Nonspecific interstitial pneumonia: survival is influenced by the underlying cause

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ABSTRACT Idiopathic, nonspecific interstitial pneumonia (NSIP) is most often associated with various clinical disorders, including connective tissue diseases (CTDs) and chronic hypersensitivity pneumonitis (cHP). Emerging evidence also suggests that "idiopathic" NSIP may be the lung manifestation of undifferentiated CTD (UCTD). However, whether or not NSIP outcome is influenced by the underlying cause remains uncertain.

This retrospective study included 127 biopsy-proven NSIP patients (65 women, mean±SD age 55 ±12 years). Survivals were estimated using a Kaplan–Meier curve and compared using the log-rank test. Multivariate analyses were based on a Cox model.

15 (11.8%) patients had cHP, 29 (22.8%) had CTD, 32 (25.2%) satisfied the Kinder criteria for UCTD and 51 (40.1%) had idiopathic NSIP. At the end of follow-up (mean±SD 64±54 months), a difference in survival was observed between aetiological groups (p=0.002). Survival was better for UCTD than for idiopathic NSIP (p=0.020) and similar to that observed for CTD. cHP survival tended to be poorer than that of idiopathic NSIP (p=0.087) and was an independent predictor of mortality (hazard ratio 2.17, 95% CI 1.05–4.47; p=0.035).

NSIP outcome is influenced by its cause. cHP exhibits the highest mortality. UCTD does not differ from CTD supporting the concept of autoimmune NSIP, with a prognosis that is better than that of idiopathic NSIP.

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NSIP patients should be investigated for the presence of an underlying cause, which significantly impacts survival http://ow.ly/F1lO2

Received: Aug 25 2014 | Accepted after revision: Nov 21 2014

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

Introduction

Nonspecific interstitial pneumonia (NSIP) remains an area of uncertainty that requires further research [1, 2]. Although most often idiopathic, the histologic pattern of NSIP is also observed in a wide variety of clinical settings, including connective tissue diseases (CTDs), chronic hypersensitivity pneumonitis (cHP), drug toxicity and slowly resolving diffuse alveolar damage [1]. NSIP is the most common histological pattern in interstitial lung diseases (ILDs) associated with CTDs, including their *forme fruste* variants. Several authors have suggested that a subset of patients previously classified as "idiopathic" NSIP meet the criteria for undifferentiated CTD (UCTD) [3–5]. UCTD is characterised by the presence of features reflecting a systemic autoimmune process that do not fulfil the accepted diagnostic criteria for differentiated CTDs, *i.e.* rheumatoid arthritis (RA), Sjögren's syndrome (SjS), systemic scleroderma (SSc), polymyositis and dermatomyositis, systemic lupus erythematosus and mixed CTD [5, 6]. Whether or not patients with CTD-associated NSIP have a better outcome than those with idiopathic NSIP remains controversial [7]. Similarly, the prognostic impact of UCTD in NSIP patients has not been fully elucidated [8–11]. Although it is now well known that NSIP can represent the sole histological expression of a percentage of patients with cHP [12–16], no studies have compared the survival of these patients with that of patients with idiopathic NSIP.

The aim of the study was to compare the prognosis of NSIP patients stratified according to the underlying cause (idiopathic, UCTD, CTDs and cHP) in terms of survival, response to therapy and long-term functional outcome.

Methods

Patient selection and data collection

This retrospective study received institutional review board approval (Comité de Protection des Personnes Ile-de-France X, No. 2012-12-01). All consecutive patients with a histological pattern of NSIP on surgical lung biopsy (SLB) examined at the Avicenne University Hospital Pathology department (Bobigny, France) were selected. The patient cohort has already been the subject of a previous study focusing on histology [17]. The diagnosis of NSIP was based on a consensus by two pathologists (M. Kambouchner and A.G. Nicholson) [1]. Clinical and laboratory characteristics, pulmonary function tests (PFTs) and bronchoalveolar lavage (BAL) findings at the time of SLB were collected from medical records. The battery of individual serological tests and serum precipitins were ordered as part of the initial workup or during follow-up on clinical grounds. Two radiologists (D. Piver and P.Y. Brillet) reviewed in consensus high-resolution computed tomography (HRCT) scans that were available within 6 months of SLB. Patients were classified as presenting a HRCT pattern either "suggestive or consistent with NSIP" or "suggestive of usual interstitial pneumonia (UIP)" [1, 2].

