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Fundamental Neurosurgery

Post-transplant aspergillosis and the role of combined neurosurgical and antifungal therapies under belatacept immunosuppression

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Abstract

Opportunistic CNS-infection represent a major threat to patients after organ transplantation due to the need for ongoing immunosuppression and belatacept is a novel CTL4A inhibitor, which is increasingly used for patients following cadaveric kidney transplantation. Among the CNS infections, intracranial Aspergillus is a particular challenge and poses difficulties for its insidious onset, a timely and accurate diagnosis, and its management due to high mortality rates. To this end we want to illustrate the management of this scenario as encountered in a 71-year-old female patient, who was admitted into our institution in June 2007 with speech difficulties and gait instability 1.5 years after cadaveric kidney transplantation. On imaging, both a mediastinal and left frontal mass were found. Radiographically guided sampling of the mediastinal mass and a stereotactic biopsy of the left frontal brain lesion revealed *Aspergillus fumigatus*. With modification of immunosuppression and directed antifungal therapy there was complete resolution of the chest lesion; the brain lesion initially responded well but later progressed in size. Surgical intervention via a left fronto-temporal craniotomy with intraoperative image guidance was performed for a gross total resection of the lesion. Twenty-four months from resection, she remains on voriconazole with no evidence of recurrence and complete neurologic recovery and preserved renal function.

Key Words: Belatacept, CNS aspergillosis, immunosuppression, neurosurgery, renal transplant, voriconazole

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INTRODUCTION

Environmental fungi account for approximately 5% of all central nervous system (CNS) infections. Most occur as opportunistic organisms in immunocompromised patients and carry a mortality rate as high as 86-95%.[1,3,8,15,18] The most common isolates are *Aspergillus spp*, presenting as either maxillary sinusitis or primary pulmonary infections.[1] CNS disease can occur via hematogenous spread from angioinvasive disease in the lungs or by direct invasion through the nasal sinus via vascular channels or bone.[13] Manifestation of CNS involvement may be subtle as a result of location (e.g., frontal disease) but can dramatically and rapidly progress to fulminant symptoms due to concurrent effects of immunosuppression.

The number of patients with invasive fungal infections appears to be rising and may be related to increases in the number of solid organ, bone marrow or stem cell transplant recipients.[10]Increased use of newer biologic immunosuppressants may also play a role in epidemiological changes. Additionally, radiographic imaging modalities and pathogen detection techniques have improved and become more sensitive, contributing to the ability to better diagnose invasive fungal infections.[3,7,18]

One such class of immunosuppressant drugs is belatacept, the costimulatory ligand blocker used to target specific signaling pathways. This review includes the first case report of an unusual presentation of an invasive *Aspergillus* infection in a renal transplant recipient receiving belatacept for immunosuppression.

CASE REPORT

The patient is a 71-year-old female with a history of adult-onset diabetes mellitus, hypertension, rectal cancer and end-stage renal disease who had a successful deceased donor renal transplant 18 months prior to presentation. Her immunosuppression included belatacept, administered as part of an institutional review board (IRB) approved study. She presented acutely with complaints of breathing difficulties and substernal chest pain that was initially pleuritic in nature, but had become constant. She was also noted to have new onset of word-finding difficulty with inappropriate word substitution approximately 7 days prior to evaluation. She denied fever, chills, weight loss, or other constitutional symptoms.

Her clinical examination was significant for the aphasia and a substernal mass, which was firm, and tender to palpation. She had no other focal neurologic or physical findings. The routine chest roentgenograph demonstrated a mediastinal mass with a left lower lobe process. A subsequent computerized tomography (CT) scan confirmed only a mediastinal mass that was adherent to the pericardium and extended anteriorly [Figure 1].

Following admission for further workup, she rapidly developed right retro-orbital pain with ipsilateral decreased vision. On re-examination, she had a predominantly expressive aphasia, a mild right pronator drift, and some slight right nasolabial fold flattening. Ophthalmologic evaluation revealed corneal erosion for which she received topical ophthalmologic polymyxin B. Head imaging with CT and magnetic resonance imaging (MRI) revealed a deep-seated left frontal lesion [Figure 2a-d]. The lesion was heterogeneously contrast enhancing after intravenous gadolinium administration, measured 25 × 18 × 10 mm and showed associated perifocal edema, resulting in a mild midline shift. She was started on dexamethasone for the edema and levetiracetam for seizure prophylaxis.

