

Allergic Bronchopulmonary Aspergillosis with Aspergilloma: An Immunologically Severe Disease with Poor Outcome

Ritesh Agarwal · Ashutosh N. Aggarwal ·
Mandeep Garg · Biman Saikia · Dheeraj Gupta ·
Arunaloke Chakrabarti

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Abstract

Background and Aims The association between allergic bronchopulmonary aspergillosis (ABPA) and aspergilloma has been proposed as a severe form of ABPA. However, this conclusion is based on single-patient case reports. In this study, we describe the clinical details and immunological findings of this association and compare patients of ABPA with aspergilloma and those without.

Methods This is a retrospective analysis of data of patients with ABPA managed in the Chest Clinic. We compared the clinical, radiological and immunological profile of patients with ABPA and central

bronchiectasis, with and without the presence of aspergilloma on HRCT scan.

Results There were 98 men and 81 women with a mean (SD) age of 33.6 (12.2) years. Eight patients were diagnosed to have aspergilloma. Sputum cultures grew *Aspergillus fumigatus* in all these eight patients. The aspergilloma was solitary in six patients, and two each in two patients. Patients with aspergilloma had higher IgE levels (both total and *A. fumigatus* specific) than those without aspergilloma. Bronchiectasis was also more extensive in patients with aspergilloma. Overall, 70 % of the ABPA patients experienced relapse during the median (interquartile range) follow-up of 27 (19–39) months. The number of relapses was significantly higher in patients with aspergilloma ($p = 0.0001$). On a multivariate linear regression analysis, high-attenuation mucus and aspergilloma were independent predictors of relapse frequency.

Conclusions The concurrent presentation of ABPA and aspergilloma is associated with an immunologically severe disease and risk of recurrent relapses.

R. Agarwal (✉) · A. N. Aggarwal · D. Gupta
Department of Pulmonary Medicine, Postgraduate
Institute of Medical Education and Research, Sector-12,
Chandigarh 160012, India
e-mail: riteshpgi@gmail.com;
agarwal.ritesh@pgimer.edu.in

M. Garg
Department of Radiodiagnosis, Postgraduate Institute
of Medical Education and Research, Chandigarh, India

B. Saikia
Department of Immunopathology, Postgraduate Institute
of Medical Education and Research, Chandigarh, India

A. Chakrabarti
Department of Medical Microbiology, Postgraduate
Institute of Medical Education and Research, Chandigarh,
India

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Introduction

Aspergillus, a genus of spore-forming fungi, is a ubiquitous mold that can affect the lung in numerous

ways. The respiratory diseases caused by *Aspergillus* can be broadly classified as simple colonization (aspergilloma), allergic (allergic bronchopulmonary aspergillosis and hypersensitivity pneumonias) and invasive (airway invasive aspergillosis, chronic cavity pulmonary aspergillosis and invasive pulmonary aspergillosis) [1]. Allergic bronchopulmonary aspergillosis (ABPA) is an inflammatory pulmonary disorder caused by immune reactions to *Aspergillus* species, mainly *A. fumigatus* [2]. It is predominantly a disease of asthmatics and complicates the course of up to 13 % of these patients [3]. High-resolution computed tomography (HRCT) of chest is the imaging modality of choice for the diagnosis of ABPA. The common findings on HRCT chest include central bronchiectasis (CB), mucoid impaction, high-attenuation mucus (HAM) and centrilobular nodules. HRCT chest findings can also predict outcome in ABPA with CB and HAM being markers of recurrent relapses [4–6]. An aspergilloma is a conglomerate of *Aspergillus* infecting preformed and poorly draining lung spaces. The development of an aspergilloma is classically associated with tubercular cavities although it is also reported in cavities due to sarcoidosis, lung abscess, pulmonary infarcts, bronchiectasis, cystic fibrosis and others [7–9].