Diagnostic criteria

Standard diagnostic criteria were applied for individual differentiated CTDs [18–24]. Patients were considered to have UCTD when they had at least one symptom suggestive of CTDs and evidence of systemic inflammation in the absence of infection, as defined by Kinder *et al.* [5]. A narrower definition of UCTD was also applied, as proposed by Corte *et al.* [8, 25]. The diagnosis of cHP was established using the criteria of Richerson *et al* [26]. In addition to clinical and radiological evidence of ILD, patients were required to have a history of exposure to an inhaled antigen known to cause cHP and either confirmatory serum precipitins or a lymphocytic BAL [26].

Patient outcome

Therapeutic response was recorded within 3–6 months of treatment initiation. Long-term functional outcome was evaluated for patients with available PFTs at least 12 months after their initial assessment. Improvement was defined as a $\geqslant$10% increase in forced vital capacity (FVC) % predicted or a $\geqslant$15% increase in diffusing capacity of the lung for carbon monoxide (*D*LCO) % predicted from initial values, and worsening was defined as >10% decrease in FVC or >15% decrease in *D*LCO.

Statistical analysis

All results are expressed as percentages or mean±SD. The various aetiological groups were compared using a Chi-squared test or Fisher's exact test for categorical variables, and Kruskal–Wallis test for continuous variables. Survival was calculated from the date of inclusion, which corresponded to the date of SLB and ranged from July 1987 to November 2011, until the end of the follow-up period. Patients were followed until death, lung transplantation or September 1, 2012, with complete follow-up for 125 out of 127 cases. Information regarding vital status and cause of death was obtained by reviewing the patient's medical charts and by contacting the referring physician and general practitioner. Transplanted patients were censored at the time of transplantation. The survival probability of aetiological groups was estimated using

DOI: 10.1183/09031936.00148613

the Kaplan–Meier method and compared by a log-rank test. Univariate analysis was based on a log-rank test. For continuous variables, patients were classified into two groups on either side of the median value. All parameters with a p-value <0.20 were then entered into the multivariate Cox proportional hazards model. Results are reported as hazard ratios (HRs) and 95% confidence intervals.

Results

Aetiological groups

136 cases with NSIP were listed in the Pathology department. Nine cases were excluded because the medical charts were not available. The study population comprised 127 patients (table 1). SLB were obtained from a single lobe in 29 (22.8%) cases, two lobes in 75 (59.1%) cases and three lobes in four (3.1%) cases. The site of SLB was not available for 19 (15.0%) patients, and for the other 108 patients corresponded to: upper lobes n=74 (68.5%); lower lobes n=90 (83.3%); middle lobe n=18 (16.7%); or lingula: n=5 (4.6%).

The study population consisted of 62 men with a mean±SD age of 55±12 years at the time of SLB. 15 (11.8%) patients had a diagnosis of cHP induced by the following antigens: birds n=12, domestic moulds n=1, hay n=1 and textile dusts n=1. 29 (22.8%) patients had a differentiated CTD (RA n=7, SjS n=7, SSc n=4, polymyositis or dermatomyositis n=7, mixed CTD n=2, systemic lupus erythematosus plus SjS n=1, and SSc plus SjS n=1). NSIP occurred during the course of a previously known CTD in nine cases, with a median time to onset of 60 months (range: 5–192 months). The two conditions were diagnosed concomitantly in 16 cases. NSIP preceded the diagnosis of CTD in four cases by 8, 48, 120 and 120 months, respectively. While one of these four patients with RA initially had no features suggestive of a

TABLE 1 Patients' characteristics at the time of surgical lung biopsy (SLB) according to aetiological groups

