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Spectrum of pulmonary aspergillosis in Hyper IgE syndrome with autosomal dominant STAT3 deficiency

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AD, CT, EC, OL, FL, CP, and MOC designed the study analysis. AD and CG collected data. The evaluation committee was AD, FL, EC, CT, and SP. AD and FL drafted the manuscript. SP and CT supported the radiological analysis. All authors provided input and reviewed and approved the final manuscript.

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Abstract

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

Main results:

Twenty-one episodes of pulmonary aspergillosis in 13 (17.5%) STAT3deficient patients were identified. The median age at first episode was 13 years (IQR 10-26). Ninety percent of patients had previous bronchiectasis or cavitations. Infections were classified as follows: five single aspergilloma, nine chronic cavity pulmonary aspergillosis (CCPA), five allergic broncho-pulmonary aspergillosis-like disease (ABPA-like), and two mixed forms of concomitant ABPA-like and CCPA. No invasive aspergillosis cases were identified. *Aspergillus sp.* 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 six patients (seven episodes) required surgery with a high rate of post-surgical complications. One patient died and six relapsed.

Conclusion:

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.

Highlights box

1. What is already known about this topic?

STAT3 deficiency predisposes to bacterial pneumonia complicated by bronchiectasis and pneumatoceles and aspergillosis is a major cause of morbidity in patients living with this primary immunodeficiency.

2. 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 two forms: chronic aspergillosis, including chronic cavitary pulmonary aspergillosis and aspergilloma, and allergic aspergillosis with overlapping forms.

3. 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.

Key words

aspergillosis, STAT3 deficient patient, allergic broncho-pulmonary aspergillosis, cavitary chronic pulmonary aspergillosis, aspergilloma

Abbreviations:

ABPA	allergic bronchopulmonary aspergillosis
AD-HIES	autosomal dominant hyper-IgE syndromes
BAL	bronchoalveolar lavage
CEREDIH	Centre de Référence des Déficits Immunitaires Héréditaires
CCPA	chronic cavitary pulmonary aspergillosis
CR	complete response
CT	computed tomography
EORTC/MSG	European Organization for Research and Treatment of Cancer/Mycoses Study Group
ESCMID/ERS	European Society of Clinical Microbiology and Infectious Diseases/ European Respiratory Society
IA	invasive aspergillosis
ICU	intensive care unit
Ig	immunoglobulins
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PR	partial response

Introduction

STAT3 (Signal Transducer and Activator of Transcription 3) deficiency is the main aetiology of autosomal dominant hyper-IgE syndromes (AD-HIES), which is responsible for a primary immunodeficiency with elevated IgE levels, hyper-eosinophilia, memory-B cell lymphopenia, and a low proportion of IL-17-producing Th17 cells. It also affects the connective tissue, skeletal system, vasculature, and dentition[1]. Ninety per cent of patients develop bacterial pneumonia complicated with frequent (67%) pulmonary sequelae, such as bronchiectasis or pneumatoceles[1]. Chronic mucocutaneous candidiasis (CMC) 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 colonisation 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, (CEDI) at Necker Hospital (CP) through the Centre de Référence des Déficits Immunitaires Héréditaires (CEREDIH) (NM) 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 CT scan or X Ray), (2) serological (*Aspergillus spp.* IgG antibody detection by immunodiffusion, counter immune-electrophoresis, particle-hemagglutination, indirect-immuno-fluorescence, radio-immunoassay, or ELISA) or microbiological evidence of *Aspergillus sp.* (direct microscopy or positive culture for *Aspergillus* in sputum, aspiration, or broncho-alveolar 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, months 3, 6, and 12, and the last follow-up. Medical records and thoracic computed tomography (CT) were centralized. An evaluation committee, including infectious disease physicians (FL, AD), respiratory medicine physicians (CT or EC), and a radiologist (SP), reviewed the clinical, microbiological, and radiological data to assess aspergillosis diagnoses, classify aspergillosis episodes, and evaluate treatment responses.

We classified patients as aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA),

allergic bronchopulmonary aspergillosis-like (ABPA-like), or invasive aspergillosis (IA). Definition criteria of pulmonary aspergillosis were based on the most recent consensus: European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) consensus definitions for invasive aspergillosis[3], European Society of Clinical Microbiology and Infectious Disease/European Respiratory Society (ESCMID/ERS) guidelines for Chronic pulmonary aspergillosis[4], and classification criteria by *Patterson et al*. for ABPA criteria [5].

