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Original Investigation

Characterization of patients with idiopathic interstitial pulmonary disease and capillary and laboratory findings in two health institutions in Medellín, Colombia: A descriptive study

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ABSTRACT

Introduction: Interstitial lung disease (ILD) usually has a poor therapeutic response and prognosis. One of the methods that could help in the diagnosis and optimize the management of these patients is capillaroscopy. The study aimed to determine the clinical and capillaroscopic characteristics of patients with ILD and the frequency of findings suggestive of autoimmune disease.

Materials and methods: A descriptive observational study that evaluated patients with ILD treated between 2010 and 2019 without a previous diagnosis of autoimmune disease. An interview, capillaroscopy, and laboratory tests were performed.

Results: 28 patients were evaluated, 16 (57.1%) were women and 17 (60.7%) had hypertension. Three patients (10.7%) reported morning stiffness for more than 60 minutes and there was

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one unexplained digital edema. There were no telangiectasias, Raynaud's phenomenon, mechanic's hands, sclerodactyly or Gottron's sign, or ANAS titres greater than 1:80. The rest of the laboratory tests were negative in 100% of the patients. In the capillaroscopies, 13 (46.4%) patients had a normal capillaroscopic pattern, and 15 (53.6%) had capillaroscopic abnormalities of undetermined significance. There were none with a pattern of systemic sclerosis or similar.

Conclusions: No laboratory or capillaroscopy findings were found that suggested interstitial disease with autoimmune features, possibly due to the low prevalence of the disease, its high mortality, and underdiagnosis. These findings reinforce the concept of capillaroscopic normality in patients with non-autoimmune ILD and call for an active search for ILD with autoimmune features for prognostic purposes.

Caracterización de pacientes con enfermedad pulmonar intersticial idiopática y hallazgos capilaroscópicos y de laboratorio en dos instituciones de salud en Medellín, Colombia: estudio descriptivo

Palabras clave:
Enfermedades pulmonares intersticiales
Angioscopía microscópica
Autoinmunidad

RESUMEN

Introducción: La enfermedad pulmonar intersticial (EPI) suele tener una pobre respuesta terapéutica y un mal pronóstico. Uno de los métodos que podrían ayudar a su diagnóstico y optimizar el manejo de estos pacientes es la capilaroscopia. El objetivo del estudio fue determinar las características clínicas y capilaroscópicas de pacientes con EPI y la frecuencia de hallazgos que sugieran enfermedad autoinmune.

Materiales y métodos: Estudio observacional descriptivo que evaluó pacientes con EPI, sin diagnóstico previo de enfermedad autoinmune, atendidos entre el 2010 y el 2019, a quienes se les realizó entrevista, capilaroscopia y se tomó laboratorio.

Resultados: Se evaluaron 28 pacientes, 16 (57,1%) de los cuales fueron mujeres y 17 (60,7%) tenían HTA. Tres pacientes (10,7%) refirieron rigidez matinal mayor de 60 min y uno edema digital inexplicable. No se encontraron telangiectasias, fenómeno de Raynaud, manos de mecánico, esclerodactilia o signo de Gottron, ni ANAS con títulos superiores a 1:80. El resto de paraclínicos fueron negativos en el 100% de los pacientes. En las capilaroscopias, 13 (46,4%) pacientes tenían un patrón capilaroscópico normal y 15 (53,6%) tenían anormalidades capilaroscópicas con significado indeterminado. No hubo ninguno con patrón de esclerosis sistémica o similar.

Conclusiones: No se hicieron hallazgos de laboratorio o capilaroscópicos que sugirieran enfermedad intersticial con características autoinmunes, posiblemente debido a la baja prevalencia de la enfermedad, su alta mortalidad y subdiagnóstico. Estos hallazgos refuerzan el concepto de la normalidad capilaroscópica en pacientes con EPI no autoinmune y constituyen un llamado a la búsqueda activa de la EPI con características autoinmunes para fines pronósticos.

