Allergic fungal sinusitis: innocence under suspicion

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The objective of this investigation was to explore the possibility of treating patients harboring invasive intracranial aspergillosis (InIA) at an early stage. Nineteen patients (age range 18–42 years) from a total of 114 cases of InIA seen from January 1999–December 2009 were included in this investigation. These individuals, all of whom had a past history of treated allergic fungal sinusitis (AFS) were evaluated as to their immune status, clinical presentations, time-intervals and radiological findings. Past records of seven patients indicated skull base erosion and extension of the paranasal (PNS) masses into intracranial cavity, but none had neurological deficits or symptoms suggestive of raised intracranial pressure. All 19 patients had undergone endoscopic clearance of PNS during their first presentations. Both AFS and InIA were found simultaneously in seven patients, while the time-interval between the two forms was as long as 10 years for two patients. Overall mortality was (8/19; 42%) with all deaths attributable to fungal meningo-encephalitis. As InIA carries a high mortality rate, it seems prudent to evaluate and treat these patients early in the course of their illness. The appearance of the invasive form of the disease in patients with a past history of AFS is not uncommon. The allergic form of disease may not be considered as a separate entity from InIA as both the pathologies may exist in same patient.

Keywords allergic fungal sinusitis, invasive aspergillosis, follow-up

Introduction

Allergic fungal sinusitis (AFS) is a well-recognized form of benign, non-invasive sinusitis, the histopathologic features of which are similar to those of allergic bronchopulmonary aspergillosis [1,2]. The typical patient is an immunocompetent adult, with bilateral proptosis, and scattered intra-sinus hyperdense areas on computerized tomography (CT) scan [3]. Generalized eosinophilia and raised serum titres of IgE antibodies directed against the fungi indicate that AFS is allergic in nature. Although an allergic etiology of AFS is currently the most accepted, there have been a few reports that document fungal invasion [3–5]. It seems plausible that there must be regions where mucosal invasion are going undetected due to insufficient material for histopathology. We at a neurosurgical centre have been involved in a number of cases involving invasive intracranial aspergillosis (InIA), which, due to the extension and invasiveness of the fungi, have poor patient outcomes.

As early initiation of anti-fungal chemotherapy may provide better patient management [6], the past medical/intervention histories of these individuals provide us with an entirely new link between these two different pathologies. In the present communication, we present a select group of InIA patients who had been treated for allergic form of disease in their past.

Materials and methods

A total of 114 InIA patients were treated since January 1999 at the Neurosurgical Centre of a tertiary care hospital in North India. The age of the individuals ranged from 6–62 years, with the cohort composed of 77 males and 37 females. All patients were harboring skull base aspergillosis/aspergillomas or intra-cerebral
mass aspergillosis lesions as proven by pathologic methods. We obtained the retrospective historical details of these patients, which included clinical symptoms pertaining to paranasal sinuses, immunological status, radiological findings (CT images) and surgical interventions performed the past. Of these 114 InIA patients, 19 had been treated for AFS by otolaryngologists. They had undergone sinuscopy, surgical clearance (partial or complete) and had pathologic evidence of AFS. The time-interval from the first diagnosis/presentation of AFS to the second diagnosis of InIA was as long as 10 years for two patients, while seven patients had the simultaneous presence of both allergic and invasive forms of fungal disease. This sub-group of 19 patients had an age range of from 18–42 years and was composed of 11 males and eight females. All patients’ previous records were compliant with the following diagnostic criteria for AFS; presence of polyps, type 1 hypersensitivity as indicated by serology, hyper-attenuating areas on the radiological scans (Figs. 1–4), documentation of scanty fungal hyphae in sinuses by special stains such as Grocott silver (Fig. 5) and allergic mucin (thick inspissated mucus, found in the sinuses, containing eosinophils and charcot-leyden crystals, recognizable as hexagonal structures in cross-section and bi-pyramidal or rectangular structures in longitudinal section).

Results

The past medical histories of all 19 patients met the pathologic criteria of AFS, but none showed vascular invasion or vasculitis. All underwent coronal sections of CT scans which showed hyper-attenuating areas within peripheral nervous system paranasal sinuses (PNS) (Figs. 1 and 2). None of these patients showed intra-cerebral extension of the PNS mass lesions. Erosion of skull base and extension of these PNS masses into intracranial cavity was noted in 7 patients (Figs. 1 and 2). Historically, there were no cranial nerve deficits, focal hemiparesis, or symptoms