Allergic bronchopulmonary aspergillosis is only occasionally been considered as a predisposing factor for an aspergilloma with only single-patient case reports describing this association [8, 10–13]. Although McCarthy et al. reported aspergilloma in eight cases in their series of 111 patients describing radiological findings in ABPA, the report provided no details regarding their clinical features and outcome [14]. The concurrent association of ABPA and aspergilloma has also been proposed as a severe form of the disease with higher likelihood of poor control of asthma and probability of life-threatening complications like massive hemoptysis and invasive aspergillosis [15]. However, no study has systematically described the clinical details and immunological findings of this association. Moreover, no study has compared patients with ABPA with concomitant aspergilloma and those without aspergilloma. ABPA is highly prevalent in India, and we have recently reported the clinical features and outcomes of more than 200 patients with ABPA [4–6, 16–18]. In this study, using the same data set, we describe the immunological findings and outcome of patients presenting with

concurrent aspergilloma and ABPA and compare the clinical findings and outcome of patients with ABPA with aspergilloma and those without aspergilloma.

Materials and Methods

The present study is a retrospective analysis of the data of all consecutive patients with ABPA diagnosed between January 2006 and December 2008 and followed till December 2010. The clinical characteristics of these patients have been previously described [4–6, 16]. The study was approved by the Local Ethics Committee, and a written informed consent was taken from all patients. All glucocorticoid naïve (glucocorticoid intake more than 3 weeks in the preceding 6 months) patients with asthma in our Chest Clinic are screened with *Aspergillus* skin test for *Aspergillus* sensitization. Those demonstrating type I reactions to *Aspergillus* antigen are further investigated with IgE levels (total and *A. fumigatus* specific), eosinophil count, *Aspergillus* precipitins and HRCT chest. Patients are diagnosed as ABPA if they meet both the following criteria: (a) total IgE levels > 1,000 IU/mL; (b) *A. fumigatus*-specific IgE levels > 0.35 kUA/L; and, two of the following criteria: (a) presence of serum precipitins against *A. fumigatus*; (b) radiographic pulmonary opacities (fixed/transient); (c) absolute eosinophil count > 1,000 cells/ μ L; (d) central bronchiectasis on HRCT [4–6, 16, 19]. All the investigations including CT scan were done prior to starting glucocorticoid therapy. The investigations were performed within a period of 2–3 days of one another. None of the patients were screened for cystic fibrosis. All patients with aspergilloma were also subjected to sputum for acid-fast bacilli and cultures for mycobacteria.

Aspergillus skin test was performed by injecting 0.2 mL of the *A. fumigatus* antigen (100 PNU/mL) intradermally in the forearm, while 0.2 mL of phosphate buffer saline in the other forearm serves as negative control [20]. The test site was examined every 15 min for 1 h. Type I reaction was said to be present if a wheal and erythema developed within 1 min, reached a maximum after 10–20 min and resolved within 1 h, with the antigen arm skin reaction diameter being at least 8 mm more than the control arm. Type III reactions were read after 6 h, and any

amount of subcutaneous edema was considered positive.

Serum IgE levels (total and *A. fumigatus* specific) were assayed using the quantitative enzyme-linked immunosorbent assay (Demeditec diagnostics GmbH, Kiel, Germany) and the fluorescent enzyme immunoassay (UniCap Systems; Pharmacia Upjohn; Stockholm, Sweden).

Aspergillus fumigatus precipitins were detected by the Ouchterlony's gel diffusion technique according to the method of Longbottom and Pepys [21].

Spirometry was performed on a dry rolling seal spirometer (Spiro RS-232; PK Morgan Limited; Kent, UK). Forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC) and FEV₁/FVC ratio were measured using the American Thoracic Society guidelines [22]. The severity of obstruction was categorized as per the standard practice in our laboratory [23]. Bronchodilator reversibility was considered to be present if the FEV₁ and/or FVC increased by $\geq 12\%$ and 200 mL after inhalation of 400 μg of salbutamol [22].

Absolute eosinophil count was estimated by counting the numbers of white blood cells (WBCs) on an automated blood cell analyzer. The differential leukocyte count involved counting and classifying 100 WBCs on a blood film stained with the Wright-Giemsa stain, which gave the percentage of each subtype of cells. By multiplying the percentage with the total leukocyte count, the total eosinophil count was obtained.

