

Chest HRCT findings in patients with primary Sjögren's syndrome

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Abstract

Background. Pulmonary manifestations (PMs) in primary Sjögren's syndrome (pSS) are among the most frequent extraglandular complications, with reported prevalence varying widely (9–75%), depending on the methods of detection.

Objectives. The aim of this study was to assess the incidence of PMs in pSS and to determine the factors predisposing to the occurrence of this complication.

Material and methods. The study group consisted of 68 patients with pSS. Among the patients who were possibly affected by PMs, chest High Resolution Computed Tomography (HRCT) was performed.

Results. In the group of all patients afflicted with pSS, 30 people indicated the need to expand medical imaging via chest HRCT scan. (The most frequent reason, in 80% of patients, was persistent, dry cough periodically waking up patients at night). The chest HRCT scan revealed lung tissue changes in the course of 29% of all examined patients (of 68). No correlation was found between the occurrence of HRCT changes and the age of patients ($p = 0.8$), increased CRP > 5 mg/l ($p = 0.1$) or ESR > 20 mm/h ($p = 0.9$), focus score ($p = 0.8$), leucopenia ($p = 0.5$), RF value ($p = 0.3$), gamma globulin value ($p = 0.5$), intensity of eye and oral cavity dryness ($p = 0.6$; 0.3), and smoking cigarettes. Additionally, no correlation was found between more frequent occurrences of antibodies anti-SSA, anti-SSB or anti-Ro52 and HRCT changes ($p = 0.3$; 0.07 ; 0.4). Pertaining to the clinical signs, HRCT changes occurred more often only in patients suffering from peripheral arthritis ($p < 0.01$).

Conclusions. PM is a frequent symptom of pSS. A factor predisposing to the development of changes in the respiratory system was not found. Changes in HRCT occur more frequently in patients with peripheral arthritis.

Key words: chest HRCT, primary Sjögren's syndrome, pulmonary manifestation

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Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease with symptoms occurring in many organs, specifically in the salivary glands, lacrimal glands and musculoskeletal system. Symptoms are often weakly expressed resulting in a mean diagnostic delay of 6–7 years.¹ Lymphocytic infiltrates characteristic of pSS may be localized in the respiratory tract. The prevalence of respiratory symptoms in pSS varies a lot (9–75%), depending on the publications and assessment methods (clinical symptoms, chest X-ray, computed tomography).² High Resolution Computed Tomography (HRCT) is a relatively noninvasive method and is currently the most important method for detecting early lung parenchymal abnormalities and reduced lung function. Common HRCT findings of pSS in the lungs include ground-glass attenuation, bronchiectasis, a reticular pattern and honeycomb appearance.³ The presence of honeycombing was associated with increased mortality in pSS. There was a fourfold increased risk of dying after 10 years of the disease among patients with lung involvement compared with those without lung involvement in a Norwegian population.⁴

Changes in the respiratory tract in pSS can occur as variable symptoms, which was considered in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).⁵ It consists of the subjective and objective symptoms including persistent dry cough, bronchial involvement, shortness of breath, radiographic abnormalities on radiography or in chest HRCT and abnormal lung function tests ($70\% > DL_{CO} \geq 40\%$ or $80\% > FVC \geq 60\%$). The pulmonary weight has a value of 5 points. A maximum total score of 15 points can be achieved. It is suggested that a score of 5 points is associated with moderate pSS activity and > 14 points with shorter survival.^{6,7}

The aim of this study was to assess the incidence of pulmonary manifestations in pSS and to determine factors predisposing to this complication.