Introduction

Interstitial lung disease is a heterogeneous group of chronic disorders characterized by involvement of the lower airway, especially the alveolar-interstitial structures, and often with poor therapeutic response, leading to a poor prognosis.[1,2] Among the multiple etiologies, its strong association with autoimmune diseases such as systemic sclerosis (SS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), characterized and Sjögren's syndrome (SS), among others, stands out; however, up to 35% of cases have been classified as idiopathic, and, in some cases, the clinical picture suggests an underlying autoimmune process without meeting the classification criteria for a specific rheumatological disease.[1] Therefore, in 2015, the *European Respiratory Society* (ERS) and the *American Thoracic Society* (ATS) published a consensus in which they proposed the term "*interstitial pulmonary disease with autoimmune features*" (IPAF) and unified the classification criteria with clinical, serological, and morphological domains.[3–5]

Among the diagnostic methods currently used for the study of patients with rheumatic diseases, there is capillaroscopy, a non-invasive technique used to visualize the

cutaneous microcirculation of the nail bed using optical magnification instruments, as well as to detect early changes in the microvasculature suggesting the presence of an underlying systemic disease.[6–8]

The objective of the study was to determine the clinical, radiological, serological, and capillaroscopy characteristics of patients with interstitial lung disease, without previous classification of autoimmune origin, who had been classified as idiopathic and not considered IPAF, to assess whether in this population, whose origin of their interstitial lung disease was unclear, there were laboratory and capillaroscopy findings that could point to IPAF in patients from 2 health institutions in Medellin during the period between 2010 and 2019.

Methodology

Design and study population

A descriptive observational study whose population consisted of all patients seen in 2 high complexity health institutions between 2010 and 2019, with a diagnosis of interstitial lung disease of no known autoimmune origin. Patients over 18 years of age with a diagnosis made by HRCT, fibrobronchoscopy, or biopsy (criteria defined by the ATS and ERS)[4,5] were included, while those with a previous diagnosis of any underlying autoimmune disease, psychiatric illness, cognitive disability, or any other condition that prevented them from giving consent to participate in the research, as well as deceased patients or without contact details, were excluded.

Collection process

Once approval was obtained from the health research committee of the Universidad Pontificia Bolivariana (UPB) and the participating institutions, the medical records were reviewed to select patients identified with the ICD-10 codes for interstitial lung disease and related diagnoses: drug-induced acute interstitial lung disorders (J702), drug-induced chronic interstitial lung disorders (J703), unspecified drug-induced interstitial lung disorders (J704), other interstitial lung diseases, other interstitial lung diseases with fibrosis (J841), other specified interstitial lung diseases (J848), interstitial lung disease, unspecified (J849), interstitial emphysema (J982), pulmonary eosinophilia not elsewhere classified (J82X), and other specified cardiopulmonary diseases (I278).

The researchers collected the information on an electronic form designed in the Magpi® tool and checked the quality of the data weekly, ensuring that errors or omissions were timely detected. From these patients, those who met the eligibility criteria for participation in the study were selected.

Subsequently, patients were contacted by telephone and invited to participate in the research. Those who accepted were invited to the health institution, where they were informed in more detail about the project, and informed consent was requested. Those who consented, underwent capillaroscopy by an experienced rheumatologist, and a sample was taken for the required laboratory tests: rheumatoid factor (RF), antinuclear antibodies (ANA), anti-deoxyribonucleic acid antibodies (anti-DNA), anti-cyclic citrullinated peptide antibodies (anti-CCP), antibodies against extractable nuclear antigens (ENA): anti-Ro/La, anti-RNP, anti-Smith, anti-SCL-70, and anti-Jo1. Once the results were obtained, they were entered into the database previously elaborated.

Variables of interest were:

a) *Socio-demographics:* age, sex, socio-economic status, occupation, occupational exposure.
b) *Clinical:* use of therapies such as oxygen, steroids, immunomodulators, antibiotics, transplant recipient, smoking, alcohol consumption, family history of RA, SLE, previous hospitalizations, presence of dyspnoea, dyspnoea grade by *Modified Medical Research Council* (mMRC), presence of inflammatory arthritis or morning joint stiffness greater than 60 min, palmar telangiectasias, Raynaud's phenomenon, unexplained digital edema, mechanic's hands, Gottron's, distal digital ulceration, sclerodactyly and family history of autoimmune disease.
c) *Capillaroscopic findings,* according to the update published by the EULAR microcirculation group, which evaluates density, dimension, abnormal morphology, and microhemorrhages.[9]
d) *Laboratory findings:* ANA, ANA titers and pattern, presence of ANE, ANE pattern, RF, anti-CCP, anticardiolipin, anti-DNA, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

After collecting all the information, it was exported to an Excel database, where the variables that required it were coded and categorized before analysis.

