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What are the characteristics of asthma patients with elevated serum IgG4 levels?

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ABSTRACT

Introduction: IgG4 has recently been a subject of great interest in human pathology. No data are available about the characteristics of asthma patients with elevated IgG4 levels.

Population and methods: An observational study was conducted from January 2006 to March 2015 in a difficult-to-treat population of asthma patients. Twenty-six difficult-to-treat asthma patients with elevated serum IgG4 levels (IgG4/IgG ratio up to 10%) were compared with a control population of 98 difficult-to-treat asthma patients with normal serum IgG4. Blood eosinophilia, total IgE and FeNO were compared between groups to better characterize asthma patients with elevated serum IgG4 levels.

Results: Median IgG4 concentrations were 1.72 g/l [1.19–2.36] and 0.22 g/l [0.10–0.49] in the elevated IgG4 group and normal IgG4 group, respectively. Median blood eosinophilia was more than three times higher in patients with elevated serum IgG4 levels than in controls ($0.75 \times 10^9/L$ [IQR 0.54–1.78] vs $0.22 \times 10^9/L$ [IQR 0.09–0.54] respectively, $p < 0.0001$). Total IgE was twice as high (264.5 kU/l [IQR 166.3–779] vs 126 kU/l [IQR 26–350] respectively; $p < 0.05$) and FeNO was nearly twice as high (61 [IQR 41–111] ppb vs 35 [IQR 23–51] ppb, $p < 0.001$). Allergic broncho-pulmonary aspergillosis (ABPA) and eosinophilic granulomatosis with polyangiitis (EGPA) were observed in the asthma patients with elevated serum IgG4. Ten patients had unexplained increased blood eosinophilia.

Conclusion: Asthma patients with elevated IgG4 levels have significantly higher blood eosinophilia, total IgE and FeNO. ABPA and EGPA are observed in patients with elevated serum IgG4.

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1. Introduction

Asthma is a heterogeneous condition covering a multitude of diseases [1]. Cluster analysis trials have revealed several phenotypes based on clinical and biological similarity [2,3]. These data highlight the importance of personalized treatment adapted to particular patients or small groups of patients with similar phenotypes [4]. To that end, phenotypes need to be better characterized, identifying new biomarkers.

The role of immunoglobulin G4 (IgG4), a subclass of

immunoglobulin G (IgG), is not clearly understood in human pathology [5]. Among all IgG subclasses, IgG1 has the highest concentration in the blood (>50%) and IgG4 the lowest concentration (classically < 5%) [5,6]. IgG4 is described as non-inflammatory IgG with low affinity for Fc receptors (FcR) [7]. Little is known about elevated concentrations of IgG4 and their role in respiratory diseases. Elevated levels of serum and tissue IgG4 are found particularly in IgG4-related disease (IgG4-RD), which is characterized by a polyclonal lymphocyte and plasma cell infiltration and perivascular sclerosis [8]. Pulmonary involvement is described in 14–54% cases of IgG4-RD [9,10]. Several clinical presentations have been identified such as inflammatory pseudotumours, idiopathic interstitial pneumonias, fibrosing mediastinitis and, inflammatory pleural lesions. Elevated IgG4 is also observed in other diseases with lung involvement, such as vasculitis, connective tissue diseases and cancer, but its role has not yet been clearly identified [6]. To the best

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of our knowledge, no data are available on the exact profile of asthma patients with high levels of IgG4.

The aim of this study is to determine the clinical, functional and biological profile of asthma patients with high levels of serum IgG4 compared to a population of asthma patients with normal levels. We particularly compared eosinophilia count, total IgE values and FeNO level. We also investigated the asthma phenotype/disease observed in patients with elevated levels of serum IgG4.

