SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2018; 35; 218-229 DOI: 10.36141/svdld.v35i3.6432

Airway-centered interstitial fibrosis – an under-recognized subtype of diffuse parenchymal lung diseases

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Abstract. Airway centered interstitial fibrosis (ACIF) has been recently suggesed as a rare histological pattern of interstitial lung disease of variable etiology and outcome. It is characterized by fibrosis of the respiratory bronchioles and the peribronchiolar interstitium. We describe the clinical features of 13 patients (7 female, mean age 55 years) with histologically proven ACIF in 12 cases and long-term follow up. In ten patients, exogenous agents could be detected (mould n=5, wood n=2, leather exposure n=1, occupational exposure n=2). Two patients had rheumatoid arthritis and 1 patient suffered from recurrent aspiration. In three patients no associated exposure could be detected. Eight patients were never-smokers, while five were ex- smokers. At time of diagnosis patients presented with a moderate restrictive ventilation impairment and sever reduction in diffusion capacity (VC 61%, TLC 66%, DLCOc-SB 38% pred.). All patients were started on immunosuppressive therapy with steroids which were combined with azathioprine in seven and with mycophenolate mofetil in one patient. Median time of follow up was 52 months (2-127 months). Patients with ACIF due to exogenous agents or associated with RA were stable with immunosuppressive therapy. One patient with idiopathic ACIF showed a progressive deterioration within 29 months despite immunosuppression and died while on a waiting-list for lung transplantation. In our experience ACIF is a rare finding, which is relatively frequently observed in the context of hypersensitivity pneumonitis, aspiration and rheumatoid arthritis, while idiopathic ACIF was a minority. In the majority of patients, ACIF showed a favorable long-term outcome with immunosuppressive therapy. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 218-229)*

Key words: bronchiolitis obliterans, hypersensitivity pneumonitis, non specific interstitial pneumonia, organizing pneumonia, respiratory bronchiolitis, usual interstitial pneumonia

Introduction

Airway centered interstitial fibrosis (ACIF) has been recently discussed as a new rare histological entity within the diffuse parenchymal lung diseases (DPLD), eventually occurring idiopathic or in the context of environmental expsoures (1).

It is histologically characterized by airway fibrosis, localized peribronchiolar interstitial pulmonary fibrosis and a moderate lymphocytic alveolitis in the bronchoalveolar lavage (BAL). There is still debate about if ACIF is a true separate subtype of IIP or is an atypical presentation of other forms of interstitial pneumonia (IP) (2).

The initial description of ACIF was published by Churg et al (3) who reported 12 patients sharing

Received: 6 May 2017
Accepted after revision: 2 March 2018
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the typical radiological and histological features of interstitial fibrosis centered on membranous and respiratory bronchioles, in many instances with prominent bronchiolar metaplasia overlying the fibrotic alveolar walls and in some cases with heavily muscularized bronchioles (table 1).

As 8 out of 12 patients had a history of environmental/occupational inhalative exposure, the authors speculate that the process may start in the bronchi with subsequent spreading into the alveolar compartment. During 3-years follow up, four patients died despite treatment suggesting ACIF as an ILD with a bad prognosis.

In the following years, several groups reported different forms of localized peribronchiolar interstitial pulmonary fibrosis with variable response to therapy and long-term outcome (4-7).

Yousem et al described 10 patients with a similar pattern of interstitial and peribronchiolar fibrosis and bronchiolar metaplasia (4). They used the term idiopathic bronchiolocentric pneumonia and discussed similarities to hypersensitivity pneumonitis. During the follow up of 4 years, 3 out of 9 patients died.

De Carvalho reported a series of 12 patients with a fibrosis localized within separate lobules, prompting the term centrilobular fibrosis (CLF) (5). The airways showed a continuous necrosis of the bronchiolar epithelium suggestive for microaspiration as a causative mechanism. The authors clearly distinguished their findings from other forms of IIP like UIP or NSIP. Follow up was not reported.

The study of Fukuoka described another cohort of 15 patients with interstitial lung disease and a characteristic histological hallmark of peribronchiolar metaplasia. All patients were elderly ladies with mild symptoms and mild radiological changes. No patient died during follow up of 2,4 (0,6-6,9) years (6).

In all those forms, the peribronchiolar pattern is suggestive for a causative role of inhalative noxious agents, possibly including aspiration. Churg suspected that the initiation of the disease is the contact of the airways with an agent that lead to chronic inflammation with subsequent fibrosis spreading into the alveolar compartment.

As the changes are primarily adjacent to the central airways, radiology shows a characteristic pattern in ACIF. On thoracic computed tomography (TCT) the typical features of ACIF are peribronchovascular fibrosis, interstitial thickening and traction bronchiectasis with thickened airway walls and surrounding fibrosis (3, 7).