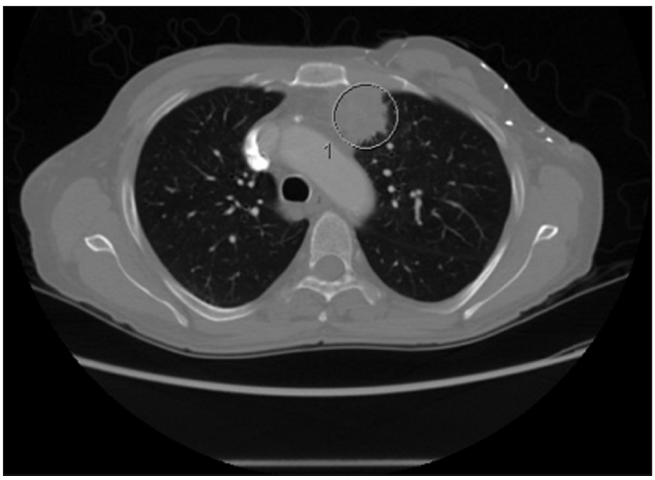

Figure 1: CT of the chest, lung window, demonstrating a mediastinal process invading into the left lung verses a primary pulmonary process invading into the mediastinal border; the appearance was concerning a neoplasm. Further images demonstrate erosion anteriorly into the posterior sternum

Routine blood work included compete blood count and differential, electrolytes and chemistries, all of which were within normal limits. Her baseline creatinine was 0.8 mg/dl. Infectious causes were considered. Blood cultures for bacteria and fungus were obtained (but showed no growth), serum toxoplasma IgG and IgM, cryptococcal antigen, galactomannan and beta-d-glucan antigen tests were negative; urinary histoplasma antigen was also negative. Sampling of her CSF was not performed because of concerns of increased intracranial pressure. Given her history of a distant squamous cell carcinoma of the anus, the presence of an erosive mediastinal mass and being a relatively recent solid organ transplant recipient, metastatic or recurrent malignancy as well as post-transplant lymphoproliferative disease were of concern and it was felt that a biopsy was needed of both foci. The patient first underwent a CT-guided transthoracic lung biopsy followed 2 days later by a stereotactic brain biopsy. Both yielded specimen demonstrating septated, branching hyphae with culture data that confirmed *Aspergillus fumigatus*. Nucleic acid testing for mycobacteria, toxoplasma, and Epstein Barr Virus from the brain biopsy specimen was negative.

Antifungal therapy was initiated and included high-dose oral voriconazole (6 mg/kg twice daily) and parenteral liposomal amphotericin B (5 mg/kg/day). Because of an acute rise in serum creatinine from 1.0 to 2.0 mg/dl the liposomal amphotericin was discontinued, and caspofungin (75 mg parenteral load, then 50 mg daily) was initiated. Her immunosuppression was changed from belatacept to mycophenolate mofetil 250 mg twice daily. The patient remained neurologically stable with resolution of her expressive aphasia within 4 weeks of initiation of dexamethasone and antifungal therapy. Repeat MRI of her CNS lesion was grossly unchanged