Material and methods

The study group consisted of 68 patients (66 women and 2 men) with a diagnosis of pSS on the basis of the American-European criteria of Sjögren's Syndrome Classification from 2002⁸, who were treated in the Department of Rheumatology and Internal Medicine, Wrocław Medical Hospital, in the years 2010–2014. Written informed consent was obtained from each patient before the study. The study was accepted by the Commission of Bioethics at Wrocław Medical University (no. 357/2010). The median age of patients was 51 (19–82) years. The median time between the onset of first symptoms and diagnosis of pSS was 7.5 years; among patients with changes in the respiratory system, the average time was 7 years and it was the shortest in comparison to other initial symptoms: changes in major salivary glands (10 years), enlarged peripheral lymph nodes (9 years), skin changes (11 years),

arthritic changes (9 years). Among the patients who were possibly affected by pulmonary manifestations, chest HRCT was performed without and with administration of contrast medium. Symptoms leading to the expanding of medical imaging by chest HRCT were dry cough not related to the infection and lasting for 3 months, dyspnea, decreasing stamina due to the symptoms of dyspnea or paroxysmal dry cough.

The efficacy of immunosuppressive therapy was assessed on the basis of the chest HRCT performed on patients who have been receiving treatment for more than 6 months (Table 1, patient number 3, 5, 6, 8–11, 13, 15 and 16). The examination was performed with the same equipment. Additionally, all of these patients underwent basic laboratory tests including a complete circumferential blood count, concentration of C-reactive protein (CRP, $nv < 5$ mg/L), erythrocyte sedimentation rate (ESR, $nv < 15$ mm/h), value of gamma globulins marked in electrophoresis of proteins ($nv 0.6$ – 1.2 g/dL), immunological panel including rheumatoid factor (RF, $nv < 14$ IU/mL) and specific antibodies anti-SSA, anti-SSB and anti-Ro52 (Anti-ENA ProfilePlus1 EUROLINE, EUROIMMUN, Lübeck, Germany) as well as the assessment of lymphoid infiltrates in minor salivary glands graded on the focus score scale (0–4). The assessment of the degree of intensity of symptoms of the oral cavity and eye dryness was based on the EULAR Sjögren's Syndrome Patient Reported Index Scale (ESSPRI).⁹ 0 points indicated no symptoms of dryness whereas 10 points indicated strong intensity of dryness which made everyday functioning difficult for patients. In statistical analysis, the Student's t-test, Kruskal-Wallis test and ANOVA were used to compare 3 groups of patients (with positive and without changes in chest HRCT and patients without chest HRCT). The assumed alpha significance level was 0.05, $p < 0.05$.

Results

In the group of all patients with pSS, 30 (44%, females only) indicated the need to expand medical imaging via chest HRCT scan. The symptoms leading to this examination were as follows: in 80% of cases it was constant, dry and persistent cough periodically waking up the patients at night. In 18% of cases it was the decreased stamina mainly due to coughing fits (91%). In 2% of cases, dyspnea not related to dry cough was reported. There were no changes in patients undergoing clinical chest examination. No correlation was found between the respiratory system symptoms and cigarette smoking. There were no other factors which were found to have an influence on the changes in the lungs, for example profession, older age and longer duration of pSS. In the group of patients with pSS who did not have a HRCT scan first, chest radiography was obtained, which were positive in all but 2 cases (a lung tumor and suspicion of in-

Table 1. Treatment of patients with changes in the chest HRCT

Patient No.	Treatment duration (months)	Treatment before chest HRCT	Efficacy of treatment (control chest HRCT)	Encorton (mg)	Cyclosporine (mg)	Azathioprine (mg)	Type of changes (chest HRCT)
1	<6	HQ	–	–	–	150	N/ F
2	<6	HQ,GKS	–	10	–	–	ML
3	12	HQ, CYC	stabile	2.5	150	–	N
4	<6	CHQ,CYC,GKS	–	10	–	150	N/ ML
5	6	CHQ,GKS	complete regression	7.5	150	–	GGO/ ML
6	9	n dgn	stabile	5	150	–	N
7	<6	HQ,AZA,	–	–	–	175	F
8	15	CHQ, GKS	stabile	10	–	100	F/ ML
9	12	n dgn	progression	10	–	150	GGO
10	13	n dgn	complete regression	5	–	150	F/ ML
11	13	CYC	–	2.5	–	100	GGO
12	<6	MTX	partial regression	–	–	100	F
13	12	MTX, GKS	–	5	–	150	LIP
14	<6	CHQ, GKS	stabile	–	100	–	N
15	12	HQ	progression	5	150	–	N/ F
16	21	CHQ	–	10	–	50	GGO/ ML
17	<6	CHQ	–	–	–	150	F
18	<6	n dgn	–	5	–	–	F
19	<6	GKS	–	15	150	–	LIP/ ML
20	<6	n dgn	–	5	–	–	F