Data about ACIF are sparse. Most of the reported patients had a history of exposure to inhalation agents, such as wood smoke, birds, cotton, pasture, chalk dust, cleaning agents, agrochemical compounds and cocaine. However, causalty could not be proven for any of these exposures yet. The majority of patients with ACIF were ex-smokers, mostly with moderate cumulative exposure. The mean age is 46 years with a female predominance. So far ACIF is reported as a disease of poor prognosis with a reported mean survival of 2,4 years (3).

We report our experience with ACIF in diagnosis and long-term follow up.

Table 1. Clinical characteristics of ACIF (adapted from 3)

Mean age 54±14
Restrictive lung pattern
Female predominance
Histology:
BAL lymphocytosis
Small airway-centered interstitial fibrosis
Metaplastic bronchiolar epithelium
Extensive bronchiolar muscularization
Radiology
Bronchial wall thickening
Peribronchovascular interstitial thickening
Traction bronchiectasis with airway thickening and surrounding fibrosis
Focal reticular changes

Methods

Study population

We reviewed the pathology reports of patients referred for workup of diffuse parenchymal lung disease between 1993 and 2013.

The description of "centrilobular fibrosis (CLF)", "peribronchiolar metaplasia (PBM)" and "bronchiolocentric interstitial pneumonia" deemed suggestive for ACIF. Thereafter, lung CT scans were reassessed to identify patterns compatible with ACIF (peribronchovascular fibrosis, interstitial thickening, traction bronchiectasis with thickened airway walls and surrounding fibrosis). When the diagnosis of ACIF

was confirmed in the multidisciplinary discussion, patients were included in this study.

We reviewed patients' chart with regard to history, especially exposure to environmental and occupational inhaled agents, smoking history and medication, clinical findings, laboratory results, PFT including exercise test if available, bronchoscopy and open lung biopsy if performed.

At time of follow up we recorded response to treatment with respect to clinical, functional and radiologic response.

Since 2013 we evaluated all patients referred for workup of diffuse parenchymal lung disease according to radiological and pathological criteria of ACIF.

We recorded patient symptoms, laboratory results, lung function tests and exercise capacity at the first visit and response to treatment during further follow up including lung function tests and radiology studies if available.

In 2016 all patients were contacted and those alive were interviewed regarding symptoms, response to therapy, potential triggers of the disease including infections or environmental or occupational inhaled agents.

The study was evaluated by the local ethical committee of the university of Munich, Germany.

Statistics

All the results are reported as mean (± standard deviation). For statistical analysis of differences between groups we used the f-test. For correlation, the Pearson correlation coefficient was calculated.

Results

Between 1993 and 2013 we detected 35 cases with pathological changes compatible with ACIF. After reviewing the patient charts, the histology and radiology results, a diagnosis of ACIF was made in 9 patients. All of them had undergone surgical lung biopsy (SBx) for diagnostic workup.

Between 1/ 2013 and 6/2015 we evaluate 620 patients for newly diagnosed ILD. Among them we prospectively detected 4 patients with ACIF. In 3 patients, the histological diagnosis was based on transbronchial cryobiopsies obtained during rigid bronchoscopy. In one patient, the diagnosis was based on clinical and radiological criteria only, since invasive procedures were contraindicated due to severity of pulmonary impairment.

All retrospective and prospective cases were discussed in the multidisciplinary ILD team.

Clinical data

At time of diagnosis, 13 patients (7 female) were 55 years (44-77 years) old. The main complains were dry cough (n=6), dyspnea at rest (n=2) and on exertion (n=7). The symptoms started about 20 months (4- 36 months) prior to initial assessment for ILD.

On auscultation, we found end-inspiratory fine crackles on the lung bases in 12 patients, in one patient who was diagnosed at a very early stage of the disease crackles were absent. One patient (no 9) developed finger clubbing 8 years after the diagnosis.

At the time of initial assessment one patient received treatment with weekly methotrexate for rheumatoid arthritis. None of the other patients were under immuno-suppressants including steroids.

Three patients reported about a recent pulmonary infection with subsequent deterioration and hospital admission leading to diagnosis of ILD.

At time of diagnosis no patient was active smoker. Eight patients were never smokers while 5 patients were previous smokers with mean cumulative exposure of 30 pack years (3-65). Patient characteristics at baseline are presented in table 2.

Comorbidities

One patient suffered from significant, endoscopically and histologically confirmed gastroesophageal reflux disease (GERD) (case 1).

Two patients suffered from rheumatoid arthritis for 14 years (case 9) and 10 years (case 12), respectively, before they developed respiratory symptoms.

Three patients reported a previous allergic reaction against antibiotics (case 4 and 5), and diclofenac (case 12), respectively. Seven patients were treated for arterial hypertension. One patient had chronic atrial fibrillation (case 11) and one patient coronary artery disease (case 12). Case 5 suffered from ichthyosis vulgaris.

