

Spectrum of Pulmonary Aspergillosis in Hyper-IgE Syndrome with Autosomal-Dominant STAT3 Deficiency



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What is already known about this topic? Signal transducer and activator of transcription 3 (STAT3) deficiency predisposes to bacterial pneumonia complicated by bronchiectasis and pneumatocoeles, and aspergillosis is a major cause of morbidity in patients living with this primary immunodeficiency.

What does this article add to our knowledge? Here, we report the first nationwide series of aspergillosis in STAT3-deficient patients with a prevalence of 17.5%. We describe 2 forms: chronic aspergillosis, including chronic cavitary pulmonary aspergillosis and aspergilloma, and allergic aspergillosis with overlapping forms.

How does this study impact current management guidelines? This study provides a precise overview of the pulmonary aspergillosis spectrum in STAT3-deficient patients, highlighting poorly reported allergic forms with clues for the clinician concerning radiological presentation, diagnostic tools, medical and surgical treatment, and outcome.

BACKGROUND: Autosomal-dominant signal transducer and activator of transcription 3 (*STAT3*) deficiency predisposes to recurrent bacterial pneumonia, complicated by bronchiectasis and cavitations. Aspergillosis is a major cause of morbidity in these patients. However, its diagnosis, classification, and treatment are challenging.

OBJECTIVE: We aimed to assess the prevalence and describe the clinical, mycological, and radiological presentation and related therapy and outcome of *Aspergillus* infections of the respiratory tract in the STAT3-deficient patients of the National French cohort. **METHODS:** We performed a retrospective study of all pulmonary aspergillosis cases in STAT3-deficient patients

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Conflicts of interest: A. Duréault and F. Danion report personal fees from Gilead, outside the submitted work. E. Catherinot reports personal fees from LVL, CSL Behring, and LFB, outside the submitted work. O. Lortholary reports grants from

Gilead science; and personal fees from Pfizer, Novartis, Astellas, Gilead Sciences, and Merck, outside the submitted work. M. Castelle reports personal fees from Jazz Pharmaceutical, outside the submitted work. F. Lanternier reports personal fees from Gilead and Basilea, outside the submitted work. B. Sendid received travel grants from Pfizer and Merck Sharp & Dohme (MSD); consulting fees from MSD; and research grants from bioMérieux and Lesaffre International, outside the submitted work. J. F. Bervar reports personal fees from Pfizer and Novartis, outside the submitted work. A. Deschildre reports personal consultancy and lecture fees from Novartis, ALK, TEVA, GlaxoSmithKline (GSK), Stallergenes Greer, Aimmune, Zambon, CHIESI, Astra Zeneca, and DBV Technologies, outside the submitted work. C. Pison reports personal fees from GSK, Novartis, Boehringer Ingelheim, and Astra Zeneca France, outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 9, 2018; revised February 26, 2019; accepted for publication February 28, 2019.

Available online March 13, 2019.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.02.041>

Abbreviations used

ABPA- Allergic bronchopulmonary aspergillosis
AD-HIES- Autosomal-dominant hyper-IgE syndrome
BAL- Bronchoalveolar lavage
CCPA- Chronic cavitary pulmonary aspergillosis
CR- Complete response
CT- Computed tomography
GM- Galactomannan
IQR- interquartile range
PR- Partial response
STAT3- Signal transducer and activator of transcription 3

(n = 74). Clinical and mycological data were collected up to October 2015 and imaging was centralized.

RESULTS: Twenty-one episodes of pulmonary aspergillosis in 13 (17.5%) STAT3-deficient patients were identified. The median age at first episode was 13 years (interquartile range, 10-26 years). Ninety percent of patients had previous bronchiectasis or cavitations. Infections were classified as follows: 5 single aspergilloma, 9 chronic cavity pulmonary aspergillosis, 5 allergic bronchopulmonary aspergillosis-like disease, and 2 mixed forms of concomitant allergic bronchopulmonary aspergillosis-like disease and chronic cavity pulmonary aspergillosis. No invasive aspergillosis cases were identified. *Aspergillus* species were isolated in 71% of episodes and anti-*Aspergillus* antibodies in 93%. Eleven episodes were breakthrough infections. Antifungal treatment was prolonged, with a median of 13 months, and 6 patients (7 episodes) required surgery, with a high rate of postsurgical complications. One patient died and 6 had a relapse. **CONCLUSIONS:** Chronic and allergic forms of aspergillosis occurred in 17.5% of STAT3-deficient patients, mostly in lung cavities. Almost half had recurrences, despite prolonged antifungal treatment and/or surgery. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1986-95)

Key words: Aspergillosis; STAT3-deficient patient; Allergic bronchopulmonary aspergillosis; Cavitary chronic pulmonary aspergillosis; Aspergilloma

INTRODUCTION

Signal transducer and activator of transcription 3 (STAT3) deficiency is the main etiology of autosomal-dominant hyper-IgE syndrome (AD-HIES), which is responsible for a primary immunodeficiency with elevated IgE levels, hypereosinophilia, memory-B-cell lymphopenia, and a low proportion of IL-17-producing T_H17 cells. It also affects the connective tissue, skeletal system, vasculature, and dentition.¹ Ninety percent of patients develop bacterial pneumonia complicated with frequent (67%) pulmonary sequelae, such as bronchiectasis or pneumatoceles.¹ Chronic mucocutaneous candidiasis of various mucosal sites and nails is observed in 85% of patients.¹

STAT3 deficiency has been previously shown to predispose patients to aspergillosis.^{1,2} Here, we report *Aspergillus*-related colonization or infection in 22% of STAT3-deficient patients (n = 13) in the first global analysis of the national French cohort. Both frequent pneumatoceles and STAT3-related immunodeficiency could be

responsible for susceptibility to lung aspergillosis. The diagnosis, classification, and treatment of aspergillosis in STAT3-deficient patients are challenging, and clinical, radiological, and mycological descriptions of aspergillosis are lacking for these patients, as well as the role of antifungal treatment and surgery in their management. This study of the STAT3 deficiency French cohort allowed us to describe the clinical, radiological, and mycological presentation of pulmonary aspergillosis and its related therapy and outcome.

METHODS

We performed a national retrospective study in France of all episodes of pulmonary aspergillosis in STAT3-deficient patients. Seventy-four STAT3-deficient patients were identified by the Study Centre for Primary Immunodeficiencies (Centre d'Etude des Déficiences Immunitaires) at Necker Hospital (C.P.) through the Centre de Référence des Déficiences Immunitaires Héritaires (N.M.) based at Necker-Enfants Malades Hospital, Paris, France. Physicians in charge of patients were contacted to report microbiological and/or radiological evidence of pulmonary aspergillosis.

