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

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Author contributions:

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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1 **Abstract**

2 **Background:**

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

7 **Objective:**

8 We aimed to assess the prevalence and describe the clinical, mycological, and radiological
9 presentation and related therapy and outcome of *Aspergillus* infections of the respiratory tract
10 in the *STAT3* deficient patients of the National French cohort.

11 **Methods:**

12 We performed a retrospective study of all pulmonary aspergillosis cases in *STAT3* deficient
13 patients (n=74). Clinical and mycological data were collected up to October 2015 and
14 imaging was centralized.

15 **Main results:**

16 Twenty-one episodes of pulmonary aspergillosis in 13 (17.5%) *STAT3*deficient patients were
17 identified. The median age at first episode was 13 years (IQR 10-26). Ninety percent of
18 patients had previous bronchiectasis or cavitations. Infections were classified as follows: five
19 single aspergilloma, nine chronic cavity pulmonary aspergillosis (CCPA), five allergic
20 broncho-pulmonary aspergillosis-like disease (ABPA-like), and two mixed forms of
21 concomitant ABPA-like and CCPA. No invasive aspergillosis cases were identified.
22 *Aspergillus sp.* were isolated in 71% of episodes and anti-*Aspergillus* antibodies in 93%.
23 Eleven episodes were breakthrough infections. Antifungal treatment was prolonged with a
24 median of 13 months and six patients (seven episodes) required surgery with a high rate of
25 post-surgical complications. One patient died and six relapsed.

26 Conclusion:

27 Chronic and allergic forms of aspergillosis occurred in 17.5% of STAT3 deficient patients,
28 mostly in lung cavities. Almost half had recurrences, despite prolonged antifungal treatment
29 and/or surgery.

30

31

32 **Highlights box**

33 1. What is already known about this topic?

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

37 2. What does this article add to our knowledge?

38 Here, we report the first nationwide series of aspergillosis in STAT3 deficient patients with a
39 prevalence of 17.5%. We describe two forms: chronic aspergillosis, including chronic
40 cavitary pulmonary aspergillosis and aspergilloma, and allergic aspergillosis with overlapping
41 forms.

42 3. How does this study impact current management guidelines?

43 This study provides a precise overview of the pulmonary aspergillosis spectrum in STAT3
44 deficient patients, highlighting poorly reported allergic forms with clues for the clinician
45 concerning radiological presentation, diagnostic tools, medical and surgical treatment, and
46 outcome.

47

48

49

50 **Key words**

51 aspergillosis, STAT3 deficient patient, allergic broncho-pulmonary aspergillosis, cavitary

52 chronic pulmonary aspergillosis, aspergilloma

53 *Abbreviations:*

54

ABPA	allergic bronchopulmonary aspergillosis
AD-HIES	autosomal dominant hyper-IgE syndromes
BAL	bronchoalveolar lavage
CEREDIH	Centre de Référence des Déficits Immunitaires Héritaires
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

55

56

57

58 **Introduction**

59 STAT3 (Signal Transducer and Activator of Transcription 3) deficiency is the main
60 aetiology of autosomal dominant hyper-IgE syndromes (AD-HIES), which is responsible for a
61 primary immunodeficiency with elevated IgE levels, hyper-eosinophilia, memory-B cell
62 lymphopenia, and a low proportion of IL-17-producing Th17 cells. It also affects the
63 connective tissue, skeletal system, vasculature, and dentition¹. Ninety per cent of patients
64 develop bacterial pneumonia complicated with frequent (67%) pulmonary sequelae, such as
65 bronchiectasis or pneumatoceles¹. Chronic mucocutaneous candidiasis (CMC) of various
66 mucosal sites and nails is observed in 85% of patients¹.