5 patients (case 1, 3, 5, 7 and 8) suffered from obesity with a BMI of 31,1kg/m^2 and two patients (case 1 and 5) received nCPAP therapy for obstruc-

Table 2. Patients characteristics

	Age (yrs)	Sex	Symptom	Smoking	Exposure	Comorbidity	PFT	Biopsy	Main Diagnosis	Treatment	FU Months	Outcome
1	44	F	DOE	Never	GERD Mould	OSAS	restrictive	OLB	GERD	P	127	unknown
2	51	M	Cough, DOE	EX	Asbestos	Osteo-arthritis	restrictive	OLB	ACIF	P + Aza	44	Deceased Pre LTX
3	64	M	DOE	EX		Obesity	restrictive/ obstructive	OLB	Hypersensitivity Pneumonitis	P + Aza	97	unknown
4	60	F	Cough	Never	Leather		restrictive	OLB	ACIF	P	65	stable
5	56	M	Cough	Never		Ichthyosis vulgaris, Myopathy, OSAS	normal	OLB	focal ACIF	P + Aza	47	Improved
6	47	M	DOE	EX	Joiner (mahagoni)		restrictive/ obstructive	OLB	Hypersensitivity Pneumonitis	P + Aza	28	improved
7	63	F	DOE	Never	Bakery		restrictive/ obstructive	OLB	Hypersensitivity Pneumonitis	P + Aza	22	stable
8	49	F	DOE	EX	Mould	PH	restrictive	OLB	Hypersensitivity Pneumonitis	P	116	stable
9	47	F	SOB	Never		Rheumatoid Arthritis	restrictive	OLB	Rheumatoid Arthritis	P	109	improved, later LTX
10	48	F	DOE	Never	Mould positive IgG		restrictive	Cryo-bx	Hypersensitivity Pneumonitis	P	9	unknown
11	76	F	Cough	Never	Mould, positive IgG		restrictive	None	Hypersensitivity Pneumonitis	P + Aza	5	stable
12	75	M	Cough	EX	Mould asbestos	Rheumatoid arthritis	restrictive	Cryo-bx	Hypersensitivity Pneumonitis	P + Aza	5	improved
13	77	M	SOB, Cough	Never	Welder		restrictive	Cryo-bx	Hypersensitivity Pneumonitis	P + MMF	2	stable

DOE: Dyspnea on exertion; SOB: Shortness Of Breath; PH: pulmonary hypertension; LTX: lung transplantation; P: Prednisone; OLB: open lung biopsy

tive sleep apnea. None of the patients had renal disease or a malignancy in their medical history.

Environmental/occupational exposure

A history of exposure to inhaled agents was present in 10 patients: either in the context of their occupation as joiner (case 6), worker in a bakery (case 7), seamstress of leather trousers (case 4), welder (case 13), exposure to mould (cases 1, 8,10-12) or asbestos (case 2,12). The patients reported a various time of exposure from 3 (case 10) to 44 years (case 4). In 3 patients we found no inhalative or environmental exposure (Case 3, 5, 9).

Laboratory

All patients had a mild increase of C-reactive protein with a mean of 6 mg/l (min. 2,3 - max. 28,7mg/l - ULN <3mg/l).

4 patients showed mildly elevated serum antinuclear antibody titers: ANA between 1:80 - 1:640 (case 2, 10-12) which deemed unspecific. Elevated titer for ANCA or ENA were not detected.

We found increased serum-concentrations of antigen-speific IgG antbodies against Aspergillus spp in 3 patients with known mould exposure (case 1, 10, 11), A. fumigatus IgG was >200 mg/l (norm <39mg/l) in case 10 and 11, while case 1 showed an IgG Aspergillus flavus of 181,7mg/l (norm <40mg/l). In 2 patients (case 8 and 12) with a history of mould exposure IgG antibodies against Aspergillus, Cladosporum and Thermoactinomyces spp could not be detected.

Pulmonary function tests

The PFT showed a moderate restrictive pattern in 8 patients and a mixed obstructive-and restrictive pattern in 4 patients, while one patient had normal parameters.

The forced expiratory volume in 1 second (FEV1) was 1,86l (68% predicted; ±21,57%), the forced vital capacity (FVC) was 2,19 l (61% predicted; ±19,06%) and the total lung capacity (TLC) was 3,63l (66% predicted; ±16,30%). The diffusing capacity for carbon monoxide corrected for hemoglobin (DLCOc-SB) was reduced to 38,66% predicted (±14,78%).

At the time of initial assessment, 6 patients were hypoxemic at rest and received long term oxygen therapy (LTOT).

Radiologic findings

On Chest X ray, we found circumscribed reticular changes in 8 patients more prominent in the upper lobes and apical areas of the lower lobe. Two patients (case 9, 13) showed a mediastinal shift due to asymmetrical shrinkage of one of the lungs. One patient presented with diffuse ground glass opacity.