	Idiopathic NSIP	UCTD[#]	CTDs	cHP	p-value	Whole population
Subjects	51	32	29	15		127
Demographics						
Males/Females	32/19	11/21[¶]	10/19[+]	9/6	0.020	62/65
Non-/current or ex-smokers	21/30	23/9[¶]	17/12	7/8	0.044	68/59
Age years	55.8±11.5	56.5±12.8	51.6±14.4	52.7±10.3	0.206	54.7±12.5
Clinical symptoms						
NYHA functional class I–II/III–IV	41/10	25/7	24/5	11/4	0.871	101/26
Squawks	4	5	3	3	0.560	15
Digital clubbing	18	9	5	4	0.402	36
Duration of symptoms months	35.4±49.2	48.1±47.7	32.4±31.0	32.5±44.0	0.445	37.7±44.5
Site of SLB					0.963	
At least two lobes	32	19	19	9		79
A single lobe or unknown	19	13	10	6		48
HRCT pattern, n					0.375	
Subjects	37	23	23	11		94
Suggestive or consistent with NSIP	36	22	20	10		88
Suggestive of UIP	1	1	3	1		6
Pulmonary function tests						
Subjects	49	31	27	15		122
FEV_1 % predicted	70.0±19.0	75.7±22.2	66.1±20.8	60.2±17.4	0.115	69.4±20.4
FEV_1/FVC %	85.2±9.6	83.5±8.2	85.1±9.9	82.9±8.5	0.830	84.5±9.2
FVC % predicted	67.4±17.3	73.6±20.3	63.3±20.0	59.0±14.3	0.071	67.1±18.8
TLC % predicted	70.6±17.5	73.8±15.7	66.6±20.2	61.4±13.8	0.081	69.4±17.6
D_{LCO} % predicted	50.0±13.8[§]	54.9±17.3[f]	47.2±14.4[##]	44.0±18.9[¶¶]	0.238	50.0±15.7[++]
Bronchoalveolar lavage						
Subjects	42	28	22	14		106
Lymphocytes %	15.6±13.3	17.1±17.2	20.1±16.7	20.6±19.7	0.861	17.6±15.9
Neutrophils %	10.7±11.5	12.3±14.4	15.5±15.2	7.0±9.2	0.198	11.7±13.1
Eosinophils %	3.5±5.3	6.9±13.2	3.7±4.7	3.0±3.0	0.835	4.4±8.1

Data are presented as n, n/n or mean±SD, unless otherwise stated. NSIP: nonspecific interstitial pneumonia; UCTD: undifferentiated connective tissue disease; CTD: connective tissue disease; cHP: chronic hypersensitivity pneumonitis; NYHA: New York Heart Association; HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. [#]: UCTD as defined by Kinder's criteria [5]; [¶]: p<0.05 for comparison between idiopathic and UCTD groups; [+]: p<0.05 for comparison between idiopathic and CTDs groups; [§]: n=46; [f]: n=28; [##]: n=24; [¶¶]: n=13; [++]: n=110.

systemic autoimmune disorder, the other three patients with dermatomyositis, RA and SjS met the criteria for UCTD prior to the onset of differentiated CTD. Among the remaining 83 patients, 32 (38.5%, *i.e.* 25.2% of the whole population) satisfied the criteria for UCTD and did not develop differentiated CTD during follow-up, and 51 (61.4%, *i.e.* 40.1% of the whole population) had idiopathic NSIP with no UCTD. 19 cases (22.9%, *i.e.* 15% of the whole population) met the definition for UCTD proposed by Corte *et al.* [8].

Clinical characteristics, PFTs, BAL and HRCT findings

Patient characteristics at the time of SLB are summarised in table 1. Overall, aetiological groups were significantly different in terms of sex ratio (p=0.020) and smoking status (p=0.048). More specifically, patients with UCTD and CTDs were more likely to be females than those with idiopathic NSIP (UCTD *versus* idiopathic NSIP: 65.6% *versus* 37.2%, p=0.014; and CTDs *versus* idiopathic NSIP: 65.5% *versus* 37.2%, p=0.020). The UCTD group comprised a significantly higher percentage of nonsmokers than the idiopathic NSIP group (UCTD *versus* idiopathic NSIP: 71.8% *versus* 41.2%; p=0.007). Conversely, no significant difference was found between the UCTD and CTDs groups, or between the cHP and idiopathic NSIP groups. HRCT was available for 94 patients, and showed a pattern "suggestive or consistent with NSIP" in 88 (93.6%) cases and "suggestive of UIP" in six (6.4%) cases. All of these six cases had a biopsy taken from two lobes, providing evidence of a concordant histological pattern of NSIP.

Systemic autoimmune symptoms and laboratory findings

The results are shown in tables 2 and 3. As expected, the aetiological groups differed in terms of the presence of systemic autoimmune symptoms (p<0.0001) and auto-antibodies (p<0.0001). All patients with UCTD and CTDs had at least one autoimmune symptom, a much higher rate than that observed in patients with idiopathic NSIP (100% *versus* 43.1%; p<0.0001). By contrast, no significant difference was observed between the cHP and idiopathic NSIP groups. The proportion of patients with at least two symptoms was higher in the CTDs group than in the UCTD group (96.5% *versus* 78.1%; p=0.033).

