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Respiratory function in patients with pemphigus vulgaris - a small clinical study

Zoi Apalla[1], *Diamantis Chloros*[2], *Paraskevi Argyropoulou*[2], *Dimitrios Georgopoulos*[2], *Dimitrios Patakas*[2], *Dimitrios Spanos*[2], *George Chaidemenos*[1]

1. Department of Dermatology, State Hospital of Thessaloniki, Greece.
2. Respiratory Laboratory of the Aristotle University of Thessaloniki, Greece.

Corresponding author:

Dr. Zoi Apalla

State Hospital for Dermatologic and Venereologic Diseases

124, Delfon str, Thessaloniki, Greece

PC: 55535

E-mail: *zoimd@yahoo.gr*

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Abstract

Background: Pemphigus vulgaris belongs to a group of rare, autoimmune, blistering disorders, requiring intensive immunosuppressive therapy. Lung infections are common in patients with pemphigus vulgaris.

Objective: To evaluate pulmonary function in patients with pemphigus vulgaris, in order to detect possible factors that might predispose PV patients to lung damage.

Methods: Ten patients first diagnosed with severe pemphigus vulgaris and 10 healthy individuals, were included in the study. Pulmonary function testing, blood gas analysis and quantification of α1-antitrypsin serum levels were performed.

Results: Mild reduction of CO diffusing capacity was recorded, compared to the mean predicted normal value. DLCOSB (single-breath carbon monoxide diffusing capacity test) values did not significantly differ between patients with pemphigus vulgaris and healthy controls, while differences regarding DLCO/VA (VA: Alveolar Volume) were statistically significant. Alpha 1-antitrypsin serum levels were decreased (<2.0g/L) in 60% (6/10) of patients with pemphigus vulgaris and were found normal in none of the healthy controls.

Conclusion: A mild reduction of pulmonary diffusing capacity was observed in patients with pemphigus vulgaris.

Introduction

Pemphigus vulgaris (PV) is an autoimmune bullous disease in which autoantibodies against molecules of the desmosomal adhesion complex perturb desmosomal function, leading to intercellular adhesion defects in the skin, oral and genital mucosa. Loss of activity of the desmosomal cadherin desmoglein 3 (DSG3) plays the central role in the pathogenesis of PV.[1]

Introduction of steroids in the treatment of PV was revolutionary, resulting in a remarkable reduction of the mortality rate. Among others, septicemia and lung infection were the commonest causes of death, during the course of the disease. However, the combination of steroids with adjuvant drugs diminished steroid-associated morbidity. Olszewska *et al.*[2] reported that among other immunosuppressants, cyclophosphamide at a dose of 1.1-1.5 mg/kg/day is an adjuvant drug of choice in the treatment of moderate-to-severe PV.[2] Furthermore, rituximab, a chimeric monoclonal antibody against CD20, has been proven to be of benefit in refractory cases, in which therapy with conventionally accepted modalities is either not efficacious or not possible because of adverse effects.[3]

Respiratory tract involvement in paraneoplastic pemphigus has been extensively studied, while there is a lack of data regarding pulmonary function in PV. The aim of the current study was to assess the respiratory function of 10 patients diagnosed with first episode of severe, long-standing PV before any treatment procedure, and quantify alpha 1-antitrypsin (α1-AT) serum levels, in order to detect possible factors that could predispose these patients to lung damage.

Patients and Methods

Ten patients (9 males and 1 female) diagnosed with first episode of severe PV were included in the study, which was

conducted in collaboration of the Dermatologic Department of State Hospital of Thessaloniki and the Respiratory Laboratory of the Aristotle University of Thessaloniki, Greece.

The study was approved by the Institutional Ethical Committee, while patients and controls provided written informed consent before any procedure. PV diagnosis was based on clinical features suggestive of pemphigus, acantholysis on histological examination, and positive direct and indirect immunofluorescence assay on monkey and guinea pig esophagus assubstrate. All patients had extensive oral lesions, expanding to the epithelium of the upper respiratory tract. Full body computerized tomography scan was performed in order to exclude paraneoplastic pemphigus. Patients' demographic and clinical characteristics are summarized in Table 1.