Inclusion criteria were the association of (all criteria were required) (1) a new radiological pattern compatible with pulmonary aspergillosis (chest computed tomography [CT] scan or X-ray); (2) serological (*Aspergillus* spp IgG antibody detection by immunodiffusion, counter immunoelectrophoresis, particle-hemagglutination, indirect-immunofluorescence, radioimmunoassay, or ELISA) or microbiological evidence of *Aspergillus* sp (direct microscopy or positive culture for *Aspergillus* in sputum, aspiration, or bronchoalveolar lavage [BAL] fluid or galactomannan [GM] antigen in plasma, serum, BAL fluid); and (3) exclusion of alternative diagnoses or histological evidence of pulmonary aspergillosis. Demographic, clinical, radiological, and mycological data were collected in a standardized case report form at diagnosis, at months 3, 6, and 12, and at the last follow-up. Medical records and thoracic CT were centralized. An evaluation committee, including infectious disease physicians (F.L. and A.D.), respiratory medicine physicians (C.T. or E.C.), and a radiologist (S.P.), reviewed the clinical, microbiological, and radiological data to assess aspergillosis diagnoses, classify aspergillosis episodes, and evaluate treatment responses.

We classified patients as suffering from aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA), allergic bronchopulmonary aspergillosis (ABPA)-like, or invasive aspergillosis. Definition criteria of pulmonary aspergillosis were based on the most recent consensus: European Organization for Research and Treatment of Cancer/Mycoses Study Group consensus definitions for invasive aspergillosis,³ European Society of Clinical Microbiology and Infectious Disease/European Respiratory Society guidelines for chronic pulmonary aspergillosis,⁴ and classification criteria by Patterson et al⁵ for ABPA criteria.

We had to adapt these criteria for the diagnosis of ABPA and CCPA, because of the specificities of STAT3 deficiency. Modified criteria are presented in Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org. Specific *Aspergillus* IgE levels, total IgE levels, and total eosinophil counts are difficult to interpret in STAT3-deficient patients. We thus designated ABPA-like episodes as those with at least asthma, positive *Aspergillus* serology (specific IgG), and consistent pulmonary opacities. Episodes with concomitant ABPA-like and CCPA criteria were designated as mixed form.

We evaluated treatment responses by chest CT and/or bronchoscopy and/or clinical response, when available, after 3, 6, and 12

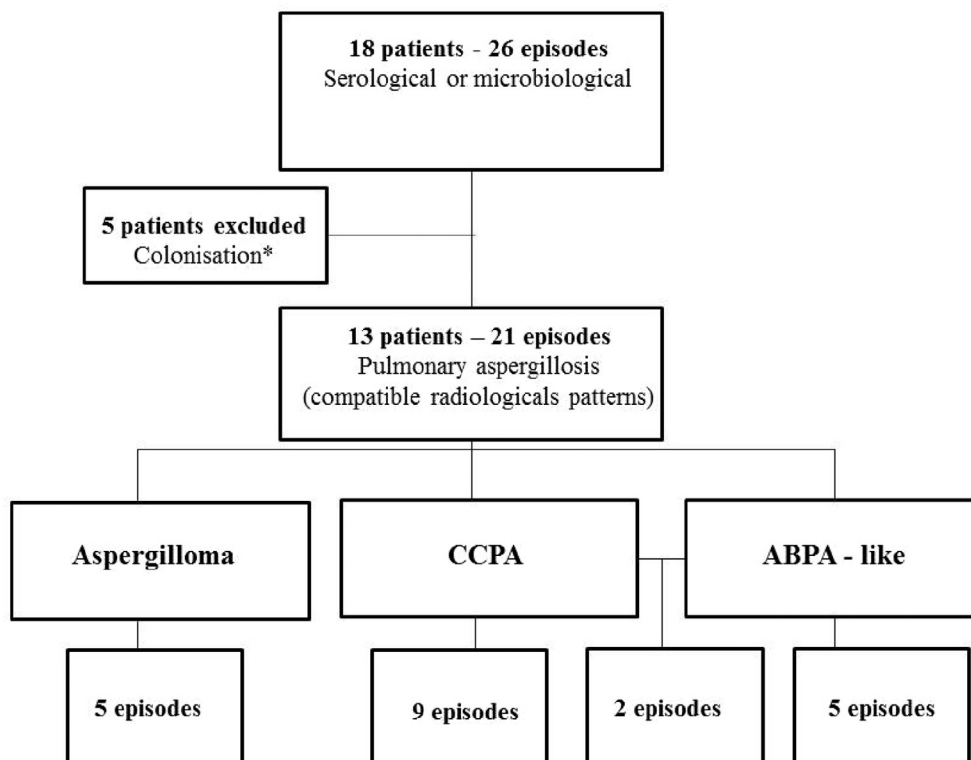


FIGURE 1. Flowchart of the cohort of STAT3-deficient patients with lung aspergillosis. *Examination of the radiological data showed 5 patients to have no CT or X-ray evidence of pulmonary aspergillosis and they were excluded.

months of treatment, and at the last follow-up. Standardized radiological criteria were not available at the beginning of the study to assess treatment response for CCPA. Thus, targets retained to assess radiological responses were size of the cavity(s), the number/size of fungus balls, pericavitary infiltrate and thickness of the cavity wall for CCPA or aspergilloma, and mosaic attenuation, centrolobular nodules, tree-in-bud opacities, nodule(s), atelectasis, and mucoid impaction⁶ for ABPA. The radiological response was defined as complete, partial, stable, or failure, and the mycological response as eradication (mycological evidence of eradication of *Aspergillus*), partial response (reduction of IgG antibody level), or persistence (mycological evidence of persistence of *Aspergillus* in samples). The clinical response was based on the assessment of cough, sputum production, hemoptysis, and dyspnea (with or without wheezing). The clinical response was defined as complete, partial, or failure. The response was defined as complete, partial, or failure as described in Table E3 in this article's Online Repository at www.jaci-inpractice.org.

Ethics board approval was obtained for research on patients cared for by the Centre de Référence des Déficits Immunitaires Héréditaires (CCTIRS 06.327; September 7, 2006).

RESULTS

Seventy-four STAT3-deficient patients were included in this study: 18 (24%) patients had at least 1 type of laboratory evidence (serological [specific IgG], microbiological, or histological) of aspergillosis. Examination of the radiological data showed 5 patients to have no CT or X-ray evidence of pulmonary aspergillosis and they were excluded. Twenty-one episodes of lung

aspergillosis were reported in 13 patients (17.5%), with an average of 1.6 episodes per patient (Figure 1).

