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Intracranial Aspergillosis in an Immunocompetent Young Woman

Prasan Kumar Panda · Sunil Kumar Mavidi · Naveet Wig · Ajay Garg · Aasma Nalwa · M. C. Sharma

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Abstract Intracranial aspergillosis (ICA) is very rare in the immunocompetent individuals, usually misdiagnosed as a tumor or an abscess. A high index of clinical suspicion is required in patients who present with focal neurological deficits, headache, or seizures. We report the case of a 25-year-old immunocompetent female, who presented with a 15-month history of headache, seizures, left-sided proptosis and ophthalmoplegia, and right hemiparesis. Recovery from the symptoms and decrease in the lesion size seen on the radiological assessment were achieved through two decompressive craniotomies followed by prolonged combined systemic antifungal therapies. Although the initial neuroimaging suggested a mitotic pathology, the surgical sample confirmed ICA. Now the patient is on single antifungal therapy (Tab. voriconazole, 200 mg twice daily) and doing her daily activities, but with a reduced intelligent quotient. We report a challenging case of ICA where multiple courses of combined antifungal therapies and repeat surgeries paved the way for a good prognosis.

Keywords Combined antifungal therapies · Craniotomy · Intracranial aspergilloma · Invasive aspergillosis · Invasive fungal disease

P. K. Panda · S. K. Mavidi · N. Wig (✉)
Department of Internal Medicine, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India
e-mail: naveet_wig@yahoo.com

A. Garg
Department of Neuro-Radiology, All India Institute of Medical Sciences, New Delhi, India

A. Nalwa · M. C. Sharma
Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

Introduction

Aspergillus is a saprophytic opportunistic ubiquitous mold/fungus found in the soil, water, and plants, and it grows on decaying vegetative matter. With varying incubation periods of 2–90 days, the organism enters the human host via an inhalation route or breaching the skin [1]. It affects a local organ or disseminates in the form of invasive aspergillosis (IA) depending upon the severity of the immunocompromised state [2].

Intracranial aspergillosis (ICA) is a form of IA, occurs more frequently in immunocompromised individuals, and takes either an acute or chronic course depending on the immune status of the patient and the mechanism of disease spread. The most common clinical symptoms are headache, fever, altered mental status, and seizures. Pathologically, it may present as meningitis, meningoencephalitis, abscess, granuloma, vasculitis (as thrombosis, hemorrhage, or aneurysm formation), and myelitis [3]. Imaging, histopathology, and isolation of the fungus from the cerebrospinal fluid (CSF) or tissue sample are useful in the diagnosis;

however, a high index of suspicion is crucial for making an early diagnosis. Early surgical treatment followed by systemic antifungal therapy remains the cornerstone of the management [4].

Here, we report an interesting case of ICA in an immunocompetent female and review the literature.

Case Report

A 25-year-old female, a computer operator and resident of north India, without prior comorbid illnesses, presented in February 2014 with a 15-month history of generalized tonic-clonic seizures (GTCS), intermittent headache, and progressive left-sided proptosis and ophthalmoplegia. She was initially evaluated in an outside hospital, suspected to have a brain tumor on the basis of imaging, started on antiepileptic agents, and planned for surgery. Meanwhile her symptoms increased, and she was referred to us after another episode of GTCS. There was no history of fever, vomiting, weight loss, or symptoms suggestive of sinusitis or chronic respiratory problems.

On examination, she was conscious and oriented with normal vital signs. There was no lymphadenopathy. Except left-sided mild proptosis and a Mini Mental State Examination (MMSE) score of 22/30, all systemic examinations including the nervous system and chest were unremarkable. Mainly attention, calculation, repetition, and copying cortical functions were disturbed in the MMSE.

Laboratory workup revealed a normal hemogram except hemoglobin 106 g/l and hematocrit 33%. Her liver and kidney function tests and electrolytes were normal. ESR was 30 mm/h with a negative Mantoux test. Nitro blue tetrazolium test for chronic granulomatous disease (CGD) was found to be normal including the dihydrorhodamine test with flow cytometry. Immunoglobulin levels (IgG, IgM, IgA, and IgE) were within normal limits. HIV was negative with a normal CD4 count. Chest radiograph was normal.