2. Population and methods

2.1. Population

From a database containing IgG subclass measurements performed from January 2006 to March 2015 in the Department of Pulmonary Medicine at the University Hospital of Tours, France, we selected difficult-to-treat asthma patients with an IgG4/IgG ratio up to 10%, which is the threshold defining elevated serum IgG4 concentrations as described previously [11]. This threshold has the advantage of avoiding false positive patients with increased polyclonal IgG. Asthma was defined according to GINA guideline criteria [12]. This study population was compared to a control population of difficult-to-treat asthma patients with normal levels of serum IgG4. French law does not require the approval of an Institutional Review Board or patient consent for this type of observational, non-interventional and retrospective analysis of medical records. The database was anonymous and complied with the restrictive requirements of the *Commission Nationale de l'Informatique et des Libertés*, the organization that ensures the application of data privacy laws in France. Our study was conducted in accordance with French legislation.

2.2. Clinical and biological data

Data regarding age, gender, body mass index and smoking status were collected for the study and control groups. Never-smoker patients were defined as patients who had smoked fewer than 100 cigarettes throughout their life. Atopy was defined as at least one positive prick test or one positive specific IgE of aeroallergen excluding aspergillus. Sensitisation to the following aeroallergens was assessed: dermatophagoides pteronyssinus, dermatophagoides farinae, cat, dog, grass, birch, ragweed, mugwort, *Aspergillus fumigatus*, *Alternaria alternata* and *Cladosporium herbarum*. The results are indicated as indoor and/or outdoor. Details of treatment were also collected. Oral steroid use was defined as a daily dose of 5 mg or more with a duration of 3 months or longer. Blood-cell count was performed using a Beckman Coulter LH 780 analyser. Immunoglobulin A, G, M and IgG subclass concentrations in serum were measured by nephelometry on BN Prospec® (Siemens Healthcare Diagnostics, Marburg, Germany).

2.3. Lung function tests

Lung function tests were performed using Sensormedics Vmax Encore plethysmography (Carefusion®, San Diego, CA). Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 s (FEV1) values were expressed as percentages of predicted values according to gender, weight and age. Measurements were performed following ATS/ERS recommendations [13]. The predicted values were those of the ERS [14].

2.4. FeNO and total IgE measurement

Total IgE levels were measured by immuno-enzymatic assay (ImmunoCAP total IgE) (Thermo Fisher Scientific. Phadia AB,

Uppsala, Sweden) and were expressed in kUI/L. FeNO values were obtained using an electrochemical device (Hypair FeNO, Medisoftware®, Sorinnes, Belgium) following ATS/ERS recommendations [15]. Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 s (FEV1) values were expressed as percentages of predicted values according to age, gender, weight, and height. Airway obstruction was defined as post-bronchodilator FEV1/FVC < 70%. Repeated and reproducible exhalations were performed until at least two NO plateau values differing by less than 10% were obtained. Flow rate exhalation was 50 ml/s. The FeNO value retained was the mean of two reproducible measurements. FeNO was expressed in parts per billion (ppb).

2.5. Asthma phenotype or associated diagnosis

To better characterize asthma patients with elevated serum IgG4 levels, we assigned for each patient a phenotype or disease that could be associated with asthma. Atopic asthma was defined as asthma with at least one positive prick test or one positive specific IgE of aeroallergen excluding aspergillus. Allergic broncho pulmonary aspergillosis (ABPA) was defined with criteria described previously [16]. Immediate hypersensitivity to *Aspergillus fumigatus* was based on a positive prick test or specific IgE. Diagnosis of eosinophilic granulomatosis with polyangiitis (EGP) was based on criteria described previously [17]. Phenotype of asthma with obesity was defined as asthma patients with a BMI up to 30 kg/m² and no atopy and blood eosinophilia < 0.5 G/L. Asthma patients who did not fit a particular phenotype but with blood eosinophilia ≥ 0.5 G/L and ≥ 1.5 G/L were classified as having asthma with mild eosinophilia and asthma with high eosinophilia respectively.