In all patients, typical radiological signs of ACIF were present on High Resolution CT scans (table 3) (Fig. 1). The predominant pattern includes bronchiectasis (8 patients), reticular infiltrates which were strictly airway-centered (12 patients), areas of ground glass opacity (6 patients) and parabronchial interstitial thickening (6 patients). In four cases these changes were predominant in cranial lung areas. Isolated decreased lung volumes in one lobe were present in three patients. The radiologic findings show mostly a bilateral distribution (84%). Only in 2 cases (15%) we found a unilateral distribution: case 5 with reticular changes in one lung lobe and case 13 with solely involvement of the right lung.

None of the patient presented with consolidations, radiological honeycombing, bronchioloectasis, lymphadenopathy, gross infiltrates or pleural effusion.

Bronchoscopy

Twelve patients underwent a bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies (forceps biopsies n=9; cryoprobe biopsies n=3).

BAL showed a total cell count of mean 282±171 /µl (ULN 100/µl) with a moderate lymphocytosis of 36±20% and a CD4 / CD 8 ratio of mean 3,58±2,75. In 11 patients a BAL eosinophilia was present with a mean of 8,6±4,7%.

In the retrospective cohort (n=9), transbronchial forceps biopsies did not provide conclusive histologic information. Conseqeuntly, all 9 patients underwent surgical lung biopsy.

In the prospective cohort (n=4), the histological diagnosis was obtained by transbronchial biopsy using a cryoprobe in three patients (case 10,12 and 13).

Table 3. Radiological signs of HRCT-scan

No	GGO	Bronchiectasis	Shrinking	Para-bronchial Interstitial thickening	Bronchio-litis	Unilaterale distribution	Bilaterale distribution	Airway-centered reticular changes
1	X	X			X		X	X
2							X	X
3			X	X	X		X	X
4	X			X			X	X
5		X			X	X		X
6				X	X		X	X
7	X		X				X	X
8	X	X	X				X	X
9	X	X	X	X			X	X
10		X		X			X	X
11		X					X	X
12		X					X	X
13	X	X	X	X		X		X
	n= 6 46%	n= 8 62%	n= 5 38%	n= 6 46%	n= 4 30%	n= 2 15%	n = 11 84%	n = 13 100%

GGO: ground glass opacity.

