ABPA Concomitantly Occurring with Invasive Sinus Aspergillosis: A Short Report on Two Patients

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Abstract Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder that is caused by hypersensitivity to *Aspergillus fumigatus* with resultant systemic immune activation, chronic asthma, recurrent pulmonary infiltrates, and bronchiectasis. First described by Hinson et al. (Thorax 7:317–333 [1]) in 1952, this disease occurs in 1–2% of patients with persistent asthma and in 2–15% of patients with cystic fibrosis (Greenberger, Front Biosci 8:s119–s127 [2]). Although the diagnostic criteria for ABPA have been laid down (and include bronchial asthma, immediate skin test reactivity to *A. fumigatus*, elevated total serum IgE level, pulmonary infiltrates, central bronchiectasis, peripheral blood eosinophilia, and positive serum precipitins [IgG] against *Aspergillus* antigen), none of these are specific for ABPA (Shah, Curr Opin Pulm Med 13(1):72–80 [3]). There is still no consensus on the number of criteria needed for diagnosis, and patients in different stages of ABPA may not fulfill all these criteria (Greenberger, Front Biosci 8:s119–s127 [2]; Chakrabarti et al., Mycoses 45:295–299 [4]). An high-resolution CT (HRCT) scan showing central bronchiectasis and high attenuation mucus is presently the investigation of choice for the diagnosis of bronchiectasis in patients with ABPA (Shah, Front Biosci 8:e138–e146 [5]). ABPA has also been reported in association with allergic fungal rhinosinusitis in English literature (Shah, Curr Opin Pulm Med 13(1):72–80 [3]).

We are reporting two patients with invasive aspergillosis of the nose, paranasal sinuses and orbit, who were diagnosed and managed successfully for ABPA, a previously unreported entity.

Keywords ABPA · Invasive aspergillosis · Itraconazole

Introduction

Aspergillus is a ubiquitous soil-dwelling organism. Because of its thermophilic nature, it has a propensity to cause a variety of clinical pulmonary syndromes (e.g., invasive aspergillosis, aspergilloma, allergic rhinosinusitis and asthma, hypersensitivity pneumonitis, chronic necrotizing aspergillosis, and allergic bronchopulmonary aspergillosis [ABPA]). ABPA is a pulmonary disorder that is caused by hypersensitivity to *Aspergillus fumigatus* with resultant systemic immune activation, chronic asthma, recurrent pulmonary infiltrates, and bronchiectasis. First described by Hinson et al. [1] in 1952, this disease occurs in 1–2% of patients with persistent asthma and in 2–15% of patients with cystic fibrosis [2].

ABPA has also been reported in association with allergic fungal rhinosinusitis in English literature [3]. We are reporting two patients with invasive aspergillosis of the nose, paranasal sinuses and orbit, who were diagnosed and managed successfully for ABPA, a previously unreported entity.

Case 1

A 30 year old female patient presented with slowly progressive swelling and severe pain, right cheek region of 2 years duration, following extraction of right upper

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premolar and molar teeth. The patient also gave history of intermittent nasal obstruction and fever. She denies any history of diabetes mellitus, tuberculosis or hypertension or drug allergy. She gave history of asthma like symptoms for 15 years for which she took steroid inhalers intermittently.

Her general physical examination and systemic examination was within normal limits. A diffuse tender firm swelling was present involving right cheek, infraorbital region and root of nose. The sensations over right side of face were reduced and there was blunting of right infraorbital margin. Anterior rhinoscopy revealed deviated nasal septum to left. Nasal endoscopic examination was grossly normal. Non-axial proptosis was seen with the eyeball pushed forwards and outwards. Visual acuity was preserved in both the eyes; right eye extraocular movements were restricted in lateral gaze. Right pupil was mid-dilated and sluggishly reacting (Fig. 1a). Biopsy of the sinonasal mucosa revealed chronic granulomatous inflammation. Fungal smear revealed septate hyphae. She underwent debridement via Caldwell luc approach and received itraconazole for 7 months; was asymptomatic for 10–12 months when she

noticed protrusion of right eye and reduced vision in right eye. She also had associated complaints of pain and diplopia.

Contrast enhanced computed tomography revealed homogenous soft tissue density in right maxilla, posterior ethmoids with intraorbital intraconal extension and extension into pterygopalatine fossa (Fig. 1b). She underwent revision debridement by Caldwell luc approach; firm gritty mass present in maxilla destroying the medial, anterior and posterior walls with disease present in subcutaneous tissue. HPE showed chronic invasive granulomatous aspergillus sinusitis collection of giant cells with negative shadows in a background of fibrosis in chronic invasive granulomatous fungal rhinosinusitis (Fig. 1c). Septate fungal hyphae were also seen on PAS staining (Fig. 1d). She received amphotericin B 2,075 g after which she developed persistent hypokalemia, raised liver enzymes and anaemia, which necessitated cessation of therapy.

