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NON-SPECIFIC INTERSTITIAL PNEUMONIA: DIFFERENTIATION OF INTERSTITIAL LUNG DISEASE FROM AUTOIMMUNE DISEASES.

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Nonspecific interstitial pneumonia: differentiation of interstitial lung disease from autoimmune diseases.

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Abstract: Recent evidence suggests that nonspecific interstitial pneumonia (NSIP) has a distinct clinical feature among other idiopathic interstitial pneumonias, and some evidence points to a possible pathogenetic role for autoimmune immunity.

In the medical database of the Samarkand City Hospital No. 1, patients diagnosed with NSIP (n=58) were identified and after their initial examination, 32 cases of NSIP were identified and re-evaluated using a dynamic integrated multidisciplinary approach and a retrospective analysis was carried out.

The aim of this study was to evaluate whether NSIP might represent an early pulmonary manifestation of an autoimmune disease. >50% of patients diagnosed with NSIP developed clinical signs of autoimmune disease within 2 years, suggesting a possible link between NSIP and autoimmune disease.

Keywords: nonspecific interstitial pneumonia (NSIP), connective tissue, autoimmune diseases.

Relevance: Nonspecific interstitial pneumonia (NSIP) is called idiopathic interstitial pneumonia. This disease occurs in idiopathic pulmonary fibrosis (IPF). Most of the patients are women aged 40-50 and there is no reason for their relationship. Similar disorders are observed in connective tissue diseases (in particular, systemic scleroderma and autoimmune myositis), some forms of pain are associated with hypersensitivity pneumonitis.

It can be found in the presence of different clinical and radiological signs [2]. Traditionally, and on clinical grounds, the recommendation that NSIP should be etiologically "idiopathic" [3] or "secondary", depending on the absence or presence of known etiological conditions for NSIP, should be the "clinical diagnosis" of NSIP is determined by Only for idiopathic and biopsy-proven cases, no causative factor is identified [2, 4].

Interestingly, a recent report from the American Thoracic Society Project showed that NSIP has a clear clinical profile, is particularly common in middle-aged and non-smoking women, and shows a good long-term prognosis [5]. In the NSIP diagnostic approach, histopathological diagnosis is still based on surgical lung biopsy [3], although the need for histological examination has been questioned in some cases [6]. Two recent studies have found an association between NSIP and autoimmune diseases [7, 8]. In a US study, more than 80% of 24 patients diagnosed with NSIP were found to have undifferentiated connective tissue disease (USD) at baseline [7], and connective tissue disease (USD) occurred in the Asian NSIP cohort. was 10% of cases during follow-up [8], suggesting a possible role of autoimmunity in NSIP.

Research purpose. The NSIP was an assessment of the possibility of early pulmonary manifestations of autoimmune disease. >50% of patients diagnosed with NSIP developed clinical signs of autoimmune disease within 2 years, suggesting a possible association between NSIP and autoimmune disease.

Research materials and methods. In the medical database of Samarkand City Hospital No. 1, patients with the diagnosis of "NSIP" (n = 58) were found and after their initial review, 32 cases of NSIP were identified and re-evaluated using a dynamic integrated multidisciplinary approach. 24 diseases with NSIP were selected for the study. Average age. The mean age at first respiratory symptom was 49.2 ± 7 years, 70% were female and 52% were never smokers. During follow-up (mean \pm standard deviation 52.7 ± 29 months, range 12-138 months), 14 (49%) patients had autoimmune diseases, seven (26%) had autoimmune thyroiditis, six (22%) had undifferentiated connective tissue. infected with immune diseases. Connective tissue disease accounted for three (11%). Patients with connective tissue autoimmune diseases were older and more often women who did not smoke. NSIP >50% of patients diagnosed with NSIP developed clinical signs of autoimmune disease within 2 years, suggesting a possible association between NSIP and autoimmune disease. Nonspecific interstitial pneumonia (NSIP) was originally defined as a histopathologic condition. Examination of each person included in the research was conducted on the basis of anamnesis collection, clinic, general laboratory analysis, and instrumental examination methods.