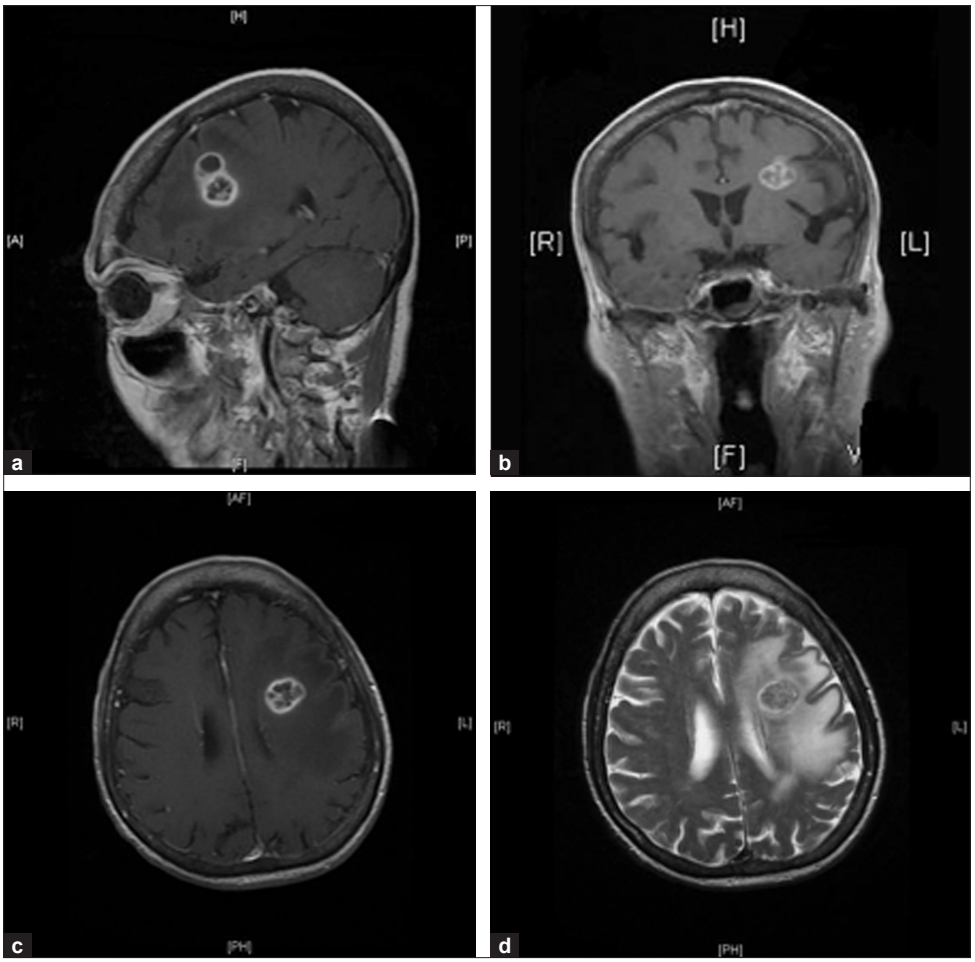

Figure 2: Cranial, sagittal and axial T1 weighted images demonstrating a 25 × 18 × 10 mm complex, lobulated, enhancing mass on post-gadolinium centered within the left frontal lobe.T2-weighted images demonstrate associated extensive vasogenic edema and mild mass effect.

at 6 weeks after initiation of antifungal therapy and by 12 weeks, the lesion regressed on MRI imaging with a concomitant decrease in edema [Figure 3]. Intravenous caspofungin was discontinued at this point, and she was continued on oral voriconazole, with trough levels in the 3-4 μg/ml range. Further chest imaging demonstrated improvement of disease with complete resolution by 6 months. However, repeat MRI of her head at 7 months demonstrated an increase in size of the lesion [Figure 4], now measuring 17 × 24 mm, with increased perilesional vasogenic edema despite medication compliance. The patient was not obviously aphasic; however, her family noted subtle word finding difficulties over the preceding 2 weeks. Because of the prior radiographic and clinical changes documenting improvement, concerns for secondary or superinfection were raised, as were CNS post-transplant lymphoproliferative disorder (PTLD), or the possibility of voriconazole-resistant *Aspergillus* infection. She underwent a second stereotactic brain biopsy and intraoperative stains were negative for organisms or leukocytes. Pathology did not reveal a neoplasm but did identify gliosis. Specific fungal stains and fungal cultures were negative, and the only recovered organism was penicillin susceptible *Proprionobacter acnes*. This could have been culture contamination but was treated as a possible pathogen with 6 weeks of parenteral penicillin, 12 million units/day.

Although clinically her aphasia had again resolved, follow up MRI of the brain failed to demonstrate improvement in the size of the lesion and showed developing areas of necrosis and edema. For this reason the patient was taken to the operating room for an image-guided, left-sided, fronto-temporal microscopic resection and duraplasty. The abscess appeared densely encapsulated at the time of surgery, but establishment of a perilesional dissection plane was complicated because of an intense inflammatory reaction of surrounding glia and its vessels, which created dense tissue adherence. Pathology demonstrated *in toto* excision of an encapsulated abscess with septated hyphae in the periphery of the abscess and culture confirmed *Aspergillus fumigatus*, with susceptibility to voriconazole. She had an unremarkable post-operative course.

