Reverse Angle: Immunological Evaluation of Patients with Bronchiectasis

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ABSTRACT

Objective: Bronchiectasis is a chronic debilitating disease of the airways that results in chronic cough and production of viscous sputum due to dilatation of the airways and bronchial wall thickening. Although bronchiectasis is a common problem in immunodeficiencies and a well-known complication of these disorders, there are a limited number of studies on the frequency of immune abnormalities in adult patients with bronchiectasis.

Materials and Methods: The records of adult patients who visited the Pulmonology Outpatient Clinic and whose immune system was assessed due to bronchiectasis at the Immunology Outpatient Clinic until June 2018 were retrospectively evaluated. The data of 84 patients with bronchiectasis (mean age: 48.5 ± 17.9 years, female: 45 [53.6%], male: 39 [46.4%]) were analyzed.

Results: Six patients (7.1%) had at least one antibody deficiency. Four patients (4.8%) had low IgG levels, one (1.2%) had low IgA level, and one (1.2%) had low IgM level. Fourteen patients (16.7%) had high IgG (16-22 g/l), 10 (11.9%) high IgA (4.08 - 6.60 g/l) and one (1.2%) high IgM (8.87 g/l). Thirty-five patients (41.7%) had at least one abnormality in the peripheral lymphocyte subset analyses.

Conclusion: Adult patients with bronchiectasis may have a variety of immunological abnormalities in addition to hypogammaglobulinemia. Therefore, clinicians should not overlook immunological evaluation in the etiological investigation of bronchiectasis, and patients with immunological abnormalities should be closely monitored.

Keywords: Bronchiectasis, hypogammaglobulinemia, common variable immune deficiency, IgG deficiency, IgM deficiency, IgA deficiency

INTRODUCTION

Bronchiectasis is a chronic debilitating disease of the airways with chronic cough and production of viscous sputum due to dilatation of the airways and bronchial wall thickening. Many factors need to come together for the development of bronchiectasis, but essential factors are an infectious agent, airway obstruction, impaired bronchial drainage and/or insufficient host defense (1). There are many elements that lead to the development of bronchiectasis and contribute negatively to this process. Airway obstruction due to foreign body aspiration, cystic fibrosis, Young's syndrome, connective tissue diseases, dyskinetic cilia syndrome, pulmonary infections, allergic bronchopulmonary aspergillosis, smoking, and impaired host defense are some of these reasons (2, 3). Impaired host defenses may be local, such as ciliary dyskinesia, or may be systemic due to prolonged immunosuppression or hypogammaglobulinemia (4). Immunological evaluation in patients with bronchiectasis has therefore become an important part of the etiological evaluation. Bronchial wall injury due to frequent and recurrent sinopulmonary infections in children with hypogammaglobulinemia predisposes the patients to bronchiectasis (5). Immunoglobulin replacement therapy specifically reduces the frequency of upper respiratory tract infections and provides protection against infections.

Although bronchiectasis is a common problem in immunodeficiencies and a well-known complication of these disorders, there are a limited number of studies on the frequency of immune abnormalities in adult patients with bronchiectasis.

In this study, we aimed to investigate the immunological parameters of patients who were referred to the Clinical Immunology Clinic from the Department of Pulmonology due to bronchiectasis.

MATERIALS and METHODS

Patients

The records of adult patients over 18 years of age who visited the Pulmonology Outpatient Clinic and whose immune system was assessed due to bronchiectasis at the Immunology and Allergic Diseases Outpatient Clinic until June 2018 were evaluated retrospectively. The study protocol was approved by the Ethics committee Informed consent was obtained from the study participants.

Patients with uremia, renal insufficiency, nephrotic syndrome, hepatic insufficiency, diabetes mellitus, HIV-AIDS (Human Immunodeficiency Virus- Acquired Immune Deficiency Syndrome), protein-losing enteropathy, malignancy and suspected malignancy, alcoholism, and malnutrition were excluded from the study. Patients taking drugs that cause hypogammaglobulinemia (antiepileptic and immunosuppressant drugs) were excluded from the study. The records of 84 patients who were found to comply with the study criteria were evaluated.