The diagnosis of NSIP was made according to the global strategy for the treatment and prevention of NSIP (GINA 2006, 2007).

The result. The diagnosis of various BTC entities was based on previously published criteria [11–14], including mixed BTC [15] and ABTC (absence of infection and symptoms associated with BTC, systemic inflammation without meeting the classification criteria evidence) was carried out according to Identified in CT [7, 16, 17]. Briefly, patients may experience Raynaud's phenomenon, arthralgia/multiple joint swelling, photosensitivity, involuntary weight loss, morning stiffness, dry mouth or dry eyes (shicca features), dysphagia, recurrent unexplained fever, asked about gastrointestinal, skin changes. (rash), mouth ulcers, nonandrogenic alopecia and proximal muscle weakness.

The diagnosis of autoimmune thyroiditis was based on the presence of anti-thyroid antibodies [18] and diffuse thyroid hypoechoogenicity on ultrasound [19].

All cases with clinical, laboratory, radiological, or pathological criteria for interstitial lung disease (ILD) other than iNSIP, or those with documented drug, airborne antigen, or occupational exposure, were excluded from the study. Cases meeting the rheumatologic criteria for BTC, ABTC, mixed BTC, and/or autoimmune thyroid disease criteria at first respiratory symptoms were also excluded from the analysis.

Further assessment.

Follow-up evaluation of patients included in the study once a year includes: Klinik va fizik tekshiruv:

Laboratory examination (including autoimmune profile, for example, rheumatoid factor, complement C3 and C4, antinuclear antigen, extractable nuclear antigens, autoantibodies against citrulline, antithyroglobulin, antithyrotropin receptors and antithyroid peroxidase (antithyroid peroxidase). TPO) autoantibodies, erythrocytes erythrocyte sedimentation rate (ECHT) and/or C-reactive protein (CRO) level and hepatitis C and B virus serology);

Pulmonary function tests;

High resolution computed tomography (CT) of the chest;

Rheumatologist's examination:

When there was an additional indication from rheumatologists and/or endocrinologists due to thyroid diseases, additional examinations were performed (for example, capillaroscopy, X-rays of the arms and legs, Schirmer's test, muscle and/or lymph biopsy, electromyography, radiography of the digestive tract and ultrasound of the thyroid gland).

Pathological and X-ray analysis.

All lung biopsy specimens were reviewed independently by two pulmonary pathologists without knowledge of the clinical or radiological findings. At least two different sections of the lung could be examined in each patient. Consensus was reached for patients with initial disagreement.

CT images were reviewed by chest radiologists in consensus at a separate workstation, and terminology was based on the Fleischner Society dictionary [20].

As previously described [19], to determine the distribution of parenchymal changes, the lungs were divided into six zones (upper, middle and lower zones in two lungs), fibrosis was scored with two points (interstitial changes and traction bronchiectasis) and images were taken. Grades 0 to 3 were scored. Scores for the five areas were summed to provide a total "roughness score" (range 0–15) [20]. Statistik tahlil.

Continuous data are expressed as mean \pm SD. Categorical data are expressed as percentages. For each patient, comparisons of clinical, functional, and radiographic parameters were made between the first respiratory symptoms and the last follow-up assessment.

The analysis was carried out in the pulmonology department of the clinic of Samarkand City Hospital No. 1. After initial review of the charts, we identified 58 patients with a pathological diagnosis of NSIP. At initial evaluation, 37 (58.7%) cases were considered to be iNSIP. Of the 37 NSIP cases classified as idiopathic, 10 patients were excluded from the analysis on multidisciplinary evaluation.

A total of 37 cases of idiopathic nonspecific interstitial pneumonia (NSIP) were identified, and 27 were finally included in the analysis. During follow-up, 52% of patients developed autoimmune diseases. BTC: connective tissue disease; DILD: drug-induced lung disease; ABTC: undifferentiated connective tissue disease; IPF: idiopathic pulmonary fibrosis; : hypersensitivity pneumonitis.