We had to adapt those criteria for the diagnosis of CCPA and ABPA, due to the specificities of STAT3 deficiency. Modified criteria are presented in Supplementary material E1. Specific *Aspergillus* IgE, total IgE levels, and total eosinophil counts are difficult to interpret in STAT3 deficient patients. We thus designated APBA-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 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 impaction[6] 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,

haemoptysis, and dyspnoea (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 Supplementary material E2.

Ethics board approval was obtained for research on patients cared for by the CEREDIH (CCTIRS 06.327; 7 September 2006).

Results

Seventy-four STAT3 deficient patients were included in this study: 18 (24%) patients had at least one type of laboratory evidence (serological (specific IgG), microbiological, or histological) of aspergillosis. Examination of the radiological data showed five 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 1. All patients had a heterozygous loss-of-function mutation in the *STAT3* gene: eight in the DNA-binding domain, four in the SH2 domain, and one in the linker domain. Seven patients were male and six were female. The median age at the first episode of lung aspergillosis was 13 years [IQR: 10-26]. Three patients were on antifungal prophylaxis at the first episode (table 1). Previous bacterial pneumonia was reported for all patients (n =11) for whom information was available. Nine patients (9/10 with prior radiological data available) had CT evidence of prior lung cavities (bronchiectasis in eight and pneumatoceles in one). Seven (54%) patients had a history of chronic mucocutaneous candidiasis (CMC) at various mucosal sites and on their nails. According to clinical, radiological, mycological, and histological data, we classified episodes as aspergilloma (n = 5), chronic cavitary pulmonary aspergillosis (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 2. One 11-year-old patient (7.7%) died.

Aspergilloma

Five episodes in five patients were classified as pulmonary aspergilloma and occurred as the first lung aspergillosis episode in four patients. One patient was on antifungal prophylaxis at diagnosis (Table 2). The median age was 20 years [15-21]. Dyspnoea and cough were reported in two cases and haemoptysis in one (Table 3). CT data was not available for one patient but aspergilloma was diagnosed based on histology. Prior lung cavities and fungus balls were present at diagnosis in all patients (Table 3, 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 three episodes and *Aspergillus* IgG serology was positive in two episodes (Table 2, Supplementary material E3.1). Three patients received voriconazole as the first-line treatment. The median duration of antifungal treatment was 16 months [12-21]. Two patients underwent surgery: lobectomy in one case and wedge resection with pleurectomy in another case complicated by pneumothorax. At one year, a partial response (PR) was reported in two patients, complete response (CR) in one, failure in one, and data was not available for one. One patient developed CCPA 30 months after surgery with complications (involving pleura) that was localized to the same territory as the aspergilloma.

CCPA

Nine pulmonary aspergillosis episodes in seven patients were classified as CCPA, of which six were breakthrough infections (patients receiving antifungal primary or secondary prophylaxis). The median age at diagnosis was 18 years [13-23] (Table 1). Five episodes were diagnosed as the first manifestation of aspergillosis. Cough was present in four and

haemoptysis in three cases. CT showed cavity thickness in eight episodes, fungus balls in six episodes, and pericavitary infiltrate in four episodes (Table 2, Figure 2). Serum was positive for GM antigen when performed at diagnosis in two cases (index: 3.1 and 3.38, both patients were on IgG substitution) and BAL GM was performed and positive in three (index: > 5; > 6, and 5.2). Serum was positive for GM antigen in two other patients at three and 10 months after diagnosis. Cultures of sputum, endotracheal aspirations, or BAL fluid were positive for *Aspergillus fumigatus* in seven episodes. Specific Aspergillus IgG antibodies were positive in all tested cases (Table 2, Supplementary material E3.1).

The first-line antifungal treatment was voriconazole in five episodes and liposomal amphotericin B in two. The median duration of treatment was 16 months [10-26]. Surgical resections were performed in five episodes for four patients: three cases of emergency surgery (severe haemoptysis (n = 2) and rapid progression (n = 1)) and two 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 two patients after surgery. In one case, recurrent pneumothorax homolateral to surgery required pleuroscopy and pleurodesis. In the other case, purulent pneumothorax required drainage. In both cases, drainage was prolonged (one and two months) and the local evolution was unfavourable, with relapse (after surgery) or persistence of lung aspergillosis.