A detailed history was obtained from the patients and a detailed physical examination was performed. The number of respiratory infections that had required patients to use antibiotics in the past year were questioned and noted in detail.

Methods

Routine laboratory tests, peripheral lymphocyte subsets, serum immunoglobulin values (IgG, IgA, IgM, IgE), complete blood count, and specific antibody responses to encapsulated pyogenic bacteria such as Streptococcus pneumoniae and Clostridium tetani were measured.

Specific antibody responses to Streptococcus pneumoniae and Clostridium tetani were measured by enzyme-linked immunosorbent assay (ELISA) using the Dynex DS2 Two-Plate Automated ELISA Processing System (Virginia, USA). A tetanus antibody level ≥ 0.04 IU/ml (6) or a pneumococcal antibody level ≥ 1.0 μg/ml was considered sufficient (7).

The isohemagglutinin titer was measured by hemagglutination at the dilution of the maximum titer. For isohemagglutinin titers, ≥1/16 was sufficient for anti-A while ≥1/8 was considered sufficient for anti-B (8).

The neutrophil respiratory burst was measured by the dihydrorhodamine (DHR) test. DHR oxidation to rhodamine during the respiratory burst was measured by flow cytometry. A stimulation index (the ratio of the mean channel fluorescence of stimulated cells versus unstimulated cells) greater than 60 was considered normal.

A quantitative determination of serum immunoglobulins (IgG, IgM, IgA, and IgE) was performed by particle-enhanced immunonephelometry using the Siemens BN II/ BN ProSpec system (Eschborn, Germany). Peripheral blood lymphocyte subsets were measured by the BD FACSCanto II 8-color configuration flow cytometer system (Erembodegem, Belgium) with fluorescence labeled antibodies.

Statistical Analyses

Statistical analysis was performed with the IBM SPSS Statistics Version 22 software (New York, United States) package. Normally distributed parameters were presented as mean ± standard deviation and skewed parameters were expressed as median (interquartile range [minimum/maximum]).

RESULTS

Baseline Demographic, Clinical, and Laboratory Parameters of the Study Population

Seventy-four patients with bronchiectasis (F: 45 [53.6%], M: 39 [46.4%]) were included in the study (age 48.5 ± 17.9). The median number of upper respiratory tract infections requiring treatment with antibiotics in the past year was 4.3 (0-20). Baseline demographic, clinical, and laboratory parameters of the study population are summarized in Table I. The most common type of bronchiectasis was tubular bronchiectasis (39.3%). Although bronchiectasis was present in all lung lobes in some patients (3 patients, 3.6%), two-lobe involvement was most common (38 patients, 45.3%) (Table II). Five patients (6%) were operated due to bronchiectasis.

Table I: Baseline demographic, clinical, and laboratory parameters of the study population.

	Total (n=84)	Normal Values
Gender (female), n (%)	45 (53.6)	
Age (years)	48.52 ± 17.91	
Number of infections requiring antibiotics in the last year	4.30 (0-20)	
Lymphopenia (Lymphocyte count <1500/mm³), n (%)	15 (17.9)	
Number of patients with bronchiectasis surgery, n (%)	5 (6)	
Leucocyte count	8887.26 ± 3665.03	4 - 10 x 10^3/µl
Neutrophil count	6008.57 ± 3550.66	1.5 - 7.3 x 10^3/µl
Lymphocyte count	1745.5 ± 1346.80	1.5 - 5.5 x 10^3/µl
IgG	12.63 ± 3.42	7 - 16 g/L
IgM	1.25 ± 0.97	0.4 - 2.3 g/L
IgA	2.57 ± 1.20	0.7 - 4 g/L
IgE	110.52 ± 181.31	5 - 150 IU/ml
CD3$^+$ T cells (%)	68.5 ± 11.9	M: 48-82.6%, F: 56.8-84.1%
CD4$^+$ T cells (%)	37.7 ± 10.5	M: 23-52.6%, F: 26.9-55.5%
CD8$^+$ T cells (%)	31.0 ± 9.7	12.8-40.2%
CD4/CD 8	1.71 (0.16-32)	0.68-3.61%
CD19$^+$ B cells (%)	11.21 (1-55)	6.3-20.8%
CD16-56 Natural Killer cells (%)	13.6 ± 9.1	M: 5-31.3%, F: 3.5-24.9%

Ig: Immunoglobulin, **CD:** Cluster of differentiation.