N – nodules; F – pulmonary fibrosis (in this, GGO – ground-glass opacity image); LIP – lymphocytic interstitial pneumonia; ML – mediastinal lymphadenopathy; GKS – corticosteroids; MTX – methotrexate; HQ – hydroxychloroquine; CHQ – chloroquine; n dgn – new diagnosis; chloroquine at a dose of 250 mg per day or hydroxychloroquine at a dose of 200 mg per day were administered in the treatment of all patients except one, number 19; cyclophosphamide at a dose of 800 mg per month was administered intravenously in the treatment of patient number 2.

terstitial changes) indicating the need for HRCT scan. The chest HRCT scan in 30 patients revealed lung tissue changes in the progress of pSS in 20 of 30 patients (66%), which made up 29% of all the examined patients (of 68). The discovered changes were: nodes (30%), emphysema (40%), fibrosis (65%), lymphocytic interstitial pneumonia (10%) and enlarged mediastinal lymph nodes (35%). Emphysema changes have never exemplified a singular pathology and they have always involved the co-occurrence of nodules and pulmonary fibrosis. The mean age of patients diagnosed with chest changes seen on HRCT scan was 52 years. No correlation was found between the occurrence of HRCT changes and the age of the patients ($p = 0.8$), CRP concentration ($p = 0.3$), increased CRP concentration $\text{CRP} > 5 \text{ mg/l}$ ($p = 0.1$), ESR ($p = 0.2$),

abnormal ESR value – $\text{ESR} > 20 \text{ mm/h}$ ($p = 0.9$), intensity of infiltration in focus score ($p = 0.8$), number of leucocytes ($p = 0.7$), leucopenia $< 4 \times 10^9/\text{L}$ ($p = 0.5$), RF value ($p = 0.3$), gamma globulin value ($p = 0.5$), intensity of eye dryness ($p = 0.6$) or intensity of oral cavity dryness ($p = 0.3$). Additionally, no correlation was found between more frequent occurrence of the antibodies anti-SSA, anti-SSB or anti-Ro52 and HRCT changes ($p = 0.3$; 0.07 ; 0.4). According to the clinical data, HRCT changes occurred more often only in patients suffering from peripheral arthritis ($p < 0.01$). The characteristics of all patients with pSS are presented in Table 2.

Treatment of lung changes and its effectiveness: 76% of 68 patients used chloroquine (250 mg/day or hydroxychloroquine (200 mg/day, 7% azathioprine (mean

Table 2. The characteristics of all patients with pSS

Patients with pSS all study groups	With changes in chest HRCT	Without changes in chest HRCT	p-value
Number of patients 68	20	10	–
Age 51 (19–80) years (min-max)	52 (31–72)	48 (27–64)	0.78
CRP (mg/L) 2.33	2.85	1.64	0.37
ESR (mm/h) 26	37	39	0.24
γ-globulin (g/dL) 1.4	1.7	1.5	0.50
RF (IU/mL) 92	66	55	0.37
Focus score (0–4 score) 2	2	2	0.87
ESSPRI (cm):			
eye dryness 4.2	4.9	4.3	0.64
oral cavity dryness 4.4	4.7	6.1	0.29
leucopenia <4000/u (n) 29	6	4	0.57
Clinical signs (number of patients):			
skin changes 23	6	3	1.0
fatigue 28	15	8	0.27
arthralgia 48	15	9	0.14
salivary gland enlargement 33	10	7	0.29
arthritis 22	15	1	<0.001
Raynaud syndrome 1	1	0	0.47
peripheral neuropathy 8	3	2	0.72
lymphadenopathy 15	6	6	0.11

CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; γ-globulin – value of gamma globulins marked in electrophoresis of proteins; RF – rheumatoid factor; ESSPRI – EULAR Sjögren's Syndrome Patient Reported Index Scale; (n) – number of patients.