High-resolution CT of the thorax (1.25 mm at 10-mm intervals) were obtained in the supine position at full end-inspiration with a scan time of 3 s. The images (from lung apex to base) were reconstructed using the high-spatial frequency algorithm (16-row, multiple detector CT scanner; LightSpeed Plus; GE Medical Systems; Slough, UK). The bronchopulmonary segments were identified by the anatomical division of the appropriate lobar and segmental bronchus, and their relationship with the major and minor fissures [24, 25]. Bronchiectasis was classified as 'central' when confined to the medial half of the lung, at a point midway between the hilum and the chest wall [26, 27]. The presence of high-attenuation mucus was considered if the mucus plugs were visually denser than the normal skeletal muscle [28]. 'Aspergilloma' was defined by the presence of eccentric soft tissue opacity within a bronchiectatic cavity.

The patients were treated with glucocorticoids (prednisolone 0.75 mg/kg for 6 weeks, 0.5 mg/kg for 6 weeks; then tapered by 5 mg every 6 weeks to continue for a total duration of at least 6–9 months) and followed up with history and physical examination, chest radiograph and total IgE levels every 6 weeks [2]. Treatment response was classified as remission if the IgE levels declined by $>35\%$, and there was clinical/radiological improvement after 3 months of glucocorticoids or relapse if there was a doubling of baseline IgE levels with clinicoradiological worsening. Patients were classified as glucocorticoid-dependent ABPA if they required oral prednisolone for recurrent relapses of ABPA. For the purpose of this study, we evaluated the clinical, radiological and immunological findings in patients with ABPA with and without aspergilloma.

Statistical Analysis

The normalcy of distribution was evaluated using Kolmogorov–Smirnov test. The continuous variables are described as mean (standard deviation [SD]) if the distribution is normal, or median (interquartile range [IQR]) if not normal. The differences between continuous variables were analyzed using Mann–Whitney *U* if not normally distributed and Student's *t*-test if normally distributed. The differences between categorical variables were analyzed using Fisher's exact test. A multivariate linear regression analysis was performed to determine whether the presence of aspergilloma is associated with frequent relapses after adjusting for eosinophil count, total and *A. fumigatus*-specific IgE levels, high-attenuation mucus and severity of bronchiectasis. Statistical significance was assumed at a *p* value of less than 0.05 (two-sided).

Results

During the study period, 234 cases of ABPA were identified. Of these, 55 patients had a normal HRCT and were excluded from the current study. The study group constitutes 179 patients with ABPA and CB (98 men, 81 women; mean [SD] age of 33.6 [12.2] years). The median duration of asthma before a diagnosis of ABPA could be established was 6 years. Forty-nine (20.9 %) patients were identified to have hyper-attenuating mucoid impaction. Eight patients were

diagnosed to have aspergilloma. Chest radiograph identified aspergilloma in four cases (Fig. 1) while all the aspergillomas could be visualized on HRCT chest (Fig. 2). The aspergilloma was solitary in six patients, and two each in two patients. Sputum cultures grew *A. fumigatus* in all these patients. Sputum for acid-fast bacilli and cultures for mycobacteria were all negative. The characteristics of patients with and without aspergilloma are depicted in Table 1. Patients with aspergilloma had higher IgE levels (both total and *A. fumigatus* specific) and a trend toward higher eosinophil counts than those without. The prevalence of precipitating antibodies against *Aspergillus* was similar in the two groups. Bronchiectasis was also more extensive in patients with aspergilloma (Table 1).

There was clinical and radiological improvement in all the patients receiving glucocorticoid therapy at 6 weeks. The median (IQR) duration of follow-up was 27 (19–39) months. One hundred and twenty (69.8 %) patients experienced relapse during the course of their treatment. All these patients were restarted on therapy

with prednisolone. The median (IQR) number of relapses was 3 (3–6) and 2 (0–2) in patients with and without aspergilloma, respectively, and was statistically significant ($p = 0.0001$). Of the 120 patients who relapsed, all could achieve remission; however, 51 patients (5 and 46 in those with and without aspergilloma, respectively; $p = 0.4$) required continuous glucocorticoid therapy for the maintenance of remission and were classified as glucocorticoid-dependent ABPA. None of the patient with aspergilloma has developed massive hemoptysis, progression of aspergilloma or invasive aspergillosis (Fig. 3).

Multivariate linear regression analysis was performed to identify risk factors associated with relapse frequency. High-attenuation mucus and aspergilloma were independent predictors of relapse frequency after adjusting for absolute eosinophil count, IgE levels (total and *Af* specific) and the extent of bronchiectasis based on the number of segments involved (Table 2).