67 STAT3 deficiency has been previously shown to predispose patients to aspergillosis^{1,2}.
68 Here, we report *Aspergillus*-related colonisation or infection in 22% of STAT3 deficient
69 patients (n = 13) in the first global analysis of the national French cohort. Both frequent
70 pneumatoceles and STAT3 related immunodeficiency could be responsible for susceptibility
71 to lung aspergillosis. The diagnosis, classification, and treatment of aspergillosis in STAT3
72 deficient patients are challenging and clinical, radiological, and mycological descriptions of
73 aspergillosis are lacking for these patients, as well as the role of antifungal treatment and
74 surgery in their management. This study of the STAT3 deficiency French cohort allowed us
75 to describe the clinical, radiological, and mycological presentation of pulmonary aspergillosis
76 and its related therapy and outcome.

77

78 **Methods**

79 We performed a national retrospective study in France of all episodes of pulmonary
80 aspergillosis in STAT3 deficient patients. Seventy-four STAT3 deficient patients were
81 identified by the Study Centre for Primary Immunodeficiencies, (CEDI) at Necker Hospital
82 (CP) through the Centre de Référence des Déficits Immunitaires Hérititaires (CEREDIH)
83 (NM) based at Necker Enfants Malades Hospital, Paris, France. Physicians in charge of
84 patients were contacted to report microbiological and/or radiological evidence of pulmonary
85 aspergillosis.

86 Inclusion criteria were the association of (all criteria were required): (1) a new
87 radiological pattern compatible with pulmonary aspergillosis (chest CT scan or X Ray), (2)
88 serological (*Aspergillus spp.* IgG antibody detection by immunodiffusion, counter immune-
89 electrophoresis, particle-hemagglutination, indirect-immuno-fluorescence, radio-
90 immunoassay, or ELISA) or microbiological evidence of *Aspergillus sp.* (direct microscopy
91 or positive culture for *Aspergillus* in sputum, aspiration, or broncho-alveolar lavage (BAL)
92 fluid or galactomannan (GM) antigen in plasma, serum, BAL fluid), and (3) exclusion of
93 alternative diagnoses or histological evidence of pulmonary aspergillosis.

94 Demographic, clinical, radiological, and mycological data were collected in a standardized
95 case report form at diagnosis, months 3, 6, and 12, and the last follow-up. Medical records
96 and thoracic computed tomography (CT) were centralized. An evaluation committee,
97 including infectious disease physicians (FL, AD), respiratory medicine physicians (CT or
98 EC), and a radiologist (SP), reviewed the clinical, microbiological, and radiological data to
99 assess aspergillosis diagnoses, classify aspergillosis episodes, and evaluate treatment
100 responses.

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

102 allergic bronchopulmonary aspergillosis-like (ABPA-like), or invasive aspergillosis (IA).
103 Definition criteria of pulmonary aspergillosis were based on the most recent consensus:
104 European Organization for Research and Treatment of Cancer/Mycoses Study Group
105 (EORTC/MSG) consensus definitions for invasive aspergillosis³, European Society of
106 Clinical Microbiology and Infectious Disease/European Respiratory Society (ESCMID/ERS)
107 guidelines for Chronic pulmonary aspergillosis⁴, and classification criteria by *Patterson et al.*
108 for ABPA criteria⁵.

109 We had to adapt those criteria for the diagnosis of CCPA and ABPA, due to the specificities of
110 STAT3 deficiency. Modified criteria are presented in Supplementary material E1. Specific
111 *Aspergillus* IgE, total IgE levels, and total eosinophil counts are difficult to interpret in
112 STAT3 deficient patients. We thus designated APBA-like episodes as those with at least
113 asthma, positive *Aspergillus* serology (specific IgG), and consistent pulmonary opacities.
114 Episodes with concomitant ABPA-like and CCPA criteria were designated as mixed form.