Characteristics of the 13 patients from 12 kindred are summarized in Table I. All patients had a heterozygous loss-of-function mutation in the *STAT3* gene: 8 in the DNA-binding domain, 4 in the SH2 domain, and 1 in the linker domain. Seven patients were male and 6 were female. The median age at the first episode of lung aspergillosis was 13 years (interquartile range [IQR], 10-26 years). Three patients were on antifungal prophylaxis at the first episode (Table I). Previous bacterial pneumonia was reported for all patients (n = 11) for whom information was available. Nine patients (9 of 10 with prior radiological data available) had CT evidence of prior lung cavities (bronchiectasis in 8 and pneumatoceles in 1). Seven (54%) patients had a history of chronic mucocutaneous candidiasis at various mucosal sites and on their nails. According to clinical, radiological, mycological, and histological data, we classified episodes as aspergilloma (n = 5), CCPA (n = 9), ABPA-like episodes (n = 5), and mixed forms (n = 2) (Figure 1). The characteristics of the 21 episodes of pulmonary aspergillosis are described in Table II. One 11-year-old patient (7.7%) died.

Aspergilloma

Five episodes in 5 patients were classified as pulmonary aspergilloma and occurred as the first lung aspergillosis episode in 4 patients. One patient was on antifungal prophylaxis at diagnosis (Table II). The median age was 20 years (IQR, 15-21 years). Dyspnea and cough were reported in 2 cases and hemoptysis in 1 (Table III). CT data were not available for 1 patient, but

TABLE I. Patients' clinical features

Patient-episode	Sex	Mutation (domain)	Previous pneumonia	Previous cavities	CMC	Antifungal prophylaxis	Age at episode (y)	Aspergillosis form	Reference
1-1	M	p.V463del (DNA-B)	Yes	Yes	Yes	No	10	Mixed form	Chandesris et al ¹
2-1	F	p.V637M	Yes	Yes	ND	No	11	CCPA	Chandesris et al ¹
2-2		(SH2)				Itraconazole	14	CCPA	
3-1	F	p.R382Q	Yes	Yes	No	Itraconazole	13	CCPA	Chandesris et al ¹
3-2		(DNA-B)				Voriconazole	15	Aspergilloma	
4-1	F	p.R382W	Yes	Yes	No	No	10	CCPA	Chandesris et al ¹
4-2		(DNA-B)				Itraconazole	20	ABPA-like	
5-1	M	p.V637M (SH2)	Yes	Yes	Yes	Itraconazole	28	CCPA	Chandesris et al ¹
6-1	M	p.R382W (DNA-B)	Yes	Yes	No	No	12	ABPA-like	Chandesris et al ¹
6-2						Itraconazole	13	ABPA-like	
6-3						Posaconazole	16	ABPA-like	
7-1	F	p.V637M (SH2)	Yes	Yes	No	Itraconazole	10	ABPA-like	Chandesris et al ¹
7-2						Itraconazole	18	CCPA	
8-1	F	p.S560del (linker)	Yes	Yes	No	No	21	Aspergilloma	This report
9-1	M	p.R382W (DNA-B)	ND	ND	ND	ND	10	Aspergilloma	Chandesris et al ¹
10-1	M	p.R382Q (DNA-B)	Yes	ND	Yes	No	33	Mixed form	Chandesris et al ¹
11-1	F	c.1282-89C>T (DNA-B)	Yes	No	Yes	No	26	CCPA	Boisson et al (unpublished data, 2019)
12-1	M	c.1282-89C>T	ND	ND	Yes	No	20	Aspergilloma	Boisson et al (unpublished data, 2019)
12-2		(DNA-B)	Yes			Voriconazole	22	CCPA	
12-3						Itraconazole	23	CCPA	
13-1	M	p.Y657C (SH2)	Yes	Yes	Yes	No	35	Aspergilloma	Chandesris et al ¹

CMC, Chronic mucocutaneous candidiasis; DNA-B, DNA-binding domain; ND, not determinate; SH2, Src homology 2.

aspergilloma was diagnosed on the basis of histology. Prior lung cavities and fungus balls were present at diagnosis in all patients (Table III; Figure 2). Serum and BAL fluid were negative for GM antigen. Cultures of sputum, endotracheal aspirations, or BAL fluid were positive for *Aspergillus fumigatus* in 3 episodes and *Aspergillus* IgG serology was positive in 2 episodes (Table II; see Table E4 in this article's Online Repository at www.jaci-inpractice.org). Three patients received voriconazole as the first-line treatment. The median duration of antifungal treatment was 16 months (IQR, 12-21 months). Two patients underwent surgery: lobectomy in one case and wedge resection with pleurectomy in another case complicated by pneumothorax. At 1 year, a partial response (PR) was reported in 2 patients, complete response (CR) in 1, failure in 1, and data were not available for 1. One patient developed CCPA 30 months after surgery with complications (involving pleura) that was localized to the same territory as the aspergilloma.

Chronic cavitary pulmonary aspergillosis

Nine pulmonary aspergillosis episodes in 7 patients were classified as CCPA, of which 6 were breakthrough infections (patients receiving antifungal primary or secondary prophylaxis). The median age at diagnosis was 18 years (IQR, 13-23 years) (Table I). Five episodes were diagnosed as the first manifestation of aspergillosis. Cough was present in 4 and hemoptysis in 3 cases. CT showed cavity thickness in 8 episodes, fungus balls in 6 episodes, and pericavitary infiltrate in 4 episodes (Table II; Figure 2). Serum was positive for GM antigen when performed at diagnosis in 2 cases (index, 3.1 and 3.38; both patients were on IgG substitution), and BAL GM was performed and positive in 3 (index, >5, >6, and 5.2). Serum was positive for GM antigen in 2 other patients at 3 and 10 months after diagnosis.

Cultures of sputum, endotracheal aspirations, or BAL fluid were positive for *A. fumigatus* in 7 episodes. Specific *Aspergillus* IgG antibodies were positive in all tested cases (Table II; see Table E4).