Now 2 years from the excision, she remains symptom free with only mild, persistent flattening of the nasolabial fold. She has no radiographic evidence of recurrence

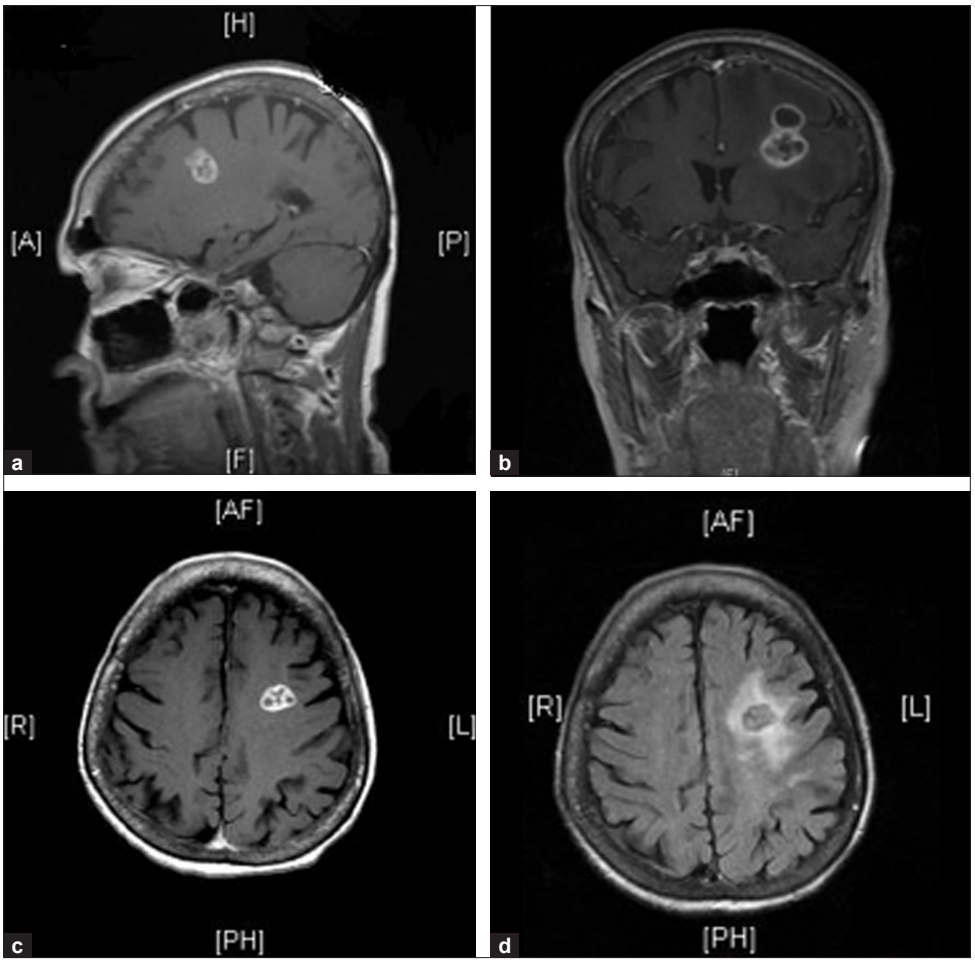

Figure 3: Sagittal and coronal T1 post-contrast MRI scans demonstrating a decrease in size of the ring enhancing lesion located deep in the left frontal lobe with decrease in surrounding edema (see FLAIR image right lower panel)

either in her CNS [Figure 5] or chest. Her renal function remains good with a serum creatinine of 1.2 mg/dl, on mycophenolate mofetil alone for immunosuppression, and voriconazole and trimethoprim/sulfamethoxazole prophylaxis.

DISCUSSION

Aspergillus

The term "Aspergillosis" typically refers to a clinical condition associated with *Aspergillus spp*, most commonly, *A fumigatus*, *A niger*, *A flavus* or *A terreus*. These are ubiquitous organisms found throughout domestic environments. Exposure to the conidia or spores, a common event, is responsible for infection. Tissue-invasive disease and more significantly angioinvasive disease occur only in specific conditions, which include acquired or medically immunosuppressed states. Other less frequently described causes have included direct inoculation or contamination of dressings in burns and surgical wounds.