115 We evaluated treatment responses by chest CT and/or bronchoscopy and/or clinical response,
116 when available, after 3, 6, and 12 months of treatment and at the last follow up. Standardized
117 radiological criteria were not available at the beginning of the study to assess treatment
118 response for CCPA. Thus, targets retained to assess radiological responses were: size of the
119 cavity(s), the number/size of fungus balls, pericavitary infiltrate and thickness of the cavity
120 wall for CCPA or aspergilloma and mosaic attenuation, centrolobular nodules, tree-in-bud
121 opacities, nodule(s), atelectasis, and mucoid impaction⁶ for ABPA. The radiological response
122 was defined as complete, partial, stable, or failure and the mycological response as eradication
123 (mycological evidence of eradication of *Aspergillus*), partial response (reduction of IgG
124 antibody level), or persistence (mycological evidence of persistence of *Aspergillus* in
125 samples). The clinical response was based on the assessment of cough, sputum production,

126 haemoptysis, and dyspnoea (with or without wheezing). The clinical response was defined as
127 complete, partial, or failure. The response was defined as complete, partial, or failure as
128 described in Supplementary material E2.

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

131

132 **Results**

133 Seventy-four STAT3 deficient patients were included in this study: 18 (24%) patients had at
134 least one type of laboratory evidence (serological (specific IgG), microbiological, or
135 histological) of aspergillosis. Examination of the radiological data showed five patients to
136 have no CT or X-ray evidence of pulmonary aspergillosis and they were excluded. Twenty-
137 one episodes of lung aspergillosis were reported in 13 patients (17.5%), with an average of
138 1.6 episodes per patient (Figure 1).

139 Characteristics of the 13 patients from 12 kindred are summarized in Table 1. All patients had
140 a heterozygous loss-of-function mutation in the *STAT3* gene: eight in the DNA-binding
141 domain, four in the SH2 domain, and one in the linker domain. Seven patients were male and
142 six were female. The median age at the first episode of lung aspergillosis was 13 years [IQR:
143 10-26]. Three patients were on antifungal prophylaxis at the first episode (table 1). Previous
144 bacterial pneumonia was reported for all patients (n =11) for whom information was
145 available. Nine patients (9/10 with prior radiological data available) had CT evidence of prior
146 lung cavities (bronchiectasis in eight and pneumatoceles in one). Seven (54%) patients had a
147 history of chronic mucocutaneous candidiasis (CMC) at various mucosal sites and on their
148 nails. According to clinical, radiological, mycological, and histological data, we classified
149 episodes as aspergilloma (n = 5), chronic cavitary pulmonary aspergillosis (n = 9), ABPA-like

150 episodes (n = 5), and mixed forms (n = 2) (Figure 1). The characteristics of the 21 episodes of
151 pulmonary aspergillosis are described in table 2. One 11-year-old patient (7.7%) died.

152

153 **Aspergilloma**

154 Five episodes in five patients were classified as pulmonary aspergilloma and occurred as the
155 first lung aspergillosis episode in four patients. One patient was on antifungal prophylaxis at
156 diagnosis (Table 2). The median age was 20 years [15-21]. Dyspnoea and cough were
157 reported in two cases and haemoptysis in one (Table 3). CT data was not available for one
158 patient but aspergilloma was diagnosed based on histology. Prior lung cavities and fungus
159 balls were present at diagnosis in all patients (Table 3, Figure 2). Serum and BAL fluid were
160 negative for GM antigen. Cultures of sputum, endotracheal aspirations, or BAL fluid were
161 positive for *Aspergillus fumigatus* in three episodes and *Aspergillus* IgG serology was positive
162 in two episodes (Table 2, Supplementary material E3.1). Three patients received voriconazole
163 as the first-line treatment. The median duration of antifungal treatment was 16 months [12-
164 21]. Two patients underwent surgery: lobectomy in one case and wedge resection with
165 pleurectomy in another case complicated by pneumothorax. At one year, a partial response
166 (PR) was reported in two patients, complete response (CR) in one, failure in one, and data
167 was not available for one. One patient developed CCPA 30 months after surgery with
168 complications (involving pleura) that was localized to the same territory as the aspergilloma.