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

ABPA-like

Five episodes in three patients were classified as ABPA-like. It was the first pulmonary aspergillosis episode in two patients. Four episodes were breakthrough infections (Table 1). The median age was 13 years [12-16]. The three patients had a history of asthma. Dyspnoea, cough, and brownish-black mucus plugs were reported in three episodes. CT showed bronchiectasis and mucoid impactions in all five episodes and tooth-paste/finger-in-glove opacities in four. When performed, serum, BAL fluid, or endotracheal aspiration were negative for GM antigen; cultures of sputum, endotracheal aspiration, or BAL fluid were positive for *Aspergillus fumigatus* in three episodes and serology (IgG) was positive for all tested episodes (Table 2). Hypereosinophilia was present in four episodes. Patients were positive for specific anti-Aspergillus IgE whenever tested (Supplementary material E3.2)**.** First-line treatment was voriconazole in one case and liposomal amphotericin B in two. One patient was hospitalized in an intensive care unit (ICU) for spastic respiratory distress. The median duration of antifungal treatment was six months [6-7]. At one year, PR was reported in three cases, CR in one, and failure in one. The evolution of ABPA-like was favourable, with 100% GR at the last follow-up. Relapses were observed in two patients: two ABPA-like episodes in the same patient and one 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 [15-27] (Table 1). Cough, dyspnoea, and haemoptysis 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 2, Figure 2). *Aspergillus* serology (IgG) was positive in both cases and the culture of BAL fluid was positive in one. Both patients were treated with voriconazole for a median of 5.5 months [5.2-5.7]. One patient (11 years old) was hospitalized in the ICU with spastic respiratory distress and died from massive haemoptysis after multiple drainage three 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 two 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 six patients had surgery with high rate post-surgery complications.

One of 13 patients died of pulmonary aspergillosis. Vinh *et al.* of the National Institute of Allergic and Infectious Disease (NIAID) described a cohort of 64 AD-HIES patients in 2010 with a prevalence of aspergillosis of 25%. They reported that mould 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]. The mortality rate was also different as we report a mortality rate of 7.7% due to lung aspergillosis *versus* 17% mould infection mortality in the American cohort[2]. This difference may be explained by the difference in median age of the two cohorts and the absence of an invasive form. In a necropsy study of six

AD-HIES patients, 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 EORTC/MSG 2008 criteria. This is a major difference relative to previously reported data; Vinh *et al.* reported 20 episodes of invasive mycosis, including 16 of aspergillosis. Infections were classified as invasive based on radiological findings as consolidation without a halo sign and the authors reported five patients with disseminated disease[2]. Furthermore, a necropsy study described three cases of aspergillosis with angio-invasion, one with dissemination (pulmonary and cerebral mycotic aneurysm) and two with local pulmonary vascular invasion in HIES patients (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 multidisciplinary reviewing, including both by lung physicians and radiologists. Ten patients developed at least one episode of CCPA or aspergilloma. Pre-existing cavitations were present in all but one case, and in the same area in 69%. In a recent review, Freeman *et al.* reported that mold infections occur in areas of pre-existing cavities (pneumatoceles or bronchiectasis), leading to chronic infection without clinic-radiological description[8]. 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 complicating sarcoidosis has been estimated to be 3 to 12% of cases[9]) 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 COPD, 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* were measured with different serological tests with different cut off depending of the laboratory. We reported those results in the table E3.1 and E3.2 (supplementary material). A prospective evaluation of these tests will be necessary both for diagnosis and follow up of Aspergillus disease in STAT 3 deficient patients

The median duration of treatment was long: 18 months for CCPA and 16 for aspergilloma, whereas itraconazole or voriconazole are recommended for a minimal duration of four to six months in CCPA[4]. Partial antifungal efficacy for aspergilloma and CCPA are associated with their weak diffusion in cavities. Half of the episodes were treated with surgery and were associated with a complete response in 71% of cases, but relapse was observed in 60% with a median of three years. Surgery was associated with complications in 28% of CCPA and 50% of aspergilloma, 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 remodelling in STAT3 deficiency[12]. However, complications are also frequent in non STAT3 deficient patients, as a recent surgery series of CPA[13] 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 favoured, but prolonged, and requires good

monitoring of tolerance and adherence. Criteria for clinical and radiological response need to be standardized.