Review of her brain computed tomography (CT) scan and magnetic resonance imaging (MRI) done a month earlier showed a nodular thick-walled cystic mass lesion of 5.5 × 5.1 × 3.7-cm size in the left parieto-occipital region with associated extensive perilesional edema and mass effect with effacement of the left lateral ventricle and right-sided midline shift of 8.2 mm (Fig. 1, a–e). MR spectroscopy (MRS) was done that revealed the high choline peaks and moderate to high lipid lactate peaks (Fig. 1f). The above features suggested the mass lesion, likely to be a mitotic pathology.

Hence, for both diagnostic and therapeutic reasons, the patient underwent left parieto-occipital decompressive craniotomy with as extensive an excision of the mass as possible and lax duraplasty. Intraoperatively, a hard, calcified, moderately vascular intra-axial non-suckable mass was found. Grossly, multiple tissue pieces were collected, all together measuring 8 × 5 × 3 cm in size, which on microscopy revealed dense granulomatous inflammation with necrosis. Ziehl Neelsen staining for acid-fast bacilli was negative. On special staining with Gomori's methenamine silver (GMS), numerous septate, dichotomously branching hyphae were identified, and a diagnosis of cranial aspergillosis was made (Fig. 2). Serum galactomannan antigen was also done, which was positive with a sera index of 2.15 (>0.5 positive). However, imaging of the paranasal sinuses (radiograph and CT) were negative for sinusitis/any pathology, although the patient had a history of recurrent cough and colds since childhood and was living in an urban area with ongoing construction/renovations.

Parenteral antifungal therapy with voriconazole, 300 mg BD after two loading doses of 400 mg (6 mg/kg IV q12h for the first 24 h, then 4 mg/kg IV q12h), was started for 5 days and continued with oral voriconazole 300 mg BD. Antiepileptic therapy was continued.

Postoperative non-contrast CT (NCCT) scan showed a cavity with minimal residual edema and mass effect (Fig. 3a). Repeat MRI brain (March 2014) showed the thin-walled enhancing resection cavity (3.9 × 2.9 cm) with multiple surrounding enhanced nodules (Fig. 3b–c) suggesting an increase in the size and spread of the disease. A simultaneous MR angiogram did not show any venous thrombosis of the brain blood vessels. Suspecting non-response to single antifungal therapy of voriconazole, parenteral amphotericin-B (deoxycholate, 1 mg/kg/day) was added and continued for 3 months. The patient improved partially till November 2014 and then deteriorated with progressive weakness of the right upper and lower limbs. CNS examination revealed hesitancy of speech and right-sided extensor plantar, brisk deep tendon reflexes, and decreased muscle

