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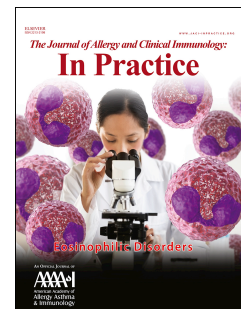
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***Aspergillus*-related diseases in a cohort of patients with severe asthma: a SANI
(Severe Asthma Network Italy) single center report.**

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28 **Clinical Implications statement:** *Aspergillus*-related diseases are frequent in severe asthma.
29 Allergists and pulmonologists involved in SA management should be aware of *Aspergillus*-related
30 disease, an underrecognized and potentially harmful disorder. Serological screening tests for
31 *Aspergillus fumigatus* should be routinely performed, together with HRCT, in asthmatic patients,
32 particularly in those with severe and/or difficult to treat asthma.

33

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56 **Key-words:**

57 *Aspergillus fumigatus*; ABPA; CPA; Bronchiectasis; Severe Asthma; *Aspergillus*-related disease;
58 SAFS.

59

60 *Aspergillus fumigatus* is a ubiquitous fungus growing in many environments including human body,
61 where it can be deposited throughout the lung. Normally, conidia are cleared by immune defenses,
62 although saprophytic noninvasive colonization often occurs in immunocompetent subjects. A
63 strong evidence links aspergillus exposure with severe asthma (SA), where defective clearance of
64 spores allows their germination into hyphae, that damage airways by producing proteases and
65 inducing inflammatory cytokines release [1]. Fungal colonization produces various clinical
66 manifestations [2] ranging from simple allergic *Aspergillus* sensitization (SAFS) to overt allergic
67 bronchopulmonary aspergillosis (ABPA). It is estimated that up to 25% of patients with difficult
68 asthma have *Aspergillus* sensitization and that 40% of them develop ABPA [2]. *Aspergillus* is also
69 implicated in the development of bronchiectasis, which is frequently found in SA [3].

70 We performed a retrospective observational study to evaluate the prevalence and clinical spectrum
71 of *Aspergillus*-related disorders in all the 74 adult immunocompetent patients included in the SANI
72 (Severe Asthma Network Italy) center of Turin, SA was diagnosed according to ERS/ATS criteria
73 [4].

74 All the patients released their informed consent, according to the SANI registry (“Area Vasta Nord-
75 Ovest Toscana”, Ethics Committee protocol number: 73714, study number 1245/2016).

76 Patients’ information, including demographics, comorbidities, spirometry, $F_{E}NO$ and asthma
77 medications were recorded as reported in Table e1. No patient was on anti-fungal therapy at the
78 time of data collection. Asthma exacerbations, expressed as number/year, were defined according to

the ATS/ERS statement [5]. The diagnostic criteria for *Aspergillus*-related conditions, that is SAFS, ABPA, chronic pulmonary aspergillosis (CPA) and bronchiectasis, are reported in Table e2.

All statistics were performed with SPSS Statistical Package software, V21 (SPSS, Chicago, Illinois, USA), using ANOVA test for parametric variables and Pearson's chi-square test for categorical ones. The results were considered statistically significant if p-value was <0.05.

Out of the 74 SA patients enrolled, 38 (51%, Group 1) had no *Aspergillus*-related disease, 6 (8%, Group 2) had SAFS, 4 (6%, Group 4) had CPA, 12 (16%, Group 5) had ABPA and 6 (8%, Group 6) had combined ABPA/CPA. The remaining 8 patients (11%, Group 3) had features that did not fit with any of the above groups, having only modest increase in total IgE, IgG-ASP and/or IgE-ASP inconsistent with ABPA, and having no HRCT sign of CPA; as they complained of chronic productive cough, reported heavy mold exposure and 6 of them had bronchiectasis, they were empirically classified as *Aspergillus*-bronchitis [7] (*Asp*-B (?), with question mark). The characteristics of the 6 groups are compared in Table 1.

Overall, 18 patients had ABPA, which in 12 was isolated and 6 it was combined with CPA.

CPA was diagnosed in 10 patients, in 4 as an isolated disease, and was characterized by markedly increased IgG-ASP. On HRCT, 3 patients had extensive cavitary disease, 6 had non-cavitary nodules with consolidations and 2 had extensive fibrotic destruction.

The 6 patients with combined ABPA/CPA had features of marked type 2 inflammation associated with chronic lung impairment; all had bronchiectasis and 5 needed chronic oral corticosteroid therapy.