Lung volumes were assessed with the closed-circuit helium dilution method using a Jaeger spirometer, while expiratory flows were recorded using pneumotachography with the same instrument. Specifically, we assessed the TLC (Total Lung Capacity), the VC (Vital Capacity) and FVC (Forced Vital Capacity), the FRC (Functional Residual Capacity), the RV (Residual Volume), the FEV1 (Forced Expiratory Volume in 1.0 sec), the FEF25-75% (Forced Mid-Expiratory Flow), the MBC (Maximal Breathing Capacity) and the Tiffeneau index (FEV1/VC x100). Diffusing capacity was evaluated using the single-breath carbon monoxide diffusing capacity test (DLCOSB) and expressed as DLCO/VA (VA=Alveolar Volume). Control group consisted of 10 healthy individuals matched for age, sex, smoking history, and clinical and anthropometric characteristics with the patients.

Arterial blood gas analysis (ABL 30 gas blood analyzer, Radiometer, Copenhagen) and quantification of α1-AT serum levels (Mancini method) were also performed.

Statistics

Student's t-test and Mann-Whitney U-test were used to compare values between patients' group and healthy controls. P-value (p) was assessed with the Ecosoft Microstat software.

Table 1. Patients' demographics and characteristics at baseline.

Patient No.	Age/sex	Skin/Oral /genital involvement	IIF titers	Smoking	Concomitant diseases	Medication
1	58/M	+/+/-	1/320	No	Seasonal rhinitis, duodenal ulcer	Ranitidine, anti-acids
2	63/M	+/+/+	1/640	40 PY	History of poliomyelitis, prostatic adenoma	None
3	37/M	+/+/+	1/320	No	History of pulmonary TBC (infanthood)	None
4	69/M	-/+/-	1/160	20 PY	None	None
5	45/M	+/+/+	1/320	50 PY	None	None
6	36/F	+/+/-	1/320	No	None	None
7	58/M	+/+/+	1/640	No	Hypertension, renal lithiasis	Atenolole
8	54/M	-/+/+	1/160	17 PY	History of pleurisy (childhood), duodenal ulcer	None
9	29/M	-/+/-	1/80	18 PY	None	None
10	63/M	+/+/+	1/160	No	Hypertension, duodenal ulcer	Indapamide

PY: pack-years, TBC: tuberculosis, M: male, F: female

Results

Our main results are summarized in Table 2. We did not observe clinically significant alterations regarding lung volumes or expiratory flows. However, in the patients' group, mild reduction of the CO diffusing capacity was recorded, compared to the mean predicted nomogram value (DLCO/VA 3.97 ± 0.58, or 70.8 ± 6.35% of the predicted).

In comparison to the controls, the DLCOSB - expressed as a % percentage of the mean predicted value - did not significantly differ between both groups, while differences regarding DLCO/VA were statistically significant (p=0.002 and p=0.0003).

With respect to the arterial blood gas levels, significant alterations were not detected (PaO2 87.1 ± 7.1 mmHg, PaCO2 35.8 ± 4.4 mmHg, pH 7.44 ± 0.03, SaO2 96.8 ± 0.8%, AaDO2 12.5 ± 8.3 mmHg). In 6 individuals α1-AT levels were lower than 2 g/L (m ± SD=2.3 ± 1.06 g/L, 1.51-5.10).

Discussion

Pemphigus is an autoimmune bullous disease of the skin and mucous membranes, affecting stratified squamous epithelium. During the course of the disease, patients often develop respiratory tract infections, which may be life-threatening. So far, there are no clinical trials, evaluating possible factors that could enhance susceptibility of PV patients to pulmonary infections.[4]

Upper and lower respiratory epithelial cells express all the plakin antigens recognized by paraneoplastic pemphigus autoantibodies. Evidence to date indicates that in paraneoplastic pemphigus, autoantibodies directed against plakin proteins may be responsible for acantholytic changes in the respiratory epithelium, pulmonary epithelial injury and subsequent progressive respiratory failure. Specifically, paraneoplastic pemphigus is classically related to bronchiolitis obliterans.[5] However, there is no evidence that antibodies against

Table 2. Anthropometric and spirometric findings, and CO diffusing capacity (m ± SD).