125 mg/day), 20% methotrexate (mean 16.5 mg/week), 4% ciclosporin (mean 145 mg/day) and 41% prednisolone (mean 6 mg/day).

Chloroquine at a dose of 250 mg per day or hydroxychloroquine at a dose of 200 mg per day were administered in the treatment of all patients except one where ophthalmic contraindications made such therapy impossible. The details of the pharmacotherapy are presented in Table 1. Additionally, cyclophosphamide at a dose of 800 mg per month was administered intravenously in the treatment of one patient (number 2) due to vasculitis manifested by palpable purpura and ulcers of the lower extremities. There was no correlation between treatment in all 68 patients and the indication to do chest HRCT ($p = 0.7$, Student's *t*-test).

Discussion

T-lymphocyte infiltration localized in airways is leading to the epithelial cells damage and to the loss of their secretory function which is primarily manifested by coughing. Respiratory manifestations in pSS are heterogeneous and may include: dry cough, diffuse panbronchiolitis (DPB), bronchiectasis, nonspecific interstitial pneumonia (NSIP), idiopathic pulmonary fibrosis (IPF), cryptogenic organizing pneumonia (COP), lung cysts, nodular opacities, follicular bronchiolitis, lymphoid interstitial pneumonia (LIP), pseudolymphoma, lymphomatoid granulomatosis, lymphoma (usually of mucosa-associated lymphoid tissue type-MALT), pulmonary amyloidosis, pulmonary hypertension and pleural involvement.^{11,12} The mediastinal manifestations of pSS include lymphadenopathy, thymic lymphoid hyperplasia, multilocular thymic cysts and, rarely, MALT lymphoma.^{11,12} Such a wide range of manifestations may lead to significant diagnostic and therapeutic difficulties. Occasionally, a histopathological assessment of lung biopsy is needed. In HRCT scans, bronchial wall thickening (8–68%), nodules (6–29%), bronchiectasis (5–46%), air trapping (32%) and ground-glass attenuation were most frequently observed.^{11–13}

According to available publications, the prevalence of respiratory manifestations in pSS is estimated to be about 9–12% and clinical features are present in about 43–75% of patients when radiology imaging such as chest X-ray, HRCT or MRI are performed.

Papiris et al. found that cough occurred in 41% of patients with pSS.¹⁰ When HRCT was performed in all patients, the findings in the lungs were observed in up to 50% of patients; and when BAL was performed, the percentage increased to 55% in patients with pSS without clinical symptoms of lung involvement. The transformation risk of BAL changes into severe lung disease is unknown, therefore this test could not be routinely used in pSS with prognostic value. The clinical symptoms of lymphoma are frequently nonspecific and include dry cough or slowly increasing dyspnea.¹⁰ Similar to Papiris et al. in a comparable percentage (44% of patients), there were indications to perform chest HRCT. We found that the most common indication in 80% of patients was a persistent dry cough for at least 3 months and rarely dyspnea, reduced exercise tolerance due to dyspnea or sudden attacks of dry coughing. In the group of 30 patients, in case of 20 of them (66%) changes on HRCT scans were found (29% of patients from the whole group with pSS). Pulmonary fibrosis, emphysematous changes and mediastinal lymphadenopathy were the most common findings. In the recent Norwegian study, the percentage of lung involvement on HRCT scans in patients with pSS was similar to our findings (23% of patients out of 217 with pSS).⁴

Contrary to our research, most other studies reported the presence of predictive factors for pulmonary involve-

ment in pSS (e.g., anti-SSB antibodies or hypergammaglobulinemia).¹⁴ Hyperglobulinemia was often observed in patients with pulmonary involvement in pSS, which was not confirmed in our study.¹¹ Unlike our results, the risk of airway involvement increased with male gender, older age at the time of diagnosis and in smokers.¹⁰

Factors such as older age and longer duration of pSS may be associated with bad prognosis but this was not confirmed in our study. Palma et al. found that the quality of life was lower in patients with pSS associated with pulmonary involvement compared to patients without airway changes, according to the Medical Outcomes Study 36-Item Short-Form Health Survey Physical Functioning ($p = 0.03$). Additionally, in patients with pulmonary findings, increased mortality was observed after 10 years ($p = 0.002$, 17% vs 4.5%).⁴

Currently, the correlation between anti-SSA and anti-SSB antibodies and airway involvement is not precisely explained and the findings from various studies contradict each other.¹⁴ Generally, the lung findings were more common when the anti-SSB antibodies were found than anti-SSA antibodies, which was not confirmed in our study, but the p -value was higher in patients with anti-SSB antibodies than with anti-SSA antibodies in our study.