2.6. Statistical analyses

Continuous data were described with median and [interquartile range]. Categorical data were expressed as number of patients and percentages. Continuous data of study and control patients were compared using the non-parametric Mann–Whitney test. Fisher exact tests were used to compare categorical data of the study and control groups. Eosinophilia, total IgE and FeNO values were available in 23 (92%), 19 (76%) and 20 (80%) patients with elevated serum IgG4 levels and 92 (94%), 71 (72%) and 65 (66%) patients with normal IgG4 levels. According to guidelines on interpretation of exhaled nitric oxide levels (FeNO) for clinical applications, a low FeNO level was defined as FeNO values ≤ 25 ppb [15]. These values are highly correlated with the absence of airway eosinophils [18]. A high FeNO level was arbitrarily defined as FeNO values > 100 ppb. Elevation of total IgE concentration is associated with Th2 inflammation. However, no specific cut-off values are identified. In normal subjects, total IgE concentration ranges from 17.8 to 40.9 kUI/l according to age [19]. The cut-off of 30 kUI/l was chosen in our study to define low total IgE concentration. High IgE values were defined as 1000 kUI/l. Normal values of blood eosinophilia is classically defined as values under a threshold of 0.5 10⁹/l [20,21]. In our study, high blood eosinophilia was defined as an eosinophil count of 0.5 10⁹/l or higher. A cut-off of 1.5 10⁹/l was used to define very high blood eosinophilia according to the definition of a large range of differential diagnoses of hypereosinophilic syndrome [21]. No statistical analysis was performed on asthma phenotype/disease assigned for each patient because of the low number of patients in some groups. Statistical significance was defined as a p value < 0.05.

3. Results

3.1. Study and control population characteristics

3.1.1. Clinical characteristics

A total of 123 asthma patients were included in the study; 25 patients had high IgG4 levels and 98 had normal levels. All characteristics are displayed in Table 1. Median age was 57 years [40.3–67.5] and 52 years [37.5–67.8] for the elevated IgG4 group and normal IgG4 group respectively. There was no difference in sex ratio between groups. There were more women than men in both groups, with 53.8% and 56.1% in the elevated and normal IgG4 groups respectively. Never-smokers predominated in both groups, but there were more former- or active-smokers in the control group (40.8%) than in the elevated IgG4 group (24.0%). The difference was not statistically significant. Atopy was observed in 52.0% and 61.5% of patients in the elevated IgG4 and control groups respectively. BMI was similar in the two groups, with a median of 26 kg/m² for each group (26 kg/m² [22.8–30.0] in the elevated IgG4 group and 26 kg/m² [22.2–30.0] in the control group).

3.1.2. Functional characteristics

Airway obstruction, defined as FEV1/FVC < 70%, was not statistically different between the two groups and was observed in 45.8% and 53.3% of patients in the elevated IgG4 and control groups respectively. Median FEV1 was 80% [62–97] and 75% [52–93] in the elevated IgG4 and control groups respectively. The proportion of patients with FEV1 < 80% did not differ between groups, with 45.8% and 55.6% in the elevated IgG4 and control groups respectively.

3.1.3. Immunoglobulin characteristics

Median IgG4 concentrations were 1.72 g/l [1.19–2.36] and 0.22 g/l [0.10–0.49] in the elevated IgG4 group and normal IgG4 group, respectively. IgA and IgM concentrations were similar in the two groups. IgG concentrations were higher in the study group than in the control group, with a median concentration of 11.10 g/l [8.44–14.00] and 8.75 g/l [6.66–11.03] respectively ($p < 0.01$).

3.1.4. Treatment characteristics

Higher doses of inhaled steroids were given to patients in the elevated IgG4 group compared to patients in the normal IgG4 group. The median daily dose was 800 µg [500–1000] and 500 µg [285–775] (beclomethasone equivalent), respectively ($p < 0.05$). Oral steroid and anti-IgE therapy did not differ between groups. Six (24.0%) and 27 (27.6%) patients were treated with oral steroids in the study and control groups respectively. Anti-IgE was administered to 4 (16.0%) and 14 (14.3%) patients in the study and control groups respectively.

Eosinophilia, total IgE and FeNO of asthma patients with elevated and normal serum IgG4 levels.