Patient had one episode of wheezing and respiratory difficulty during her hospital stay for which pulmonary consultation was taken. IgE levels against *A. fumigatus* were mildly raised. High-resolution CT (HRCT) chest

Fig. 1 **a** Clinical photograph of the patient showing nonaxial proptosis and upward and outwards deviation of the eyeball. **b** Coronal section of the CT scan showing an enhancing soft tissue density in the right maxillary sinus and the orbit. **c** Photomicrograph showing

collection of giant cells with negative shadows in a background of fibrosis in chronic invasive granulomatous fungal rhinosinusitis (haematoxylin and eosin, $\times 200$). **d** Photomicrograph showing septate fungal hyphae (PAS stain, $\times 400$)

revealed central bronchiectasis and high attenuation mucus suggestive of ABPA (Fig. 2a). *Aspergillus* skin test type 1 was positive while type 3 and type 4 were negative. She was treated with prednisolone in a dose of 0.5 mg/kg for a period of 6 weeks during which she had improvement in her chest symptoms. Post therapy HRCT chest revealed resolution of central bronchiectasis and high attenuation mucus (Fig. 2b). Patient is on regular follow up after discharge and shows no signs of active disease.

Case 2

A 32 year old female patient presented with complaints of swelling right side face of 3 months duration and pain at the local site for 15 days. No history of chronic URTI, visual or dental problems. On local examination, a diffuse firm nontender swelling present involving the right cheek and infraorbital region. CT scan revealed homogenous soft tissue density involving right maxilla with intraorbital and intraconal extension (Fig. 3a). Nasal endoscopy and biopsy was done which revealed chronic invasive granulomatous aspergillosis (Fig. 3b). Debridement was done by Weber Ferguson approach; extensive firm gritty fungal mass was present in the maxillary sinus eroding the anterior wall (involving the subcutaneous tissue), roof and going intraorbitally through inferior orbital fissure. Disease at the orbital apex was left as such.

She was discharged on oral itraconazole. Repeat CT scan at 1 month post op showed recurrence of disease for which she underwent revision endoscopic debridement and was started on amphotericin B. She completed 2.5 g of amphotericin B and was discharged.

On one of her follow up visits, she complained of recurrent wheezing for 7 days; pulmonary consultation was sought and she was diagnosed to have ABPA. *Aspergillus* skin tests were negative; IgE levels were raised (600 IU). HRCT chest showed features suggestive of ABPA (Fig. 3c). She was started on oral steroids (0.5 mg/kg for a period of 6 weeks) under antifungal cover. She has been on follow up for the past 2 years without any local or systemic recurrence of disease. Post therapy HRCT chest revealed a normal CT chest (Fig. 3d).

Discussion

ABPA is a pulmonary disorder that is caused by hypersensitivity to *A. fumigatus* with resultant systemic immune activation, chronic asthma, recurrent pulmonary infiltrates, and bronchiectasis. First described by Hinson et al. [1] in 1952, this disease occurs in 1–2% of patients with persistent asthma and in 2–15% of patients with cystic fibrosis [2]. In most cases, a lung biopsy is not required for diagnosis, and the diagnosis can be made on clinical, radiologic, and serologic grounds. Although the diagnostic criteria for ABPA have been laid down (and include bronchial asthma, immediate skin test reactivity to *A. fumigatus*, elevated total serum IgE level, pulmonary infiltrates, central bronchiectasis, peripheral blood eosinophilia, and positive serum precipitins [IgG] against *Aspergillus* antigen), none of these are specific for ABPA [3]. There is still no consensus on the number of criteria needed for diagnosis, and patients in different stages of ABPA may not fulfill all these criteria [2, 4]. The disease is arbitrarily classified into three subtypes: ABPA-seropositive (ABPA-S), ABPA with central bronchiectasis (ABPA-CB),

Fig. 2 a HRCT chest showing central bronchiectasis and high attenuation mucus suggestive of ABPA. b Post therapy HRCT chest showing recovery of central bronchiectasis and high attenuation mucus suggestive of ABPA

Fig. 3 **a** Coronal section of the CT scan of case 2 showing an enhancing soft tissue density in the right maxillary sinus and the orbit. **b** Photomicrograph showing collection of giant cells and fungal

profiles in chronic invasive granulomatous fungal rhinosinusitis (haematoxylin and eosin, $\times 200$). **c** HRCT chest showing central bronchiectasis. **d** Post therapy HRCT chest showing normal picture

and ABPA-CB with other radiologic findings (ABPA-CB-ORF) based on the HRCT findings by Aggarwal et al. [6].