169

170 **CCPA**

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

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

183 The first-line antifungal treatment was voriconazole in five episodes and liposomal
184 amphotericin B in two. The median duration of treatment was 16 months [10-26]. Surgical
185 resections were performed in five episodes for four patients: three cases of emergency surgery
186 (severe haemoptysis (n = 2) and rapid progression (n = 1)) and two cases of planned surgery
187 after failure of medical treatment. The procedure included lobectomy (n = 3), segmentectomy
188 (n = 1), and pleurectomy (n = 1). Pneumothorax occurred in two patients after surgery. In one
189 case, recurrent pneumothorax homolateral to surgery required pleuroscopy and pleurodesis. In
190 the other case, purulent pneumothorax required drainage. In both cases, drainage was
191 prolonged (one and two months) and the local evolution was unfavourable, with relapse (after
192 surgery) or persistence of lung aspergillosis.

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

199

200 **ABPA-like**

201 Five episodes in three patients were classified as ABPA-like. It was the first pulmonary
202 aspergillosis episode in two patients. Four episodes were breakthrough infections (Table 1).
203 The median age was 13 years [12-16]. The three patients had a history of asthma. Dyspnoea,
204 cough, and brownish-black mucus plugs were reported in three episodes. CT showed
205 bronchiectasis and mucoid impactions in all five episodes and tooth-paste/finger-in-glove
206 opacities in four. When performed, serum, BAL fluid, or endotracheal aspiration were
207 negative for GM antigen; cultures of sputum, endotracheal aspiration, or BAL fluid were
208 positive for *Aspergillus fumigatus* in three episodes and serology (IgG) was positive for all
209 tested episodes (Table 2). Hypereosinophilia was present in four episodes. Patients were
210 positive for specific anti-*Aspergillus* IgE whenever tested (Supplementary material E3.2).
211 First-line treatment was voriconazole in one case and liposomal amphotericin B in two. One
212 patient was hospitalized in an intensive care unit (ICU) for spastic respiratory distress. The
213 median duration of antifungal treatment was six months [6-7]. At one year, PR was reported
214 in three cases, CR in one, and failure in one. The evolution of ABPA-like was favourable,
215 with 100% GR at the last follow-up. Relapses were observed in two patients: two ABPA-like
216 episodes in the same patient and one CCPA episode.

217

218 **Mixed- form**

219 Two episodes were classified as mixed-form, as patients had criteria for ABPA-like and
220 CCPA. It was the first and single episode in both cases. No patient was on antifungal
221 prophylaxis at diagnosis. The median age was 21 years [15-27] (Table 1). Cough, dyspnoea,
222 and haemoptysis were present in both cases at diagnosis. Both patients had a history of
223 asthma and presented brownish-black mucus plugs at diagnosis. Cavitations with wall

224 thickness were described in both cases. Radiological opacities consistent with ABPA were a
225 consolidation in one case and toothpaste/finger-in-glove opacities in the second (Table 2,
226 Figure 2). *Aspergillus* serology (IgG) was positive in both cases and the culture of BAL fluid
227 was positive in one. Both patients were treated with voriconazole for a median of 5.5 months
228 [5.2-5.7]. One patient (11 years old) was hospitalized in the ICU with spastic respiratory
229 distress and died from massive haemoptysis after multiple drainage three months after
230 diagnosis. The other patient had PR at the last evaluation, without other episodes of
231 aspergillosis.

232

233 **Discussion**

234 This study describes the prevalence, presentation, and outcome of pulmonary aspergillosis
235 in the French cohort of 74 STAT3-deficient patients. We report a prevalence of 17.5% for
236 lung aspergillosis, with two different clinical entities: chronic aspergillosis (n = 14), including
237 CCPA and aspergilloma, and allergic aspergillosis (n = 5) with overlapping forms (n = 2).

238 Antifungal treatment was long, with a median of 13 months, and six patients had surgery with
239 high rate post-surgery complications.