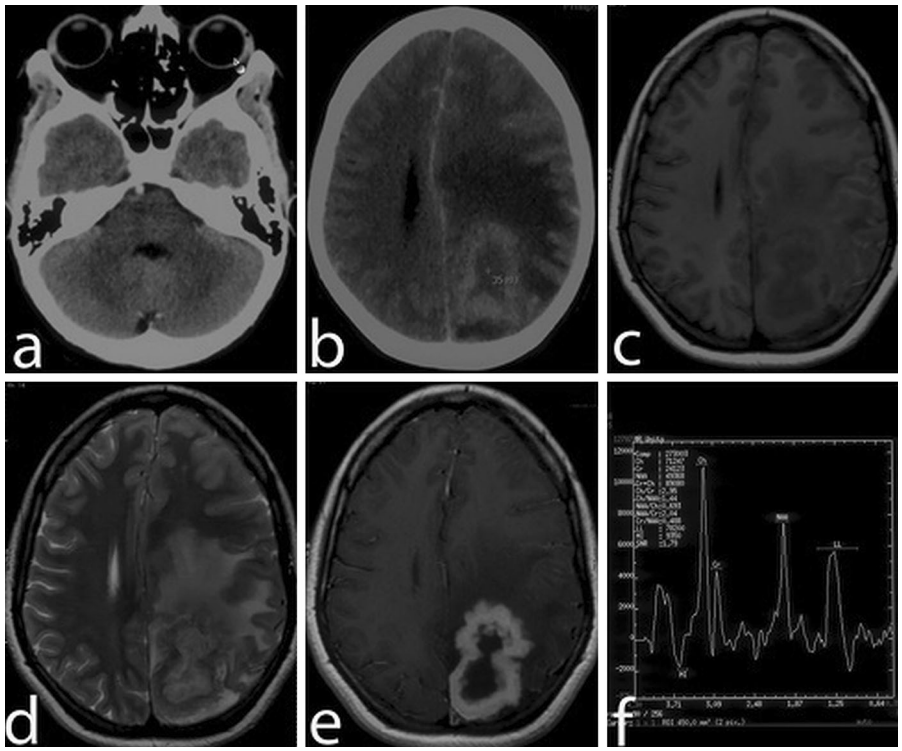

Fig. 1 Axial CT (**a**) at the level of the skull base shows no evidence of paranasal sinus disease. CECT (**b**) reveals a nodular ring-enhancing lesion with an isodense core and perilesional edema in the left parieto-occipital region. The wall of the lesion is hyperintense on the T1-weighted image (WI) (**c**), hypointense on T2-WI (**d**), and shows enhancement following gadolinium administration (**e**). On MR spectroscopy, choline is elevated, and there is presence of lipid-lactate

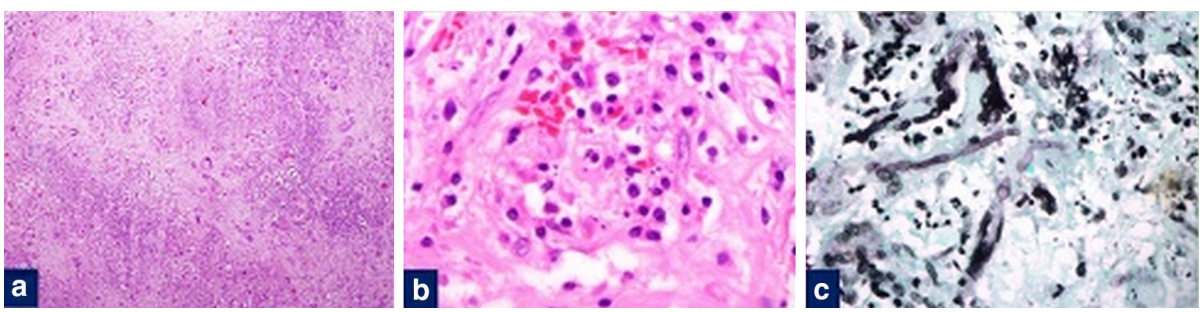

Fig. 2 Photomicrographs (**a**) shows epithelioid cell granulomas with foreign body type giant cells and large areas of necrosis (H&E, ×40); higher magnification (**b**) shows perivascular inflammatory cell infiltrates along with fungal hyphae (H&E, ×600); Gomori's methenamine silver stain (**c**) reveals numerous septate, acute-angled, dichotomously branching hyphae of *Aspergillus* (×400)

power (grade 3/5). Detailed neuropsychological evaluations revealed an MMSE score of 15/30 and mean intelligence quotient (IQ) of 79/110. These suggested a moderately impaired mental status with borderline intellectual ability. The patient deteriorated suddenly with multiple GTCS episodes, altered sensorium, headache, and persistent vomiting. NCCT showed an increase in the size of the lesion with contrast enhancement (Fig. 3d–f) and mass effect. She again underwent a left fronto-temporo-parietal decompressive craniotomy. Her symptoms improved following surgery. Simultaneously, she was started on injection