Therapeutic response and long-term functional outcome

14 (11%) patients did not receive any specific treatment for NSIP during the study period, 106 (83.5%) patients were given corticosteroids (n=99) and/or at least one immunosuppressive agent (azathioprine: n=52, cyclophosphamide: n=33, mycophenolate mofetil: n=24, methotrexate: n=4, rituximab: n=3, cyclosporine: n=1, leflunomide: n=1 and plasmapheresis: n=1), and information was not available in seven

TABLE 2 Distribution of autoimmune symptoms according to aetiological groups

	Idiopathic NSIP	UCTD[#]	CTDs	cHP	p-value
Subjects	51	32	29	15	
Symptoms associated with CTD					
Raynaud's phenomenon	2	5	15[¶,+]	1	<0.0001
Arthralgias/multiple joint swelling	5	19[§]	20[¶]	3	<0.0001
Morning stiffness	1	6[§]	14[¶,+]	1	<0.0001
Proximal muscle weakness	0	5[§]	13[¶,+]	1	<0.0001
Sicca features	2	15[§]	15[¶]	2	<0.0001
Dysphagia	2	2	2	0	0.780
Gastro-oesophageal reflux	13	8	12	1	0.096
Photosensitivity	0	2	1	0	0.226
Skin changes (rash)	1	3	7[¶]	0	0.006
Oral ulceration	0	0	1	1	0.118
Nonandrogenic alopecia	0	0	1	0	0.346
Recurrent unexplained fever	0	3	5	0	0.005
Unintentional weight loss	6	9	8	1	0.096
Number of symptoms					
⩾1	22	32[§]	29[¶]	7	<0.0001
⩾2	8	25[§]	28[¶,+]	3	<0.0001
⩾3	0	12[§]	21[¶,+]	1	<0.0001

Data are presented as n, unless otherwise stated. NSIP: nonspecific interstitial pneumonia; UCTD: undifferentiated connective tissue disease; CTD: connective tissue disease; cHP: chronic hypersensitivity pneumonitis. [#]: UCTD as defined by Kinder's criteria [5]; [¶]: p<0.05 for comparison between idiopathic and CTDs groups; [+]: p<0.05 for comparison between UCTD and CTDs groups; [§]: p<0.05 for comparison between idiopathic and UCTD groups.

DOI: 10.1183/09031936.00148613

TABLE 3 Distribution of autoimmune laboratory signs according to aetiological groups

	Idiopathic NSIP	UCTD[#]	CTDs	cHP	p-value
Subjects	51	32	29	15	
Auto-antibody					
Rheumatoid factor	2/47	13/31[¶]	13/27[+]	2/15	<0.0001
Anti-CCP antibody	0/17	3/17	7/14[+]	0/6	0.002
Antinuclear antibody	8/46	22/31[¶]	24/28[+]	3/15	<0.0001
Antinuclear antibody titer	120 (80–320)	160 (80–1600)	320 (80–2650) [+]	80 (80–320)	0.05
Anti-dsDNA antibody	1/8	0/21	3/24	0/3	0.356
Anti-Sm antibody	0/40	0/29	3/24[+]	0/14	0.012
Anti-SSA antibody	0/40	0/29	8/25[+]	0/14[§]	<0.0001
Anti-SSB antibody	0/40	0/29	3/25[+]	0/14	0.024
Anti-RNP antibody	0/40	1/29	2/24	0/14	0.065
Anti-Scl 70 antibody	0/29	3/21	2/24	0/8	0.153
Anti-Jo-1 antibody	0/30	2/24	2/25	0/10	0.337
Anti-PL7 antibody	0/10	0/4	0/8	0/4	1
Anti-PL12 antibody	0/10	0/5	0/8	0/4	1
Anti-PM-ScL antibody	0/10	0/7	0/9	0/4	1
Anti-Mi2 antibody	0/10	0/3	0/9	0/4	1
Anti-Ku antibody	0/9	0/3	1/9	0/4	1
Anti-SRP antibody	0/9	0/4	0/9	0/4	1
ANCA	4/33	7/27	1/22	1/11	0.194
Elevated erythrocyte sedimentation rate (⩾2 times normal) or CRP in the absence of infection	7	19[¶]	20[+]	3	<0.0001
At least one auto-antibody	12	29[¶]	28[+]	4	<0.0001