Fig. 1  (a) Axial section of CT scan at the level of ethmoid sinuses and orbits showing, left intra-orbital mass with extensive AFS involving bilateral ethmoid sinuses. (b) Axial section of T2-weighted MRI scan showing AFS at the level of ethmoid sinuses and involved left orbit. (c) Axial section of contrast CT scan showing a large left frontal lobe mass, with extensive peri-lesional edema, indicating aspergilloma of left frontal lobe. (d) Axial section of T2 weighted MRI scan, showing massive cerebral edema around left frontal aspergilloma. (e) Coronal section of contrast-enhanced MRI scan showing extension of PNS disease (AFS) into intracranial compartment (InIA). (f) Coronal section of T2-weighted scan showing intense frontal lobe edema, with a mass extending into frontal lobe (InIA).
suggestive of raised intracranial pressure. The clinical histories of all patients did not reveal any evidence that they were immunocompromised. None had diabetes mellitus, taken any immune-suppressive drugs including corticosteroids or chemotherapeutic agents or recurrent or atypical site infections which excluded most of the congenital immune-deficiency syndromes. Since systemic evaluations for immunological deficiencies were not performed, it is possible that rare immuno-deficient syndromes might have been missed. Biochemical work up and hematological cell counts for all these patients remained within normal acceptable limits and none tested positive for human immuno-deficiency virus.

All patients had undergone sinuscopic clearance of the PNS during their first presentation. Operative findings included the presence of greenish-brown, sludge-like material filling sinus cavities. Seven patients with skull-base erosion had also undergone successful PNS clearance, without suffering from any dural breech or cerebrospinal fluid leakage. Surgically cleared debris from five patients yielded *Aspergillus flavus* on culture and fungal hyphae were observed on histology in such material of the remaining 14 patients. With the diagnostic criteria of AFS met for all these patients, these were discharged on long-term topical steroids and nasal douches. Itraconazole was also prescribed for a period ranging from 3–6 months, but Amphotericin B was not used in any treatment protocol.

During the same hospital admission, seven of these 19 patients had developed neurological deficits suggestive of invasive form of disease rather than allergic type. In two patients, the invasive form of fungal disease presented after a follow-up of 10 years. Neither of these individuals was immunocompromised prior to development of invasive form of disease. During neurosurgical admission, all patients had undergone plain and contrast enhanced MRI scans of the skull base (Figs. 1–4) which revealed discrete intra-cerebral mass lesions, intense brain edema and midline shifts.

Of these 19 patients, eight died due to the onset of fulminant fungal meningo-encephalitis, while receiving parenteral amphotericin B. All 11 remaining patients recovered to near normal neurological state after receiving
amphotericin B (cumulative drug administration of 5.0 g) and voriconazole (loading of 400 mg/twice a day, followed by 200 mg/twice a day for 6 months; body weight at least 40 kg). Therapeutic response to antifungal drugs correlated well with disappearance of intensely enhancing skull base masses (Fig. 3) and decrease in cerebral edema.

Discussion

Recurrent and severe fungal infections like aspergillosis may occur as a result of defects anywhere in the neutrophil life-cycle, including adherence-aggregation, deformability, chemokinesis-chemotaxis or microbicidal activity. These deficient functions may result from high-dose glucocorticoids, cochinine or cytotoxic drugs like cyclophosphamide.

Neutrophil dysfunctions are part of hematological malignancies like leukemia, diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, Down’s syndrome or influenza virus infection. Chronic granulomatous disease represents a group of patients with disorders of neutrophils and monocyte oxidative metabolism. Inherited as an X-linked recessive pattern, leukocytes from these patients have severely diminished hydrogen-peroxide production.

The patients are predisposed to infections caused by catalase-positive microorganisms (Aspergillus species) resulting in extensive inflammatory reactions and lymph node suppuration. Although aphthous ulcers and chronic inflammation of the nares are usually present, they were not seen in the patients in this report. T-lymphocyte dysfunction predisposing to Aspergillus infections may occur as a part of thymic hypoplasia, Hodgkin’s disease, sarcoid or leprosy, were not present in any of the patients in our case series.

Subgrouping mycotic disease of paranasal sinuses into benign (AFS) and invasive intracranial aspergillosis (InIA) is an oversimplified description. The present study describes 114 InIA patients of whom 19 had a history of AFS. This is 16.7% of patients who had presented to clinicians well before the onset of InIA and had had sufficient time for disease management through the administration of antifungal treatment.

Co-existent AFS and InIA in seven patients further supports the hypothesis that these two entities representing the extremes of same disease. Numerous published case series have indicated the non-invasive nature of AFS [4,7]. Despite massive bony destruction associated with AFS, it is primarily the result of fungal hypersensitivity [8]. Radiologically visible bony destruction has been shown to
be completely benign and patients have been placed in the category of allergic fungal disease [8,9].