3.1.5. Eosinophilia

Median blood eosinophilia was more than three times higher in the elevated IgG4 group, with 0.75 10⁹/L [0.54–1.78] compared to 0.22 10⁹/L [0.09–0.54] in the control group ($p < 0.0001$) (Table 2 and Fig. 1). Blood eosinophilia ≥ 0.5 10⁹/L was observed in nearly three quarters of the asthma patients with elevated IgG4 and 28.3% in patients with normal IgG4 ($p < 0.001$). The proportion of patients with very high blood eosinophilia (≥ 1.5 10⁹/L) was 21.7% in patients with elevated IgG4 and only 3.3% in patients with normal IgG4 ($p < 0.001$).

3.1.6. Total IgE

Total IgE was twice as high in asthma patients with elevated IgG4 levels than in patients with normal levels (264.5 kUI/L [166.3–779] and 126 kUI/L [26–350] respectively; $p < 0.05$). Low total IgE was rare in patients with elevated IgG4, as only one (5.3%) patient had total IgE < 30 kUI/L, compared to 20 (28.2%) patients with normal IgG4 ($p < 0.05$). However, high total IgE was quite frequent in patients with elevated IgG4, as 5 (19.2%) patients in the study group and 5 (5.1%) patients in the control group had total IgE > 1000 kUI/L ($p < 0.05$).

3.1.7. FeNO

FeNO was nearly twice as high in the study sample, with a median value of 61 [41–111] ppb compared to 35 [23–51] ppb in the control group ($p < 0.001$). No patient in the study group had

Table 1

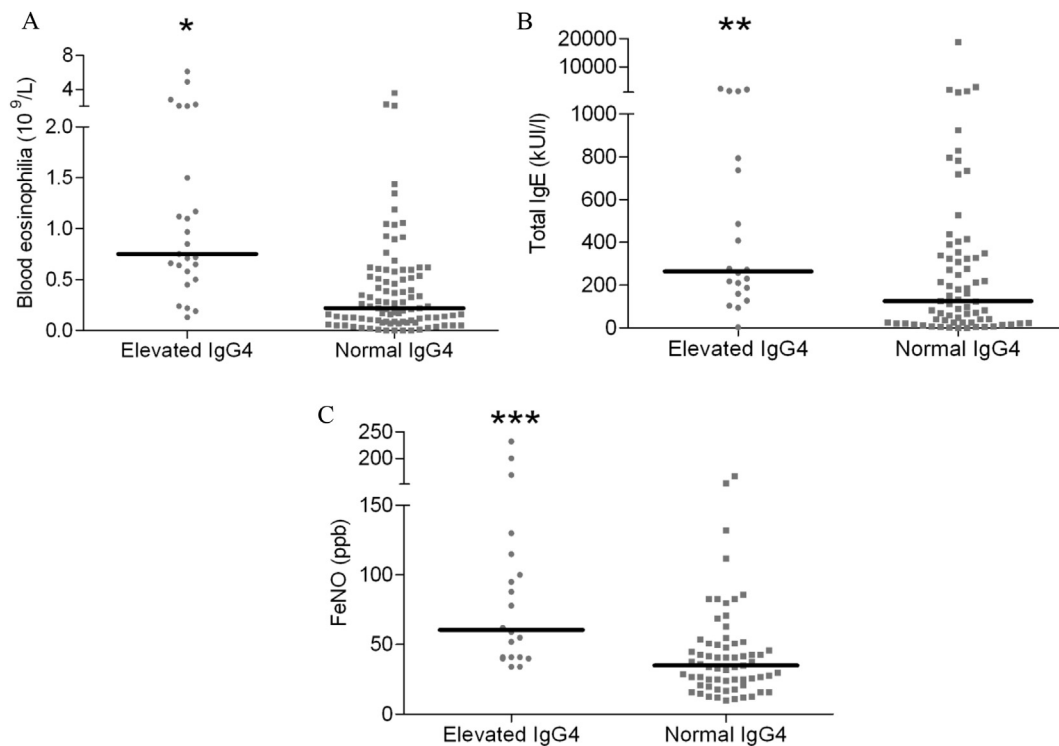
Characteristics of asthma patients with elevated and normal levels of serum IgG4. Data are expressed in median [interquartile range] or number of patients (%). FEV1 is expressed as % of predicted values. All immunoglobulin concentrations are expressed in g/L. FEV1: forced expiratory volume, VC: vital capacity, NS: not significant.