240 One of 13 patients died of pulmonary aspergillosis. Vinh *et al.* of the National Institute of
241 Allergic and Infectious Disease (NIAID) described a cohort of 64 AD-HIES patients in 2010
242 with a prevalence of aspergillosis of 25%. They reported that mould infections were
243 diagnosed in the fourth decade of life, whereas the median age at first episode of pulmonary
244 aspergillosis in our series was 13 years [IQR:10-26]. The mortality rate was also different as
245 we report a mortality rate of 7.7% due to lung aspergillosis *versus* 17% mould infection
246 mortality in the American cohort². This difference may be explained by the difference in
247 median age of the two cohorts and the absence of an invasive form. In a necropsy study of six

248 AD-HIES patients, the first case of *Aspergillus* pneumonia was reported 17 years after the
249 first case of bacterial pneumonia and the mean age at diagnosis was 27 years⁷.

250 In contrast, we do not report here any invasive aspergillosis, based on the EORTC/MSG 2008
251 criteria. This is a major difference relative to previously reported data; Vinh *et al.* reported 20
252 episodes of invasive mycosis, including 16 of aspergillosis. Infections were classified as
253 invasive based on radiological findings as consolidation without a halo sign and the authors
254 reported five patients with disseminated disease². Furthermore, a necropsy study described
255 three cases of aspergillosis with angio-invasion, one with dissemination (pulmonary and
256 cerebral mycotic aneurysm) and two with local pulmonary vascular invasion in HIES patients
257 (diagnosis by scoring, not genetically proven)⁷. These infections were all associated with
258 cavitory lung disease. Our study is the first to use centralized medical records, mycological,
259 and radiological data. Differences between lung aspergillosis classifications may be due, in
260 part, to multidisciplinary reviewing, including both by lung physicians and radiologists. Ten
261 patients developed at least one episode of CCPA or aspergilloma. Pre-existing cavitations
262 were present in all but one case, and in the same area in 69%. In a recent review, Freeman *et*
263 *al.* reported that mold infections occur in areas of pre-existing cavities (pneumatoceles or
264 bronchiectasis), leading to chronic infection without clinic-radiological description⁸. Lung
265 cavities appear to be one of the necessary underlying conditions for the development of lung
266 aspergillosis in STAT3 deficient patients, as for sarcoidosis (the burden of CPA complicating
267 sarcoidosis has been estimated to be 3 to 12% of cases⁹) and sequelae of tuberculosis (authors
268 have established the global incidence of CCPA to be 21% in residual cavitations after
269 tuberculosis). In a recent study of 127 patients with CPA (including simple aspergilloma); the
270 median age was 58 years and the underlying conditions were COPD, tuberculosis sequelae,
271 and corticosteroid use¹⁰. These patients were more symptomatic than STAT3 deficient
272 patients, but the radiological presentation was similar. In our study, the *Aspergillus*-specific

273 IgG antibody assay was positive in 84% of cases. The combination of a chest CT scan with
274 the performance of an *Aspergillus* specific IgG antibody assay are key diagnostic features for
275 establishing the diagnosis of CPA, including in STAT3 deficient patients. In this retrospective
276 study, IgE and IgG specific *Aspergillus* were measured with different serological tests with
277 different cut off depending of the laboratory. We reported those results in the table E3.1 and
278 E3.2 (supplementary material). A prospective evaluation of these tests will be necessary both
279 for diagnosis and follow up of *Aspergillus* disease in STAT 3 deficient patients