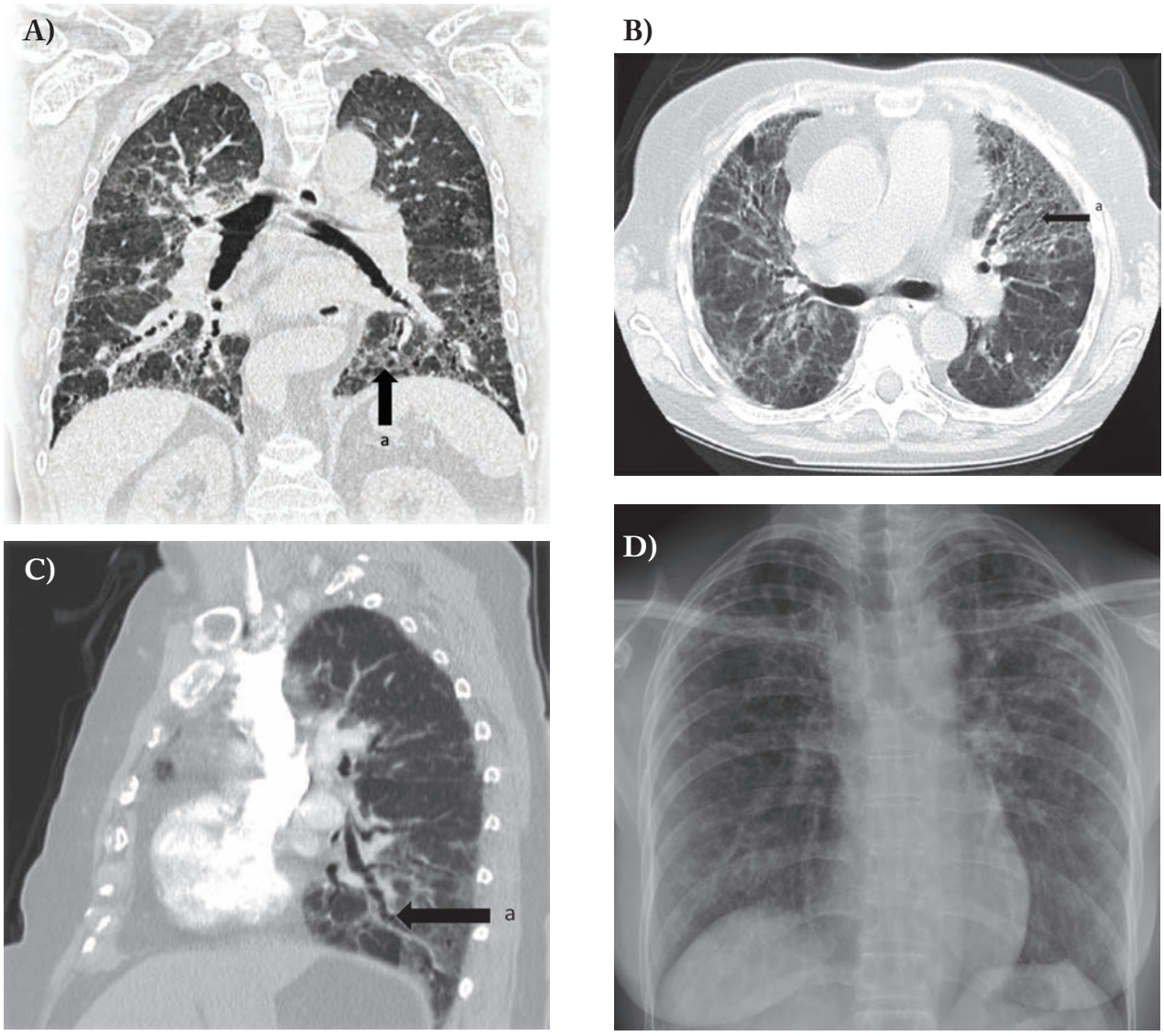

Fig. 1. A) High Resolution CT-Scan (coronar plane)): a = occasional interstitial thickening; B) Hight Resolution CT-Thorax (axial plane): a = thickened airway walls, traction bronchiectasis; C) Hight Resolution CT-Thorax (sagittal plane): a = thickened airway walls; D) Chest radiograph: cranial accentuation

One patient underwent a fiberoptic bronchoscopy with BAL only; transbronchial or surgical lung biopsy were contraindicated due to advanced pulmonary disease (case 11).

Video-assisted thoracoscopic lung biopsy

Nine patients underwent video assisted surgical lung biopsy in general anesthesia for a definite histological diagnosis. During VATS tissue samples have been obtained from the areas of most altered lung as well as from 2 other less affected parts of the lung. Postoperatively the chest tube could be removed after 3±1.7 days. None of the patients experienced postoperative complications.

Histopathology

All tissue samples were stained with hematoxylin-eosin and Elastic-van-Gieson and were examined for foreign bodies (Figs. 2, 3).

Two pathologists conducted histological exami-

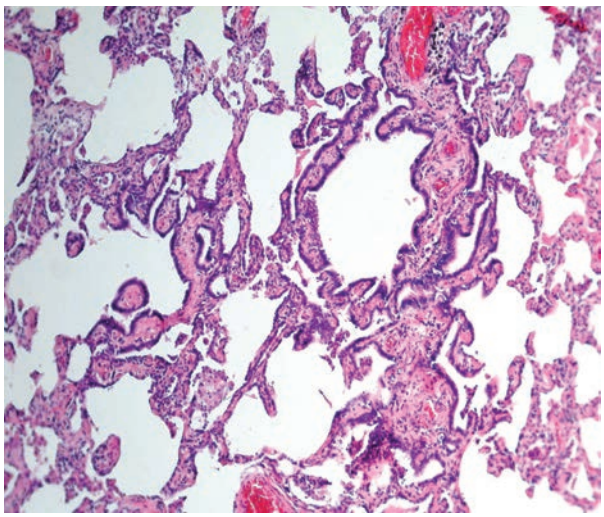

Fig. 2. Centribular (airway centered) fibrosis of the interstitium with (peri-)bronchiolar metaplasia. With courtesy of Alicia Morresi - Hauf

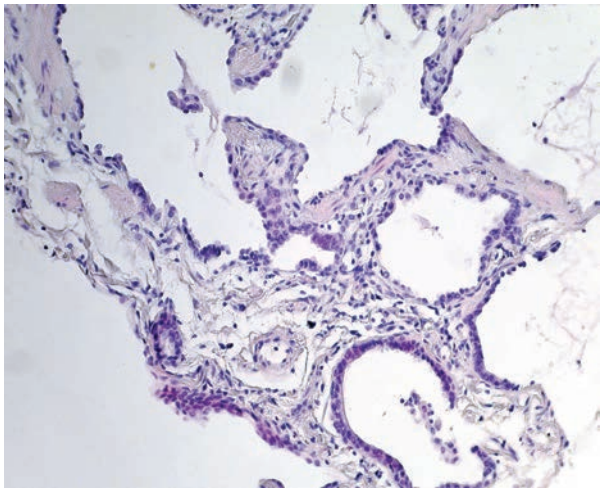

Fig. 3. Interstitial fibrosis. With courtesy of Alicia Morresi - Hauf

nations separately, the morphologic patterns were documented, and the final pathology diagnoses were made in consensus after a telephone conference.