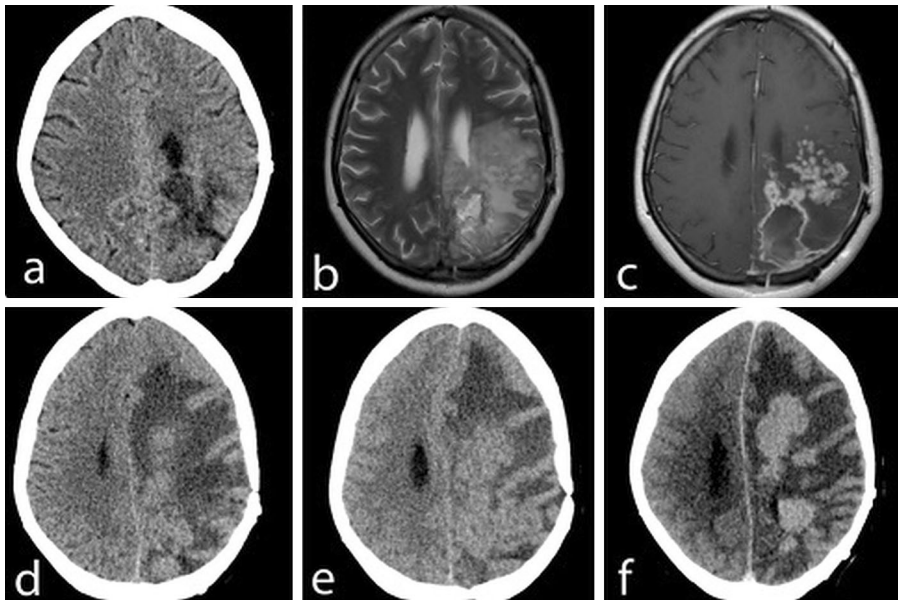

Fig. 3 Postoperative NCCT (**a**) shows the resection cavity with minimal residual mass effect and edema (February 2014). A later MRI (**b**) revealed a resection cavity with associated edema and T2-isointense nodular lesions (March 2014) that enhanced following gadolinium administration (**c**). Follow-up NCCT (**d**–**e**) shows an increase in the size of the lesion and mass effect (September and November 2014, respectively), which (**f**) enhanced following contrast administration (November 2014)

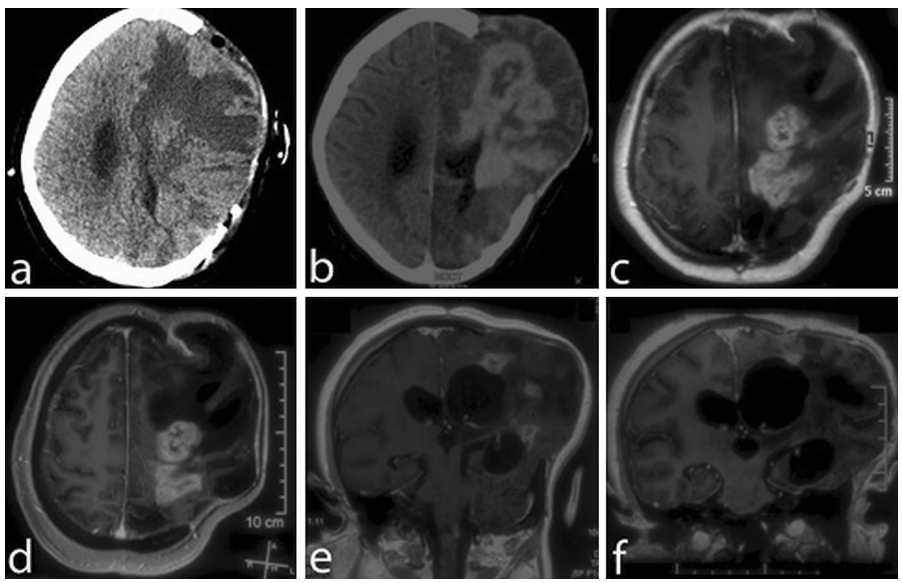

Fig. 4 Postoperative NCCT (**a**) shows evidence of the left fronto-parietal craniotomy and a residual lesion (November 2014), which increased on follow-up CT (December 2014) (**b**). Further follow-up MRI (**c**–**e**) shows continued reduction in the size of the lesion (February, May, and November 2015). The last MRI (**f**) shows the maximal reduction of the size of the lesion (May 2016)

caspofungin (70 mg loading dose followed by 50 mg OD for 5 months) and continued with oral voriconazole and antiepileptic agents. Her clinical condition gradually improved.