Discussion

The results of this study suggest that concomitant presentation of ABPA-CB and aspergilloma is associated with severer immunological findings compared to those without aspergilloma. Moreover, this association is a risk factor for higher frequency of relapses compared to patients with ABPA-CB without aspergilloma. ABPA is a disorder characterized by recurrent remissions and relapse. As spontaneous improvement of symptoms and pulmonary opacities characterize an important aspect of the disease, the natural history of ABPA is often difficult to predict [29–34]. Few studies have described factors that can predict outcome in ABPA complicating bronchial asthma. In a previous study, we had reported that the HRCT findings of CB and HAM at presentation are predictors of frequent relapses in patients with ABPA [6]. This study suggests that aspergilloma is another indicator of poor prognosis in ABPA. The probable reason for aspergilloma being associated with immunological severity is due to the high fungal burden in aspergilloma, which makes phagocytosis of conidia by macrophages difficult [35]. A persistent heavy fungal burden leads to greater release of antigens with greater immune responses being mounted against the organism.

The terminology of aspergilloma remains complex and confusing, and it has been suggested that the term

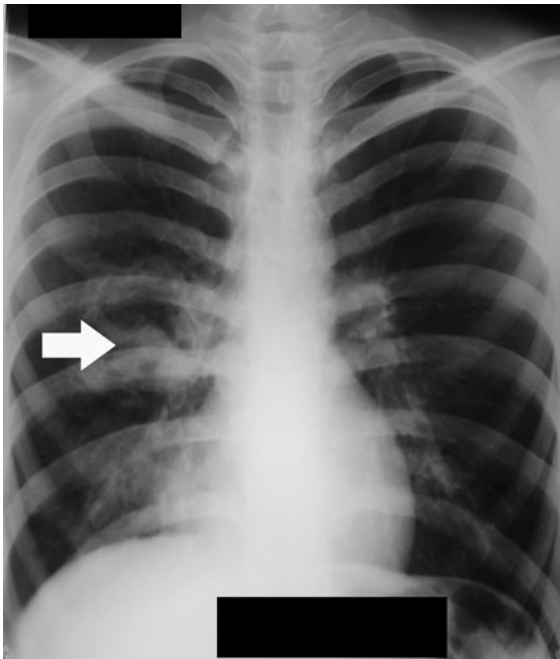


Fig. 1 Chest radiograph PA view of a 34-year-old male patient who presented with poorly controlled asthma and had received antituberculous therapy for the radiological opacities. There is a large cavity in the right mid-zone with intracavitary content suggesting a fungal ball (arrow). Also seen are numerous cystic opacities in the right lower zone

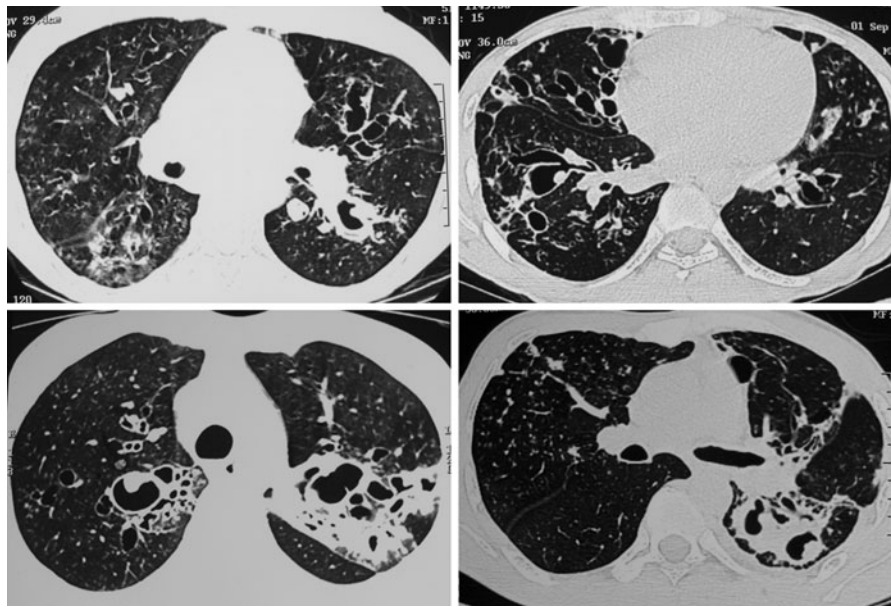


Fig. 2 High-resolution computed tomography scan images of four different patients with concomitant ABPA and aspergilloma. The *top panel* shows single aspergilloma, while the *bottom panel* shows the presence of two aspergillomas