Data are presented as n positive/N tested, median (range) or n, unless otherwise stated. NSIP: nonspecific interstitial pneumonia; UCTD: undifferentiated connective tissue disease; CTD: connective tissue disease; cHP: chronic hypersensitivity pneumonitis; CCP: cyclic citrullinated peptide; dsDNA: double stranded DNA; RNP: ribonucleoprotein; SRP: signal recognition particle; ANCA: anti-neutrophil cytoplasmic antibodies; CRP: C-reactive protein. [#]: UCTD as defined by Kinder's criteria [5]; [¶]: p<0.05 for comparison between idiopathic and UCTD groups; [+]: p<0.05 for comparison between idiopathic and CTDs groups; [§]: xxxxxx.

cases. All cHP patients had been removed from antigen exposure. 101 patients were evaluated for therapeutic response based on PFTs. Overall, responses were not different between groups the (p=0.219) (table 4). However, when patients with UCTD and CTDs were pooled and compared with the rest of the population, they presented a significantly higher rate of response (43.7% *versus* 24.5%; p=0.041). Long-term functional follow-up (⩾12 months) was available for 105 patients. At the last follow-up, the distribution of patients according to functional evolution outcome and the annual decline in FVC and *D*LCO were similar between groups (table 4).

Survival and causes of death

Mean follow-up after SLB was 63.7±54.2 months. At the end of the study, 75 patients were alive, 40 patients had died, 10 had undergone transplant and two were lost to follow-up. 2-, 5- and 10-year overall survival was 89.0%, 65.6% and 49.2%, respectively. Survival was significantly different between groups (p=0.002) (fig. 1a), with an even more marked difference when patients with UCTD and CTDs were pooled (p=0.0006) (fig. 1b). Patients with cHP exhibited the poorest survival (2-, 5- and 10-year survival of 73.3%, 41.9% and 27.9%, respectively), followed by patients with idiopathic NSIP (2-, 5- and 10-year survival of 87.7%, 60.7% and 35.9%, respectively) and patients with autoimmune NSIP (2-, 5- and 10-year survival of 94.5%, 77.1% and 72.5%, respectively). A side-by-side comparison showed that UCTD survival was significantly better than that of idiopathic NSIP (p=0.020), but similar to that of CTD (p=0.583). cHP patients tended to have a worse survival than patients with idiopathic NSIP (p=0.087). Similar results were observed according to the criteria proposed by CORTE *et al.* [8], with a tendency towards better survival in the UCTD group than in idiopathic NSIP group (p=0.090) and no significant difference between the UCTD and CTDs groups (p=0.614).

The causes of death were as follows: end-stage respiratory failure n=13; acute exacerbation n=11; respiratory tract infection n=2; pulmonary hypertension n=1; sudden death n=1; pneumothorax n=1; neoplasia n=5 (lung n=2, pancreas n=1, nasopharynx n=1 and colon n=1); upper gastrointestinal tract haemorrhage n=1; and unknown n=5.

TABLE 4 Patient outcomes according to aetiological groups

	Idiopathic NSIP	UCTD#	CTDs	cHP	p-value
Subjects	51	32	29	15	
Duration of follow-up months	66.7±58.0	64.3±49.3	67.1±61.7	45.8±31.5	0.716
Treatment at some point during follow-up					
Corticosteroids	39	26	21	13	0.849
Azathioprine	20	14	12	6	0.966
Cyclophosphamide	12	6	11	4	0.352
Mycophenolate mofetil	8	8	7	1	0.341
Response to first or second-line treatment n/N	10/39	10/25	11/23	3/14	0.219
Long-term evolution of PFTs					
Subjects	43	26	23	13	
Interval between PFTs years	4.6±3.9	5.2±4.0	5.6±3.8	3.7±2.4	0.485
Annual FVC decline %	−3.2±7.2	−1.5±3.9	−2.0±3.5	−2.0±4.6	0.562
Annual *D*LCO decline %	−4.5±13.2	−1.5±5.2	−0.8±1.9	−3.1±7.2	0.304
Improvement/stability/worsening	6/11/26	5/8/13	1/12/10	2/4/7	0.396

Data are presented as n or mean±SD, unless otherwise stated. NSIP: nonspecific interstitial pneumonia; UCTD: undifferentiated connective tissue disease; CTD: connective tissue disease; cHP: chronic hypersensitivity pneumonitis; PFTs: pulmonary function tests; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide. #: UCTD as defined by Kinder's criteria [5].

Predictive factors of mortality

Results of the univariate analysis are presented in table 5. In multivariate analyses independent predictors of mortality were absence of response to therapy (HR 10.38, 95% CI 3.1–34.2; p=0.0001) (fig. 2) and a diagnosis of cHP (HR 2.17, 95% CI 1.05–4.47; p=0.035) (fig. 3).