Demographic and clinical characteristics of the 27 NSIP cases selected for analysis. The age at first respiratory symptoms (mean \pm SD) was 54.2 ± 8 years, and the majority of patients were female and never smokers. Mean follow-up (mean \pm SD) was 59.7 ± 29 months, with a range of 12–13 months. At the first presentation, most patients presented with shortness of breath (85% of patients) and 33% with cough. One patient died after 11 months of follow-up due to severe acute respiratory failure associated with an acute exacerbation of NSIP (mortality rate 3.7%).

All 27 patients were treated with tapering doses of systemic corticosteroids (prednisolone $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) for at least 1 year. In addition to prednisolone, 12 of a total of 15 patients with "fibrotic NSIP" and three patients with "fibrotic NSIP and other symptoms" also received cyclophosphamide ($100 \text{ mg} \cdot \text{day}^{-1}$) for at least 1 year (when observed). . Azathioprine was added to prednisolone in two of nine patients with NSIP and cyclophosphamide in three cases to prednisolone for 1 year.

Autoimmune findings.

Among 27 patients diagnosed with NSIP, a total of 14 (52%) patients subsequently developed autoimmune disease. The mean \pm SD (range) interval to the onset of autoimmune disease was 22 ± 18 months (range 12–14 months) from the initial diagnosis of NSIP. At the time of the current analysis, 15 patients had <14 months of follow-up (eight of whom had not developed any autoimmune disease).

At the time of first respiratory symptoms, four (14.8%) patients had symptoms and signs suggestive of an autoimmune disease in the absence of positive serological results, three (11%) patients had positive serological results, and seven patients An increase in ECHT levels was observed. (26%), in the complete absence of any signs or symptoms of autoimmune disease (Table 2).

At follow-up, autoimmune thyroiditis was observed in seven (26%) patients, ABTK in six (22%) and CT in three (11%) patients. In two cases, patients developed two different autoimmune diseases: autoimmune thyroiditis, combined with rheumatoid arthritis and ABTK, respectively. The type of autoimmune thyroiditis was chronic Hashimoto's thyroiditis in all seven patients. In detail, we observed clinical hypothyroidism in four cases with low T4 and elevated thyroid-stimulating hormone (TSH) levels.

In the remaining three cases, patients have subclinical hypothyroidism, thyroid hormone levels are normal, and TTG levels are elevated. TPO and thyroglobulin

antibodies were positive at follow-up in five of seven patients, with only one thyroid antibody positive in two patients. Ultrasound examination of the thyroid gland showed diffuse hypoechoicity in all cases.

Two out of three patients (66%) who presented with positive serological results at baseline developed complications of CKD during follow-up. Of the eight patients with elevated ECHT levels, seven (87.5%) developed autoimmune disease (SRB 13; p = 0.03).

Three of four patients (75%) with systemic symptoms (and negative serology) at the time of first respiratory symptoms developed autoimmune diseases during follow-up.

Characteristics of patients with and without autoimmune diseases

Characteristics of patients who developed autoimmune diseases after the initial diagnosis of NSIP. Patients who developed autoimmune diseases at later follow-up were more likely to be older women and never smokers than those who did not.

Characteristics of patients with autoimmune diseases compared with those without.

A trend toward less severe restrictive disorder was observed in the group of patients who developed autoimmune diseases during follow-up. Analysis of the final CT scan score did not show a statistically significant difference between the two groups, but there was a trend toward lower interstitial scores in patients who subsequently developed autoimmune disease compared to other patients. No differences were found in terms of pathological signs.

Pathological and radiological signs.

Among 37 NSIP cases initially selected from the database, the histopathology of 30 patients was reviewed. In two cases, finally, the histological findings were defined as unusual interstitial pneumonia in both lobes, and one case had a high-sensitivity pneumonitis pattern in one lobe (these three patients were excluded from the final analysis in a multidisciplinary approach, 15 of the 27 NSIP selected were "fibrous NSIP" `` appearance and nine cases showed "cellular NSIP" appearance, while three cases were defined as "fibrosis NSIP and other appearances". The specimen was a common histopathological pattern [12]; however, in these cases, also in one case with multiple fibroblastic foci (patient 3) and in two cases (patients 13 and 18) with peribronchiolar metaplasia, multiple pits and follicular bronchiolitis associated with signs of organizing pneumonia.).