chronic cavitary pulmonary aspergillosis (CCPA) should be used instead of aspergilloma [35]. For instance, in patients without ABPA, the presence of fever, chronic cough along with positive serum *Aspergillus* precipitins and growth of *Aspergillus* in the sputum is sufficient to make a presumptive diagnosis of aspergilloma even in the absence of fungus ball. However, this concept is difficult to extrapolate in patients with ABPA as the disorder per se is characterized by the presence of fever, serum *Aspergillus* precipitins and growth of *Aspergillus* in the sputum. Hence, a diagnosis of aspergilloma/CCPA complicating ABPA can only be made by the radiographic presence of a fungal ball.

An intriguing aspect of the combination of ABPA and aspergilloma is the uncertainty of the temporal association between the two entities. It is not clear whether ABPA occurred prior to aspergilloma or vice versa or whether both occurred simultaneously. There are reports of development of aspergilloma consequent to ABPA [8, 36], whereas some authors have reported ABPA secondary to aspergilloma [11, 37]. The mechanism of aspergilloma causing ABPA is due to continuous release of fungal antigens resulting in immune activation and ABPA. In a study, Jewkes et al. demonstrated immediate cutaneous hyperreactivity to *Aspergillus* antigens in 39 of the 56 patients [38].

Similarly, McCarthy et al. demonstrated immediate type 1 skin reactions in 21 of the 28 patients with aspergilloma [39]. However, immediate cutaneous reactivity and circulating levels of IgG and IgE against *A. fumigatus* are encountered to a greater degree in ABPA compared to aspergilloma [40].

On the contrary, the development of aspergilloma can follow colonization of *Aspergillus* in the bronchiectatic cavities of ABPA with subsequent formation of a fungus ball. In our series, it seems that ABPA preceded aspergilloma in view of long history of asthma, but it is difficult to be certain of the course. Whether the concomitant presentation of ABPA and aspergilloma represent a unique subset of patients remains unclear. Patients with CF and mutation classes I–III develop colonization with *A. fumigatus* early in their disease course compared to those with mutation classes IV–V [41]. It is possible that one of this specific genetic polymorphism predisposes to excessive *Aspergillus* colonization in ABPA leading to the formation of aspergilloma. Future research should aim to identify these polymorphisms in patients with ABPA and aspergilloma.

Although majority of the patients with ABPA have bronchiectatic cavities, the coexistence of ABPA and aspergilloma is a rare finding despite the presence of a favorable milieu. Campbell et al. reported one case of

Table 1 Baseline characteristics of 179 patients with ABPA-CB stratified based on the presence or absence of aspergilloma

	ABPA-CB without aspergilloma (n = 171)	ABPA-CB with aspergilloma (n = 8)	p value
Demographic details			
Age (years), mean (SD)	33.7 (12.3)	31.6 (11.3)	0.68
Male gender, no. (%)	92 (53.8)	6 (75)	0.47
History			
Duration of asthma (years), median (IQR)	6 (4–14)	10.5 (5.8–21)	0.21
Hemoptysis, no. (%)	72 (42.1)	5 (62.5)	0.29
Expectoration of brownish black mucous plugs, no. (%)	69 (40.4)	3 (37.5)	1
Spirometry, no. (%)			
Normal	37 (21.6)	0	0.36
Mild obstruction	44 (25.7)	3 (37.5)	
Moderate obstruction	54 (31.6)	4 (50)	
Severe obstruction	36 (21.1)	1 (12.5)	
Serological findings			
<i>Aspergillus</i> skin test, no. (%)			
Type I	171 (100)	8 (100)	
Type III	129 (75.4)	5 (62.5)	0.42
Absolute eosinophil count (cells/ μ L), median (IQR)	978 (529–1,778)	1,771 (857–2,665)	0.05
<i>Aspergillus</i> precipitins, no. (%)	138 (81.2)	6 (75)	0.65
Total IgE levels (IU/mL), median (IQR)	5,400 (2,890–10,128)	20,229 (11,526–23,743)	0.0001
<i>A. fumigatus</i> -specific IgE levels (kUA/L), median (IQR)	4.8 (1.7–18.3)	22.1 (4.9–42.6)	0.03
HRCT findings			
No. of lobes, median (IQR)	3 (2–4)	5 (4–5)	0.001
No. of segments, median (IQR)	7 (5–10)	10 (8–16)	0.01
High-attenuation mucus, no. (%)	46 (26.9)	3 (37.5)	0.69