In all biopsy samples, we detected a bronchiolar or peribronchiolar fibrosis with low or mild inflammatory cell infiltration, partially with muscle-proliferation and with variable degree of scarring of the bronchioles as well as interstitial fibrosis.

An architectural disruption was observed in 10 cases, with presentation of microscopic honeycomb like changes in 4 cases.

A metaplastic bronchiolar epithelium was present in 9 of 11 cases, in 3 cases it was remarkable (case 4, 7, 9).

Further histological findings included granulomatous lesions (n=4), giant cells (n=4), as well as focal proliferating fibroblasts compatible with fibroblast foci (n=2), and organizing pneumonia (n=3). All observed changes were only of minor significance and were assessed as nonspecific tissue reaction.

A detailed description of the histological changes is shown in table 4.

Diagnosis of ACIF

ACIF has been suggested by either histological or radiological signs but a final diagnosis has been obtained in the multidisciplinary team discussion (8).

In 3 cases, the histological findings provided the definite diagnosis of ACIF (case no 7-9). In 3 additional cases (case no 1, 4, 5) the differential diagnosis of chronic bronchiolitis has been raised by pathology, but the clinical and radiological data confirmed ACIF. In one patent without histology, radiological pattern was consistent with ACIF (Case 11).

In 4 other patients (case 3, 6, 10, 12) diagnosis of ACIF was made, and late forms of bronchiolitis or hypersensitivity pneumonitis were discussed as differential diagnoses. In the MDD, after full consideration of all available data, all cases were classified as ACIF.

Treatment

At time of diagnosis all patients were started on immunosuppressive therapy with prednisone at an initial daily dose of 0,5 mg/kg BW for 4-6 weeks with subsequent tapering to a maintenance dose of 5-10 mg/week. While 5 patients remained stable on low-dose prednisone monotherapy (n=5), 8 patients were consecutively started on combination therapy with either azathioprine 150 mg/day (n=7) or mycophenolate mofetil (2000 mg/day; n=1) due to progressive disease under reduced prednisone doses. One patient received a combination with azithromycin three times weekly due to side effect of azathioprine or mycophenolate (case 7).

Case 12 with history of a rheumatoid arthritis without elevated titers for CCP we assigned to the group of chronic hypersensitivity pneumonitis ac-

Table 4. Histological findings

No	Structural lung changes			Bronchioli				Distinct histological changes								Histological differential diagnosis		
								Granulomatous changes			Inflammation			Fibrosis				
	Distribution of fibrosis	Honey combing	Disruption of lung structure	Bronchiolitis	Scarring, muscular proliferation	Bronchioloectasia	Bronchiolar metaplasia	Granuloma Giant cells	Cholesterol granuloma	Foreign material	Lymphocyte accumulation	OP	DIP-like	IF	Fibroblast foci	ACIF	HP	Bronchiolitis
1	pb, ps	++	++	+	++	+	++	-	+	-	+	-	+	++	-	++		+
2	pb, ps	-	+	+	+++	-	-	-	-	-	-	+	++	++	-	+ (late)		++ (late)
3	pb, sp	-	+	+	+	-	+	++	-	-	+	-	+	++	-	+	+ (late)	
4	pb, ps	-	+	+	+	+	+++	+	-	-	++	-	-	+	-	++		+
5	pb, ps	-	-	+	+	+	+	-	+	-	+	-	+	+	-	++		+
6	pb, ps, pl	+	++	++	++	+	+	+	++	-	++	+	+	++	+	+	++	+
7	pb, pl	+	+	+	+	+	+++	-	+	-	++	-	++	+	-	+++		
8	pb, pl	-	+	+	+	+	++	+	++	-	-	-	-	++	-	+++		
9	pb, pl	-	+	+	+	+	+++	-	+	-	+	-	+	+	+	+++		
10	pb, ps	-	+	+	+	-	-	-	-	-	+	-	-	+	-	+		+
11	no biopsy																	
12	pb	-	-	+	+	-	+	-	-	-	+	+	-	+	-	+		++
13	pb, ps	-	-	-	+	+	-	-	-	-	-	+	-	+	-	+		

pb: peribronchial; pl: pleural; ps: paraseptal; -: not existing; +: low expression; ++: moderate expression; +++: strong expression
Favoured diagnosis +++: ACIF; ++: problably ACIF; +: ACIF possible

cording to the radiological findings and the exposure to mould.

If applicable, patients were asked to avoid a further exposure of noxious inhalation.

Follow-up

Overall, patients were on follow-up for a mean of 52 months (2-127 months). Two patients (Case 5 and 7) experienced a significant and sustained symptomatic and functional improvement in terms of increase of DLCO and VC on pharmacological treatment and cessation of exposure.

Three patients (Case 4, 6 and 8) remained stable concerning pulmonary function test and imaging studies over a time course up to 116 months but remained restricted in their daily activities with persistent exertional dyspnoe.