	Patients with elevated IgG4 n = 25	Patients with normal IgG4 n = 98	p
Age (years)	57 [40.3–67.5]	52 [37.5–67.8]	NS
Female	14 (56.0)	55 (56.1)	NS
Never-smokers	19 (76.0)	58 (59.2)	NS
Former- or active-smokers	6 (24.0)	40 (40.8)	
Atopy	13 (52.0)	59 (61.5)	NS
No atopy	12 (48.0)	37 (38.5)	
Outdoor allergens	4	7 (11.9)	NS
Indoor allergens	4	35 (59.9)	
Outdoor and indoor allergens	5	17 (28.8)	
Body mass index (kg/m ²)	26 [22.8–30.0]	26 [22.2–30.0]	NS
FEV1/FVC (%)	70 [58–77]	68.5 [55–79]	NS
FEV1/FVC < 70%	11 (45.8)	48 (53.3)	
FEV1/FVC $\geq$ 70%	13 (54.2)	42 (46.7)	NS
FEV1 (% predicted values)	80 [62–97]	75 [52–93]	NS
FEV1 < 80% (n)	11 (45.8)	50 (55.6)	NS
	13 (54.2)	40 (44.4)	
IgM (g/l)	0.88 [0.53–1.15]	0.83 [0.65–1.20]	NS
IgA (g/l)	2.28 [2.00–2.85]	1.95 [1.19–2.57]	NS
IgG (g/l)	11.1 [8.44–14.00]	8.75 [6.66–11.03]	<0.01
IgG4 (g/l)	1.72 [1.19–2.36]	0.22 [0.10–0.49]	–
Inhaled steroid doses (µg/d) (beclomethasone equivalent)	800 [500–1000]	500 [285–775]	<0.05
Oral corticosteroid (n)	6 (24.0)	27 (27.6)	NS
Anti-IgE (n)	4 (16.0)	14 (14.3)	NS

Table 2

Blood eosinophilia, total IgE and FeNO values of asthma patients with elevated and normal levels of IgG4. Data are expressed in number of patients (%).

	Patients with elevated IgG4 n = 25	Patients with normal IgG4 n = 98	p
Eosinophilia	n = 23	n = 92	
Eosinophilia <0.5 10 ⁹ /L	5 (21.7%)	66 (71.7%)	<0.0001
Eosinophilia 0.5–1.5 10 ⁹ /L	13 (56.6%)	23 (25.0%)	<0.01
Eosinophilia ≥1.5 10 ⁹ /L	5 (21.7%)	3 (3.3%)	<0.01
Total IgE	n = 19	n = 71	
Total IgE < 30 kUI/L	1 (5.3%)	20 (28.2%)	<0.05
Total IgE 100–1000 kUI/L	13 (68.4%)	33 (46.5%)	0.12
Total IgE > 1000 kUI/L	5 (26.3%)	5 (7.0%)	<0.05
FeNO	n = 20	n = 65	
FeNO ≤ 25 ppb	0 (0.0%)	21 (32.3%)	<0.01
FeNO 25–100 ppb	14 (70%)	40 (61.5%)	NS
FeNO > 100 ppb	6 (30.0%)	4 (6.2%)	<0.01

**Fig. 1.** Blood eosinophilia (A), Total IgE (B) and FeNO (C) in asthma patients with elevated and normal levels of serum IgG4. Results are expressed in median and interquartile range. * $p < 0.0001$, ** $p < 0.05$, *** $p < 0.001$.

FeNO ≤ 25 ppb, compared to 21 (32.3%) patients in the control group ($p < 0.01$). High levels of FeNO (> 100 ppb) were observed in 6 (30.0%) patients with elevated IgG4 compared to only 4 (6.2%) in the control group.

Diagnosis associated with asthma patients with elevated and normal IgG4 levels.