280 The median duration of treatment was long: 18 months for CCPA and 16 for aspergilloma,
281 whereas itraconazole or voriconazole are recommended for a minimal duration of four to six
282 months in CCPA⁴. Partial antifungal efficacy for aspergilloma and CCPA are associated with
283 their weak diffusion in cavities. Half of the episodes were treated with surgery and were
284 associated with a complete response in 71% of cases, but relapse was observed in 60% with a
285 median of three years. Surgery was associated with complications in 28% of CCPA and 50%
286 of aspergilloma, with pneumothorax in all cases, prolonged bronchopleural fistulae, and
287 homolateral recurrence. Post-pulmonary surgery complications in AD-HIES have previously
288 been reported to occur in more than 50%¹¹. This may be due to abnormal tissue remodelling
289 in STAT3 deficiency¹². However, complications are also frequent in non STAT3 deficient
290 patients, as a recent surgery series of CPA¹³ reported prolonged air leak in 33% of cases,
291 empyema in 20%, and recurrence in 26%¹³. There is no consensus concerning the role of
292 surgery in the management of CCPA or aspergilloma. Surgery for pulmonary aspergillosis is
293 often challenging but offers the chance of a permanent cure, particularly for aspergilloma, but
294 recurrences are not rare. Given the young age of STAT3 deficient patients at the time of the
295 surgical procedure, the high rate of complications, and the frequency of recurrence, it is
296 crucial to discuss surgery and drainage indications for emergencies or failure of medical
297 treatment. Medical treatment should be favoured, but prolonged, and requires good

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

300 We report five ABPA-like episodes. These patients present features of allergic broncho-
301 pulmonary disease with bronchiectasis, toothpaste or finger-in-glove characteristic imaging
302 on CT in most cases, associated with positive sputum cultures for *Aspergillus fumigatus* or
303 specific IgG antibodies and a history of treated or untreated asthma^{11,14}. Allergic aspergillosis
304 in STAT3 deficiency patients is poorly described^{8,14}. Eppinger *et al.* reported sensitization to
305 *Aspergillus* in two patients with hyper-IgE syndrome by the presence of precipitating A.
306 *fumigatus* antibodies associated with bronchiectasis and a history of asthma in one case,
307 assuming an overlap between ABPA and HIE. In a recent review, Freeman *et al.* reported a
308 case of a 15-year-old with AD-HIES who presented a CT scan with the plugging
309 characteristic of ABPA associated with a sputum culture positive for *Aspergillus fumigatus*
310 and compatible clinical features⁸. In our experience, asthma can be difficult to manage, with
311 two patients hospitalized in the ICU for spastic respiratory distress. The diagnosis of ABPA-
312 like in STAT3 deficiency is challenging due to high concentrations of total serum IgE (> 1000
313 UI/L), an obligatory criterion for ABPA, and hyper-eosinophilia (> 500/mm³), a minor
314 criterion, which are both characteristics of STAT3 deficiency. STAT3 deficient patients were
315 tested for specific anti-*Aspergillus* IgE. They were found to be weakly positive in four
316 patients without any history of *Aspergillus* colonisation or asthma. Therefore, in our study
317 none of these exams can be used as diagnostic criteria in STAT3 deficient patients. In ABPA,
318 bronchiectasis is present in 73 to 95% of patients and was found in 100% of our STAT3
319 deficient patients in association with toothpaste or finger-in-glove radiological patterns.
320 Improvement of ABPA-like diagnosis will require *Aspergillus*-specific IgG antibodies follow
321 up with careful CT examination by an experienced radiologist. These patients require regular
322 pulmonological follow-up with respiratory functional tests. Furthermore, endoscopic

323 examination, when performed, showed characteristics of ABPA disease, with brownish-black
324 mucus. This exam appears to be useful in helping clinicians diagnose ABPA in STAT3
325 deficient patients.

326 Relapses were observed in three of five (60%) patients and the response was 60% at three
327 months in our cohort *versus* 100% at six weeks in an Indian cohort of ABPA patients.

328 Allergic forms of aspergillosis in STAT3 deficiency represent a major management dilemma
329 because corticosteroids, cornerstone of ABPA treatment, may accelerate pulmonary damage,
330 invasive fungal infections, and bone fracture, particularly in these patients with underlying
331 immune deficiency and osteopenia. That's why we used only antifungal therapy for treatment
332 of those patients. On the other hand, prolonged antifungal therapy could induce resistance and
333 result in toxicity. The efficacy and safety of corticosteroids and alternative treatments such as
334 monoclonal anti IgE, anti IL4 receptor, anti IL5, and anti IL5 receptor α antibodies, or
335 antifungal nebulisation (liposomal amphotericin B, itraconazole)¹⁶ need to be evaluated.