Repeated endoscopic clearances for AFS [10] as a management protocol in situations of the recurrence of the disease is well-established and accepted, thereby obscuring its natural history. Patients in the eastern part of the world, as a result of poor access to healthcare, follow-up and infrastructure, fail to obtain repeat sinuscopies, which provides the opportunity for AFS to present as InIA. It seems plausible that patients in Western countries obtain the needed repeated endoscopic clearances, thereby nullifying any chance of progression of their cases into InIA. In other words, the neglected or poorly followed cases of AFS tend to contribute to poor outcomes due to conversion into invasive form of disease. However, a subset of seven patients had concomitant AFS and InIA diseases which could suggest that the former is not benign.

Bony erosion of the skull base in AFS cases is described in many reports [8,11,12]. A new entity ‘SBAFS’ [8] describes patients with pathologic evidence of the presence of branching septate fungal filaments interspersed with eosinophilic mucin and charcot-leyden crystals without invasion of soft-tissues, with intracranial extension. Erosion of median orbital wall leading to proptosis has also been described [12].

There continues the enigma of uncertainty in pathogenesis of AFS [10]. Management of AFS includes complete elimination of all allergic mucin, along with long-term administration of short-term systemic steroids and nasal steroid spray [10]. The literature does not support systemic administration of antifungal drugs, even when there is substantial support of the recurrence of the disease. Anecdotal cases of AFS involving the isolation of the suspected etiologic agent have been described. These continue to suggest the hypothesis of the growth of a saprophytic fungus in atopic patients [13]. Furthermore, the presence of fungi in nasal secretions of these AFS patients does not appear to correlate the allergic status with the isolated fungus [1].

Pathological diagnostic criteria (Fig. 5) of invasive fungal sinusitis require demonstration of hyphal invasion of sinus mucosa, submucosa, blood vessels or bone. Although such findings are usually not considered essential in cases of AFS [14], they have been demonstrated in the present series/cases over long-term follow-up (Table 1). In addition, long-term follow-up of cases of AFS is not clearly described/presented in literature. The natural history of AFS remains unknown as a result of endoscopic clearances being performed by rhinoscopists.
As a result of several factors, we agree that the ‘pathological failure’ to detect the invasiveness of these fungal infections has resulted in cases being falsely labeled as AFS. There are studies in which pathologic proof of fungal invasion was documented in cases of AFS [5,15,16]. These instances were attributed to invasive chronic granulomatous fungal disease and its consequent inflammatory response. Two features, i.e., orbital involvement and extra-sinusoidal disease extension, have been cited as indicating the presence of invasive form of disease [3]. Varying incidence of detection of these two features in cases of AFS has been attributed to sampling errors [3]. Even when both these features found through radiological studies and can be well documented at presentation, they are correlated with pathological proof of invasiveness of the etiologic agent. Rather, these findings should prompt clinicians to institute aggressive management. The long-term follow-up simply downgrades the utility/importance of pathological findings of AFS and suggests real caution in managing these patients with antifungal therapy or topical steroids.