Postoperative CT scan showed evidence of the craniotomy and a residual lesion (Fig. 4a), which increased on follow-up after 3 months (Fig. 4b) without clinical deterioration. Follow-up MRI done

on February, May and November 2015 (Fig. 4c–e) showed continued reduction in the size of the lesion. Functional MRI brain was done to plan further removal of the granulomatous lesions, but it could not be completed because of lack of patient compliance. She continued with tablet voriconazole (300 mg BD). During a follow-up visit, she developed asymptomatic transaminitis, so the voriconazole dose was reduced to 200 mg BD, and after 15 days, the transaminitis resolved. We could not analyze the serum voriconazole level because of the practical constraints. The patient's last MRI (May 2016) showed a further reduction of the fungal mass (Fig. 4f). Presently, she is being followed up and has greatly improved power in the limbs, but the MMSE and IQ still indicate borderline intellectual ability. We do not know how long to continue antifungal therapy because of the lack of a definitive guideline; repeat imaging at 3–6-month intervals may help to make decisions about further management plans.

Discussion

Invasive aspergillosis (IA) is increasing in prevalence similar to systemic fungal infections because of the rise in the number of immunosuppressed patients. In addition to particular immunodeficienct states predisposing to IA, it has been observed that intracranial aspergillosis (ICA) is more commonly seen in alcoholics, IV drug abusers, malnourished subjects, and those with previous brain pathology, diabetes, HIV, TB, a solid organ transplant especially the kidney, lymphoma, autoimmune diseases, Cushing's syndrome, liver failure, and COPD [5, 6]. However, 23.6% cases have no comorbidities, similar to our case [6]. The truth is that there is no large systematic review, meta-analysis, or observational study to aid determining the etio-pathogenesis of ICA in patients having apparently normal immunity except based on a few case reports/series and narrative reviews. Here we have reviewed all the published ICA cases (PubMed/MEDLINE databases) in immunocompetent patients excluding diabetes in the last 2 decades (Table 1, [6–35]). Although the word immunocompetent is used in all the cases in this review, the investigations done to determine this are not clearly documented. Sinus exposure/pathology is the major risk factor in the majority of cases similar to our case. However, considering environmental factors is more important in this subset of patients. The hot, humid climate, and high spore content resulting from increased agricultural and industrial activities are contributing factors to the seasonal variation and risk exposure of aspergillosis [36, 37].

Clinical presentation of ICA is highly variable and nonspecific. It depends on the individual immune status, route of spread, and underlying pathology,which that can be hemorrhagic infarct (most common finding on autopsy), granulomas, abscess, meningitis, meningoencephalitis, arachnoiditis, or ventriculitis [38, 39]. Immunosuppressed patients present with an acute onset, having severe symptoms, and a rapid deteriorating course; unless suspected, death precipitates early. Fulminant disease in the chronic form has also been reported after months to years. Route of spread, at times, helps to localize the pathology. One study suggested that the simultaneous involvement of the para-nasal sinus (PNS, 27.6%) or lung (26.8%) with the CNS is seen more often than isolated intracranial involvement (22.8%) [6].

The diagnosis of ICA is very difficult, as most cases are diagnosed postmortem. The index of suspicion must be high. Therefore, intracranial space-occupying lesions (ICSOLs) should be approached systematically with a good history taking and examination rather than moving directly to an operation [40]. Non-culture assays, such as galactomannan (GM), β(1,3)-D-glucan, and *Aspergillus* polymerase chain reaction (PCR), all have a high negative predictive value and are ideally suited to screening to exclude IA, and they should be done prior to the initiation of antifungal therapy [41]. Serial samples for a positive GM test are recommended to avoid a false positivity, to define whether the patient is colonized or not, to monitor the disease progression and therapeutic response, and to predict the outcome [42, 43]. A combination of biomarkers increases the confidence in the diagnosis by increasing the sensitivity and enables more rational use of antifungal agents. As per the recent IA guideline, serum and bronchoalveolar lavage GM is recommended as an accurate marker for the diagnosis only in certain patient subpopulations (hematologic malignancy, HSCT). However, GM is not recommended in patients who are single organ transplant recipients, CGD, and already on antifungal therapy except for bronchoscopy specimens [43].