We report five ABPA-like episodes**.** These patients present features of allergic broncho-pulmonary disease with bronchiectasis, toothpaste or finger-in-glove characteristic imaging on CT in most cases, associated with positive sputum cultures for *Aspergillus fumigatus* or specific IgG antibodies and a history of treated or untreated asthma[11,14]. Allergic aspergillosis in STAT3 deficiency patients is poorly described[8,14]. Eppinger *et al.* reported sensitization to *Aspergillus* in two patients with hyper-IgE syndrome by the presence of precipitating *A. fumigatus* antibodies associated with bronchiectasis and a history of asthma in one case, assuming an overlap between ABPA and HIE. In a recent review, Freeman *et al.* reported a case of a 15-year-old with AD-HIES who presented a CT scan with the plugging characteristic of ABPA associated with a sputum culture positive for *Aspergillus fumigatus* and compatible clinical features[8]. In our experience, asthma can be difficult to manage, with two patients hospitalized in the ICU 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 four patients without any history of *Aspergillus* colonisation 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% 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 exam appears to be useful in helping clinicians diagnose ABPA in STAT3 deficient patients.

Relapses were observed in three of five (60%) patients and the response was 60% at three months in our cohort *versus* 100% at six weeks in an Indian cohort of ABPA patients. 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's why we used only antifungal therapy for treatment of those patients. On the other hand, 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 IL4 receptor, anti IL5, and anti IL5 receptor α antibodies, or antifungal nebulisation (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 immunological defect including the impairment of Th17 differentiation. Indeed, data suggest that respiratory epithelia (with cutaneous epithelia) are mostly dependent on cytokines of the Th17 pathway (IL-22), in particular for the synthesis of antimicrobial peptides and PMN chemotaxis[17]. Both the persistence of cavities and innate and adaptative anti-fungal immunity defects are probably responsible for the non-effective clearance and persistence of *Aspergillus sp.* in the airways of STAT3 deficiency patients. 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 Th2 response and eosinophilic inflammation[18]. In ABPA, it is hypothesized that defects in innate and adaptive immunity cause the persistence of *Aspergillus 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 Th17 response may also be involved, as the suppression of STAT3 in a multi-allergen 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, as it is necessary to avoid resistance to antifungal treatment while preserving lung function. We report in the table 4 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.

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Figure 1. Flow chart of the cohort of STAT3-deficient patients with lung aspergillosis

* Examination of the radiological data showed five patients to have no CT or X-ray evidence of pulmonary aspergillosis and they were excluded

Table 1. Patient clinical features

Patient-Episode	Gender	Mutation (Domain)	Previous pneumonia	Previous cavities	CMC*	Antifungal prophylaxis	Age at episode (years)	Aspergillosis form	Reference
1-1	M	p.V463del (DNA-B)	Yes	Yes	Yes	No	10	Mixed form	1
2-1	F	p.V637M	Yes	Yes	ND	No	11	CCPA†	1
2-2		(SH2)				Itra.	14	CCPA	
3-1	F	p.R382Q (DNA-B)	Yes	Yes	No	Itra.	13	CCPA	1
3-2						Vori.	15	Aspergilloma	
4-1	F	p.R382W	Yes	Yes	No	No	10	CCPA	1
4-2		(DNA-B)				Itra.	20	ABPA‡-like	
5-1	M	p.V637M (SH2)	Yes	Yes	Yes	Itra.	28	CCPA	1
6-1	M	p.R382W (DNA-B)	Yes	Yes	No	No	12	ABPA-like	1
6-2						Itra.	13	ABPA-like	
6-3						Posa.	16	ABPA-like	
7-1	F	p.V637M (SH2)	Yes	Yes	No	Itra.	10	ABPA-like	1
7-2						Itra.	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	1
10-1	M	p.R382Q (DNA-B)	Yes	ND	Yes	No	33	Mixed Form	1
11-1	F	c.1282-89C>T (DNA-B)	Yes	No	Yes	No	26	CCPA	Boisson et al. in preparation
12-1	M	c.1282-89C>T	ND	ND	Yes	No	20	Aspergilloma	Boisson et al. in preparation
12-2		(DNA-B)	Yes			Vori.	22	CCPA	
12-3						Itra.	23	CCPA	
13-1	M	p.Y657C (SH2)	Yes	Yes	Yes	No	35	Aspergilloma	1

*CMC: mucocutaneous candidiasis, † CCPA: chronic cavitary pulmonary aspergillosis, ‡ABPA: allergic broncho-pulmonary aspergillosis, ND: not determinate, SH2: Src homology 2; DNA-B: DNA-binding domain, Itra.: itraconazole, Vori.: voriconazole, Posa.: posaconazole.