336 STAT3 plays a critical role in the maintenance of surfactant homeostasis and lung function
337 during oxygen injury. In STAT3 deficient patients, structural lung disease is associated with
338 an immunological defect including the impairment of Th17 differentiation. Indeed, data
339 suggest that respiratory epithelia (with cutaneous epithelia) are mostly dependent on
340 cytokines of the Th17 pathway (IL-22), in particular for the synthesis of antimicrobial
341 peptides and PMN chemotaxis¹⁷. Both the persistence of cavities and innate and adaptive
342 anti-fungal immunity defects are probably responsible for the non-effective clearance and
343 persistence of *Aspergillus sp.* in the airways of STAT3 deficiency patients. In contrast to
344 chronic granulomatous disease, preserved efficient polymorphonuclear killing of *Aspergillus*
345 has been demonstrated in STAT3 deficiency².

346 ABPA is a hypersensitivity reaction to *Aspergillus sp.* and results from an altered host
347 response to colonization of the bronchial mucus by *Aspergillus* with an exaggerated Th2
348 response and eosinophilic inflammation¹⁸. In ABPA, it is hypothesized that defects in innate
349 and adaptive immunity cause the persistence of *Aspergillus fumigatus* and are associated with
350 genetic defects, which have been documented in ABPA, complicating cystic fibrosis⁹. The
351 mechanism leading to ABPA in STAT3-deficient patients is unknown. The colonization of
352 cavities associated with a defect in the IL-10 response, an anti-inflammatory cytokine, may be
353 involved in this exaggerated immune response¹⁹. Dysregulation of the Th17 response may
354 also be involved, as the suppression of STAT3 in a multi-allergen mouse model inhibited
355 airway inflammation²⁰. Both IL-17A and IL-17F cytokines activate innate epithelial immune
356 responses and make different contributions to allergic responses and protection against
357 infection²¹.

358 STAT3 deficiency is due to different types of mutations but we were unable to find any
359 correlation between specific mutations and the form of aspergillosis. Lung aspergillosis in
360 STAT3 deficiency is challenging to manage, as it is necessary to avoid resistance to
361 antifungal treatment while preserving lung function. We report in the table 4 relevant
362 diagnosis clues (clinical, radiological and mycological) and our first-line treatment
363 recommendations based on this retrospective study. However, complementary studies are
364 needed. Antifungal prophylaxis is necessary in STAT3 deficiency with lung abnormalities,
365 despite the frequency of breakthrough aspergillosis. Collaboration between pneumologists
366 and infectious disease clinicians is needed to improve the diagnosis and treatment of these
367 *Aspergillus* related diseases.

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

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

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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 (SH2)	Yes	Yes	ND	No	11	CCPA†	1
2-2						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 (DNA-B)	Yes	Yes	No	No	10	CCPA	1
4-2						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 (DNA-B)	ND	ND	Yes	No	20	Aspergilloma	Boisson et al. in preparation
12-2			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)
<i>A. fumigatus</i>		1/1 (100)			
<i>Aspergillus sp.</i>			1/3 (33)		
<i>A. fumigatus</i> + <i>A. niger</i>			1/3 (33)		
<i>A. fumigatus</i>			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)
<i>A. fumigatus</i>	3/3 (100)	6/6 (100)	2/2 (100)	1/1 (100)	
Specific <i>Aspergillus</i> 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 <i>Aspergillus</i> Specific <i>Aspergillus</i> IgG	Sputum or BAL culture positive for <i>Aspergillus</i> Specific <i>Aspergillus</i> IgG GM Ag in BAL	Sputum or BAL culture positive for <i>Aspergillus</i> Specific <i>Aspergillus</i> IgG	Sputum or BAL culture positive for <i>Aspergillus</i> Specific <i>Aspergillus</i> IgG
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 (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 cavitory 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.