Discussion

Only limited data are available in the literature on whether patients with secondary NSIP have a different outcome to those with idiopathic NSIP. The present study demonstrates that, despite similar baseline functional impairment and long-term functional decline, the prognosis of NSIP is influenced by the underlying cause of the disease. Patients with cHP appear to have a poorer outcome, while a diagnosis of cHP is independently associated with a higher mortality. Although patients with autoimmune NSIP, *i.e.* NSIP associated with CTDs or UCTD, have a better survival than those with cHP and idiopathic NSIP, the impact of a diagnosis of autoimmune NSIP is no longer significant on multivariate analysis. The absence of response to therapy is the strongest independent determinant of mortality.

A NSIP pattern is observed on histology in 16–50% of cases of cHP [12–16]. Hypersensitivity pneumonitis is traditionally thought to be associated with a good prognosis, but a wide range of mortality rates are

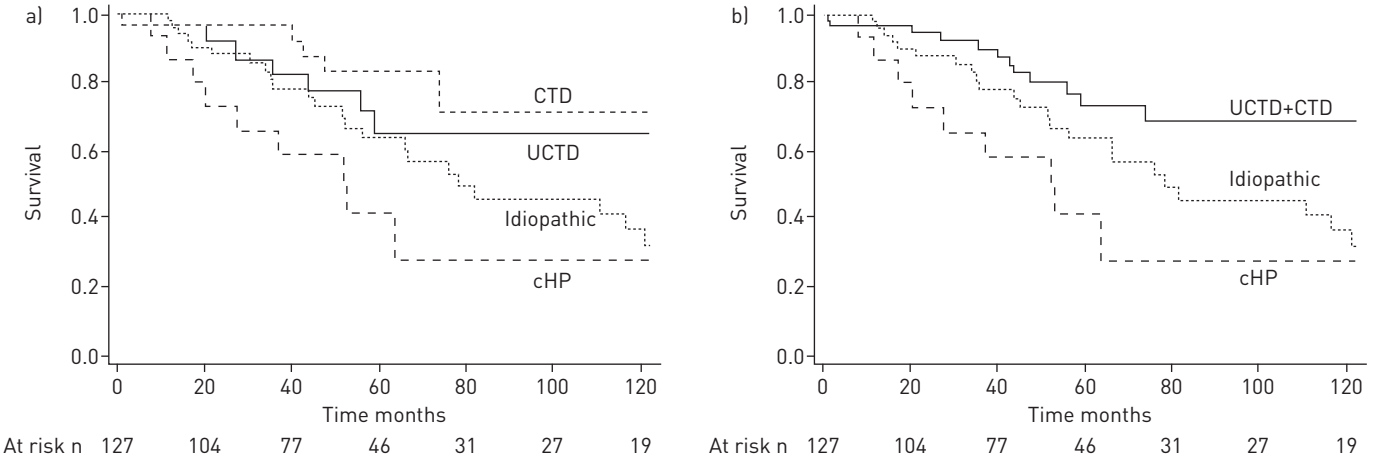

FIGURE 1 Patient survival according to aetiological group. a) Patients with undifferentiated connective tissue disease (UCTD) (as defined using Kinder's criteria [5]) and connective tissue diseases (CTDs) are separated. b) Patients with UCTD and CTDs are pooled (autoimmune). cHP: chronic hypersensitivity pneumonitis.

DOI: 10.1183/09031936.00148613

TABLE 5 Univariate analysis of factors associated with mortality

Variable	p-value
Males	0.910
Current or ex-smoker	0.162
Age >56.1 years	0.139
Absence of systemic autoimmune symptoms	0.017
Absence of auto-antibody	0.013
No diagnosis of UCTD[#] or CTDs	0.001
Diagnosis of cHP	0.004
Duration of symptoms >22.5 months	0.839
Digital clubbing	0.067
FVC <65.2% predicted	0.125
***D*LCO <50.0% predicted**	0.062
Alveolar lymphocytosis >20%	0.019
Alveolar neutrophilia >5%	0.090
No response to therapy	<0.0001

UCTD: undifferentiated connective tissue disease; CTDs: connective tissue diseases; cHP: chronic hypersensitivity pneumonitis; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide. [#]: UCTD as defined by Kinder's criteria [5].

actually reported [27]. Most recent studies have estimated the 5-year survival to be between 25% and 55% in the presence of histological signs of fibrosis [12, 15, 28, 29]. A similarly poor outcome is observed in the present series, with a 5-year survival of 41.9%. This may partly reflect the large number of patients with bird exposure (12 (80%) out of 15), which has been suggested to be linked with a more severe course [27]. It is remarkable that the disease progressed in the majority of our patients, all of whom presented with avian cHP, despite exposure avoidance, which raises the hypothesis that, once NSIP is established, the disease may become independent of continuing exposure [15].