Table II: Type and lung involvement of bronchiectasis.

Type of bronchiectasis	n	%	Lung involvement	n	%
Tubular bronchiectasis	33	39.3	Two lobe involvement	38	45.2
Cystic bronchiectasis	29	34.5	Single lobe involvement	22	26.2
Varicose bronchiectasis	3	3.6	Three lobe involvement	12	14.3
Tubulo-saccular bronchiectasis	2	2.4	Four lobe involvement	9	10.7
Tubulocystic bronchiectasis	4	4.8	Five lobe involvement	3	3.6
Varicose+cystic bronchiectasis	5	6.0			
Tubulo-varicose bronchiectasis	4	4.8			
Tubular+cystic+varicose bronchiectasis	4	4.8			

Total Serum Immunoglobulins

Clinical and laboratory parameters of the study population are summarized in Table I. Four patients (4.8%) had low IgG levels. These patients did not meet the CVID (Common Variable Immune Deficiency) criteria as they were not accompanied by low IgM and/or IgA levels (9). These patients were therefore considered to have IgG deficiency. One patient (1.2%) had low IgA level. The patient was considered to have selective IgA deficiency with the current clinical and laboratory findings (10). Only one patient (1.2%) had low IgM level. The patient was considered to have possible selective IgM deficiency due to abnormalities in the peripheral lymphocyte subset analysis (Table II). Fourteen patients (16.7%) had a high IgG level (16-22 g/l), 10 (11.9%) had a high IgA level (4.08 - 6.60 g/l), and one (1.2%) had a high IgM level (8.87 g/l).

Table III: Peripheral lymphocyte subset analyses of patients.

Total (n=84)	n (%)
At least one antibody decrease	6 (7.1)
Low IgG	4 (4.8)
Low IgA	1 (1.2)
Low IgM	1 (1.2)
At least one abnormality in peripheral lymphocyte subsets	35 (41.7)
Low CD3	7 (8.3)
Low CD4	10 (11.9)
Low CD8	1 (1.2)
Low CD19	16 (19.1)
Low CD16-56	6 (7.1)
Low CD4/CD8	14 (16.7)
Reduced neutrophil functions	3 (3.6)

Ig: Immunoglobulin, **CD:** Cluster of differentiation

Peripheral Lymphocyte Subset Analyses

Peripheral lymphocyte subset analyses of the patients are summarized in Table III. Thirty-five patients (patients 1-35) (41.7%) had at least one abnormality in the peripheral lymphocyte subset analyses (Table III). The most frequent abnormality in this patient group was a reduced percentage of CD19(+) B cells (16 patients, 45.7% of the patients with peripheral lymphocyte subset anomalies, 19.1% of all patients). Reduced neutrophil functions were observed in three patients (3.6%).

Specific Antibodies

Pneumococcal and tetanus antibodies were evaluated in 43 (51.2%) and 67 (79.8%) patients, respectively, and were adequate in all the patients and 33 patients (39.3%) patients, respectively. After appropriate immunization, all 34 patients with inadequate tetanus antibodies produced adequate tetanus antibody responses.

Isohemagglutinin titers were studied in 80 patients (95.2%). Isohemagglutinin titers were evaluated in only 65 patients as 15 patients had blood type AB, where isohemagglutinin titers could not be evaluated. Isohemagglutinin antibody titers were adequate in 45 patients (69.2%). All immunological abnormalities in the study population are summarized in Table IV.