Atopic asthma was observed in 9 (34%) patients with high IgG4

and in 57 (58%) patients with normal IgG4 (Table 3). In the study group, there were 4 (16.0%) patients with severe eosinophilia (≥ 1.5 10⁹/l) with no atopy, whereas none of the patients in the control group showed this characteristic. Four patients in each group, representing 15.4% of the study group and 4.1% of the control group, had allergic broncho pulmonary aspergillosis. Two (7.7%) patients with elevated IgG4, but none of the control patients, had an

Table 3

Phenotypes/diseases associated with asthma patients with elevated and normal IgG4.

	Patients with elevated IgG4 n = 25	Patients with normal IgG4 n = 98
Atopic asthma	8 (32.0%)	57 (58.2%)
Asthma associated with obesity	1 (4.0%)	8 (8.2%)
Non-atopic asthma with mild blood eosinophilia increase	6 (24.0%)	5 (5.1%)
Non-atopic asthma with severe blood eosinophilia increase	4 (16.0%)	0 (0%)
Non-atopic and non-eosinophilic asthma	0 (0%)	24 (24.5%)
Allergic broncho pulmonary aspergillosis	4 (16.0%)	4 (4.1%)
Eosinophilic granulomatosis with polyangiitis	2 (8.0%)	0 (0%)

eosinophilic granulomatosis with polyangiitis (EGPA). The proportion of patients with a phenotype of asthma and obesity was low in both groups (4.0% and 8.2% in patients with elevated and normal IgG4, respectively).

4. Discussion

In difficult-to-treat asthma patients with elevated serum IgG4 levels, clinical and functional characteristics do not seem to be very different from those of a control group with normal IgG4. However, blood eosinophilia was more than three times higher, total IgE more than twice as high, and FeNO nearly twice as high in asthma patients with elevated serum IgG4 levels than in the control group.

Atopy does not explain these results, because it was found less in asthma patients with elevated serum IgG4 levels than in the control group. We found that ABPA and EGPA were more frequent in patients with elevated serum IgG4, which could partly explain the high levels of blood eosinophilia and total IgE.

The real involvement of IgG4 in ABPA is still unknown. All IgG subclasses, particularly IgG4, are significantly higher in ABPA than in controls, although one study found no difference with other asthma patients [22,23]. It has been suggested that specific IgG4 responses to *Aspergillus fumigatus* (Af) antigen are found in chronic exposure to this fungus and could protect the host from protracted inflammation [24,25]. A link between elevated specific IgG4 concentrations and chronic exposure to *Aspergillus fumigatus* antigen has also been observed in cystic fibrosis patients [26]. It has been demonstrated that regulatory T cells may contribute to the suppression of allergic diseases by induction of IgG4 [27]. Elevated IgG4 levels in ABPA could reflect an attempt by the immune system to reduce the allergic reaction. In our study, ABPA patients had elevated serum IgG4, although low levels were observed in some. Note that elevated total IgE and specific IgE positivity to Af could have appeared several months after IgG4 increase in our patients. In difficult-to-treat asthma patients associated with elevated serum IgG4 levels, ABPA should be considered initially and also during regular follow-ups.

High levels of serum IgG4 are classically observed in EGPA [28,29]. One study found that serum IgG4 was particularly high in active EGPA and correlated with disease activity [30]. In that study, serum IgG4 seemed to decrease during disease remission [30]. However, in another study, the serum IgG4 and IgG4/IgG ratio did not clearly differentiate active from inactive EGPA [31]. Further research is required to clarify the role of serum IgG4 in EGPA.