There is emerging evidence that so-called "idiopathic" NSIP is frequently associated with an autoimmune "flavour" [3–5]. KINDER *et al.* [5] first applied a set of diagnostic criteria for UCTD to an American cohort with idiopathic interstitial pneumonias (IIPs), and found that 88% of cases with NSIP had UCTD. In two other Japanese [10] and British series [8] the proportion of UCTD patients was 47% and 71%, respectively. CORTE *et al.* [8] emphasised the highly nonspecific nature of Kinder's criteria, which were met by one third of patients with idiopathic pulmonary fibrosis (IPF). Using a more stringent definition, the frequency of UCTD dropped from 71% to 31% [8]. In our series, the proportion of UCTD patients was 38.5% and 22.9% using the Kinder criteria and the Corte criteria, respectively. No clearly validated criteria for the diagnosis of UCTD are available at the present time.

As in previous studies, our patients with UCTD were more likely to be females [5, 8, 30] and nonsmokers [5, 30] than those with idiopathic NSIP. UCTD patients were similar to CTDs patients, including in terms of demographic characteristics and survival. In line with previous observations [10], three cases with UCTD developed differentiated CTD over time. Taken together, these observations support the grouping of these patients into a subset of "autoimmune NSIP".

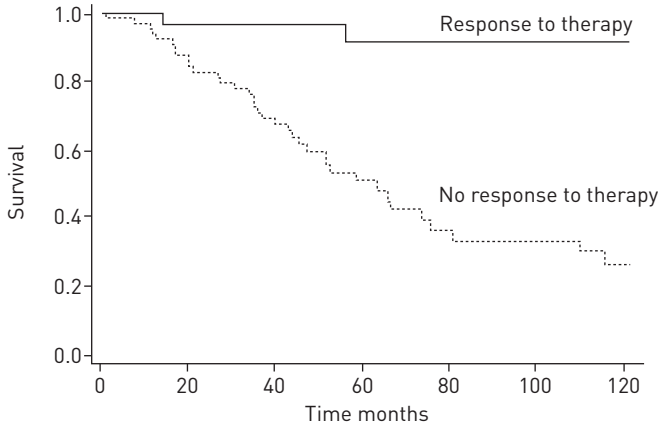

FIGURE 2 Patient survival according to the response to first- and/or second-line therapy.

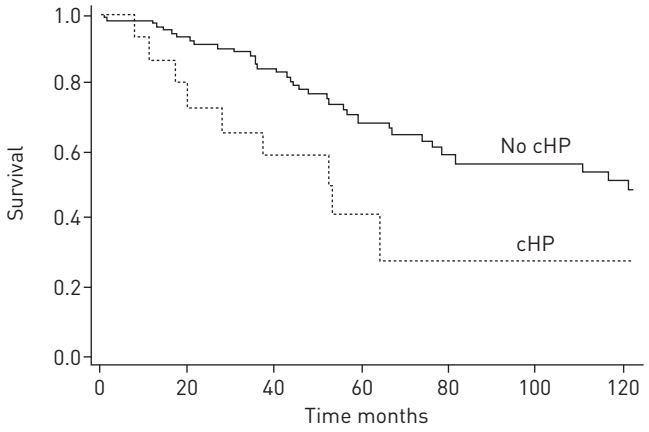

FIGURE 3 Patient survival according to the presence or absence of chronic hypersensitivity pneumonitis (cHP).

Most studies have shown that individuals with CTDs-ILD live significantly longer than patients with IIPs [7, 31], but in the study of PARK *et al.* [7] this difference disappeared in cases diagnosed by histology as NSIP. However, the absence of distinction of UCTD in this study may have led to overestimation of the survival of patients with "idiopathic" NSIP. In fact, the prognostic significance of a concomitant diagnosis of UCTD has been questioned in a small number of studies [8–11]. CORTE *et al.* [8] showed that the presence of UCTD was not associated with a survival advantage in IIP patients taken as a whole, but this association was not tested in the NSIP subset. In the study by VIJ *et al.* [11], no difference was observed between IIPs with autoimmune features (with a similar definition to Kinder's definition of UCTD) and IPF. It is, however, noteworthy that 80.6% of cases of IIPs with autoimmune features who underwent SLB displayed an UIP pattern [11]. By contrast with these papers, SUDA *et al.* [10] demonstrated that UCTD patients had a significantly lower mortality compared with patients with NSIP not fulfilling the criteria for UCTD. Similarly, in our study, UCTD patients had a significantly better survival than those with idiopathic NSIP ($p=0.002$) and this survival difference persisted when patients with UCTD and CTD were pooled ($p=0.0006$). Comparable results were observed when the definition of UCTD was restricted to the criteria proposed by CORTE *et al* [8]. Univariate analysis revealed that the presence of auto-antibodies as well as the presence of systemic autoimmune symptoms was significantly correlated with a lower risk of death. We failed to establish the role of a diagnosis of autoimmune NSIP on multivariate analysis, possibly because of a link with the response to therapy.