The first-line antifungal treatment was voriconazole in 5 episodes and liposomal amphotericin B in 2. The median duration of treatment was 16 months (IQR, 10-26 months). Surgical resections were performed in 5 episodes for 4 patients: 3 cases of emergency surgery (severe hemoptysis [$n = 2$] and rapid progression [$n = 1$]) and 2 cases of planned surgery after failure of medical treatment. The procedure included lobectomy ($n = 3$), segmentectomy ($n = 1$), and pleurectomy ($n = 1$). Pneumothorax occurred in 2 patients after surgery. In 1 case, recurrent pneumothorax homolateral to surgery required pleuroscopy and pleurodesis. In the other case, purulent pneumothorax required drainage. In both cases, drainage was prolonged (1 and 2 months) and the local evolution was unfavorable, with relapse (after surgery) or persistence of lung aspergillosis.

At 1 year of treatment, PR was reported in 2 cases, CR in 3, and failure in 1 (data not available for 3 cases). Four patients developed another episode of lung aspergillosis after CCPA (in 3 of 4 cases after surgical treatment). Subsequent episodes were classified as CCPA in 2 cases (homo and bilateral), ABPA-like (bilateral) in 1, and aspergilloma (contro-lateral) in 1. The median interval between 2 episodes was 45.5 months (IQR, 30.7-70.7 months).

Allergic bronchopulmonary aspergillosis—like

Five episodes in 3 patients were classified as ABPA-like. It was the first pulmonary aspergillosis episode in 2 patients. Four episodes were breakthrough infections (Table I). The median age was 13 years (IQR, 12-16 years). The 3 patients had a history of

TABLE II. Clinical, radiological, and mycological data, according to the presentation of aspergillosis

Episodes	Aspergilloma (n = 5)	CCPA (n = 9)	ABPA-like (n = 5)	Mixed form (n = 2)	Total (n = 21)
Clinical presentation					
Age (y), median (IQR)	20 (15-21)	18 (13-23)	13 (12-16)	21 (15-27)	16 (12-22)
Dyspnea	2 of 3 (66)	1 of 8 (12)	3 of 5 (60)	2 of 2 (100)	8 of 18 (44)
Cough	2 of 3 (66)	4 of 8 (50)	3 of 5 (60)	2 of 2 (100)	11 of 18 (61)
Asthma	0 of 3	0 of 8	5 of 5 (100)	2 of 2 (100)	7 of 18 (39)
Hemoptysis	1 of 3 (33)	3 of 8 (37)	0 of 5	2 of 2 (100)	6 of 18 (33)
Brownish-black mucus plugs	0 of 3	0 of 8	3 of 5 (60)	2 of 2 (100)	5 of 18 (28)
Radiological findings					
Bronchiectasis	1 of 4 (25)	4 of 9 (44)	5 of 5 (100)	2 of 2 (100)	12 of 20 (60)
Mucoid impactions	0 of 4	1 of 9 (11)	4 of 5 (75)	0 of 2	5 of 20 (25)
Toothpaste or finger-in-glove	0 of 4	0 of 9	4 of 5 (75)	1 of 2 (50)	5 of 20 (25)
Micronodules	0 of 4	2 of 9 (22)	1 of 5 (25)	1 of 2 (50)	4 of 20 (20)
Cavitation(s)	4 of 4 (100)	9 of 9 (100)	5 of 5 (100)	2 of 2 (100)	20 of 20 (100)
Prior cavity in infection territory	3 of 4 (75)	6 of 9 (66)	3 of 5 (75)	2 of 2 (100)	14 of 20 (70)
Cavity's wall thickness	0 of 4 (40)	8 of 9 (88)	1 of 5 (20)	2 of 2 (100)	11 of 20 (55)
Fungal balls	4 of 4 (100)	6 of 9 (67)	0 of 5	0 of 2	10 of 20 (50)
Pericavitary infiltrate	0 of 4	4 of 9 (44)	0 of 5	1 of 2 (50)	5 of 20 (25)
Consolidation	0 of 4	2 of 9 (22)	1 of 5 (20)	1 of 2 (50)	4 of 20 (20)
Bilateral localization	0 of 4	1 of 9 (11)	3 of 5 (60)	1 of 2 (50)	5 of 20 (25)
Mycological results					
GM antigen serum (>0.5)	0 of 3	2 of 6 (33)	0 of 3	0 of 2	2 of 14 (14)
GM antigen BAL (>1)	0 of 2	3 of 3 (100)	0 of 0	0 of 0	3 of 5 (60)
Sputum, direct microscopy	0 of 0	0 of 1	0 of 2	0 of 0	0 of 3
Sputum, culture	0 of 0	1 of 1 (100)	3 of 4 (66)	0 of 0	3 of 4 (75)
<i>A fumigatus</i>		1 of 1 (100)			
<i>Aspergillus sp</i>			1 of 3 (33)		
<i>A fumigatus</i> + <i>A niger</i>			1 of 3 (33)		
<i>A fumigatus</i>			1 of 3 (33)		
BAL, direct microscopy	0 of 4	3 of 5 (60)	1 of 3 (33)	0 of 2	4 of 14 (28)
BAL, culture	3 of 4 (75)	6 of 7 (88)	2 of 3 (67)	1 of 2 (50)	12 of 16 (75)
<i>A fumigatus</i>	3 of 3 (100)	6 of 6 (100)	2 of 2 (100)	1 of 1 (100)	
Specific <i>Aspergillus</i> IgG*	2 of 3 (75)	7 of 7 (100)	4 of 4 (100)	2 of 2 (100)	15 of 16 (94)
Total IgE	2 of 2 (100)	2 of 2 (100)	2 of 2 (100)	2 of 2 (100)	8 of 8 (100)
Histology	1 of 1 (100)	4 of 4 (100)	0 of 0	0 of 0	5 of 5 (100)

CPA, Chronic pulmonary aspergillosis.

All results are presented on the basis of total (denominator) available data.

**Aspergillus* spp antibody (IgG) detection by immunodiffusion, counter immunoelectrophoresis, particle-hemagglutination, indirect immunofluorescence, radioimmunoassay, or ELISA.

asthma. Dyspnea, cough, and brownish-black mucus plugs were reported in 3 episodes. CT showed bronchiectasis and mucoid impactions in all 5 episodes and toothpaste/finger-in-glove opacities in 4. When performed, serum, BAL fluid, or endotracheal aspiration were negative for GM antigen; cultures of sputum, endotracheal aspiration, or BAL fluid were positive for *A fumigatus* in 3 episodes, and serology (IgG) was positive for all tested episodes (Table II). Hypereosinophilia was present in 4 episodes. Patients were positive for specific anti-*Aspergillus* IgE whenever tested (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). First-line treatment was voriconazole in 1 case and liposomal amphotericin B in 2. One patient was hospitalized in an intensive care unit for spastic respiratory distress. The median duration of antifungal treatment was 6 months (IQR, 6-7 months). At 1 year, PR was reported in 3 cases, CR in 1, and failure in 1. The evolution of ABPA-like was favorable, with 100% GR at the last follow-up. Relapses were

observed in 2 patients: 2 ABPA-like episodes in the same patient and 1 CCPA episode.