One patient (case 13) did deteriorate on treatment with prednisone monotherapy; but improved on combination treatment with mycophenolate mofetil.

Four patients (Case 2, 3, 11 and 13) required long-term-oxygen-therapy at time of diagnosis and 2 patients (case 8+9) developed hypoxaemia and were started on O2 supplementation during follow up. 4 patients (case 2, 8, 9 and 11) developed a significant precapillary pulmonary hypertension after a mean duration of the disease of 7 years. 2 patients were treated for pulmonary hypertension with sildenafil (case 2 and 8).

Two patients (case 2, 9) deteriorated despite treatment and required subsequent non-invasive ventilation. Case 9 was treated with steroid monotherapy and oxygen supplementation. Eight years after diagnosis, she deteriorated with development of hypercapnic respiratory failure but refused to increase immunosuppressive therapy. She was started on noninvasive ventilation and listed for lung transplantation. One year later she successfully underwent single lung transplantation.

Case 2 was treated with steroids and azathioprine but deteriorated 2.5 years after diagnosis. He required oxygen therapy and was listed for lung transplantation. Within 1 year he developed pulmonary hypertension and hypercapnic respiratory failure. He died due to pneumonia with septic multi organ failure.

The other 11 patients are currently alive with a mean of 52 (2 - 127) months after diagnosis.

A follow up telephone interview has been performed mean 37 months after initial diagnosis. Seven patients answered, while 2 patients did not respond to the questionnaire (23%) and 2 were diseased.

Three patients did not experience a subjective long-term benefit from individual therapy with persistent restriction in daily activities. Patients complaints of side effects due to long-term steroid therapy, e.g. osteoporotic fractures and impaired wound healing. Pulmonary function tests improved in 3 cases and remained stable in further 3 patients.

Discussion

Firstly described 10 years ago, ACIF as a new entity of ILD is still under discussion (1). However, clinical data remain sparse and limited to case series mainly focused on histological descriptions.

In the current manuscript, we report a case series of 13 ACIF patients, reflecting on the origin of the disease, treatment and long-term prognosis. Retrospectively, we identified nine patients over 20 years but another four patients prospectively within 2 ½ years, who fulfilled the histological and radiological characteristics for ACIF adapted from Churg et al. (3)(Table 1).

While there is variability in histology, radiology pattern and prognostic implication between the different forms of bronchocentric fibrotic pulmonary changes we agree with Virk et al. (8) considering the five reports (table 5) to be variants of the same type of DPLD . The histological hallmark is the bronchiolocentric patterns of interstitial pneumonia as outlined in the most recent international statement on DPLD classification (1, 9).

Among the other forms of IIP with airway involvement, RB-ILD is significantly associated with active cigarette smoking with detected of pigmented macrophages in the BAL. In our cohort, we neither found radiological or histological signs of RB-ILD nor the presence of smoker-macrophages in the BAL.

Bronchiolitis interstitial pneumonitis (BIP) is characterised by interstitial fibrosis and bronchiolitis obliterans, but no peribronchiolar fibrosis, a significant difference from ACIF (10). Peribronchiolar metaplasia (PBM) can be frequently found in several interstitial lung diseases especially in the context of

Table 5. Overview over current studies on Airway-centric Interstitial Lung diseases – (modified by 17)

	De Carvalho et al (8)	Yousem et al (7)	Churg et al (3)	Fukuoka et al (9)	Kuranishi et al (4)	Our group
No.	12	10	12	15	68	13
m/f	6/6	2/8	4/8	13/2	29/39	6/7
Age (years) mean (SD)	58 (11,4)	47 (12,8)	54 (13,8)	57 (9,1)	57 (12)	55 (7,33)
Smokers	4 (33%)	4 (40%)	3 (25%)	5 (33%)	1 (1,47%)	5 (42%)
FEV1 % pred mean (SD)	74 (20,8)	n/a	53 (15,5)	n/a	69 (18)	68 (21)
FVC % pred mean (SD)	63+/- 18,9	restriction (n=6)	51+/-15,8	n/a	66 +/-18	61+/-19,06
Disease distribution	Lower zones, asymmetric	Bibasilar	Central	Diffuse	Lower lobe (38), central + peripheral (45)	Diffuse, cranial attenuation
Radiology	Subpleural consolidation, bronchial wall thickening	interstitial and alveolar infiltrates	Reticonodular infiltrates, Bronchial wall thickening, Ring shadows, bronchi(olo)ectasis	Mosaic attenuation patchy subpleural ggo	peribronchovascular infiltrates, ggo, bronchiectasis, centrilobular nodules	peribronchiolar reticular infiltrates, ggo, bronchiectasis, sublobar shrinking
Died due to ILD	n/a	3 of 9	4 of 10	0 of 11	22 of 68	2 of 13

exposition to inhaled noxious agents as well as in ACIF like in our cohort. However, we regard the presence of PBM as such only as an associated but not specific histological finding in ACIF (9).

