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► **To cite this version:**

Amélie Duréault, Colas Tcherakian, Sylvain Poiree, Emilie Catherinot, François Danion, et al.. Spectrum of Pulmonary Aspergillosis in Hyper-IgE Syndrome with Autosomal-Dominant STAT3 Deficiency. *Journal of Allergy and Clinical Immunology: In Practice*, 2019, 7, pp.1986 - 1995.e3. 10.1016/j.jaip.2019.02.041 . hal-03487994

**HAL Id: hal-03487994**

**<https://hal.science/hal-03487994v1>**

Submitted on 20 Dec 2021

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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.

### *Sources of funding:* none

Dr. Duréault and Dr Danion reports personal fees from Gilead, outside the submitted work.

Dr. Catherinot reports personal fees from LVL, CSL Behring, and LFB, outside the submitted work. Pr. Lortholary reports grants from Gilead science, personal fees from Pfizer, Novartis, Astellas, Gilead Sciences, and Merck, outside the submitted work. Pr. Lanternier reports personal fees from Gilead and Basilea, outside the submitted work. Pr. Sendid received travel grants from Pfizer and MSD, consulting fees from MSD, and research grants from bioMérieux and Lesaffre International, outside the submitted work. Pr. Pison reports personal fees from GSK, Novartis, Boehringer Ingelheim, and Astra Zeneca France, outside the submitted work. Dr. Castelle reports personal fees from Jazz Pharmaceutical, outside the submitted work. Dr. Deschildre reports personal consultancy and lecture fees from Novartis, ALK, TEVA, GSK, Stallergenes Greer, Aimmune, Zambon, CHIESI, Astra Zeneca, and DBV technologies, outside the submitted work. Dr Bervar reports personal fees from Pfizer and Novartis, outside the submitted work.

Dr Tcherakian, Dr Poiree, Dr Jouvion, Dr Bougnoux, Dr Mahlaoui, Dr Givel, Pr Picard, Dr Chansdesris, Dr. Coignard, Dr Amazzough, Pr Suarez, Pr Blanche, Dr Cornu, Dr Wemeau, Pr Fieschi, Pr A. Alanio, Dr Menetrey, Dr Senechal, Pr Ader, Pr Tattevin, Dr Grandiere-Perez , Dr Garcia-Hermoso, Pr F. Botterel - Chartier have no conflict of interest to disclose.

*Summary word count: 252*

*Total word count: 3707*

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 dentition<sup>1</sup>. Ninety per cent of patients  
64 develop bacterial pneumonia complicated with frequent (67%) pulmonary sequelae, such as  
65 bronchiectasis or pneumatoceles<sup>1</sup>. Chronic mucocutaneous candidiasis (CMC) of various  
66 mucosal sites and nails is observed in 85% of patients<sup>1</sup>.

67 STAT3 deficiency has been previously shown to predispose patients to aspergillosis<sup>1,2</sup>.  
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 Héritaires (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 aspergillosis<sup>3</sup>, European Society of  
106 Clinical Microbiology and Infectious Disease/European Respiratory Society (ESCMID/ERS)  
107 guidelines for Chronic pulmonary aspergillosis<sup>4</sup>, and classification criteria by *Patterson et al.*  
108 for ABPA criteria<sup>5</sup>.

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 impaction<sup>6</sup> 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 cohort<sup>2</sup>. 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 years<sup>7</sup>.

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 disease<sup>2</sup>. 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)<sup>7</sup>. 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 description<sup>8</sup>. 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 cases<sup>9</sup>) 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 use<sup>10</sup>. 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 CCPA<sup>4</sup>. 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%<sup>11</sup>. This may be due to abnormal tissue remodelling  
289 in STAT3 deficiency<sup>12</sup>. However, complications are also frequent in non STAT3 deficient  
290 patients, as a recent surgery series of CPA<sup>13</sup> reported prolonged air leak in 33% of cases,  
291 empyema in 20%, and recurrence in 26%<sup>13</sup>. 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<sup>11,14</sup>. Allergic aspergillosis  
304 in STAT3 deficiency patients is poorly described<sup>8,14</sup>. 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 features<sup>8</sup>. 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/mm<sup>3</sup>), 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  $\alpha$  antibodies, or  
335 antifungal nebulisation (liposomal amphotericin B, itraconazole)<sup>16</sup> 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 chemotaxis<sup>17</sup>. 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 deficiency<sup>2</sup>.

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 inflammation<sup>18</sup>. 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 fibrosis<sup>9</sup>. 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 response<sup>19</sup>. Dysregulation of the Th17 response may  
354 also be involved, as the suppression of STAT3 in a multi-allergen mouse model inhibited  
355 airway inflammation<sup>20</sup>. Both IL-17A and IL-17F cytokines activate innate epithelial immune  
356 responses and make different contributions to allergic responses and protection against  
357 infection<sup>21</sup>.

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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369 **Acknowledgment:** C. Godet (Poitiers).