DISCUSSION

Bronchiectasis is a common and well-known clinical entity in immunodeficiency patients. Dilated and thickened airways and thus the development of bronchiectasis is a common pathological response to recurrent pyogenic infections and/or airway inflammation. Bronchiectasis may also develop due to any immunodeficiency that predisposes the patient to recurrent pyogenic infections in the lungs. Patients with primary antibody deficiencies (such as X-linked agammaglobulinemia, CVID, IgA deficiency, IgG subclass deficiency), combined immunodeficiencies (e.g., signal transducer and activator of transcription 5b [STAT5b] deficiency, activating mutations of phosphoinositide 3-kinase delta [PI3KD] syndrome [APDS]), and phagocyte dysfunction (e.g., chronic granulomatous diseases) are particularly predisposed to bronchiectasis (11). Although different rates are reported in various studies, bronchiectasis occurs in 11 to 51% of immunodeficiency cases (12). Despite all this information, mostly from small series and case reports, large studies on the prevalence of hypogammaglobulinemia and immunological abnormalities in patients with bronchiectasis are relatively rare.

There are several studies investigating the prevalence of antibody deficiency in bronchiectasis patients and different results have been obtained from various groups of patients. Stanley et al. compared 47 patients with chronic respiratory tract infections and 53 healthy individuals in terms of serum IgG subclasses and IgG, IgM and IgA. They found no difference between the two groups in terms of IgG, IgM and IgA while five patients had selective IgA deficiency (13). De Garcia et al. observed deficiencies in at least one IgG subclass (IgG1, IgG2, IgG3, IgG4) in 31 (48%) of 65 patients with bronchiectasis (12). In another study, three of 56 patients with bronchiectasis had low IgG level and 13 patients had at least one IgG subclass deficiency (11). The largest study of bronchiectasis revealed a hypogammaglobulinemia (IgG < 5 g/l) prevalence of 1.4% in 1254 patients. In this patient group, the prevalence of hypogammaglobulinemia was 1.6% in 245 patients with non-mycobacterial tuberculosis and bronchiectasis, and 1.3% in 1009 patients with only bronchiectasis. In the same study, the IgM deficiency (IgM < 0.2 g/l) rate was 0.6% and the IgA deficiency (IgA < 0.5 g/l) rate was 0.3% in patients with only bronchiectasis, whereas the patients with non-mycobacterial tuberculosis and bronchiectasis had no IgA or IgM deficiency (14). In our study, the rates of IgG, IgM and IgA deficiency were 4.8%, 1.2% and 1.2%, respectively.

Table IV: Summary of immunological abnormalities in patients with bronchiectasis.

	Low IgG	Low IgM	low IgA	Low CD3	Low CD4	Low CD8	Low CD4/8	Low CD19	Low CD16-56	Reduced Neutrophil Functions
Patient 1							x		x	
Patient 2				x					x	
Patient 3					x		x		x	
Patient 4									x	
Patient 5									x	
Patient 6	x				x		x			
Patient 7	x			x	x		x			
Patient 8								x		x
Patient 9							x			
Patient 10							x			
Patient 11							x			
Patient 12							x			
Patient 13					x		x			x
Patient 14					x		x			
Patient 15					x		x			
Patient 16				x	x		x			
Patient 17				x	x	x				
Patient 18		x		x	x			x		
Patient 19				x						
Patient 20				x						
Patient 21					x		x	x		
Patient 22								x		
Patient 23								x		
Patient 24								x		
Patient 25								x		
Patient 26								x		
Patient 27								x		
Patient 28								x		
Patient 29	x							x	x	
Patient 30					x		x	x		
Patient 31								x		
Patient 32	x							x		
Patient 33								x		
Patient 34								x		
Patient 35								x		
Patient 36			x							
Patient 37										x

Our study is the one of the rare studies on investigating peripheral lymphocyte subsets in bronchiectasis patients without a known immunodeficiency. King et al. reported that both the count of CD19(+) B cells and the number of patients with low CD19 (+) B cells were significantly lower in patients with bronchiectasis than the control group. In the same study, immune abnormalities were detected in 45 patients out of 103 patients with bronchiectasis, and the most frequent abnormality was low neutrophil oxidative burst (33 patients) (15). In our study, we detected at least one abnormality in peripheral lymphocyte subsets in 35 patients (41.7%). The most frequent abnormality in this patient group was a reduced percentage of CD19(+) B cells (16 patients, 45.7% of patients with peripheral lymphocyte subset anomalies, 19.1% of all patients). CD19 is considered a B lymphocyte marker and is used to count and classify B lymphocytes in flow cytometry in clinical practice (16). In animal studies, CD19 deficiency has been shown to result in unresponsiveness to transmembrane signals and a reduced T-cell mediated humoral response, which lead to a general humoral deficiency (17). In addition, decreased CD19(+) B cell counts may result in poor antibody response to pathogens and reduced B-cell and T-cell interaction. Although not all cases of immunodeficiency have a low CD19(+) B cell count, this value is low in many immunodeficiency cases with antibody deficiency, particularly in adults, and adult patients with low CD19(+) B cell counts should be monitored for possible hypogammaglobulinemia. In our study, one patient (patient 32) had a low IgG level as well as a low CD19 (+) B cell value while another patient (patient 18) had a low IgM level as well as a low CD19 (+) B cell value. Close clinical monitoring was necessary for these patients.