Primary host defense lies in the alveolar macrophages, which engulf and neutralize *Aspergillus conidia*. There is significant surface antigen processing, ultimately resulting in a complex array of T- and B-lymphocyte responses. In the settings where macrophage number or function or both are impaired, or an overwhelming exposure to conidia occurs, the conidia or spores will germinate resulting in the mycelial or hyphal elements which are the vegetative form of the mold. In early invasive disease, neutrophils are recruited by regulatory cytokines and neutrophil chemotactic factors. The hyphae release a series of metabolites in response, including galactomannan, a surface glycoprotein that can be used in diagnosing angioinvasive infection and also serves as an evasion factor to macrophages. Other metabolites include complement inhibitors, mycotoxins including aflatoxin, a potent neurotoxin, and gliotoxin, which have extensive immunosuppressive qualities. Pathologically, once hyphal disease develops in an overwhelmed host, they typically ignore tissue planes, and rapidly invade vessels. This results in local necrosis ("Black eschars") but also permits the hyphae to spread to other organs and distant sites, including brain, spinal cord, visceral organs, and extremities.

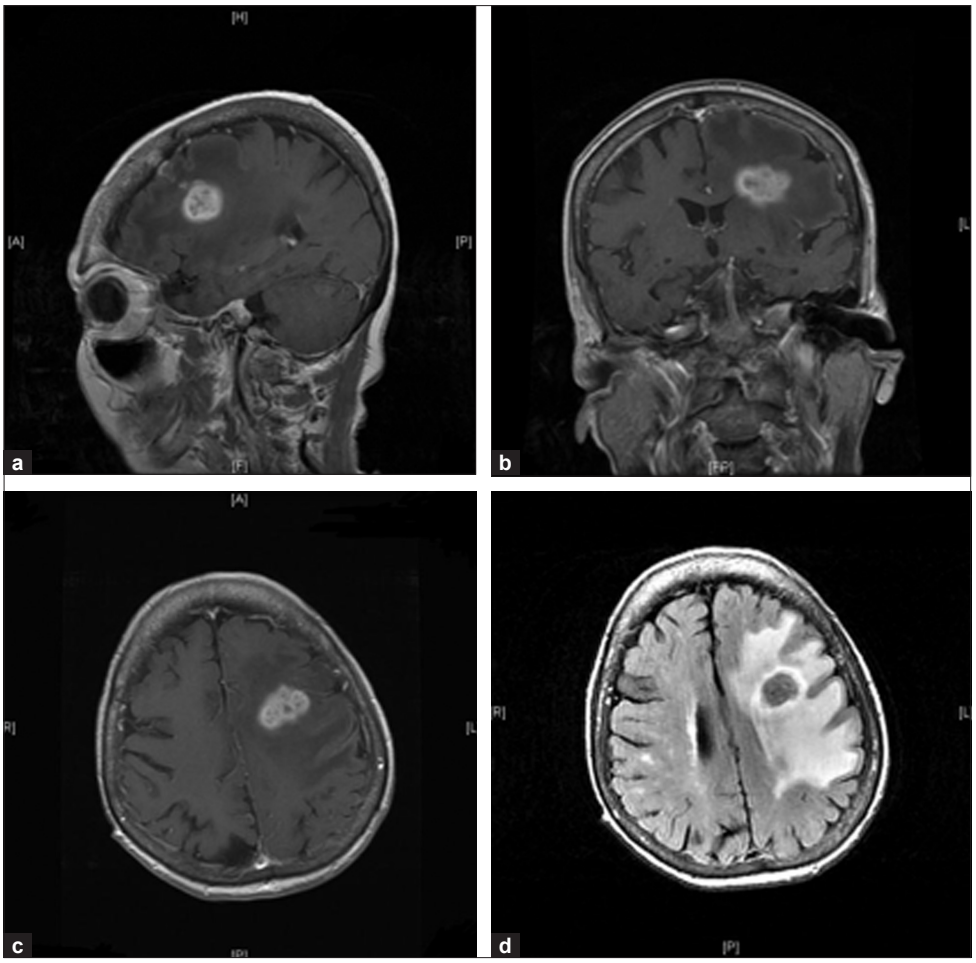

Figure 4: Follow-up MRIT1 post-contrast demonstrate an increase in size of the left frontal lesion with much increased surrounding edema (see FLAIR image right lower panel)

