue diagnosis is highly recommended. Though voriconazole is the treatment of choice for invasive aspergillosis, resistance is common and can lead to rapid disease progression and mortality. Additionally it is critical to monitor therapeutic drug levels, where available, during voriconazole therapy to ensure clinical efficacy and decrease adverse effects. Hence close monitoring for clinical and radiological resolution, as well as, alternate drug therapy are strongly advised. Transitioning treatment from voriconazole to amphotericin B along with early surgical intervention may improve the chance of resolution and survival.

Conflict of Interest

There are none.

Acknowledgements

The authors would like to acknowledge the efforts of Dr Prasanth Ariyannur, Staff scientist, Molecular Oncology Lab and Fabia E T, Lecturer, Allied Health Sciences for manuscript preparation and submission.

References

[1] S. Chen, J.L. Pu, J. Yu, J.M. Zhang, Multiple Aspergillus cerebellar abscesses in a middle-aged female: case report and literature review, Int J. Med. Sci. 8 (7) (2011) 635–639.
[2] S.-J. Lin, J. Schranz, S.M. Teutsch, Aspergillosis case-fatality rate: systematic review of the literature, Clin. Infect. Dis. 32 (3) (2001) 358–366.
[3] S. Schwartz, M. Ruhnke, P. Ribaud, L. Corey, T. Driscoll, O.A. Cornely, et al., Improved outcome in central nervous system aspergillosis, using voriconazole treatment, Blood 106 (8) (2005) 2641–2645.
[4] D.W. Denning, D.A. Stevens, Antifungal and surgical treatment of invasive aspergillosis: review of 2121 published cases, Rev. Infect. Dis. 12 (6) (1990) 1147–1201.
[5] J.M. Son, W.H. Lee, C.K. Jung, S.I. Kim, K.Y. Ha, Aspergillosis spondylitis involving the cervico-thoraco-lumbar spine in an immunocompromised patient: a case report, Korean J. Radiology. 8 (5) (2007) 448–451.
[6] D.R. DeLone, R.A. Goldstein, G. Petermann, M.S. Salamat, J.M. Miles, S.J. Knechtie, et al., Disseminated aspergillosis involving the brain: distribution and imaging characteristics, AJNR Am. J. Neuroradiol. 20 (9) (1999) 1597–1604.
[7] J.F. Camargo, V. Seriburi, M. Tenner, M.Y. El Khoury, Aspergillus osteomyelitis of the lumbar spine complicated with orbital apex syndrome: a potential role of the Batson’s plexus in disease propagation, Med Mycol. Case Rep. 1 (1) (2012) 9–12.
[8] G.J. Lee, T.Y. Jung, S.M. Choi, M.Y. Jung, Cerebral aspergillosis with multiple enhancing nodules in the right cerebral hemisphere in the immune-competent patient, J. Korean Neurosurg. Soc. 53 (5) (2013) 312–315.
[9] D.W. Denning, Therapeutic outcome in invasive aspergillosis, Clin. Infect. Dis. 23 (3) (1996) 608–615.
[10] M. Cuenca-Estrella, M. Bassetti, C. Lass-Flörl, Z. Ráfi, M. Richardson, T.R. Rogers, Detection and investigation of invasive mould disease, J. Antimicrob. Chemother. 66 (suppl 1) (2011) i15–i24.
[11] R. Herbrecht, V. Lettscher-Bru, C. Oprea, B. Louzé, J. Waller, F. Campos, et al., Aspergillus galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients, J. Clin. Oncol. 20 (7) (2002) 1898–1906.
[12] M. Kami, S. Ogawa, Y. Kanda, Y. Tanaka, U. Machida, T. Matsumura, et al., Early diagnosis of central nervous system aspergillosis using polymerase chain reaction, latex agglutination test, and enzyme-linked immunosorbent assay, Br. J. Haematol. 106 (2) (1999) 536–537.
[13] L. Ostrosky-Zeichner, B.D. Alexander, D.H. Kett, J. Vazquez, P.G. Pappas, F. Saeki, et al., Multicenter clinical evaluation of the (1→3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans, Clin. Infect. Dis. 41 (5) (2005) 654–659.
[14] J.W.M. van der Linden, R.R. Jansen, D. Breesters, C.E. Visser, S.E. Gerverings, E.J. Kuiper, et al., Azole-Resistant Central Nervous System Aspergillosis, Clin. Infect. Dis. 48 (8) (2009) p1111–p1113.
[15] M.J. Dolton, J.E. Ray, S.C. Chen, K. Ng, L.G. Pont, A.J. McLachlan, Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring, Antimicrob. Agents Chemother. 56 (9) (2012) 4793–4799.
[16] M.H. White, E.J. Anaissie, M. Tenner, D. Siegler, B. Wingard, J.W. Hiemenz, A. Cantor, et al., Amphotericin B colloidal dispersion vs. amphotericin B as therapy for invasive aspergillosis, Clin. Infect. Dis. 24 (4) (1997) 635–642.
[17] O.A. Cornely, J. Maertens, M. Bresnik, R. Ebrahimi, A.J. Ullmann, E. Bouza, et al., Detection and investigation of invasive mould disease, J. Antimicrob. Chemother. 36 (3) (1995) 608–615.
[18] A.S. Janoff, W.R. Perkins, S.L. Saletan, C.E. Swenson, Amphotericin B lipid complex (AmBiLoad trial), Clin. Infect. Dis. 44 (10) (2007) 1289–1297.
[19] A.S. Janoff, W.R. Perkins, S.L. Saletan, C.E. Swenson, Amphotericin B lipid complex (AmBiLoad trial), Clin. Infect. Dis. 44 (10) (2007) p1111–p1113.
[20] J.F. Camargo, V. Seriburi, M. Tenner, M.Y. El Khoury, Aspergillus osteomyelitis of the lumbar spine complicated with orbital apex syndrome: a potential role of the Batson’s plexus in disease propagation, Med Mycol. Case Rep. 1 (1) (2012) 9–12.
[21] F. Cowie, S.T. Meller, P. Cushing, R. Pinkerton, Chemoprophylaxis for pulmonary aspergillosis during intensive chemotherapy, Arch. Dis. Child. 70 (2) (1994) 136–138.