Table 1 Reported cases of intracranial aspergillosis in immunocompetent patients in the literature in the last 2 decades

Citations (year-wise)	Age, sex, country	Presence of comorbidites	Possible route of spread	Pathological type	Immunological workup	Medical/surgical treatment	Outcome
Al-Maskari et al. [7]	12 years, M, Saudi Arabia	None	NA	Brain abscess	Immunoglobulin levels, lymphocyte markers, blastogenic response, complement deficiency, oxidative burst, polymorphonuclear chemotaxis, HIV test	Two surgeries, 2 years of antifungals	Survived
Beraldo et al. [8]	59 years, M, Brazil	None	Unknown	Aspergillosis	NA	Surgery only	Survived
Rasoolinejad et al. [9]	29 years, F, Iran	None	Unknown	Aspergilloma	NA	Three surgeries, 19 months of antifungals	Survived, at 2-year follow-up
Mohammadi et al. [10]	11 years, M, Iran	None	Through lungs	Aspergilloma	HIV negative, immunoglobulin levels-normal	Two surgeries, 2 years of antifungals	Survived, at last follow-up
Ellenbogen et al. [11]	67 years, M, UK	Operated otitis media and mastoiditis, simultaneous detection of prostate cancer	Local spread	Brain abscess/ aspergillosis	Details—NA	Surgery, 6–7 years of antifungals	Survived, declared posaconazole responsive
Khandelwal et al. [12]	4 months, NA, India	None	Transplacental	Brain abscess	Immunoglobulin levels, viral markers	Surgery, 6 months of antifungals, on follow-up	Survived
Bao et al. [13]	42 years, M, China	Meningioma, glucocorticoid	Through intraoperative wound	Brain abscess/ aspergilloma	NA	Five surgeries, 2 years of antifungals	Death
Leyngold et al. [14]	61 years, M, Ukraine,	Hypertension	Sino-orbital spread (18 cases in this review are described with same spread in immunocompetents)	Aspergillosis/ abscess	NA	Surgery, 1-year combined antifungals, on follow-up	Survived, however other reported cases in this review (death, 11; survived, 7)

Table 1 continued

Citations (year-wise)	Age, sex, country	Presence of comorbidites	Possible route of spread	Pathological type	Immunological workup	Medical/surgical treatment	Outcome
Bokhari et al. [15]	5 case series, all F, Saudi Arabia	None	Unknown	Aspergillosis	NA	Surgery, antifungals	Death, 1; survived, 4
Xiao et al. [16]	57 years, M, China	NA	Local spread through pterygopalatine fossa following a tooth extraction	Aspergillosis	NA	Surgery, 42-day combined antifungals	Death
Pelaez et al. [17]	45 years, M, Spain	Chronic otits media, operated	Local spread	Aspergilloma	NA	Two surgeries, 1-year antifungals at writing report	Survived, voriconazole resistance declared
Li et al. [18]	72 years, F, China	Hypertension	Through lungs?/sinus after near drowning	Brian abscess	NA	2-days antifungals	Death, disseminated involvement with lungs, kidneys, and heart
Ederies et al. [19]	75 years, F, Canada	Hypertension, hepatitis C positive	Local spread	Aspergillosis	NA	Surgery, antifungals, steroid, interferon-beta	NA
Genzen et al. [20]	37 years, F, West Africa	Cesarean section at delivery	Inoculation by epidural analgesia	Hydrocephalus	NR	CSF drainage, 9-months antifungals at follow-up	Survived
Narayan et al. [21]	30 years, F, India	None	Unknown	Aspergillosis	NA	Surgery, antifungals—defaulter	Death
Del Gaudio et al. [22]	47 years, M, Italy	None	Unknown	Aneurysm/ abscess	NA	Surgery	Death early, genetic predisposition suspected
Hiraga et al. [23]	74 years, M, Chiba	Hypertension, cerebellar infarct	Sinus, local spread	Aspergillosis	NA	Sphenoidotomy, corticosteroid, 2-year antifungals at follow-up	Survived, role of steroid in some CNS aspergillosis
Ducolin et al. [24]	53 years, M, Italy	None	Disseminated from lungs	Cerebral abscess	NA	Postmortem diagnosis	Death
Martins et al. [25]	53 years, M, Brazil	None	NA	Cerebral vasculitis	HIV negative, others—NA	Surgery, antifungals	Death