The comparison between patients with and without *Aspergillus*-related disease, see Table 2, indicates that the coexistence of *Aspergillus*-related disease is associated with poorer outcomes in patients with severe asthma, including more severe airway obstruction, higher number of exacerbations, and higher prevalence of the observed bronchiectasis. Most bronchiectasis was in patients with ABPA, a fact not surprising since bronchiectasis is among the ABPA diagnostic criteria. We cannot know whether in CPA and *Asp*-B(?) associated with bronchiectasis, the fungus

had a pathogenetic role or it simply complicated preexisting bronchiectasis. Curiously, despite different clinical features, the prevalence and severity index of bronchiectasis [8] were quite similar in all the groups, including that without *Aspergillus*-related diseases.

In summary, we found high prevalence of *Aspergillus*-related diseases (40%) among our 74 SA patients, the most common being ABPA, which affected 18 (24%) of them. This is in agreement with the literature reporting that ABPA is the most frequent form of allergic bronchopulmonary mycosis [3]. Unfortunately, ABPA is often misdiagnosed or undiagnosed, and failure to treat it favors the development of bronchiectasis and the evolution towards permanent lung damage [3,4]. Retrieving clinical data of our 18 ABPA patients prior to entry into the SANI register, revealed that 8 of them were supposedly at their first episode, triggered by acute heavy mold exposure, 4 were probably on their second episode, while the remaining 6 patients had several documented ABPA episodes. These 6 patients are very intriguing as, besides relapsing ABPA with extremely high values of IgE, IgE-ASP, IgG-ASP, circulating eosinophils, severe airway obstruction and bronchiectasis, all also had CPA. This strongly supports the hypothesis that repeated episodes of ABPA led to the development of irreversible bronchopulmonary disease. Bronchiectasis itself, acting as a fungus reservoir, could have contributed to ABPA relapses, as well as chronic oral steroid therapy that could have impaired local *Aspergillus* phagocytosis by reducing the IL17A response [8].

The clinical picture of the four patients with CPA but no history of ABPA was distinctly different, being dominated by chronic interstitial and/or cavitary lung disease, with no feature of type 2 inflammation. All patients had increased IgG-ASP, which, at present, is considered to be the most reliable method for diagnosing CPA. CPA is the least common *Aspergillus*-related disease, and it is considered one of the most refractory pulmonary infectious diseases, with an estimated 5-year survival similar to that of idiopathic pulmonary fibrosis [3].

In conclusion, our findings indicate that in patients with SA, *Aspergillus*-related disease is a relevant negative prognostic factor and can promote the development of irreversible lung disease.

Allergists and pulmonologists involved in SA management should be aware of *Aspergillus*-related disease, an underrecognized and potentially harmful disorder. Serological screening tests for *Aspergillus fumigatus* are crucial for diagnosing *Aspergillus*-related disease and should be routinely performed, together with HRCT, in asthmatic patients, particularly in those with severe and/or difficult to treat asthma.

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1 TABLE E1

2 INFORMATION COLLECTED FROM ENROLLED PATIENTS.

3

Information collected	Data assessment and definition
Demographic data	Number of patients, Age, Sex
Smoking habits	Yes/no
Atopy	Defined as presence of at least one positive skin prick test, according to the EAACI consensus on allergy testing [Bousquet J et al. Allergy 2012;67:18-24].
Asthma control	Assessed through Asthma Control Test (ACT)
Asthma exacerbations (numbers/years)	Defined as unscheduled physician visit for acute or subacute asthma worsening of respiratory symptoms, associated with airflow obstruction, requiring changes or stepping-up of medications, need for oral corticosteroid or antibiotic, and/or hospitalization.
Mold exposure	Questionnaire based on four questions (score from 0 to 4) on the presence at home or in working place of: mold odor, visible mold, dampness damage, any mold or dampness indicator [Thacher JD, et al. Allergy 2017;72:967-974].
Lung function tests	Lung function test (Baires System, Biomedin, Padua, Italy) were performed according with Quanjer PH, et al. Eur Respir J Suppl 1993; 16: 5-40. Bronchodilator response was diagnosed according with Global Initiative for Asthma. GINA. Available at http://ginasthma.org/ .
F _E NO (NO electrochemical analyzer: Hypair, Medisoft, Sorinnes, Belgium).	Bronchial F _E NO was assessed according to the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations [Am J Respir Crit Care Med 2005; 171: 912-930].
Total IgE and Aspergillus fumigatus specific IgE (IgE-ASP)	ImmunoCap TM Phadia (Thermo Fisher Scientific, Uppsala, Sweden). Total IgE were considered increased if over 100 kUA/L. IgE-ASP were considered increased if over 0.35 kUA/L.
Aspergillus fumigatus specific IgG (IgG-ASP)	IgG-ASP were considered increased if over 12 U/ml. (DRG Instruments GMBH, Germany)
Chest radiologic examination	Chest X-rays were available in all the patients. High resolution chest CT scan (HRCT) was available in 67/74 patients (7 had normal chest X-rays and no clinical suspicion for aspergillosis or other lung diseases).