Concomitant association of ABPA with afirs of the paranasal sinuses though rare, has been reported by a few investigators. Since asthma and sinusitis are often seen by two different specialities, the occurrence of AAS in ABPA and ABPA in AAS may easily be overlooked. In one of the studies [7] out of 95 patients with ABPA, 22 had radiological evidence of sinusitis. Nine consented to surgery, seven of whom were diagnosed as concomitant AAS. Nasal symptoms preceded chest symptoms in two patients, vice versa in one and occurred simultaneously in four. Familial occurrence of ABPA, middle lobe syndrome and collapse with effusion along with an operated aspergilloma were seen in one patient each. Transient pulmonary infiltrates and central bronchiectasis were seen in all patients. Computed tomography of the paranasal sinuses, carried out in six patients, revealed mucosal thickening with hyperdense lesions, without any bony erosion or destruction. All

patients had positive skin tests, positive precipitin study and raised total and specific IgE. Allergic mucin was seen in all patients, fungal hyphae in five, and culture grew *Aspergillus* spp. in four. All patients responded favourably to oral prednisolone [7].

Patients of chronic sinusitis confirmed by diagnostic imaging and positive isolates of *Aspergillus* from paranasal sinus material and histopathological evidence of hyphal elements within the sinus mucosa, sub-mucosa, blood vessels or bone are said to have invasive aspergillosis of the nose and paranasal sinuses. Association of ABPA in such patients in any form has not been previously reported. We are here reporting two such patients with ABPA diagnosed during the course of management of invasive aspergillosis who have been successfully managed. According to Aggarwal et al. [6] patients were considered to have ABPA if they met four of the following criteria: clinical diagnosis of asthma; elevated total IgE level (i.e., $>1,000$ IU/ml); presence of specific IgE against

A. fumigatus detected (by enzyme-linked immunosorbent assay; >0.35 kU/l), serum precipitating antibodies against *A. fumigatus*; radiographic pulmonary infiltrates (fixed/transient); and proximal or central bronchiectasis seen on HRCT scan. Both our patients were being managed for chronic invasive granulomaosis of the paranasal sinuses with intraorbital invasion when they were diagnose to have ABPA. Both the patient had elevated of specific IgE against *A. fumigatus* detected (by enzyme-linked immunosorbent assay; >0.35 kU/l), and CT Scan showed evidence of central bronchiectasis in both the patients.

The *Aspergillus* skin test was performed using *A. fumigatus* antigen (Aspergillin; Hollister-Stier Laboratories; Spokane, WA). The test was read every 15 min for 1 h, and then after 6–8 h. For delayed-type reactions, the text was read after 24, 48, and 72 h. The reactions were classified as type I if a wheal and erythema developed within 1 min, reached a maximum after 10–20 min, and resolved within 1–2 h; a type III reaction was read after 6 h, and any amount of subcutaneous edema was considered to be a positive result; and a type IV reaction was read after 72 h, and an induration of >5 mm was considered to be a positive result [4]. Our first patient showed type I skin test as positive but type III and IV could not be interpreted due to thrombophlebitis and in patient no 2 *Aspergillus* skin test was negative.

An HRCT scan is presently the investigation of choice for the diagnosis of bronchiectasis in patients with ABPA [5]. The characteristic radiologic findings described for ABPA have been reported extensively in literature [8–10]. Central bronchiectasis (i.e., bronchiectasis confined to the medial half of the lung) with normal peripheral bronchi is a characteristic feature of ABPA, which was seen in both of our patients. High-attenuation mucus, which is the most characteristic (if not pathognomonic) finding of ABPA, a finding which has been reported [11] to occur in as high as 28% of patients was also seen in our patients.

Oral glucocorticoids are currently the drug treatment of choice for ABPA as they suppress both immune function and inflammation [12, 13] administration of oral glucocorticoids in patients with invasive aspergillosis carries with it the risk of disease activation in the paranasal sinuses. So, we administered oral glucocorticoids under anti-fungal cover. Antifungal agents, especially itraconazole, have been suggested to modify the immunologic activation associated with ABPA and to improve clinical outcome [14]. We tried to follow this observation to be on the safer side. Both our patients showed complete remission of the disease with no activation of the sinus pathology. Both are presently on regular follow up for the past 2 years.

The cause effect relationship seems to be very complicated. One of our patients gave a history of bronchial asthma with irregular but prolonged use of inhalers over the past few years. The development of invasive

aspergillosis could be secondary to the use of inhalers which has the maximum impact on the nasal mucosa. This association needs to be examined in detail which can only be done if we keep a high index of suspicion and try to diagnose these patients in early stages, before they develop permanent and extensive lung damage.

Conclusion

ABPA though uncommonly seen in India is probably underdiagnosed. It has sparingly been reported in afirs of nose and apranasal sinuses. A working knowledge of the entity is very important which can be commonly confused with tuberculosis and bronchial asthma. It needs to be recognized in patients with invasive aspergillosis for optimal treatment.

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