Mixed form

Two episodes were classified as mixed form, as patients had criteria for ABPA-like and CCPA. It was the first and single episode in both cases. No patient was on antifungal prophylaxis at diagnosis. The median age was 21 years (IQR, 15-27 years) (Table I). Cough, dyspnea, and hemoptysis were present in both cases at diagnosis. Both patients had a history of asthma and presented brownish-black mucus plugs at diagnosis. Cavitations with wall thickness were described in both cases. Radiological opacities consistent with ABPA were a consolidation in one case and toothpaste/finger-in-glove opacities in the second (Table II; Figure 2). *Aspergillus* serology (IgG) was positive in both cases, and the culture of BAL fluid was positive in 1 case. Both patients were treated with voriconazole for a median of 5.5 months (IQR,

TABLE III. Treatment and outcome according to the form of aspergillosis

Treatment and outcome	Aspergilloma (n = 5)	CCPA (n = 9)	ABPA-like (n = 5)	Mixed form (n = 2)	Total (n = 21)
Treatment (first line)					
AmB	—	2	2	—	4
Voriconazole	3	5	1	2	11
Median total duration (mo)	16 (12-21)	18 (12-36)	6 (6-7)	5.5 (5.2-5.7)	
Surgery	2 (40)	5 (55.5)	0	0	7
Outcome					
M3					
Response	2 of 5	4 of 9	3 of 5	—	9 of 21
PR	1 of 5	4 of 9	2 of 5	—	7 of 21
CR	1 of 5	—	1 of 5	—	2 of 21
Failure	—	3 of 9	—	1 of 2	4 of 21
NA	3 of 5	2 of 9	2 of 5	1 of 2	8 of 21
M6					
Response	1 of 5	7 of 9	4 of 5	1 of 2	13 of 21
PR	—	5 of 9	3 of 5	1 of 2	9 of 21
CR	1 of 5	2 of 9	1 of 5	—	4 of 21
Failure	—	1 of 9	—	1 of 2	2 of 21
NA	4 of 5	1 of 9	1 of 5	—	6 of 21
M12					
Response	3 of 5	5 of 9	4 of 5	1 of 2	13 of 21
PR	2 of 5	2 of 9	3 of 5	1 of 2	8 of 21
CR	1 of 5	3 of 9	1 of 5	—	5 of 21
Failure	1 of 5	1 of 9	1 of 5	1 of 2 (death)	4 of 21
NA	1 of 5	3 of 9	—	—	4 of 21
Last news					
Response	4 of 5	6 of 9	5 of 5	1 of 2	16 of 21
PR	1 of 5	3 of 9	4 of 5	1 of 2	9 of 21
CR	3 of 5	3 of 9	1 of 5	—	7 of 19
Failure	1 of 5	3 of 9	—	1 of 2 (death)	5 of 21
NA	—	—	—	—	—

AmB, Amphotericin B; NA, not available.

5.2-5.7 months). One patient (11 years old) was hospitalized in the intensive care unit with spastic respiratory distress and died from massive hemoptysis after multiple drainage 3 months after diagnosis. The other patient had PR at the last evaluation, without other episodes of aspergillosis.

DISCUSSION

This study describes the prevalence, presentation, and outcome of pulmonary aspergillosis in the French cohort of 74 STAT3-deficient patients. We report a prevalence of 17.5% for lung aspergillosis, with 2 different clinical entities: chronic aspergillosis (n = 14), including CCPA and aspergilloma, and allergic aspergillosis (n = 5) with overlapping forms (n = 2). Antifungal treatment was long, with a median of 13 months, and 6 patients had surgery with a high rate of postsurgery complications.

One of 13 patients died of pulmonary aspergillosis. Vinh et al² of the National Institute of Allergic and Infectious Disease described a cohort of 64 patients with AD-HIES in 2010 with a prevalence of aspergillosis of 25%. They reported that mold infections were diagnosed in the fourth decade of life, whereas the median age at first episode of pulmonary aspergillosis in our series was 13 years (IQR, 10-26 years). The mortality rate was

also different as we report a mortality rate of 7.7% due to lung aspergillosis versus 17% mold infection mortality in the American cohort.² This difference may be explained by the difference in median age of the 2 cohorts and the absence of an invasive form. In a necropsy study of 6 patients with AD-HIES, the first case of *Aspergillus* pneumonia was reported 17 years after the first case of bacterial pneumonia and the mean age at diagnosis was 27 years.⁷

In contrast, we do not report here any invasive aspergillosis, based on the European Organization for Research and Treatment of Cancer/Mycoses Study Group 2008 criteria. This is a major difference relative to previously reported data; Vinh et al² reported 20 episodes of invasive mycosis, including 16 of aspergillosis. Infections were classified as invasive on the basis of radiological findings as consolidation without a halo sign and the authors reported 5 patients with disseminated disease.² Furthermore, a necropsy study described 3 cases of aspergillosis with angio-invasion, 1 with dissemination (pulmonary and cerebral mycotic aneurysm), and 2 with local pulmonary vascular invasion in patients with HIES (diagnosis by scoring, not genetically proven).⁷ These infections were all associated with cavitary lung disease. Our study is the first to use centralized medical records, mycological, and radiological data. Differences between lung aspergillosis classifications may be due, in part, to