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**References:**

1. Chandesris M-O, Melki I, Natividad A, Puel A, Fieschi C, Yun L, et al. Autosomal Dominant STAT3 Deficiency and Hyper-IgE Syndrome: Molecular, Cellular, and Clinical Features From a French National Survey. *Medicine (Baltimore)*. 2012 Jul;91(4):e1–19.
2. Vinh DC, Sugui JA, Hsu AP, Freeman AF, Holland SM. Invasive fungal disease in autosomal-dominant hyper-IgE syndrome. *J Allergy Clin Immunol*. 2010 Jun;125(6):1389–90.
3. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008 Jun 15;46(12):1813–21.
4. Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S, et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. *Eur Respir J*. 2016 Jan;47(1):45–68.
5. Patterson R, Greenberger PA, Halwig JM, Liotta JL, Roberts M. Allergic bronchopulmonary aspergillosis. Natural history and classification of early disease by serologic and roentgenographic studies. *Arch Intern Med*. 1986 May;146(5):916–8.
6. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy*. 2013 Aug;43(8):850–73.
7. Freeman AF, Kleiner DE, Nadiminti H, Davis J, Quezado M, Anderson V, et al. Causes of death in hyper-IgE syndrome. *J Allergy Clin Immunol*. 2007 May;119(5):1234–40.
8. Freeman AF, Olivier KN. Hyper-IgE Syndromes and the Lung. *Clin Chest Med*. 2016 Sep;37(3):557–67.
9. Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis complicating sarcoidosis. *Eur Respir J*. 2013 Mar 1;41(3):621–6.
10. Godet C, Laurent F, Béraud G, Toper C, Camara B, Philippe B, et al. Phenotyping chronic pulmonary aspergillosis by cluster analysis. *Eur Respir J*. 2015 Nov 1;46(5):1509–12.
11. Freeman AF, Renner ED, Henderson C, Langenbeck A, Olivier KN, Hsu AP, et al. Lung parenchyma surgery in autosomal dominant hyper-IgE syndrome. *J Clin Immunol*. 2013 Jul;33(5):896–902.
12. Sekhsaria V, Dodd LE, Hsu AP, Heimall JR, Freeman AF, Ding L, et al. Plasma metalloproteinase levels are dysregulated in signal transducer and activator of transcription 3 mutated hyper-IgE syndrome. *J Allergy Clin Immunol*. 2011 Nov;128(5):1124–7.
13. Farid S, Mohamed S, Devbhandari M, Kneale M, Richardson M, Soon SY, et al. Results of surgery for chronic pulmonary Aspergillosis, optimal antifungal therapy and proposed high risk factors for recurrence - a National Centre's experience. *J Cardiothorac Surg*. 2013 Aug 5;8:180.
14. Eppinger TM, Greenberger PA, White DA, Brown AE, Cunningham-Rundles C. Sensitization to *Aspergillus* species in the congenital neutrophil disorders chronic granulomatous disease and hyper-IgE syndrome. *J Allergy Clin Immunol*. 1999 Dec;104(6):1265–72.
15. Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in north India. *Chest*. 2006 Aug;130(2):442–8.
16. Godet C, Meurice J-C, Roblot F, Kauffmann-Lacroix C, Verdaguer M, Frat J-P, et al.

420 Efficacy of nebulised liposomal amphotericin B in the attack and maintenance treatment of  
421 ABPA. *Eur Respir J*. 2012 May 1;39(5):1261–3.

422 17. Minegishi Y, Saito M, Nagasawa M, Takada H, Hara T, Tsuchiya S, et al. Molecular  
423 explanation for the contradiction between systemic Th17 defect and localized bacterial  
424 infection in hyper-IgE syndrome. *J Exp Med*. 2009 Jun 8;206(6):1291–301.

425 18. Becker KL, Gresnigt MS, Smeekens SP, Jacobs CW, Magis-Escurra C, Jaeger M, et  
426 al. Pattern recognition pathways leading to a Th2 cytokine bias in allergic bronchopulmonary  
427 aspergillosis patients. *Clin Exp Allergy J Br Soc Allergy Clin Immunol*. 2015 Feb;45(2):423–  
428 37.

429 19. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-  
430 negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome.  
431 *Nature*. 2007 Aug 30;448(7157):1058–62.

432 20. Yuan S, Cao S, Jiang R, Liu R, Bai J, Hou Q. FLLL31, a derivative of curcumin,  
433 attenuates airway inflammation in a multi-allergen challenged mouse model. *Int*  
434 *Immunopharmacol*. 2014 Jul;21(1):128–36.

435 21. Ishigame H, Kakuta S, Nagai T, Kadoki M, Nambu A, Komiyama Y, et al.  
436 Differential Roles of Interleukin-17A and -17F in Host Defense against Mucoepithelial  
437 Bacterial Infection and Allergic Responses. *Immunity*. 2009 Jan;30(1):108–19.

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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	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
<b>Clinical presentation</b>					
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)
<b>Radiological findings</b>					
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)
<b>Mycological results</b>					
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**

	<b>Aspergilloma n = 5</b>	<b>CCPA n = 9</b>	<b>ABPA-like n = 5</b>	<b>Mixed-form n = 2</b>	<b>Total n= 21</b>
<b>Treatment (1<sup>st</sup> line)</b>					
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
<b>Outcome</b>					
<b>M3</b>					
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
<b>M6</b>					
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
<b>M12</b>					
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
<b>Last news</b>					
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.**

	<b>Aspergilloma n=5</b>	<b>CCPA n=9</b>	<b>ABPA-like n=5</b>	<b>Mixed form (CCPA+ABPA- like) n=2</b>
Age (median, IQR)	20 [15-21]	18 [13-23]	13 [12-16]	21 [15-27]
<b>Diagnosis</b>				
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.