Table 2. 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 (years), median (IQR)	20 [15-21]	18 [13-23]	13(12-16)	21 [15-27]	16 [12-22]
Dyspnoea	2/3 (66)	1/8 (12)	3/5 (60)	2/2 (100)	8/18 (44)
Cough	2/3 (66)	4/8 (50)	3/5 (60)	2/2 (100)	11/18 (61)
Asthma	0/3	0/8	5/5 (100)	2/2 (100)	7/18 (39)
Haemoptysis	1/3 (33)	3/8 (37)	0/5	2/2 (100)	6/18 (33)
Brownish-black mucus plugs	0/3	0/8	3/5 (60)	2/2 (100)	5/18 (28)
Radiological findings					
Bronchiectasis	1/4 (25)	4/9 (44)	5/5 (100)	2/2 (100)	12/20 (60)
Mucoid impactions	0/4	1/9 (11)	4/5 (75)	0/2	5/20 (25)
Toothpaste or finger-in-glove	0/4	0/9	4/5 (75)	1/2 (50)	5/20 (25)
Micronodules	0/4	2/9 (22)	1/5 (25)	1/2 (50)	4/20 (20)
Cavitation(s)	4/4 (100)	9/9 (100)	5/5(100)	2/2 (100)	20/20 (100)
Prior cavity in infection territory	3/4 (75)	6/9 (66)	3/5 (75)	2/2 (100)	14/20 (70)
Cavity's wall thickness	0/4 (40)	8/9 (88)	1/5 (20)	2/2 (100)	11/20 (55)
Fungal balls	4/4 (100)	6/9 (67)	0/5	0/2	10/20 (50)
Pericavitary infiltrate	0/4	4/9 (44)	0/5	1/2 (50)	5/20 (25)
Consolidation	0/4	2/9 (22)	1/5 (20)	1/2(50)	4/20 (20)
Bilateral localization	0/4	1/9 (11)	3/5 (60)	1/2 (50)	5/20 (25)
Mycological results					
GM antigen serum (> 0.5)	0/3	2/6 (33)	0/3	0/2	2/14 (14)
GM antigen BAL (>1)	0/2	3/3 (100)	0/0	0/0	3/5(60)
Sputum, Direct Microscopy	0/0	0/1	0/2	0/0	0/3
Sputum, culture	0/0	1/1(100)	3/4 (66)	0/0	3/4(75)
A. fumigatus		1/1 (100)			
Aspergillus sp.			1/3 (33)		
A. fumigatus + *A. niger*			1/3 (33)		
A. fumigatus			1/3 (33)		
BAL, Direct Microscopy	0/4	3/5 (60)	1/3 (33)	0/2	4/14(28)
BAL, culture	3/4 (75)	6/7 (88)	2/3 (67)	1/2 (50)	12/16(75)
A. fumigatus	3/3 (100)	6/6 (100)	2/2 (100)	1/1 (100)	
Specific *Aspergillus* IgG*	2/3 (75)	7/7 (100)	4/4 (100)	2/2 (100)	15/16(94)
Total IgE	2/2 (100)	2/2 (100)	2/2(100)	2/2 (100)	8/8 (100)
Histology	1/1 (100)	4/4 (100)	0/0	0/0	5/5 (100)

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

**Aspergillus spp.* antibody (IgG) detection by immunodiffusion, counter immune-electrophoresis, particle-hemagglutination, indirect-immuno-fluorescence, radio-immunoassay, or ELISA

GM: galactomannan, BAL: broncho-alveolar lavage, CPA: chronic pulmonary aspergillosis, ABPA: allergic broncho-pulmonary aspergillosis