Table 1 continued

Citations (year-wise)	Age, sex, country	Presence of comorbidites	Possible route of spread	Pathological type	Immunological workup	Medical/surgical treatment	Outcome
Kulkarni et al. [26]	23 years, M, India	None	Disseminated from lungs	Aspergilloma	HIV negative, others—NA	Surgery, 1-year of antifungals, at reporting time	Survived
Challa et al. [27]	8 case series, India	None	None, sinus/lung origin suspected	Aspergilloma	NA	Surgery, antifungals	Survived, 4; death, 4
Taşdelen Fişgin et al. [28]	43 years, M, Turkey	Intracranial tumor, operated	Sinus local spread or intraoperative inoculation	Aspergillosis	Immunoglobulin levels—N, complements—N, HIV negative	Two operations, 4–5 months of antifungals	Death
Sood et al. [29]	43 years, M, India	None	Sinus local spread	Aspergilloma	HIV negative, others—NA	Surgery, 20 days of antifungals at reporting time	Survived
Cho et al. [30]	61 years, M, Korea	Chronic otitis media, operated	Local spread or intraoperative inoculation	Aspergillosis	NA	Ear-based surgery, 45-day antifungals	Death
Aslam et al. [31]	2 cases, 57 and 38 years, M-2, Pakistan	None	Local spread (sinus), another—unknown	Aspergilloma	NR	Surgery, antifungals	Survived, high-dose itraconazole (16 mg/kg) alleged to play a role
Siddiqui et al. [32]	25 case series, Pakistan	None	Local spread (sinus)	Variable	NR	Surgery, antifungals	Intracerebral aspergillosis type having worst prognosis > intracranial extradural type > cranial base aspergillosis
Pongbhaesaj et al. [33]	65-67 years, M, F, Thailand	None	Local spread (ear and sinus)	Brain abscess	NR	Surgery, 6–12 months antifungals	Survived
Srinivasan et al. [34]	4 cases considered, 40–50 years, M-1, F-1, NR-2, India	Chronic sinusitis	Local spread, unknown	Apergilloma, infarct	NR	Surgery, antifungals—at least 6 months	Survived, 3; died, 1

NA not available

Radiological findings are useful, but no pathognomonic findings allow differentiation from other infections causing ICSOL [6]. It depends on the route of spread of the organism and immune status. There are four general patterns: (1) single or multiple infarcts, (2) ring lesions (single or multiple) consistent with abscess formation, (3) solid enhancing lesions referred to as aspergilloma or "tumoral" form, and (4) dural or vascular infiltration arising from the adjacent PNS or orbits [44]. Other findings include mycotic aneurysms and hemorrhagic transformation of the infarcted areas. If the disease spreads from the PNS, eye, or middle ear, it manifests as a single or multiple abscesses, often occurring in the frontal or temporal lobe, and a hematogenous spread often leads to multiple abscesses at the gray-white junction and putamen-striatal arterial distribution [45]. In immunocompromised patients, MR imaging shows patchy or punctate T2 hyperintensity with rarely seen enhancement on postcontrast images, whereas in immunocompetent patients, it shows solid or ring-enhancing lesions with or without a granuloma [46]. Granulomas are virtually indistinguishable from tubercular granulomas or other chronic granulomas. However, the presence of the concomitant PNS involvement and dural enhancement hints at a fungal etiology. In our case, radiologically suspected to be immunocompetent, the route of spread may have been through the PNS.

Histopathology is essential to diagnose an invasive fungal disease. The diagnosis is frequently suspected when *Aspergillus* is isolated from non-sterile body sites, particularly tracheal or bronchial aspirates, which may only represent colonization if without tissue involvement [47]. Similar to the radiological findings, the pathology depends on the route of spread and host immunity. Contiguous spread and immunocompetence usually lead to a well-defined granuloma/aspergilloma as seen in our case, while hematogenous dissemination leads to ischemia and hemorrhage [48]. Immunocompromised patients have variable characteristics. There is a lack of clear distinction between aspergilloma and aspergillosis in the brain as compared to the lungs; hence, the terms are used interchangeably in various case reports. The prominence of multinucleated giant cells with an admixture of neutrophils, plasma cells, and eosinophils and relatively fewer epithelioid cells favor the *Aspergillus* granuloma in contrast to tubercular granuloma (the most common differential diagnosis). Giant cells contain thin (3–12 μm), septate, and acute-angled (45°) or dichotomous branching hyphae on GMS and PAS stains, suggesting *Aspergillus* [1]. *Aspergillus* should be identified to the species complex level by referral to a specialist laboratory if necessary, be susceptibility tested for antifungals if suspected to have an azole-resistant isolate or for patients who are unresponsive to antifungal agents, or for epidemiological purposes, and be stored for 6 months in case of additional susceptibility if needed [43, 49]. We could not culture our patient's tissue sample.