4

5 TABLE E2

6 DIAGNOSTIC CRITERIA FOR ASPERGILLUS-RELATED DISEASES

7

Aspergillus-related disorder	Diagnostic criterion
Severe asthma with Aspergillus sensitization (SAFS)	Positive IgE-ASP <i>Aspergillus fumigatus</i> specific IgE test (over 0.35 IU/mL), who did not meet the criteria for ABPA and had total serum IgE below <1000 IU/ml in the absence of any Aspergillus-related disease. [Agarwal R. Curr Allergy Asthma Rep 2011;11: 403-413. Agarwal R, et al. Clin Exp Allergy, 2013; 43: 850–873]
Allergic bronchopulmonary aspergillosis (ABPA)	Serum total IgE over 1000 IU/ml (in patients receiving oral corticosteroids, a documented historical IgE >1000 IU/mL) and elevated specific serum IgE to <i>A. fumigatus</i> (or positive skin prick test for <i>A. fumigatus</i>) plus at least two of the following supportive criteria: total circulating eosinophils count over 500 cells/ μ L (for patients receiving oral corticosteroids, a documented historical eosinophil count over 500 cells/uL within previous 12 months) and/or increased serum IgG antibodies to <i>Aspergillus fumigatus</i> , and/or documented HRCT findings consistent with ABPA (such as fleeting pulmonary parenchymal opacities, mucoid impaction, high-attenuation mucus, centrilobular nodular opacities, atelectasis, bronchiectasis, etc). [Agarwal R et al. Clin Exp Allergy, 2013; 43: 850–873].
Chronic pulmonary aspergillosis (CPA)	Presence of symptoms (sputum, cough, shortness of breath, fever, fatigue) for at least 3 months and HRTC lung lesions presenting as one or more cavities, non-cavitary nodules below 3 cm, consolidations, or severe fibrotic destruction of at least two lobes seen on HRCT imaging [Denning DW, et al. Eur Respir J 2016; 47: 45–68].
Bronchiectasis	Bronchiectasis were defined according to Pasteur MC et al. Thorax. 2010; 65 Suppl 1:1–58. Bronchiectasis severity was classified into three degrees (1=mild, 2=moderate, 3=severe), based on Chalmers JD et al. Am. J. Respir. Crit. Care. Med. 2014;189: 576–585.