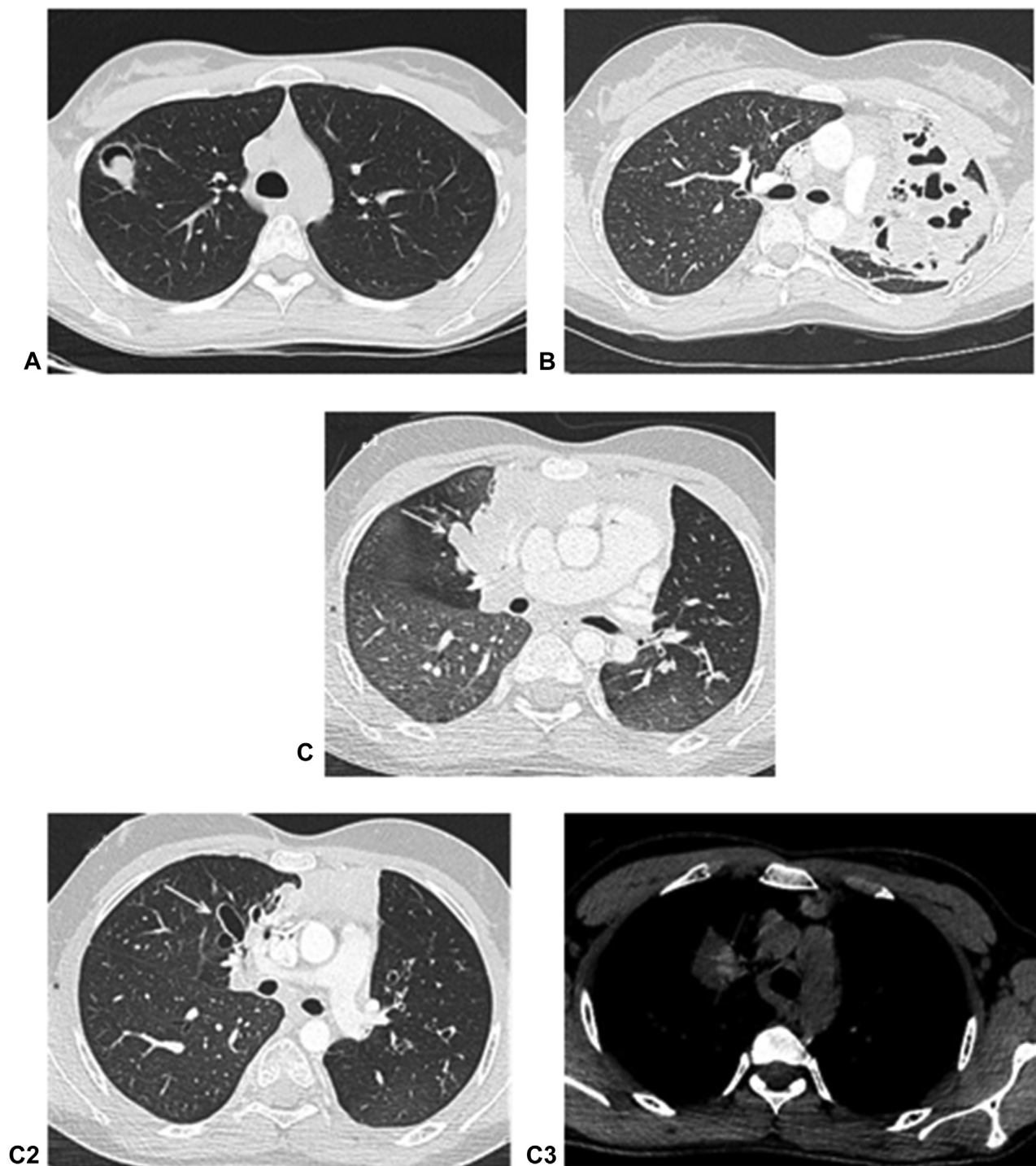


FIGURE 2. CTscans. **A**, Aspergilloma (patient 8, episode 1). Fungus ball inside a single small cavity. **B**, CCPA (patient 7, episode 2). Large cavities of the upper left lobe containing mass-like fungus ball with cavity wall thickness and pericavitary infiltrate. **C1**, ABPA-like (patient 6, episode 2); **C2**, partial resolution after 1 month of therapy, showing the disappearance of several impactions and air trapping; **C3**, same patient with high attenuation mucoid impaction in the right upper lobe.

multidisciplinary reviewing, including both by lung physicians and by radiologists. Ten patients developed at least 1 episode of CCPA or aspergilloma. Preexisting cavitations were present in all but 1 case, and in the same area in 69%. In a recent review, Freeman and Olivier⁸ reported that mold infections occur in

areas of preexisting cavities (pneumatocoles or bronchiectasis), leading to chronic infection without clinic-radiological description. Lung cavities appear to be one of the necessary underlying conditions for the development of lung aspergillosis in STAT3-deficient patients, as for sarcoidosis (the burden of CPA

TABLE IV. Diagnosis and therapeutic clues according to aspergillosis form in STAT3-deficient patients

Diagnosis and therapeutic clues	Aspergilloma (n = 5)	CCPA (n = 9)	ABPA-like (n = 5)	Mixed form (CCPA + ABPA-like) (n = 2)
Age (y), median (IQR)	20 (15-21)	18 (13-23)	13 (12-16)	21 (15-27)
Diagnosis				
Clinical presentation	Asymptomatic or dyspnea, cough	Asymptomatic or dyspnea, cough	Dyspnea, cough, asthma, brownish-black mucus plugs	Dyspnea, cough, asthma, brownish-black mucus plugs
Radiological presentation (CT scan)	Cavitation + fungus ball	Cavitation (1 or more) + wall thickness, progression	Mucoid impactions, toothpaste or finger-in-glove	Mix of CCPA + ABPA-like radiological findings
			Bilateral localization	
Mycological	Sputum or BAL culture positive for <i>Aspergillus</i>	Sputum or BAL culture positive for <i>Aspergillus</i>	Sputum or BAL culture positive for <i>Aspergillus</i>	Sputum or BAL culture positive for <i>Aspergillus</i>
	Specific <i>Aspergillus</i> IgG	Specific <i>Aspergillus</i> IgG	Specific <i>Aspergillus</i> IgG	Specific <i>Aspergillus</i> IgG
		GM antigen in BAL		
Therapy	Any triazole active against <i>Aspergillus</i>	Any triazole active against <i>Aspergillus</i>	Itraconazole ± corticosteroids	Any triazole active against <i>Aspergillus</i>
Median length of treatment (mo)	16 (12-21)	18 (12-36)	6 (6-7)	5.5 (5.2-5.7)

complicating sarcoidosis has been estimated to be 3%-12% of cases⁹) and sequelae of tuberculosis (authors have established the global incidence of CCPA to be 21% in residual cavitations after tuberculosis). In a recent study of 127 patients with CPA (including simple aspergilloma), the median age was 58 years and the underlying conditions were chronic obstructive pulmonary disease, tuberculosis sequelae, and corticosteroid use.¹⁰ These patients were more symptomatic than STAT3-deficient patients, but the radiological presentation was similar. In our study, the *Aspergillus* specific IgG antibody assay was positive in 84% of cases. The combination of a chest CT scan with the performance of an *Aspergillus* specific IgG antibody assay are key diagnostic features for establishing the diagnosis of CPA, including in STAT3-deficient patients. In this retrospective study, IgE and IgG specific *Aspergillus* antibodies were measured with different serological tests with different cutoffs depending on the laboratory. We reported those results in Tables E4 and E5. A prospective evaluation of these tests will be necessary both for diagnosis and for follow-up of *Aspergillus* disease in STAT3-deficient patients.