aspergilloma in their series of 88 cases of ABPA, whereas McCarthy could identify aspergilloma in only eight of their 111 patients with ABPA [10, 14]. We could identify aspergilloma in only eight of the 234 cases of ABPA. Interestingly, half of the patients with fungal balls on chest CT had no visible aspergillomas on chest radiograph. It is well recognized that plain chest radiography is not sufficiently sensitive compared to HRCT chest, and the latter not only allows better assessment of the pattern and distribution of bronchiectasis but also detects abnormalities that are not apparent on chest radiography [42]. Moreover, it has been seen that the CT appearance of the parenchymal abnormalities on HRCT reflects the macroscopic pathologic findings [43].

The combination of ABPA and aspergilloma represents a challenge for the clinician as glucocorticoids are the cornerstone of therapy in ABPA, whereas it has been suggested that glucocorticoid therapy may lead to the formation (or increase the size) of an aspergilloma in ABPA [44, 45]. However, the occurrence of aspergilloma in glucocorticoid naïve patients in our study goes against this finding. Moreover, all the patients in our series improved with glucocorticoid therapy with decrease in size of aspergilloma, simultaneous decline in levels of total IgE and clinical remission. In addition, there are numerous cases on record of patients with ABPA and aspergilloma who have been treated with corticosteroids and have attained remissions [11–13, 37, 44–51]. Hence, there is a poor



Fig. 3 Serial chest radiographs of a patient with ABPA and aspergilloma showing clearance of the fungal ball after 3 months of glucocorticoid therapy

Table 2 Effect of immunological and radiological findings on frequency of relapses: multivariate linear regression model

	Regression coefficient	SE	<i>p</i> value
Eosinophil count (cells/ μ L)	−0.056	0.105	0.60
Total IgE levels (IU/mL)	0.1	0.135	0.46
<i>A. fumigatus</i> -specific IgE levels (kUA/L)	−0.007	0.073	0.92
Extent of CB based on the number of involved segments	0.03	0.025	0.25
Severity of asthma	0.044	0.131	0.74
Presence of high-attenuation mucus	1.416	0.229	0.0001
Presence of aspergilloma	2.061	0.466	0.0001

evidence to support the hypothesis of steroids as a risk factor for aspergilloma formation, and we believe that the use of steroids is safe in patients with ABPA and aspergilloma. It has been hypothesized that administration of glucocorticoids alleviates the asthma thus decreasing sputum production; this alters the bronchial environment, producing a more hostile milieu for *Aspergillus* and eliminating the fungus from the lungs [37]. Whether these patients will also benefit from concomitant azole therapy or aerosolized amphotericin B remains unknown? Surgical intervention is another option but should be generally reserved for patients with aspergilloma who have massive hemoptysis, those failing to respond to conventional therapy with steroids or azoles, or in those with localized disease [52–54].

Finally, our study is not without limitations. The retrospective nature of the study limits the analysis to the available data, and it may be possible that certain

important information has been missed. For example, we do not have serial CTs of the chest as we follow these patients only with symptoms, chest radiograph and IgE levels. It is difficult to establish cause and effect, and thus our results are at best, hypothesis-generating. The strength of the multivariate linear regression analysis is limited by the small number of patients in the aspergilloma group as it does not allow for a valid assessment of the identified risk factors in the study population being strong contributing factors. Hence, a larger prospective study is required to confirm our findings.

Conclusions

In conclusion, our study confirms that the concomitant presentation of ABPA and aspergilloma is uncommon.

However, the simultaneous presentation is associated with immunologically severe disease and also predisposes a patient to risk of recurrent relapses. Glucocorticoid therapy is safe in ABPA with aspergilloma. More studies are required to confirm our findings and defining the best treatment approach in this group of patients.

Conflicts of interest None.

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