On radiology studies, we found the characteristic changes of ACIF in all patients using high-resolution chest CT, as demonstrated in table 3. However, several radiological features previously describe were not present in our patients, such as consoldiations, honeycombing or bronchioloectasis (7). This might be due to detection of the disease at different stages. There was a clear association between the extent of the radiological changes and degree of pulmonary functional impairment.

Although the diagnosis ACIF can be suggested based on clinical and radiological characteristics, a histological confirmation of the diagnosis should be attempt if the patient is fit for invasive workup. During the era when transbronchial lung cryobiopsy was not available all our patients underwent surgical VATS lung biopsy to provide a representative biopsy specimen. Although this procedure is associatied with an increased risk of exacerbation of IIP, we did not observe postoperative complications in our patients (11, 12).

Bronchoscopic transbronchial forceps/biospies are of limited value in IIP, and indeed in none of our patient histological diagnosis was obtained with this technique. In contrast, use of tranbronchial cryobiopsy allowed the histological confirmation of ACIF even in central parabronchial areas in three out of three patients (cases 10, 12 and 13). This underlines the potential role of transbronchial cryobiopsy in the histological evaluation of even complex histological patterns (13).

The etiology in ACIF is still a matter of debate. The peribronchiolar pattern is suggestive for a causative inhalative exposure, and indeed, in our study 69% of the patients had a history of an exposure to inhalative noxious agents, similar to previous reports (3, 14). Noteworthy, in none of the patients, termination of noxious exposure deemed to had an influence of the interstitial process.

The association of ACIF pattern to different forms of ILD including HP, rheumatological disorders and chronic aspiration has been recently found in a large Brazilian population. Kuranishi et al. reported a high number of 68 cases with ACIF diagnosed by surgical lung biopsy. They described a mixed etiology including HP (42,6%), GERD (25%) and collagen vascular disease (5,9%) with a 5 years mortality of 32,5% (14).

ACIF has been suggested as a subtype of chronic HP However, the histological hallmarks of HP such as granulomatous lung disease and lymphocytic alveolitis have not been described in the previous case series of ACIF. Churg et al. already pointed out that the histological hallmarks of ACIF such as small airway scarring or the peculiar pattern of bronchiolar metaplasia are not observed in HP (3).

In our cohort, we found only a moderate BAL lymphocytes of mean 36% not predictive of HP (15),

but 8 cases with a history of exposure and specific precipitins, compatible with HP as underlying ILD. Indeed, ACIF pattern has been described in 2% of lung specimen in chronic pidgeon breeder`s disease (16).

Other explanation includes GERD with micoraspiration, as present in our study (case 1) and previously reported (9, 13, 14). This pathogenetic concept is supported by an interesting study of de Souza et al. They reported about 6 patients with ILD in systemic sclerosis and a histologically confirmed centrilobular fibrosis resembling ACIF pattern. All patients responded well to antireflux therapy alone (17).

Cases of ACIF in association with rheumatoid arthritis have been reported previously, as also observed in our study (case 9) (11).

In our study, 3 ACIF patients (cases 2, 4 and 5) did not present with an underlying disorder or a distinct form of ILD. Two of them reported potential contact to inhaled agents (case 4 leather fabrication, case 2 asbestos), but not suggestive of a causal relationship. In case 5, ACIF was diagnosed as an incidental finding at an early stage of the disease with focal radiological changes but no underlying disorder. One might speculate about a hidden and unrevealed exposure, but we consider these 3 cases as idiopathic at present. Taken together, ACIF often occurs in conjunction with different clinical conditions, such as environmental exposure (then resembling chronic HP), rheumatoid diseases or chronic aspiration, but can also present as idiopathic disease.

In most cases, patients responded well to immunosuppressive therapy with corticosteroids monotherapy or in combination with azathioprine or mycophenolate mofetil, respectively. One patient (case 7) received intermittent azithromycin due to intolerance of combination immunosuppression. A beneficial effect of clarithromycin has been previously reported (18). During follow up of 52 months (min. 2, max. 127) one patient successfully underwent lung transplantation due to progressive disease despite immunosuppression (case 9) and one patient died but the reminder had a favorable prognosis. The favorable treatment response underlines the primary inflammatory nature of ACIF.

Reported factors associated with better prognosis include presence of peribronchiolar metaplasia (4, 5), but this could not be confirmed in our case series.

Our study combines two groups of patients: 9 patients have been retrospectively identified within 20 years, while prospectively we identified 4 newly patients within 13 months. ACIF might be still sporadic, but not so rare as suggested.

In summary in our case series of 13 patients, ACIF is a rare form of IP associated with environmental exposure, GERD and rheumatoid arthritis, but idiopathic in 23%. 77% of patients showed a favorable long-term outcome on immunosuppressive therapy.

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