The authors presented 19 cases which met criteria of AFS (past history) or concurrent diagnosis of AFS at time of invasive fungal disease. We propose the hypothesis that invasive fungal infection may fall within the same disease spectrum as allergic fungal sinusitis rather than
<table>
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<th>Treatment of allergic disease</th>
<th>Time interval (First-second presentation)</th>
<th>Skull base radiology</th>
<th>Treatment of invasive disease</th>
<th>Outcome/ follow-up</th>
<th>Cause of death</th>
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<td>18/F</td>
<td>B/L ethmoids</td>
<td>pan-sinusoidal</td>
<td>sinusectomy + steroids</td>
<td>co-existent</td>
<td>B/L frontal lobes intense brain edema</td>
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<td>death</td>
<td>meningo-encephalitis</td>
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<tr>
<td>26/F</td>
<td>Sphenoid sinus</td>
<td>sphenoid sinus</td>
<td>sphenoidectomy</td>
<td>co-existent</td>
<td>PNS + cav sinus + hydrocephalus</td>
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<td>22/M</td>
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<td>left ethmoid</td>
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</tr>
<tr>
<td>19/F</td>
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<td>sinusectomy + steroids</td>
<td>co-existent</td>
<td></td>
<td></td>
<td>Amphoterecin B</td>
<td>favorable (5 years)</td>
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<tr>
<td>18/M</td>
<td>B/L ethmoids</td>
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<td>co-existent</td>
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<td>favorable (5 years)</td>
<td></td>
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<tr>
<td>27/M</td>
<td>B/L ethmoids</td>
<td>sinusectomy + steroids</td>
<td>5 years</td>
<td></td>
<td></td>
<td>Amphoterecin B + craniotomy (pre-surgical loading 1.6 gm)</td>
<td>favorable (4 years)</td>
<td></td>
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<tr>
<td>28/F</td>
<td>Expansile Sinusoidal mass</td>
<td>sinusectomy +itraconazole</td>
<td>6 months</td>
<td></td>
<td></td>
<td>Amphoterecin B + voriconazole (2 gm)</td>
<td>favorable (2 years)</td>
<td></td>
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<td>40/M</td>
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<td>co-existent</td>
<td></td>
<td>B/L cavernous sinus B/L ICA encased</td>
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<td>favorable (4 years)</td>
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<tr>
<td>20/F</td>
<td>Left maxillary sinus</td>
<td>B/L ethmoid+</td>
<td>sinusectomy + steroids</td>
<td>6 months</td>
<td>B/L orbits + clivus + pre-pontine cistern</td>
<td>Amphoterecin B + temporal lobe lobectomy</td>
<td>death</td>
<td>meningo-encephalitis severe hyperkalemia</td>
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<tr>
<td>20/M</td>
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<td>sinusectomy</td>
<td>co-existent</td>
<td></td>
<td>PNS + left temporal lobe</td>
<td>Amphoterecin B + Frontal craniotomy</td>
<td>favorable (3 years)</td>
<td></td>
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<tr>
<td>36/M</td>
<td>B/L ethmoids</td>
<td>sinusectomy</td>
<td>6 months</td>
<td></td>
<td>PNS + left temporal Lobe</td>
<td>Amphoterecin B (2 gm) + Voriconazole</td>
<td>favorable (2 years)</td>
<td></td>
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<tr>
<td>42/F</td>
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<td>sphenoidectomy</td>
<td>15 months</td>
<td></td>
<td>B/L orbits + clivus + pre-pontine cistern</td>
<td>Amphoterecin B (2 gm) + voriconazole</td>
<td>death</td>
<td>acute 4th ventricular dilatation</td>
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<tr>
<td>25/M</td>
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<td>sinusectomy</td>
<td>2 years</td>
<td></td>
<td>PNS + frontal lobe invasion</td>
<td>Amphoterecin B (400 gm)</td>
<td>death</td>
<td>meningo-encephalitis</td>
</tr>
<tr>
<td>35/M</td>
<td>left ethmoid</td>
<td>sinusectomy</td>
<td>Itraconazole (6 mths)</td>
<td>2 years</td>
<td>B/L frontal lobes</td>
<td>Amphoterecin B (3 gm)</td>
<td>favorable (3 months)</td>
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<tr>
<td>26/F</td>
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<td>sinusectomy</td>
<td>Itraconazole</td>
<td>2 years</td>
<td>left frontal lobe</td>
<td>Amphoterecin B (1 gm)</td>
<td>death</td>
<td>meningo-encephalitis</td>
</tr>
<tr>
<td>36/M</td>
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<td>sphenoidectomy + Itraconazole, steroids</td>
<td>sinusectomy + steroids</td>
<td>10 years</td>
<td>right orbital + cav sinus mass</td>
<td>Amphoterecin B (1.5 gm)</td>
<td>favorable (6 months)</td>
<td></td>
</tr>
<tr>
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<td>frontal sinuses</td>
<td>sinusectomy + steroids</td>
<td>5 years</td>
<td>B/L frontal lobes</td>
<td>voriconazole</td>
<td>favorable (6 months)</td>
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representing two separate disease processes. With a mortality rate of nearly 100% in cases of InIA, we intend to treat all AFS patients with great caution, as 19 (16.7%) of the patients in the present study who presented with ample treatment time and good clinical status, failed to receive appropriate therapy. Henceforth, our correlation puts the innocence of AFS under strong suspicion and discrete categorization of fungal sinusitis into invasive and non-invasive forms as over-simplification. We propose and support that these two entities are merely the extremes of same pathology and tend to shift as probably the result of host defenses [13,17]. Breach in the mucosal barrier, brought about by inflammation or a proliferation of fungal elements in the sinus lumen has been cited as the precipitating factor, upsetting the equilibrium of host-agent interactions and resulting in the progression from non-invasive disease to invasive form [17].

The exact incidence of invasive aspergillosis developing in instances of AFS is not known. The co-existence of both forms of disease has been described earlier [3]. None of the patients with co-existent forms of disease were administered antifungals and one of the six had a fatal outcome [3]. We propose long-term follow-up of these patients as the disease may tend to behave aggressively in later part of life. Patients may be administered antifungal drug therapy after surgical debridement and not left merely after surgical debulking. The use of steroids in such patients should be employed cautiously and discouraged.

Conclusion

The present analysis/findings causes us to be highly cautious of the ‘allergic nature’ of AFS as an entity and certainly requires high dose of antifungal therapy for all patients, keeping an eye on near-fatal outcome of invasive intracranial aspergillosis [6]. As InIA carries a high mortality rate, it seems prudent to initiate treatment earlier in the course of illnesses. The appearance of invasive form of disease in the past setting of AFS is not uncommon. The allergic form of disease may not be considered a separate entity from InIA, but rather both pathologies may co-exist in the same patient.

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