Control of biases

- Population selection bias: this bias was reduced by including the entire population that met the eligibility criteria; the population was not sampled due to the low prevalence of these diseases and the small number of patients who met the inclusion criteria. It was also controlled by exclusion criteria and a rigorous evaluation of each patient's medical history. However, it was not possible to control for the fact that not all patients were screened, but only those who wished to attend.
- Data bias: To control for bias on the part of the investigators, standardization of the data collection process was carried out so that there would be clarity on how the study variables should be recorded. In addition, capillaroscopy was performed by a rheumatologist certified by the University of Genoa (Italy) to perform this procedure.
- Observer information bias was controlled by confirming information provided by patients in medical records, physical examinations, and previous laboratories.
- Bias of the measuring instrument: an Optilia video capillaroscope was used, which complied with the standards established for its proper use and was maintained. Likewise, all laboratory tests were taken by a single entity to maintain the same reference values.

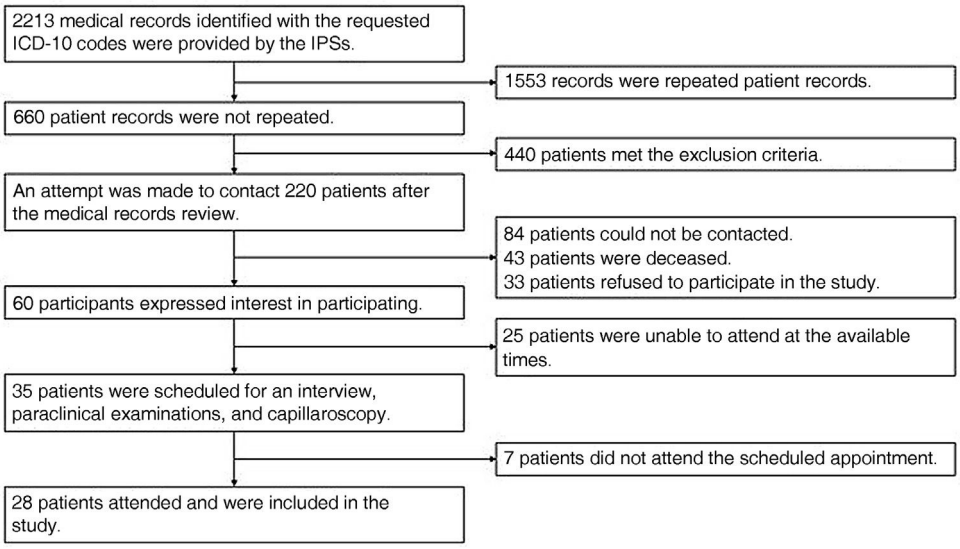

Fig. 1 – Process for recruiting participants.

Statistical analysis

Qualitative variables were expressed as relative frequencies and absolute frequencies, while quantitative variables were presented as averages and standard deviations, or medians and interquartile ranges, according to the distribution of the data. The analyses were performed with the statistical package IBM SPSS 22, licensed from UPB.

Ethical considerations

According to Resolution 8430 of 1993, the present investigation was considered a minimal risk because patients were exposed to the application of vegetable oil on the nail edge, and a venous puncture was performed for sample collection. Patient autonomy was granted by informed consent. Ethical approval was obtained from the different participating institutions.

Results

Patient recruitment

A total of 2,213 medical records provided with the ICD 10 diagnoses previously described were reviewed, and 220 patients were included after applying the exclusion criteria. The total number of patients who were interested in participating in the study was 60, and 28 finally attended, each of whom underwent an interview, paraclinical tests, and capillaroscopy (Fig. 1).

Sociodemographic and clinical characteristics

Out of the 28 patients, 16 were female (57.1%). Among the most relevant pathological antecedents, 17 (60.7%) presented arterial hypertension, followed by hypothyroidism (10; 35.7%) (Table 1). Regarding family history of rheumatological disease, 8 patients (28.5%) reported rheumatoid arthritis and 2

Table 1 – Sociodemographic and epidemiological characteristics of the patients with interstitial lung disease.