The median duration of treatment was long: 18 months for CCPA and 16 for aspergilloma, whereas itraconazole or voriconazole is recommended for a minimal duration of 4 to 6 months in CCPA.⁴ Partial antifungal efficacy for aspergilloma and CCPA is associated with their weak diffusion in cavities. Half of the episodes were treated with surgery and were associated with a CR in 71% of cases, but relapse was observed in 60%, with a median of 3 years. Surgery was associated with complications in 28% of CCPA and 50% of aspergilloma cases, with pneumothorax in all cases, prolonged bronchopleural fistulae, and homolateral recurrence. Post-pulmonary surgery complications in AD-HIES have previously been reported to occur in more than 50%.¹¹ This may be due to abnormal tissue remodeling in STAT3 deficiency.¹² However, complications are also frequent in non-STAT3-deficient patients, as a recent surgery series of CPA¹³ reported prolonged air leak in 33% of cases, empyema in 20%, and recurrence in 26%.¹³ There is no

consensus concerning the role of surgery in the management of CCPA or aspergilloma. Surgery for pulmonary aspergillosis is often challenging but offers the chance of a permanent cure, particularly for aspergilloma, but recurrences are not rare. Given the young age of STAT3-deficient patients at the time of the surgical procedure, the high rate of complications, and the frequency of recurrence, it is crucial to discuss surgery and drainage indications for emergencies or failure of medical treatment. Medical treatment should be favored, but is prolonged, and requires good monitoring of tolerance and adherence. Criteria for clinical and radiological response need to be standardized.

We report 5 ABPA-like episodes. These patients present features of allergic bronchopulmonary disease with bronchiectasis and toothpaste or finger-in-glove characteristic imaging on CT in most cases, associated with positive sputum cultures for *A fumigatus* or specific IgG antibodies and a history of treated or untreated asthma.^{11,14} Allergic aspergillosis in patients with STAT3 deficiency is poorly described.^{8,14} Eppinger et al¹⁴ reported sensitization to *Aspergillus* in 2 patients with hyper-IgE syndrome by the presence of precipitating *A fumigatus* antibodies associated with bronchiectasis and a history of asthma in 1 case, assuming an overlap between ABPA and HIE. In a recent review, Freeman and Olivier⁸ reported a case of a 15-year-old patient with AD-HIES who presented a CT scan with the plugging characteristic of ABPA associated with a sputum culture positive for *A fumigatus* and compatible clinical features. In our experience, asthma can be difficult to manage, with 2 patients hospitalized in the intensive care unit for spastic respiratory distress. The diagnosis of ABPA-like in STAT3 deficiency is challenging due to high concentrations of total serum IgE (>1000 UI/L), an obligatory criterion for ABPA, and hyper-eosinophilia (>500/mm³), a minor criterion, which are both characteristics of STAT3 deficiency. STAT3-deficient patients were tested for specific anti-*Aspergillus* IgE. They were found to be weakly positive in 4 patients without any history of *Aspergillus* colonization or asthma. Therefore, in our study, none of these exams can be used as diagnostic criteria in

STAT3-deficient patients. In ABPA, bronchiectasis is present in 73% to 95%¹⁵ of patients and was found in 100% of our STAT3-deficient patients in association with toothpaste or finger-in-glove radiological patterns. Improvement of ABPA-like diagnosis will require *Aspergillus* specific IgG antibodies follow-up with careful CT examination by an experienced radiologist. These patients require regular pulmonological follow-up with respiratory functional tests. Furthermore, endoscopic examination, when performed, showed characteristics of ABPA disease, with brownish-black mucus. This examination appears to be useful in helping clinicians diagnose ABPA in STAT3-deficient patients.

Relapses were observed in 3 of 5 (60%) patients, and the response was 60% at 3 months in our cohort versus 100% at 6 weeks in an Indian cohort of patients with ABPA. Allergic forms of aspergillosis in STAT3 deficiency represent a major management dilemma because corticosteroids, cornerstone of ABPA treatment, may accelerate pulmonary damage, invasive fungal infections, and bone fracture, particularly in these patients with underlying immune deficiency and osteopenia. That is why we used only antifungal therapy for the treatment of those patients. However, prolonged antifungal therapy could induce resistance and result in toxicity. The efficacy and safety of corticosteroids and alternative treatments such as monoclonal anti-IgE, anti-IL-4 receptor, anti-IL-5, and anti-IL-5 receptor α antibodies, or antifungal nebulization (liposomal amphotericin B, itraconazole)¹⁶ need to be evaluated.

STAT3 plays a critical role in the maintenance of surfactant homeostasis and lung function during oxygen injury. In STAT3-deficient patients, structural lung disease is associated with an immunologic defect including the impairment of T_H17 differentiation. Indeed, data suggest that respiratory epithelia (with cutaneous epithelia) are mostly dependent on cytokines of the T_H17 pathway (IL-22), in particular for the synthesis of antimicrobial peptides and polymorphonuclear leucocytes chemotaxis.¹⁷ Both the persistence of cavities and innate and adaptive antifungal immunity defects are probably responsible for the noneffective clearance and persistence of *Aspergillus* sp in the airways of patients with STAT3 deficiency. In contrast to chronic granulomatous disease, preserved efficient polymorphonuclear killing of *Aspergillus* has been demonstrated in STAT3 deficiency.²

ABPA is a hypersensitivity reaction to *Aspergillus* sp and results from an altered host response to colonization of the bronchial mucus by *Aspergillus*, with an exaggerated T_H2 response and eosinophilic inflammation.¹⁸ In ABPA, it is hypothesized that defects in innate and adaptive immunity cause the persistence of *A fumigatus* and are associated with genetic defects, which have been documented in ABPA, complicating cystic fibrosis.⁹ The mechanism leading to ABPA in STAT3-deficient patients is unknown. The colonization of cavities associated with a defect in the IL-10 response, an anti-inflammatory cytokine, may be involved in this exaggerated immune response.¹⁹ Dysregulation of the T_H17 response may also be involved, as the suppression of STAT3 in a multiallergen mouse model inhibited airway inflammation.²⁰ Both IL-17A and IL-17F cytokines activate innate epithelial immune responses and make different contributions to allergic responses and protection against infection.²¹

STAT3 deficiency is due to different types of mutations, but we were unable to find any correlation between specific mutations and the form of aspergillosis. Lung aspergillosis in STAT3 deficiency is challenging to manage, because it is necessary to

avoid resistance to antifungal treatment while preserving lung function. We report in Table IV relevant diagnosis clues (clinical, radiological, and mycological) and our first-line treatment recommendations based on this retrospective study. However, complementary studies are needed. Antifungal prophylaxis is necessary in STAT3 deficiency with lung abnormalities, despite the frequency of breakthrough aspergillosis. Collaboration between pneumologists and infectious disease clinicians is needed to improve the diagnosis and treatment of these *Aspergillus*-related diseases.