The CD4/CD8 ratio is calculated by dividing the CD4(+) cell count by the CD8(+) cell count, and is expected to be 0.68 to 3.61 in immunocompetent individuals (18). This ratio can be reversed with the death of CD4(+) cells circulating in the plasma, CD8(+) cell expansion, or both. A low or inverted CD4/CD8 ratio is an immune risk phenotype that indicates an imbalance between humoral immunity and cell-mediated immunity, and is associated with altered/impaired immune functions, immune aging, and chronic inflammation. King et al. reported that the levels of CD4(+) T cells were similar between patients with bronchiectasis and controls but the number of patients with low CD4(+) T cells were significantly lower in patients with bronchiectasis than the ones in the control group (15). There was a low CD4/CD8 ratio in 14 patients

(16.7%) in the current study. In terms of the age of the study population (mean age: 48.5 ± 17.9 years), this ratio may be an indicator of immune aging and may also indicate chronic inflammation caused by recurrent stimulation of the respiratory mucosa by pathogens.

Neutrophils are a very important group of cells in the host defense against pathogenic microorganisms. In addition to phagocytizing the microorganisms, they can kill microorganisms by producing oxygen radicals, which is called oxidative burst. Recurrent lung infections and bronchiectasis can be seen in immunodeficiency states such as chronic granulomatous disease where oxidative burst decreases (19). In a cohort study involving 103 patients with bronchiectasis, King et al. reported that the most common immune disorder in these patients was decreased neutrophil oxidative burst (33 patients, 32%) (15). In the current study, reduced neutrophil functions were observed in three patients (3.6%).

Increased immunoglobulin levels in patients with bronchiectasis have also been shown in several studies (11, 14, 20) and are thought to show a reactive response to airway inflammation in patients with bronchiectasis. Due to recurrent antigenic stimuli to the surface of the bronchial mucosa, increased IgA levels predominantly occur in these cases (11). Consistent with this information, Ruffner et al. reported increased IgA levels in 9.8%, increased IgG levels in 9.2%, and increased IgM levels in 6.4% of patients with bronchiectasis in cohort studies evaluating 1254 patients with bronchiectasis (14). In another study, Stead et al. reported increased IgA levels in 33.9%, increased IgG levels in 12.5%, and increased IgM levels in 1.8% of patients with bronchiectasis (11). Our results are in line with those reports.

Limitations of the study include the retrospective design, the study being performed at a tertiary university hospital where the tertiary patients were more complicated and medically fragile, and some patients being unable to complete the immunological evaluation. We could not evaluate IgG subgroups because of technical issues and some cases of IgG subgroup deficiency might therefore have been left undiagnosed. Although patients using drugs for hypogammaglobulinemia were excluded from the study, some treatments such as inhaler steroids may have affected the peripheral lymphocyte subset analysis. In addition, we measured total pneumococcal IgG levels for all 23 pneumococcal serotypes, which may have masked the unresponsiveness to one or more serotypes.

In conclusion, adult patients with bronchiectasis may have a variety of immunological abnormalities in addition to hypogammaglobulinemia. Clinicians should therefore not overlook immunological evaluation in the etiological investigation of bronchiectasis, and patients with immunological abnormalities should be closely monitored.

Statement of Ethics: The study protocol was approved by the Ethics Committee. An informed consent form was obtained from all the patients participating in the study.

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CONFLICT of INTEREST: None

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