This is the first study to show that the response to therapy is the most robust prognostic predictor. The response rate of 25.6% observed in idiopathic NSIP was similar to that reported in several previous studies (between 25% and 33.3%) [32–34], but lower than that estimated by PARK *et al.* [35] (53%). Importantly, none of these studies had distinguished UCTD. The response rate observed in this study for patients with UCTD was comparable to that observed by KINDER *et al.* (40% *versus* 38%, respectively). Interestingly, when patients with UCTD and CTD were pooled, *i.e.* patients with autoimmune NSIP, they responded more frequently to therapy than those with other forms of NSIP (43.7% *versus* 24.5%; $p=0.041$).

Our group has previously published a study based on the same cohort concerning the histological findings, in which we clearly demonstrated that NSIP subdivision into histological subgroups was clinically relevant for prognostic and aetiological purposes [17]. In addition to the widely accepted NSIP criteria, several histological subgroups could be identified according to superimposed minor histological features, which were associated with significantly different survivals. NSIP/organising pneumonia overlap was significantly associated with CTDs and NSIP/cHP overlap with a clinical diagnosis of cHP. Interestingly, only five out of the 15 patients with a clinical diagnosis of cHP presented a histological pattern of NSIP/cHP overlap [17]. These two studies, therefore, provide different and complementary information and support the role of thorough clinical investigation of the underlying cause of NSIP as well as a detailed examination of SLB.

Our study encompasses several limitations. First, we cannot exclude that some cases with UCTD or cHP have escaped diagnosis. Nevertheless, in our routine practice, we systematically question patients with ILDs about the presence of symptoms of CTD and exposures, and almost all patients were evaluated for at least antinuclear antibody and rheumatoid factor. One of the strengths of our study is the fairly long duration of follow-up, which decreases the risk of missing patients with late development of CTD. Secondly, interpretation of survival is limited by the small number of patients with cHP. Thirdly, SLB is rarely performed in the context of CTD and cHP, creating a potential selection bias. This issue has already been extensively discussed in CTD. In our patients with identifiable exposures, the decision to perform SLB may have been dictated by a particular clinical presentation or disease course, so that our findings may not

DOI: 10.1183/09031936.00148613

be extrapolated to all cHP patients. Lastly, it is recognised that a histological pattern of NSIP and UIP may coexist in the same patient and, in the presence of interlobar variability, the outcome is that of IPF [36]. As SLBs were performed in various centres using different procedures over a long period of time, specimens were not taken from two lobes in all of our patients. However, the overall survival of our cohort is much better than expected for IPF, and 93.6% of our patients presented a pattern of NSIP on HRCT.

In conclusion, the outcome of NSIP is influenced by the underlying aetiology, with a poorer survival for cHP patients and better survival for patients with autoimmune NSIP. In addition to autoimmune signs and the recognition of *forme fruste* variants of CTD and UCTD, NSIP compels the clinician to be vigilant in questioning patients about environmental or occupational exposures. As the antigenic source frequently remains undetected and as new causative agents continue to be identified, so-called "idiopathic" NSIP may simply conceal a *forme fruste* of cHP. The role of detailed evaluation based on a systematic questionnaire for home and workplace exposures and a panel of serum precipitins needs to be investigated by further studies.

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 DOI: 10.1183/09031936.00148613

Author Queries

Journal: ERJ

Manuscript: ERJ-01486-2013

Q1 I have changed references to the "idiopathic group" to "idiopathic NSIP group" throughout, is this okay?

Q2 Which is the correct reference by Kinder *et al.* to include here? "... observed by KINDER *et al.* (40% *versus* 38%, respectively)."

Q3 Table 3: what does the § symbol indicate? No explanatory footnote was included in the submitted manuscript.