In our study, 10 (38.5%) patients with elevated serum IgG4 had unexplained high levels of blood eosinophilia ($>0.5 \times 10^9/L$), which did not meet the criteria for atopic asthma, ABPA or EGPA. Mild to moderate blood eosinophilia is classically observed in IgG4-RD patients, and in one study, the proportion of patients with eosinophilia $>0.5 \times 10^9/L$ was 27% [8,32]. High levels of IgE concentration, sometimes more than 10 times higher than the upper limit of normal, have also been observed in 35% of IgG4-RD patients [8,32]. IgG4-RD patients had high levels of blood eosinophilia and total IgE, but with no evidence of atopy, which is consistent with our results [32]. Two case reports describe IgG4-RD patients with authentic symptoms of asthma [33,34]. In one, blood eosinophilia was $>1.5 \times 10^9/L$ and total IgE was 913 kU/L [34]. In our opinion, if blood eosinophilia is found in asthma patients with no obvious aetiology, histological tissue should be sampled to look for IgG4-RD. None of the patients in our retrospective study had had bronchial biopsy, so it is not possible to ascertain from these cases whether there is any involvement of IgG4-related disease in asthma with high levels of serum IgG4.

Moreover, the frontier between EGPA and IgG4-RD could be unclear. In one case report, Ayuzawa et al. described a patient with

a diagnosis of EGPA based on asthma, eosinophilia, mono-neuropathy, pulmonary opacities on imaging, and biopsy-proven leukocytoclastic vasculitis [35]. This patient had no MPO- or PR3-ANCA, and a combination of salivary gland swelling, interstitial pneumonia, tubulointerstitial nephritis with membranous glomerulonephropathy, a high serum IgE level, a good response to steroid therapy, and a marked elevation of the serum IgG4 level (275 mg/dL), which could suggest a diagnosis of IgG4-related disease. However, IgG4-positive plasma cells in the tubulointerstitium accounted for about 10% of all IgG-positive plasma cells, which was too low to make a diagnosis of IgG4-RD.

The pathophysiological role of IgG4 in human disease is not clearly known but could be very complex [36]. In IgG4-RD, a high expression of Th2 cytokines (interleukin (IL)-4, IL-5, and IL-13) has been widely observed which could explain eosinophilia, total IgE and FeNO in patients with elevated serum IgG4 level in our study [37–39]. However, Foxp3+ Treg cells are also seen in IgG4-RD lesions and may account for the increased levels of IL-10 and transforming growth factor (TGF)- β [37,39]. Expression levels of IL-4 and IL-10 correlate with the ratio of IgG4 to IgG within the labial salivary gland lesions of patients with Mikulicz's disease (IgG4-related dacryoadenitis and sialadenitis) [40]. Moreover, an increase in the number of circulating Th2 and Treg cells is observed in IgG4-RD [41]. IgG4 seems to be linked to Th2 expression, but it is also induced by Treg cells, suggesting that IgG4 production could be the consequence of several mechanisms. No data are currently available to confirm the pathogenic role of IgG4.

Our study has several limitations. First, asthma patients were selected on the basis of IgG4 concentrations, and specific indications of IgG sub-class levels were not available. This introduces a bias, because it is possible that analysis of IgG sub-class concentrations is only indicated for a limited number of diseases. However, we compared patients with elevated and normal serum IgG4 levels. Therefore, this bias is probably present in both groups and does not modify the results concerning total IgE, eosinophilia and FeNO. Secondly, we found a large proportion of patients with elevated serum IgG4 levels who had unexplained high blood eosinophilia. No diseases were clearly identified in these patients and we postulated that IgG4-RD could be a possible diagnosis, but no histological tissues were available in our study. However, obtaining bronchial tissue is not currently recommended in asthma. Our results could modify the management of asthma patients in clinical practice. Finally, the phenotype/disease used in our study to describe the asthma population is probably restricted, but we tried to take an approach similar to clinical practice and cluster analysis studies [2,3].

In conclusion, asthma patients with elevated levels of serum IgG4 had higher blood eosinophilia, total IgE and FeNO than a control group of asthma patients with normal levels of IgG4. Allergic broncho pulmonary aspergillosis and eosinophilic granulomatosis with polyangiitis were observed in asthma patients with elevated levels of IgG4. A non-negligible number of patients had unexplained high levels of blood eosinophilia. The involvement of an IgG4-related disease in these patients should be considered, but no bronchial tissues were available. In order to better characterize asthma patients with elevated levels of serum IgG4, future studies should collect data of histological findings.

5. Conflict of interest

None.

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