Radiological analysis at baseline and follow-up was available in 21 of 27 cases. Descriptive and scoring characteristics of chest CT scans are summarized in Table 4. No statistically significant differences were assessed between patients with and without autoimmune disease either at first respiratory symptoms or at last follow-up; no statistically significant differences were found between patients with autoimmune diseases and patients without progression (at first assessment or follow-up).

Summary.

In this study, we hypothesized that the clinically distinct NSIP entity may be associated with autoimmune diseases. Our findings showed that after a

multidisciplinary approach in a group of NSIP patients systematically screened for the development of autoimmune diseases: 1) > 50% develop an autoimmune disease (autoimmune thyroiditis, ABTK and BTK) after a mean follow-up. 14 months; 2) autoimmune thyroiditis is the most common autoimmune disease (26% of cases); and 3) patients with autoimmune diseases are older and often women who do not smoke.

It is estimated that 15–20% of patients with idiopathic NSIP have latent BTC or develop BTC later [23]. Thus, occult BTK can mimic idiopathic interstitial pneumonias, as pulmonary manifestations can often dominate the clinical presentation or precede systemic findings [24]. However, these previously published data relate to idiopathic NSIP in general, and evidence for autoimmune involvement in “idiopathic” NSIP is limited.

Data on autoimmunity in NSIP have been presented in three previously published studies [7, 8, 20]. A small series of six patients with histologically and clinically confirmed NSIP who subsequently developed typical collagen vascular disease was published by a group of Japanese authors in 2006 [20]. Recently, in a retrospective analysis and evaluation of the clinical presentation and pulmonary function changes of NSIP in an Asian population, Park et al. [8] found that 10% of cases developed CT clinical manifestations during follow-up. A study published by Kinder et al. [7] found that the majority (88%) of patients classified as NSIP met ABTK criteria at first pulmonary presentation. However, the characteristics of these three studies were significantly different from those of our study, because, firstly, they were not specifically designed to carefully look for the development of autoimmune diseases in the long-term follow-up of NSIP, and secondly, the diagnosis. NSIP was not based on a multidisciplinary approach [5]. A study by Sato et al. [17] was a retrospective analysis including 26 patients with secondary NSIP who had underlying diseases at the time of histological diagnosis, including Ktida.

In six of the 26 patients studied, NSIP occurred 6 months before the onset of BTK. However, this article does not provide a description of the methods used, nor the results showing the CT findings [16]. The aim of our study was completely different from the American study [7], because we deliberately excluded patients with CT and clinical and serological manifestations of autoimmune thyroiditis at the first presentation of the lungs.

Thus, the aim of our study was to assess whether patients diagnosed with NSIP may subsequently develop an autoimmune disease. The development of an autoimmune disease, e.g. Found by BTKs, Park et al. [8] was a randomized observational retrospective analysis of the clinical course and pulmonary function changes of NSIP. In fact, this study [8] was not designed to assess autoimmunity in this NSIP population.

Furthermore, these patients belonged to an Asian population, in contrast to the Caucasian population in our study, and there is no evidence of possible ethnic differences in autoimmunity in NSIP. Despite the differences between the aforementioned [7, 8, 16] methodology and our current study, all these findings together support the hypothesis that the autoimmune background may play an

important role in the pathogenesis of NSIP and NSIP. Although the exact pathogenetic mechanisms are still unknown, it is thought to be an early pulmonary manifestation of autoimmune disease.

The association between CT and autoimmune thyroid disease is well recognized. The most common is the association of rheumatoid arthritis, Sjögren's syndrome, and autoimmune thyroiditis [16,17] and is frequently seen on CT in patients with autoimmune thyroiditis [18]. The specific rationale for investigating thyroid autoimmune disease in our NSIP patients was based on the hypothesis of its possible association with thyroid disease, as both the lung and thyroid express thyroid transcription factor-1, which plays a role in thyroid development and physiology.