	Patients (N=10)	Controls (N=10)	*p value*
Age (y)	51.2±13.5	50.8±12.5	NS*
Height (cm)	170.3±6.7	168.4±8.5	NS
Weight (Kg)	71.8±12.0	71.8±8.2	NS
Hb (g/dL)	14.3±0.8	14.5±0.5	NS
FVC (L)/FVC%	4.5±0.6/112.1±12.8	4.2±0.8/106.0±10.5	NS
FRC (L)/FRC%	3.9±0.8/118.9±25.9	3.7±0.9/114.3±25	NS
RV (L)/RV%	2.2±0.5/107.1±26.3	2.4±0.7/116.8±23.9	NS
TLC (L)/TLC%	6.7±1.0/104.8±14.9	6.6±0.9/105.7±6.0	NS
FEV1 (L)/FEV1%	3.2±0.5/100.3±10.2	3.1±0.7/95.9±17.2	NS
FEV1/FVC (%)	72.8±6.6	73.4±8.2	NS
FEF25-75% (L/s)/ FEF25-75% %	2.8±1.0/76.2±22.1	2.6±1.2/73.6±33.8	NS
DLCOSB (mL/min/mm Hg)	23.83±4.46	27.48±6.17	NS
DLCOSB %	85.00±15.31	101.20±17.44	0.0200
D/VA	3.97±0.58	4.75±0.53	0.0020
D/VA%	70.80±6.35	84.80±8.87	0.0003

* NS: non-significant (level of significance, $p > 0.05$)

desmogleins play any part in the induction of respiratory lesions. Even though in patients with PV the lungs are exposed to autoantibodies against desmoglein 3, respiratory involvement has not been observed.[5] These observations are supported by studies which confirm that desmogleins 3 and 1 are not expressed in respiratory epithelium.[6]

According to our data only a mild reduction of the diffusing capacity was recorded (DLCOSB% and DLCO/VA %). When these values were compared to the controls', were found significantly lower ($p=0.02$ and $p=0.0003$, respectively). The DLCOSB reduction became more obvious when it was expressed as a DLCO/VA ratio, which is a more reliable parameter for evaluating diffusion variations (given that DLCOSB increases with the pulmonary volume). Taking into account personal history (including smoking habit), clinical and laboratory findings, none of the already known mechanisms provoking diffusion disturbances can explain the above mentioned observation.

An interesting finding is the detection of low α1-AT serum levels (<2.0g/L) in 6 out of 10 patients.

Previous studies have demonstrated that proteolytic activity of blister fluid in PV is gradually decreased, subsequent to the elevation of anti-proteases, such as α1-AT. According to recent literature data α1-AT and α1 antichymotrypsin are implicated in the inhibition of matrix metalloproteinase-9 (MMP-9) in skin tissue.[7] MMP-9 is found over-expressed in experimental models of PV.[8,9] Imbalance between MMP-9 and α1-AT concentrations might contribute to blister formation in PV.

During the course of a lung infection, α1-AT level increases in the bronchoalveolar secretion, in order to protect it from topically produced proteolytic enzymes. In case of imbalance between proteinases and their inhibitors, the former damage respiratory epithelium, resulting in enhancement of microorganism colonization. It is believed that insufficient production, or prolonged consumption of α1-AT, might predispose these patients for lung infection and/or for asymptomatic obstructive pulmonary damage that are emerged as early deregulation of diffusing capacity.[10]

In our PV patients, only a mild reduction of pulmonary diffusing capacity was observed. We assume that this is due to mucosal involvement of the upper respiratory tract rather than a consequence of pulmonary impairment. In the light of these observations, respiratory dysfunction seems not to be critical feature in PV. The role of α1-AT remains unclear.

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