8

TABLE 1

CHARACTERISTICS OF PATIENTS BY *ASPERGILLUS*-RELATED DISEASE

	NO-ASP Group 1	SAFS Group 2	ASP-B(?) Group 3	CPA Group 4	ABPA Group 5	ABPA+CPA Group 6
NUMBER (%)	38 (51.5)	6 (8)	8 (11)	4 (5.5)	12 (16)	6 (8)
Women, n (%)	28 (74)	5 (83)	6 (75)	3 (75)	7 (58)	2 (33)
Age years, mean (SD)	60.8 (13)	59.3 (11)	59.5 (9)	61.3 (10)	66.0 (12)	56.0 (15)
Never-smoker, n (%)	28 (74)	5 (83)	5 (63)	3 (75)	6 (50)	2 (33)
Atopy n (%)	21 (55)	6 (100)	7 (88)	4 (100)	12 (100)	6 (100)
ACT score mean (SD)	17.8 (5)	18.2 (1.5)	16.6 (3.1)	19.8 (2.2)	18.1 (3.5)	15.7 (4.9)
Mold exposure index, mean(SD)	0.53 (1.1) ^{3,4,5,6}	0.67 (1.0) ^{3,4,5,6}	3.25 (1.4) ^{1,2}	3.75 (0.5) ^{1,2}	3.17 (1.3) ^{1,2}	4.00 (0.0) ^{1,2}
FENO ppb mean (SD)	42.4 (37) ⁶	35.7 (32.9)	28.9 (24.4)	15.3 (11.1)	30.8 (36.1)	93.8 (108) ¹
Eosinophils cells/ml	477.5 (393) ⁶	423.3 (263)	292.5 (224) ⁵	320.0 (230)	568.5 (267)	1258 (1390) ^{1,3}
Total IgE U/ml mean (SD)	262 (314) ^{2,5,6}	560.5 (422) ¹	297.8 (221)	268.5 (338)	2906 (3595) ¹	5779 (10522) ¹
IgE-ASP,IU/ml mean (SD)	0.06 (0.04) ^{2,3,5,6}	0.70 (0.47) ^{1,4}	0.38 (0.31) ¹	0.11 (0.06) ²	4.9 (6.60) ¹	20.6 (39.6)
IgG-ASP U/ml mean (SD)	12.4 (7.8) ^{3,4,5,6}	11.0 (6.5) ⁶	74.9 (73) ^{1,6}	66.0 (90) ¹	47.4 (55) ^{1,6}	177.3 (90) ^{1,2,3,5}
AE n/year mean (SD)	2.3 (1.3) ^{4,6}	2.0 (0.9) ⁶	2.6 (1.2) ⁶	4.0 (2.9) ¹	2.5 (1.2)	4.2 (1.7) ^{1,2,3,5}
VC % pred mean (SD)	85.0 (16) ⁴	90.7 (3.1) ⁴	79.5 (18)	65.0 (12) ^{1,2}	80.5 (24)	82.7 (17)
FEV1 % pred mean (SD)	71.0 (16) ^{4,6}	76.5 (12) ^{3,4,6}	63.0 (7) ²	52.8 (9) ^{1,2}	59.3 (21)	54.8 (15) ^{1,2}
FEV1/VC% mean (SD)	63.9 (11) ^{5,6}	66.7 (19) ⁵	61.6 (14)	61.5 (11)	51.6 (11) ^{1,2}	52.8 (4.5) ¹
FEV1 PB % mean (SD)	17.3 (11)	15.0 (10)	20.3 (9)	11.5 (10)	20.5 (14)	24.8 (10)
Bronchiectasis n (%)	5 (13) ^{3,4,6}	0 (0)	6 (75) ¹	3 (75) ¹	4 (33)	6 (100) ¹
CRSwNP N (%)	19 (50)	2 (33)	2 (25)	1 (25)	8 (67)	4 (67)
OCS n (%)	14 (37)	2 (33)	1 (13)	3 (75)	5 (42)	5 (83)
Biologic therapy n (%)	26 (68)	3 (50)	5 (63)	3 (75)	7 (58)	6 (100)

Superscript numbers in cells indicate the significant differences between groups (i.e. 1 means significantly different from group 1, 2 from group 2, and so on).

NO-ASP: patients without SAFS nor Aspergillus-related disease. SAFS: severe asthma with fungal sensitisation. ASP-B(?): Aspergillus-bronchitis, with question mark. CPA: Chronic Pulmonary Aspergillosis. ABPA: Allergic bronchopulmonary aspergillosis. ABPA - Allergic bronchopulmonary aspergillosis.

ACT: Asthma control test. FeNO: Exhaled nitric oxide. IgE-ASP: Aspergillus fumigatus specific IgE. IgG-ASP: Aspergillus fumigatus specific IgG. AE: Asthma exacerbations. VC: Slow vital capacity. FEV1: Forced expiratory volume in one second. CRSwNP: Chronic sinusitis with nasal polyps. OCS: Oral corticosteroids therapy.

TABLE 2

Comparison between patients with and without aspergillus-related diseases

	ASP-related disease Group 3, 4, 5, 6	No ASP-related disease Groups 1, 2	P
	30	44	
Age years, mean (SD)	61.6 (12)	60.6 (12)	NS
BMI, mean (SD)	24.9 (5.5)	25.0 (4.1)	NS
Females n (%)	18 (60)	33 (75)	NS
Mold exposure index, mean (SD)	3.43 (1.1)	0.55 (1.1)	<0.001
IgG-ASP U/ml, mean (SD)	83.2 (84.1)	12.2 (7.6)	<0.001
Total IgE U/ml, mean (SD)	2433 (5322)	302.7 (341.2)	<0.001
IgE-ASP UI/ml, mean (SD)	6.18 (18.59)	0.15 (0.28)	0.034
Eosinophil cells/ml , mean (SD)	599.7 (710.4)	470.1 (375.6)	0.311
FENO, ppb	40.8 (58.3)	41.5 (36.5)	NS
FEV1 %pred, mean (SD)	58.4 (15.3)	71.8 (15.9)	0.001
VC % pred , mean (SD)	78.5 (19.8)	85.8 (14.9)	0.077
FEV1/VC%, mean (SD)	56.0 (11.2)	64.3 (12.3)	0.005
AE n, mean (SD)	3.07 (1.60)	2.25 (1.24)	0.016
Bronchiectasis, n (%)	19 (63)	5 (11)	<0.001
OCS, n (%)	14 (47)	16 (36)	NS
Biologic therapy n (%)	21 (70)	29 (66)	NS
Chronic Sinusitis, n (%)	20 (67)	31 (71)	NS
CRSwNP, n (%)	15 (50)	21 (48)	NS