Characteristic	n = 28 n (%)
[0,1–2] *Gender*	
Female	16 (57.1)
Age, years	65.7 (10.2)[a]
Occupational exposure	16 (57.1)
[0,1–2] *Comorbidities*	
Hypertension	17 (60.7)
Hypothyroidism	10 (35.7)
Dyslipidemia	6 (21.4)
Coronary heart disease	3 (10.7)
Diabetes mellitus	3 (10.7)
COPD	1 (3.5)
Tuberculosis	1 (3.5)
Other[b]	8 (28.5)
[0,1–2] *Use of therapies*	
Oxygen at home	11 (39.2)
Steroids	8 (28.5)
Immunomodulator	4 (14.2)
Antibiotics	3 (10.7)
Transplant receptor	4 (14.2)
[0,1–2] *Smoking*	
Active	2 (7.1)
Non-smoker	11 (39.2)
Former smoker	15 (53.5)
Alcohol consumption	7 (25)
[0.1-2] *Family history*	
Rheumatoid arthritis	8 (28.5)
Systemic lupus erythematosus	2 (7.1)
Previous hospitalisations	19 (67.8)
Previous ICU stays	5 (17.8)

[a] Mean with standard deviation (SD).
[b] Other comorbidities: stroke, vertigo, neuropathy, portal hypertension, obesity, heart failure, fibromyalgia, psoriasis, depression, and osteoarthritis.

Table 2 – Capillaroscopic findings in patients with interstitial lung disease.

Characteristic	Frequency	%
Density	≥7	100
Dimension 20–50	10	35.7
Abnormal morphology	11	39.2
Microhemorrhages	3	10.7
Normal pattern	13	46.4
Unspecific pattern	15	53.6

No capillaries larger than 50 μm were found and are therefore not reported.

Table 3 – HRCT findings in patients with interstitial lung disease.

HRCT results	n = 20 n (%)
Non-specific interstitial pneumonia	7 (35)
Usual interstitial pneumonia	5 (25)
Hypersensitivity pneumonitis	4 (20)
Organized pneumonia	1 (5)
Pulmonary fibrosis plus pulmonary hypertension	1 (5)
Other[a]	2 (10)

[a] Other: signs of small airway disease and chronic obstructive pulmonary disease.

(7.1%) SLE. The most common medication used by patients was home oxygen, in 11 cases (39.2%), followed by systemic corticosteroids, used by 8 people (28.5%). In addition, 4 patients (14.2%) were found to be lung transplant recipients. Regarding toxicological history, 15 patients (53.5%) reported being ex-smokers, 2 (7.1%) reported active smoking, and 16 (57.1%) reported occupational exposure to possible pulmonary noxious agents (Table 1).

Regarding clinical characteristics, 3 patients (10.7%) reported morning stiffness greater than 60 minutes, and one patient had unexplained digital edema; 11 patients (39.2%) had NYHA I functional class, 9 (32.1%) NYHA II, 5 (17.8%) NYHA III, and 2 (7.1%) NYHA IV. Telangiectasias, Raynaud's phenomenon (referred to or evidenced), mechanic's hands, sclerodactyly, or Gottron's sign were not found in any patient.

Serological markers

No patient with ANA titers higher than 1:80 was found. Among the other tests performed, only one patient (3.5%) had positive anti-La, while the rest of the tests (anti-DNA; Sm, Scl 70, PmScl, Jo1, RNP, anti-CCP, or FR) were negative in 100% of the patients.

Capillaroscopic findings

In the capillaroscopies performed, 15 patients (53.6%) were found to have a capillaroscopic pattern with non-specific abnormalities, mostly due to capillary dimensions between 20 and 50 μm and abnormal capillary morphology. No patient had a capillary dimension greater than 50 μm (Table 2).

Imaging findings

Regarding imaging findings, 15 patients had X-ray reports at the time of evaluation, with the following findings: interstitial infiltrates in 9 patients (60%), bronchitis in 2 (13.3%), emphysema in one (6.6%), and other findings, such as the presence of atelectasis and consolidations, in 3 (20%).

On the other hand, 20 patients had reported HRCT at the time of consultation, and the most frequent finding was non-specific interstitial pneumonia (35%), followed by usual interstitial pneumonia (25%), and hypersensitivity pneumonitis (20%) (Table 3).