Our data on the development of autoimmune thyroiditis in NSIP support single case reports describing the association of NSIP and chronic/autoimmune thyroiditis [15,18]. In autoimmune thyroiditis (an organ-specific autoimmune disease), the histopathological appearance of the thyroid gland and the histopathological appearance of the salivary glands and lymph nodes in Sjögren's syndrome are similar, showing characteristic focal or diffuse T-lymphocyte infiltrates [17,18]. share pathogenetic pathways. Surprisingly, NSIP typically shows T-lymphocyte infiltrates in the lung interstitium, as well as focal B-cell accumulation and fibrosis [1]. Based on these observations, we hypothesize that "NSIP" may not be a latent autoimmune disease but a hitherto unrecognized organ-specific autoimmune disease such as autoimmune pneumonitis [7].

However, we know that there is currently no real evidence to prove or disprove this hypothesis.

The NSIP population of this analysis showed clinical similarities with recently described study populations [5, 8], dominated by never-smoking, middle-aged women, with significantly stable pulmonary function at follow-up [4, 18] . Compared to the study by Park et al. [8], we found a higher frequency of BTC development during follow-up (in our analysis, a total of 33%, including BTC and ABTC, compared to 10% in their study, including BTC and mixed BTC), probably to identify possible ethnic differences in the development of autoimmune diseases. as a result of our systematic approach. In the polyclinic, an increase in patients with interstitial lung diseases, which are more common in women of working age, was observed, in which shortness of breath, weakness, cough, etc. prevailed. The importance of using imaging technologies was shown. Consultation with a pulmonologist is recommended in the treatment of patients with rheumatic diseases [16,13].

Furthermore, the most important difference between our autoimmune results and those of Park et al. [8] was the high rate of autoimmune thyroiditis we found (26% of the total, which is almost half of the total autoimmune diseases), which was not considered and investigated in the previous study [8].

This study has a number of limitations, such as the following: it is a descriptive study that only speculates about possible pathogenetic mechanisms and includes a relatively small number of patients. However, although the population of this analysis

was relatively small, it was carefully characterized in a multidisciplinary approach, and it should be noted that NSIP is a rare disease and therefore it is very difficult to collect many patients. This analysis was performed only in patients with complete autoimmune data (seven patients were excluded due to incomplete data), which, as noted earlier, is a bias of the "complete case" analysis. can cause deafness [17].

However, even if no autoimmune disease had developed in these excluded patients, the proportion of cases developing autoimmune disease would still have been more than one-third of the total study population. Conversely, given that the median time to develop autoimmune disease is 12 to 14 months from the initial diagnosis of NSIP, some of our patients may still develop autoimmune disease in the future.

Despite these limitations, this study is the only analysis that presents serological and clinical data of autoimmune diseases carefully and systematically collected during long-term follow-up of patients with NSIP, characterized by surgical lung biopsies and leading to the final diagnosis. based on in a multidisciplinary approach. The results of this study emphasize the need for a complete autoimmune evaluation in the follow-up of patients with NSIP, including thyroid disease. Thus, the development of autoimmune thyroiditis in 26% of cases of this study population represents a new finding. Clinical studies have shown that depending on the age of the patient, individual phases of COVID-19 can be more or less virulent: if tolerance to the first virulent phase decreases with age, the last hypervirulent phase can be life-threatening. [14]. threatens small patients. To our knowledge, no previously published articles on NSIP have demonstrated this finding. Data from a group of patients who did not develop any autoimmune disease (younger, mostly smokers) may support the hypothesis of a different NSIP phenotype with smoking pathogenesis as previously proposed [9, 10].

In conclusion, we present here the largest cohort of patients systematically investigated for the development of autoimmune diseases of NSIP. The study highlights the high prevalence of autoimmune manifestations in patients initially diagnosed with "idiopathic" NSIP and adds to the existing literature the remarkable frequency of autoimmune thyroiditis, suggesting long-term follow-up with a multidisciplinary clinical approach and evaluation. It is mandatory for patients with autoimmune diseases. Although a definite conclusion cannot be drawn due to limited data, this study suggests a possible association between NSIP and the clinical presentation of autoimmune diseases. Future studies should confirm these findings.

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