Due to frequent non-specific clinical manifestations, CNS aspergillosis is difficult to diagnose and is often mistaken for pyogenic abscess, tuberculosis, toxoplamosis, or a neoplasm. Histopathologically, CNS aspergillosis typically generates large septal hyphae that show a dichotomous branching pattern creating granuloma formation with a perilesional giant cell reaction.[8] Such vascular extension of fungal invasion into neural tissue and blood vessels frequently promotes hemorrhage, thrombosis, infarction, necrosis, and meningitis with ventriculitis causing various clinico-pathological features of CNS aspergillosis.[15,18]

Risk factors in solid organ transplantation

Immunosuppression in solid organ transplantation recipients continues to evolve in an effort to minimize infectious complications and to improve graft survival and function. Belatacept has proven to be an effective agent in the prevention of acute rejection following renal transplantation and minimizing effects on glomerular filtration rates as compared to calcineurin inhibitors.[16] This is a human fusion protein that combines the cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) with the constant-region fragment (Fc) of human IgG. The interaction of these surface proteins with the CD28 receptor on T-cells is necessary for T-cell activation and subsequent recognition of the presented foreign antigen. Blocking this interaction prevents antigen recognition and thereby rejection of the transplanted tissue or organ. While the acute rejection rates have been low, reports of infections remain limited though suggestive of potentially persistent T-cell functional defects even after withdrawal of the agent. These infections to date have been limited to late onset *Pneumocystis carinii* pneumonia and CMV.[6,20]

Diagnostics

Early diagnosis is generally achieved by high level of suspicion and demonstration of organism by biopsy or culture from what should be a sterile site (e.g., lung biopsy). Hyphal elements can be seen by silhouette on routine hematoxylin and eosin staining, or more directly with fungal specific stains such as period acid Schiff. The hyphae are characterized as thin and filamentous with regular septation and branches occurring at acute angles. A diagnosis of Aspergillus cannot be made without culture demonstration of the fruiting bodies or macroconidiae.