Table 3. Treatment and outcome according to the form of aspergillosis

	Aspergilloma n = 5	CCPA n = 9	ABPA-like n = 5	Mixed-form n = 2	Total n= 21
Treatment (1st line)					
AmB	-	2	2	-	4
Voriconazole	3	5	1	2	11
Median total Duration (months)	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	2/5	4/9	3/5	-	9/21
PR	1/5	4/9	2/5	-	7/21
CR	1/5	-	1/5	-	2/21
Failure	-	3/9	-	1/2	4/21
NA	3/5	2/9	2/5	1/2	8/21
M6					
Response	1/5	7/9	4/5	1/2	13/21
PR	-	5/9	3/5	1/2	9/21
CR	1/5	2/9	1/5	-	4/21
Failure	-	1/9	-	1/2	2/21
NA	4/5	1/9	1/5	-	6/21
M12					
Response	3/5	5/9	4/5	1/2	13/21
PR	2/5	2/9	3/5	1/2	8/21
CR	1/5	3/9	1/5	-	5/21
Failure	1/5	1/9	1/5	1/2 (death)	4/21
NA	1/5	3/9	-	-	4/21
Last news					
Response	4/5	6/9	5/5	1/2	16/21
PR	1/5	3/9	4/5	1/2	9/21
CR	3/5	3/9	1/5	-	7/19
Failure	1/5	3/9	-	1/2 (death)	5/21
NA	-	-	-	-	-

PR: partial response, CR: complete response, CCPA: chronic cavitary pulmonary aspergillosis, NA: not available
ABPA: allergic bronchopulmonary aspergillosis, AmB: Amphotericin B

Table 4. Diagnosis and therapeutic clues according to aspergillosis form in STAT3-deficient patients.

	Aspergilloma n=5	**CCPA n=9**	**ABPA-like n=5**	**Mixed form (CCPA+ABPA-like) n=2**
Age (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, Tooth paste or finger in glove Bilateral localization	Mix of CCPA + ABPA like radiological findings
Mycological	Sputum or BAL culture positive for Aspergillus Specific Aspergillus IgG	Sputum or BAL culture positive for Aspergillus Specific Aspergillus IgG GM Ag in BAL	Sputum or BAL culture positive for Aspergillus Specific Aspergillus IgG	Sputum or BAL culture positive for Aspergillus Specific Aspergillus IgG
Therapy	Any triazole active against *Aspergillus*	Any triazole active against *Aspergillus*	Itraconazole + /- corticosteroids	Any triazole active against *Aspergillus*
Median length of treatment (months)	16[12-21]	18 [12-36]	6 [6-7]	5.5 [5.2-5.7]