Discussion

Interstitial lung disease is closely related to connective tissue pathologies and may even precede the debut of autoimmune disease for years.[10] Such a pattern of lung dominance has major prognostic and treatment implications, which is why great importance has been given to a multidisciplinary study that takes into account clinical, morphological, and serological characteristics to differentiate idiopathic interstitial lung disease from IPAF.[11]

In recent years, the role of capillaroscopy in the early diagnosis of connective tissue diseases has been strengthened, and systemic sclerosis is the most studied disease. In patients with systemic sclerosis, capillaroscopy not only has a clearly defined pattern but is also part of the classification criteria. Also, those with interstitial involvement have been found to have more capillary loss, more avascular areas, and more abnormal capillary shapes.[12] From this postulate, it is thought that patients with IPAF and not idiopathic interstitial lung disease may have specific capillaroscopic alterations; however, few studies perform capillaroscopy in patients with interstitial lung disease in general, as well as in patients with IPAF, making it difficult to establish precedents for defining whether a capillaroscopic pattern exists.

In a study comparing 45 patients with IPAF and 143 with idiopathic pulmonary fibrosis, it was found that in patients with IPAF, women were predominant, ANA positivity in 17.8% (n = 8), and 68.9% reported non-specific interstitial pneumonia, while the main clinical finding was Raynaud's in 31.11% of patients, followed by arthralgia in 26.7%, which is quite different from our patients, in whom the main finding was joint pain, no Raynaud's and negative ANAs. Out of the patients with IPAF, only 2 had alterations in capillaroscopy at the onset of the disease, and another 2 had alterations during the disease[13]; however, it should be noted that the definition of alterations was taken with the criteria proposed by Cutolo et al.[14] in 2013, which prevents accurate comparisons, due to the changes in definitions that have occurred in recent years.

In a cohort of patients with IPAF and idiopathic pulmonary fibrosis, patients with IPAF also had Raynaud's as the main clinical characteristic, followed by joint pain, whereas 83% were ANA positive and 42% had NINE on CT. In this series, capillaroscopy was performed on 30 of the 57 IPAF patients, of whom 16 had Raynaud's phenomenon. Giant capillaries were

found in 13 patients; however, the definition of giant capillaries is unclear. Again, the difficulty of standardizing definitions limits the comparisons.[15]

In another study, comparing interstitial lung disease associated with connective tissue disease and idiopathic interstitial lung disease with patients with Sjögren's and RA without interstitial lung disease (the latter as controls), it was found that median capillary density was significantly reduced in patients with connective tissue disease compared to controls. Similarly, there were more major capillaroscopic abnormalities (decreased capillary density, more than 50% tortuous capillaries, hemorrhages, more than 50% neoangiogenesis, ectasia, and microhemorrhages) in these patients compared to controls.[16] In our study, more than half of the patients were found to have a non-specific pattern on capillaroscopy, which would necessitate a repeat capillaroscopy in the next 6 months. However, this is not necessarily in agreement with the international literature, and is perhaps secondary to the difficulties of standardization of capillaroscopy, especially since the last update was in 2020. In this sense, there is a need to re-evaluate what has been published and also to conduct studies in which patients can be followed to see if the alterations can be a predictor or a consequence of interstitial lung disease.

Although the study aimed to find patients with IPAF in the group of patients previously classified as having interstitial lung disease of unclear or idiopathic cause, which was not achieved; the fact that the capillaroscopic pattern was normal or with non-specific alterations, without megacapillaries, highlights the specificity of megacapillary changes in connective tissue diseases and, therefore, the usefulness of video capillaroscopy to help rule out this disease. Although this test is not considered within the formal criteria, it is possible that in the future it will be included in them.

Another relevant finding is that no capillaroscopic changes were found in patients who were lung transplant recipients, which is important since, in clinical practice, it may be possible for a patient to undergo transplantation and then consider the option of IPAF. These data, although limited by the type of study and number of patients, show that video capillaroscopy would continue to be useful in this subgroup.

Limitations of the study include the usually aggressive course of interstitial lung disease, which may have led to selection bias, as it is possible that, when searching the databases, patients with more aggressive disease may have already had a negative outcome. To try to minimize this, the bias control included the entire population and covered all costs associated with the study, including travel to try to minimize the loss of patients.

Finally, according to the literature search, this is the first study in patients with idiopathic interstitial lung disease that aimed to look for findings suggestive of autoimmune disease, including laboratory profile and capillaroscopy, in Colombia and Latin America. IPAF remains a major challenge for clinicians today and should be systematically searched for as it has demonstrated utility and could have prognostic and treatment implications.

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Conflict of interests

The authors declare that they have no conflict of interest that would compromise the veracity and disclosure of the results obtained in this study.

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