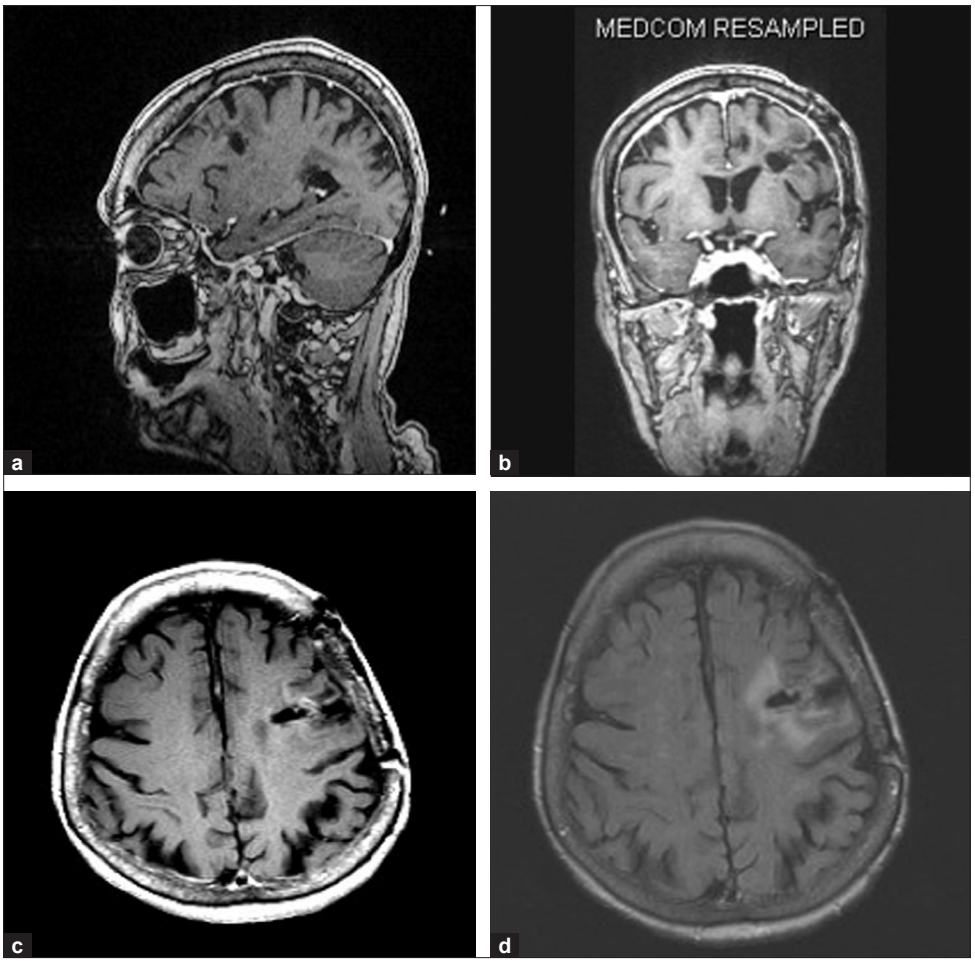

Figure 5: Resolution of T1-contrast enhancing abscess in the left frontal lobe 12 months postoperatively s/p open resection; only mild residual gliosis is visible on FLAIR (lower right)

If isolated in a specimen, Aspergillus species grow rapidly. Recovery from direct plating of lavage fluid from bronchoscopy or from biopsied tissue is possible. Recovery from sputum should be scrutinized carefully as airway colonization or contamination with spores is not uncommon particularly in conditions such as chronic lung disease.

More recently, direct antigen detection assays including galactomannan and beta-D-glucan have become FDA approved for the diagnosis of invasive fungal infections. Galactomannan is a water-soluble glycopeptide that is largely specific to *Aspergillus* species and appears to be closely linked with early immunologic invasion. Random sampling in otherwise immunocompetent patients may result in false positive results from various bacterial infections including *Staphylococcus aureus*, streptococci, Pseudomonas, and unusual oral organisms such as *Alcaligenes* spp. Other false positive results have been reported in conjunction with hemodialysis, receipt of intravenous gamma globulin, methylcellulose filters, and some parenteral antibacterial agents such as piperacillin-tazobactam, ampicillin-clavulanate, and trimethoprim-sulfamethoxazole. However, in the highly immunosuppressed patient or one that is neutropenic, the presence of a positive serum galactomannan, fever, and radiographic findings suggesting invasive disease carries a very high positive-predictive value.

Another surface carbohydrate that may be measured in invasive disease is the beta-D-glucan. This is a ubiquitous carbohydrate with a variety of different conjoiners that is present in the cell wall of many different fungi and yeast. Clinically relevant yeast including Candida species, *Pneumocystis jirovecii* (carinii), and Histoplasma, as well as molds such as Aspergillus, elaborate the 1,3 beta-glucan on their surface, which can be measured in serum by ELISA. Utility again is limited to the high-risk host. Sensitivity and specificity as well as both positive and negative predictive values drop dramatically when used in the non-neutropenic, non-immunocompromised settings.

In order to provide guidance and definitions for infection, the Bacterial and Mycoses Study Group at the National Institutes of Health (BAMSG), in conjunction with the Infectious Diseases Society of America (IDSA) and the European Organization of Research and Treatment of

Cancer (EORTC), created an algorithm for criteria for defining likelihood of disease. This includes:

Proven disease

Evidence of infection on histopathology of deep tissue sampling, or recovery and culture of organism from a deep tissue biopsy or cavity (this excludes recovery from sinus cavity, urine, or single bronchoalveolar lavage (BAL).

Probable disease

The presence of at least one host factor including neutropenia for more than 10 days, receipt of human stem cell transplantation, or corticosteroid exposure at greater than the 0.3 mg/kg/day prednisone equivalent for more than 3 weeks, or treatment with T-cell suppressants such as cyclosporine A, tacrolimus, tumor necrosis factor (TNF)-alpha blockers, alemtuzumab or inherited severe immunodeficiencies. Radiographic suggestion of disease including mass lesion in the lung or brain by CT scan or invasive disease on sinus imaging and either recovery of organism in culture of sputum or BAL, or the presence of galactomannan or beta-D-glucan in two serial serum samples.

Possible disease

Presence of one of the host factors listed in probable disease and either one clinical criterion or one microbiological criterion.

Treatment of CNS disease

Antifungal drugs and neurosurgical intervention have both been used to treat CNS aspergillosis in the past.[4,5,14]Medical management alone of invasive Aspergillus infection is ineffective. The effect of ongoing immunosuppression on mortality is most clearly demonstrated by the multicenter, multinational Aspergillus Study Group outcome report. In 525 patients with proven invasive aspergillosis, outcome was clearly influenced by the severity of immunosuppression. Mortality was 72% vs. 49% in high vs. low-level immunosuppression.