The treatment and prognosis of IA depend on the type and severity of the disease, immune status of the patient, and timing of interventions—prophylactic, empirical, preemptive, or targeted. As per two large trials, empirical therapy may be advocated in high-risk patients, whereas a preemptive approach may be started in low-risk patients based on biomarkers such as GM or PCR, radiographic signs such as the halo/air crescent sign, and clinical symptoms [4, 50]. In the management of ICA, early and optimal neurosurgery, antifungal therapy, treatment of the source of infection, and correction of underlying risk factors are the cornerstone. Combining medical and surgical treatment appears to be the most successful approach since the mortality has decreased from 60.4–100 to 28.6–25% in comparison to medical treatment alone [6]. This is especially true for immunocompetent patients as advocated by a recent narrative review [35]. Since antifungal therapy is needed in almost all ICA cases, physiochemical properties such as the molecular size, lipophilicity, plasma protein binding, efflux pump affinity, molecular charge, and cerebral blood flow are given higher consideration because of better penetration of the drugs into the CNS [51]. Considering all the above factors, voriconazole is a better drug than amphotericin-B, which is better than caspofungins. Voriconazole therapy requires regular monitoring of the drug levels in the serum since a low level has been linked to clinical failure. Although in vitro and animal studies and a few human observation studies favor combination therapy, having a complementary/synergistic mechanism of action such as mold-active azoles or polyenes with echinocandins, antagonism has been suggested in higher doses by some studies, especially between polyenes and certain azoles; hence, it is not recommended in the recent guideline [43, 52, 53]. Total duration of the medical

treatment is uncertain in all types of IA; however, it is to be continued for a minimum of 6–12 weeks, which largely depends on the degree and duration of immunosuppression, site of disease, and evidence of disease improvement [43]. ICA may need a longer duration of treatment.

Surgery offers the theoretical advantage of decreasing the fungal load, allowing better antifungal penetration, relieving the mass effect, and decreasing the local neurotoxic and inflammatory effects exerted by the fungal infection; however, there are debates between the conservative and aggressive approach, with anecdotal reports of postoperative complications of ischemic deficits and malignant brain edema. Although the Infectious Diseases Society of America (IDSA) has given a rational choice for adjunctive surgery in cases of focal ICA, other indications are less clear and require consideration of the patient's immune status, comorbidities, confirmation of a single focus, and the risks of surgery [43]. Patient fatality is as high as 100% in immunosuppressed and 5–30% in immunocompetent ICA patients, the highest among all forms of aspergillosis [15]. Good prognostic factors are noted in a small series of the immunocompetent patients, viz. (1) good functional status at presentation; (2) radiologic findings of contrast enhancement; (3) pathologic characteristics of lack of angioinvasiveness and robust granulomatous response; (4) treatment options such as preoperative antifungals followed by adequate removal of the fungal mass [15]. Our patient had a mix of these factors; however, she responded and was on oral antifungal therapy. In the follow-up, one should keep in mind the possibility of a post-infectious inflammatory response syndrome after starting the treatment, especially in immunocompetent patients, in the differential diagnosis of non-responders to the treatment [54]. This syndrome is more likely to obtain benefit from an adjunctive corticosteroid rather than an aggressive medical/surgical therapy.

Conclusion

This case study exemplifies the importance of a high index of suspicion for ICA in an immunocompetent patient who presents with headache, seizures, and mass effect. Surgery may be repeated, and combined antifungal therapies offer the best choice of treatment. The small number of successfully treated cases give hope that an aggressive therapy can provide a cure to what is frequently thought of as a fatal disease.

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Authors' Contributions PKP searched the literature, analyzed and drafted the study; SK collected data and drafted the study; NW provided the concept, analyzed, interpreted and revised the work; AG interpreted, including the literature search, especially the radiology data and critically revised the work; MCS and AN searched literature for the pathology part and drafted the work. PKP, SK, and NW were the physicians involved in patient management. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflicts of interest We declare that we have no conflicts of interest.

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