Many types of cytokines, such as IL-10, IL-6 and TGF- β , INF- γ , a unique chimera-type member of the β -galactoside-binding soluble lectin family galectin-3 and lymphocytes Th1 and Th17 have been known to regulate the pathogenic process of ILD.^{15–17}

Lin Yang et al. suggested the protective role of autoantibodies against interferon- γ , which significantly reduces the frequency of pulmonary fibrosis and concentration of C-reactive protein in patients with pSS. Autoantibodies against interferon- γ may become a prognostic marker of pulmonary manifestations and have a close correlation with autoimmune inflammation in pSS.¹⁸ In patients with pSS without prior ILD, the cumulative incidence of ILD in patients with pSS was 10% ($\pm 3\%$) 1 year after diagnosis of pSS and increased to 20% ($\pm 4\%$) 5 years after diagnosis of pSS. The development of lung disease in pSS was associated with poor survival.¹⁹ Thus, repeated pulmonary function tests and diagnostic radiology are necessary and should be the preferred methods to monitor pSS-specific organ involvement.

Pulmonary involvement in pSS may present in various forms and clinical manifestations that were included in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI); this index includes clinical symptoms and objective tests such as persistent cough, shortness of breath on exercise, radiological or HRCT evidence of interstitial lung disease and abnormal lung function tests ($DL_{co} < 70\%$, $FVC < 80\%$).⁵ Pulmonary domain weight stands at 5 points. Patients can accumulate 15 points in the case of the highly active pulmonary involvement. Five points in the ESSDAI index is considered to be a moderate activity of pSS and 14 points or more are cor-

related with increased mortality.⁶ According to Ramos-Casals et al., the clinical domain with greatest activity during follow-up in comparison to the activity measured at diagnosis was the pulmonary part. At the beginning of the study, changes were observed only in 6% of patients and after 75 months the percentage increased to 15%. The mean total ESSDAI score for this domain was low (2–5). Older patients at the time of diagnosis (> 70 years) were less active during follow-up, but had a higher pulmonary activity score.⁷

Findings on the chest HRCT scan in our study were more common in patients with arthritis, but the group with these complications was relatively small.

For the time being, treatment of the pulmonary manifestations is undefined and is based on clinical experience. The explicit guideline (algorithm) does not exist yet. In patients with pSS and changes in the upper respiratory tract the most common symptoms are associated with dryness. Thus, muscarinic receptor agonists (pilocarpine and cevimeline) in nasal or throat sprays and humidifiers may be used in therapy. In pulmonary involvement, the treatment consists of immunosuppressive drugs such as hydroxychloroquine, azathioprine, cyclosporine and, in life-threatening cases, cyclophosphamide and corticosteroids. Isolated reports have suggested the benefits of using an oral cyclosporine in pSS patients with interstitial cystitis. In patients with active pSS, rituximab, belimumab and abatacept have also been used, but this treatment is uncommon due to its high cost, and questions relating to its usefulness in pSS still remain unanswered.^{21–24}

In conclusion, pulmonary involvement in pSS is common and occurs in around 30% of patients. This represents one of the most intriguing aspects of the disease. The main symptom is persistent dry cough that periodically wakes up patients at night. Radiological tests in daily clinical practice allow diagnosis of pulmonary findings, even if the changes are not very advanced. Additionally, they enable monitoring of pSS activity, because a factor or factors predisposing to the development of changes in the respiratory system have not been found. Changes in HRCT occur more frequently only in patients with peripheral arthritis.

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