Central nervous system involvement with *Aspergillus* is a devastating complication, and historically carried a mortality rate of >90%. CNS involvement develops either from direct extension from sinus disease or from hematogenous dissemination as a result of pulmonary angioinvasion.[18] The medical monotherapy of immunocompromised patients suffering from aspergillosis has been far from satisfactory with are responses reported using liposomal amphotericin.[9] More recently, survival from CNS invasion was seen with the use of voriconazole as compared to amphotericin or liposomal amphotericin.[7] When voriconazole was combined with surgery, the long-term survival rate was reported to be 31%.[11] Neurosurgical treatment options have consisted of either stereotactic or open craniotomy for abscess drainage, catheter insertion for direct drug administration, or excision of the lesion. Although technically possible, surgical approaches to eloquent areas of the dominant hemisphere are technically challenging even for the experienced neurosurgeon and may remain associated with a high morbidity for deep-seated lesions. Because such lesions are also not frequently encountered, open techniques are in general not widely reported and hence not well established when compared to experience from medical treatment. A retrospective multifactorial analysis by Schwartz *et al*. found a significant survival benefit in patients who underwent neurosurgical intervention (P=0.02) in addition to antifungal therapy.[11] In their report, a total of 31 patients had neurosurgical procedures performed, including full craniotomy with attempted abscess resections (n=14), abscess drainage (n=12), ventricular shunt insertion (n=4), and placement of an Ommaya reservoir (n=1). Coleman *et al*. reported a review of 25 CNS aspergilloma-survivors of which 20 underwent some form of neurosurgical treatment (15 craniotomies and 6 stereotactic drainage procedures or insertion of intracavitary catheters) as a complement to antifungal treatment.[2] More recently, Wasay *et al*. have shown that neurosurgical intervention as first line treatment, which is supported by peri- and post-operative antifungal therapy, also resulted in a good outcome.[19] Srinivasan *et al*. reported a study of three cases with near complete or radical surgical removal of CNS aspergilloma combined with monotherapy using either itraconazole or voriconazole.[12]

Antifungal agents with anti-Aspergillus therapy include polyenes (amphotericin deoxycholate and liposomal amphotericin B), echinocandins (caspofungin, micafungin and anidulafungin), and triazole agents (itraconazole, voriconazole and posaconazole). Until the last decade, most of the medical experience was with amphotericin deoxycholate or amphotericin B. Despite efficaceous eradication of the fungus, the overall mortality rates remained high, and outcomes were further complicated by dose-limiting end-organ complications from the agent itself. These include cytopenias, transaminitis, cholestasis, and acute renal failure. The lipid formulations have improved the infusion-related toxicities, and in most cases shown superiority in outcome as compared to conventional amphotericin B.[9]

The echinocandins are agents having a similar spectrum of activity, being effective in treating invasive candidal and Aspergillus infections. The class is well tolerated with minimal drug-drug interactions and significantly fewer infusion-related toxicities. Voriconazole more so than posaconazole or itraconazole has demonstrated proven superiority in the treatment of invasive Aspergillus infection and was recommended by the Infectious Diseases Society of America as the antifungal of choice.[17] In a retrospective review of 81 patients with proven or probable CNS aspergillosis, 1/3rd of those who received

voriconazole survived a median of 390 days as compared to only 31 days in those who received alternative antifungal agents.[11] Posaconazole is a reasonable alternative agent, although limitations of the drug include its formulation as liquid agent with limited bioavailability. Itraconazole is a reasonable second line agent and like voriconazole is available in a parenteral or enteral formulation. But unlike voriconazole, its effectiveness against Aspergillus is limited.[17]

CONCLUSION

Although newer antifungal agents such as voriconazole are more efficacious and have improved the outcome of invasive *Aspergillus* infection, it is important to understand that neurosurgical intervention in combination with antifungal therapy remains the treatment of choice to improve survival in CNS aspergillosis. It is also noteworthy that modern and minimally invasive neurosurgical techniques may significantly improve the outcome in this challenging patient population and might play a larger role in the future. Only with a high index of suspicion, an aggressive approach to diagnosis and combined medical and surgical therapy may we hope to alter the clinical course in this group of patients.

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