Acknowledgments

We acknowledge C. Godet (Poitiers).

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ONLINE REPOSITORY

DIAGNOSTIC CRITERIA

See [Table E1](#) for diagnostic criteria for ABPA and [Table E2](#) for diagnostic criteria for CCPA.

TABLE E1. Diagnostic criteria for ABPA

ABPA criteria according to Patterson et al ^{E1} : 6 major = likely, 7 major = certain		Modified criteria for ABPA-like episodes in STAT3-deficient patients: 4 major criteria or 3 major plus 2 minor	
Major criteria			
- Bronchial asthma		- Present or past history of bronchial asthma	
- Immediate cutaneous Hypersensitivity to <i>A fumigatus</i>		- Bronchiectasis	
- Serum total IgE levels (>1000 IU/mL)		- Serum precipitins or IgG against <i>A fumigatus</i>	
- Central bronchiectasis		- Consistent abnormalities on TDM†	
- Serum precipitins against <i>A fumigatus</i>			
- Consistent opacities on radiography or TDM*			
- Eosinophil count > 1000 cells/μL			
Minor criteria			
Sputum cultures demonstrating growth of <i>A fumigatus</i>		Sputum cultures demonstrating growth of <i>A fumigatus</i>	
- Expectoration of brownish-black mucus plugs		- Expectoration of brownish-black mucus plugs or compatible aspect in fibroscopy	
- Type III skin reaction to <i>A fumigatus</i> antigen			

*Radiographic pulmonary opacities consistent with ABPA: transient as consolidation, nodules, tram-track opacities, toothpaste/finger-in-glove opacities, fleeting opacities or permanent as parallel line and ring shadows, bronchiectasis, and pleuropulmonary fibrosis.

†Bronchial involvement (mucoid impactions, with high attenuation mucoid impaction, toothpaste/finger-in-glove) and/or pulmonary consolidation (as fleeting or atelectasia).

TABLE E2. Diagnostic criteria for CCPA

CCPA criteria according to Denning et al ^{E2}		Modified CCPA criteria for STAT3- deficient patients	
- One or more pulmonary cavities (with either a thin or thick wall) possibly containing 1 or more aspergillomas or irregular intraluminal material		- One or more pulmonary cavities (with either a thin or thick wall) possibly containing 1 or more aspergillomas or irregular intraluminal material	
- Serological or microbiological evidence implicating <i>Aspergillus</i> spp		- Serological or microbiological evidence implicating <i>Aspergillus</i> spp	
- Significant pulmonary and/or systemic symptoms		- Radiological progression (new cavities, increasing pericavitary infiltrates, or increasing fibrosis) over at least 3 mo of observations	
- Radiological progression (new cavities, increasing pericavitary infiltrates, or increasing fibrosis) over at least 3 mo of observations			

TABLE E3. Definition of global response according to clinical, radiological, and mycological response^{E3-E5}

Failure	At least 1 criteria:
	– Clinical failure
	– Radiological stabilization or failure
	– Mycological persistence
Partial response	– Partial clinical response with complete or partial radiological response and mycological eradication or PR
	OR
	– Partial radiological response with complete clinical response and mycological eradication
	OR
	– Partial mycological response with partial radiological response with complete or partial clinical response
Complete response	– Complete clinical response
	AND
	– Complete radiological response (with or without sequelae)
	AND
	– Mycological eradication

TABLE E4. Levels of specific *Aspergillus* IgG in aspergilloma and CCPA in STAT3-deficient patients

Patients-episode	Type of episode	At diagnosis	After treatment	Time of evaluation
2-1	CCPA	Precipitins: 3 bands	5 bands	M6
2-2	CCPA	Precipitins: 6 bands	7 bands	M6
3-1	CCPA	Precipitins: 3 bands	NA	M6
3-2	Aspergilloma	Precipitins: 4 bands	4 bands	M3
4-1	CCPA	Precipitins: 4 bands	2 bands	M3
5-1	CCPA	Precipitins: NA	NA	M6
7-2	CCPA	Precipitins: 1 band HAI: 320	NA NA	M6
8-1	Aspergilloma	NA	NA	M3
9-1	Aspergilloma	NA	NA	NE
11-1	CCPA	Precipitins: 6 bands ELISA: 80	0 band <50	M6
12-1	Aspergilloma	Precipitins: 3 bands ELISA: 351	1 band 93	M3
12-2	CCPA	Precipitins: 3 bands	NA	M3
12-3	CCPA	NA	NA	M3
13-1	Aspergilloma	NA	NA	M3

NA, Not applicable/available.

TABLE E5. Levels of total IgE and specific *Aspergillus* IgE and IgG in ABPA-like and mixed form in STAT3-deficient patients

Patients-episode	Type of episode	At diagnosis	After treatment	Time of evaluation
1-1	Mixed form	Precipitins: 3 bands	NA	M3
		ELISA: NA	78 UI/L	
		IgE total: NA	NA	
		IgE specific: 12.9	11.3	
4-2	ABPA-like	Precipitins: NA	NA	NE
		IgE total: NA	NA	
		IgE specific: NA	NA	
6-1	ABPA-like	ELISA: NA	169 UI/L	M3
		IgE total: 700	2369	
		IgE specific: NA	19	
6-2	ABPA-like	ELISA: 206 UI/L	NA	M3
		IgE total: NA	NA	
		IgE specific: NA	NA	
6-3	ABPA-like	Precipitins: 2 bands	1 band	M3
		ELISA: 327 UI/L	300 UI/L	
		IgE total: 1585	1270	
		IgE specific: 43	30	
7-1	ABPA-like	HAI: 320	NA	M3
		IgE total: 900	NA	
		IgE specific: 61	NA	
10-1	Mixed form	Precipitins: 3 bands	NA	NE
		IgE total: 5000	NA	
		IgE specific: 6.1	NA	

NA, Not available/applicable; NE, nonevaluable.

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