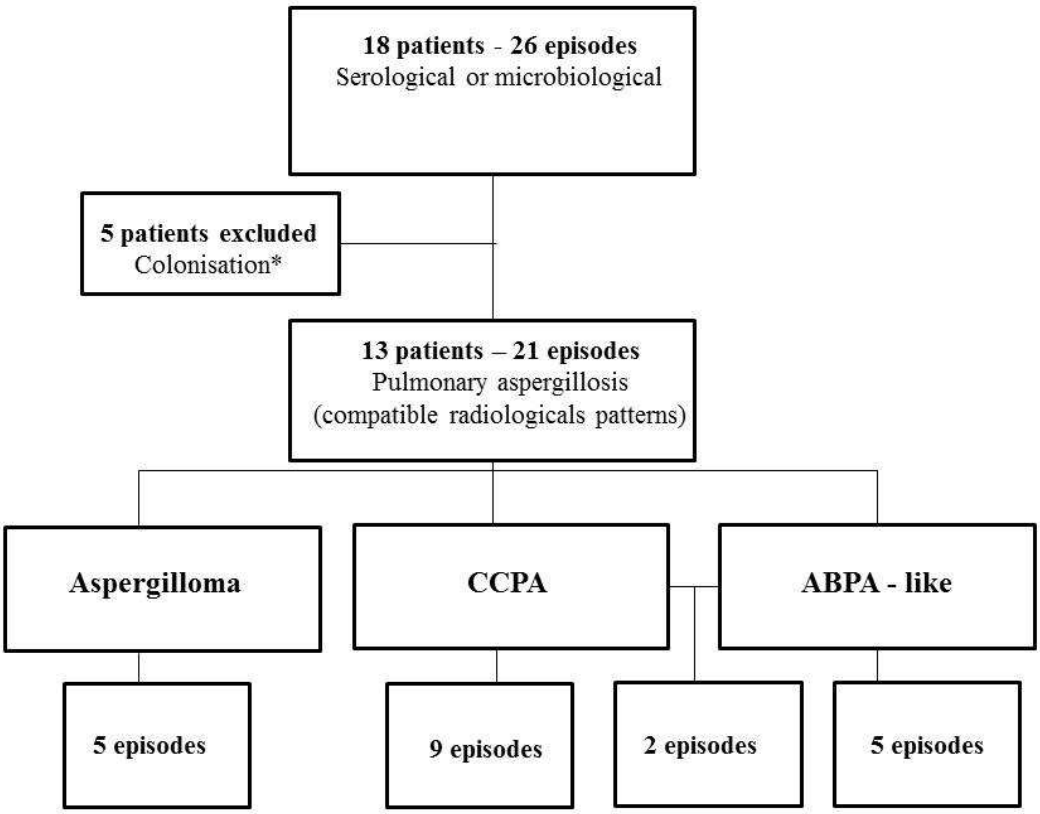
Figure 2: CT scans

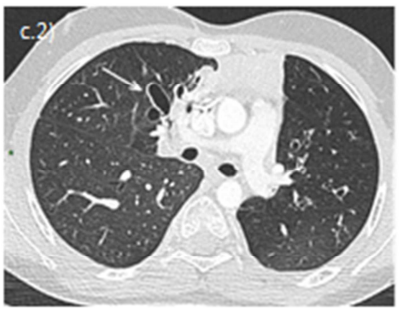
a) Aspergilloma (Patient 8, episode 1). Fungus ball inside a single small cavity.

b) Chronic cavitary pulmonary aspergillosis (Patient 7, episode 2). Large cavities of the upper left lobe containing mass-like fungus ball with cavity wall thickness and pericavitary infiltrate.

c.1) ABPA-like (Patient 6, episode 2).

c.2) Partial resolution after one month of therapy, showing the disappearance of several impactions and air trapping.
c.3) Same patient with high attenuation mucoid impaction in the right upper lobe.
d) Mixed Form (Patient 1, episode 1). Mucoid impaction with "finger-in-glove" aspect in the right middle lobe. Air trapping is seen in the lower right lobe.


18 patients - 26 episodes
Serological or microbiological
5 patients excluded
Colonisation*
13 patients – 21 episodes
Pulmonary aspergillosis
(compatible radiologicals patterns)
Aspergilloma
CCPA
ABPA - like
5 episodes
9 episodes
2 episodes
5 episodes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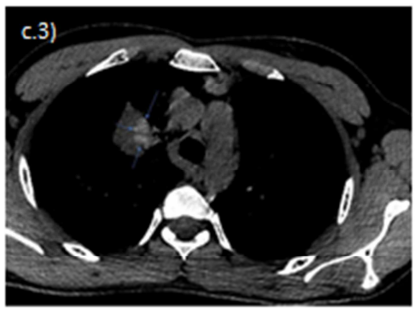
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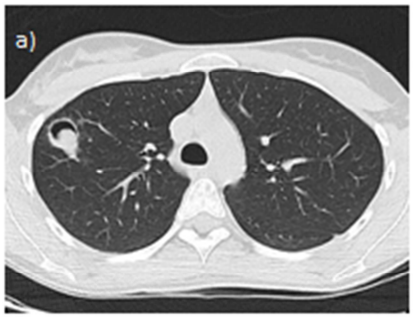
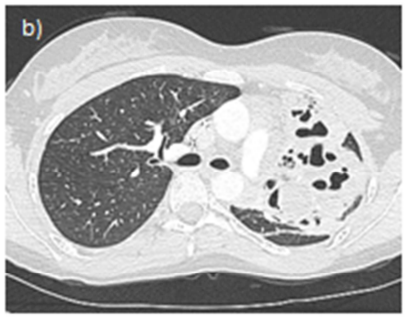

a)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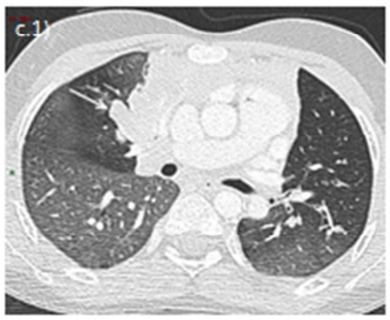
c.1)