Journal of Clinical Immunology (2019) 39:849–851
https://doi.org/10.1007/s10875-019-00708-2

LETTER TO EDITOR

Interstitial Lung Disease Frequently Precedes CVID Diagnosis

Leif G. Hanitsch[1] · Kirsten Wittke[1] · Anna Barbara Stittrich[1] · Hans Dieter Volk[1,2] · Carmen Scheibenbogen[1,2]

Received: 25 July 2019 / Accepted: 11 October 2019 / Published online: 22 October 2019

To the editor:

Common variable immunodeficiency disorder (CVID) is the most frequent clinically relevant primary immunodeficiency, and pulmonary infections, often leading to the development of bronchiectasis, are a major clinical finding in CVID patients [1]. However, non-infectious manifestations of the lung occur frequently too, with previous studies reporting interstitial lung diseases (ILD) in 10–20% of patients with CVID [1–3] and a disease onset of non-infectious pulmonary manifestations after 8 years [2]. CVID patients suffering from ILD have a poorer clinical prognosis [4]. Due to its main clinical manifestations, the term "granulomatous lymphocytic interstitial lung disease (GLILD)" was coined; however, clinical and histopathological findings show substantial heterogeneity, and a clear and universal definition is missing.

Other non-infectious manifestations, like immune thrombocytopenia or autoimmune hemolytic anemia, often precede the clinical symptoms and diagnosis of CVID [5], an observation that helps to improve early recognition of this rare disease. It is unknown what percentage of CVID patients presents with clinical symptoms of interstitial lung diseases preceding the diagnosis of immunodeficiency.

We conducted a cross-sectional study on non-infectious respiratory manifestations, i.e., the presence of ILD, in 105 adult patients with CVID. CVID was diagnosed according to ESID (European Society for Immunodeficiencies) criteria at the Outpatient Clinic for Immunodeficiencies, Charité Universitätsmedizin Berlin, Germany. Patient charts were reviewed for clinical courses, immunological parameters, pulmonary function tests, radiological features in CT scan, differential cytology in bronchoalveolar lavage fluid (BALF), histopathological findings, treatment, and results of genetic testing. Thoracic CT scans were part of the routine diagnostics at the time of PID diagnosis in our clinic. Three patients without pulmonary symptoms had not undergone thoracic CT scans and were excluded from the study. ILD was diagnosed in patients with radiomorphological changes in their CT scans and clinical symptoms (coughing, dyspnea) +/− impairment in pulmonary function testing (TLC (total lung capacity) < 80% and/or KCO (transfer coefficient of the lung for carbon monoxide) < 75%). For thoracic CT analysis, both mediastinal and lung window setting images were reviewed by different radiologists and all images were re-evaluated by a respiratory physician. Apart from solitary micronodules, there were no accidental findings of ILD in CT scans in asymptomatic patients. All patients were non-smokers. The study was approved by the local ethics committee, and informed consent was obtained from all individual participants included in the study.

In our cohort of 105 adult CVID patients, we identified 19 patients (18%) with interstitial lung diseases. In 53% (10/19 patients), a pulmonary diagnosis of ILD had preceded the diagnosis of CVID with a median delay of 36 months (see Table 1).

Demographic and clinical characteristics are listed in supplemental table S1. Patients affected with ILD presented with a much higher frequency of splenomegaly (74% vs. 31%; p value < 0.001) and lymphadenopathy (63% vs. 14%; p value < 0.001). Bronchiectasis occurred more frequently in patients with ILD than without ILD (37% vs. 16%; p value 0.04). Rates for autoimmune cytopenia and recurrent pneumonias did not differ significantly (supplemental table S1). In contrast to the recently described significant T-lymphopenia in patients with ILD [1], in our cohort, no significant differences in the immunological phenotype between patient groups were found (see supplemental table S2).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10875-019-00708-2) contains supplementary material, which is available to authorized users.

✉ Leif G. Hanitsch
leif-gunnar.hanitsch@charite.de

[1] Outpatient Clinic for Immunodeficiencies, Institute for Medical Immunology, Charité-Universitätsmedizin, Augustenburger Platz 1, 13353 Berlin, Germany

[2] Berlin Institute of Health (BIH), Center for Regenerative Therapies (BCRT), Charité-Universitätsmedizin Berlin and Max Delbrück Center, Berlin, Germany

Table 1 Data on diagnostic delay, pulmonary changes in CT, pulmonary function, BALF, histology, and genetics of all 19 CVID patients with GLILD

	Sex	Age	CVID diagnosis delayed (in months)	CT scan 1: nodular 2: ground glass 3: reticular 4:honey combing	Restriction 0: TLC > 80% +: TLC < 80% ++: TLC < 60%	Impaired diffusion capacity 0: KCO > 75% +: KCO < 75% ++:KCO < 60%	BALF 0: normal 1: lymphocytes > 20% n.d.: not done	Histology P: lung biopsy L: lymph node n.d.: not done	Immuno-suppressive therapy	Genetic results
1	F	46	52	2, 3 (bilateral lower lobes)	+	++	1 (CD4/8-ratio: normal)	COP: granulomatous lesions (P); LIP (P)	Steroids	*NFKB1*
2	M	55	36	1 (right upper and lower lobe)	0	0	n.d.	n.d.	Steroids	n.d.
3	M	35	0	1 (bilateral lower lobes)	0	0	1 (CD4/8-ratio: 1,7)	Sarcoid-like (L)	None	Neg.
4	F	54	0	2 (bilateral upper lobes), 3 (bilateral lower lobes)	0	+	1	Sarcoid-like (P)	Steroids, RTX, Aza, Cycloph.	Neg.
5	F	66	24	1 (bilateral lower lobes)	0	0	1 (CD4/8-ratio: 5,0)	n.d.	None	Neg.
6	M	46	36	1 (subpleural)	0	+	1 (CD4/8-ratio: 1,4)	Sarcoid-like (L)	None	Neg.
7	F	59	0	1 (multiple nodules bilateral)	0	+	n.d.	n.d.	None	Neg.
8	F	31	104	1, 2, 3 (bilateral with predominance in lower lobes)	0	+	1 (CD4/8-ratio: 3,7)	COP: granulomatous lesions (P)	Steroids	Neg.
9	F	28	44	2 (bilateral peribronchial and subpleural)	0	0	1 (CD4/8-ratio: 2,2)	n.d.	None	Neg.
10	F	34	0	2, 3 (bilateral lower lobes)	+	0	0	Sarcoid-like (L)	TNFa	Neg.
11	M	39	0	2 (bilateral)	0	0	1 (CD4/8-ratio: 5,2)	Lymphocytic infiltrates (P)	None	Neg.
12	F	55	5	2, 3, 4 (bilateral)	++	++	1 (CD4/8-ratio: 0,5)	n.d.	Steroids, RTX	Neg.
13	M	44	0	3, 4 (bilateral lower lobes)	+	++	0	n.d.	Steroids	*NFKB2*
14	M	36	72	1 (multiple nodules bilateral)	0	0	0	NSIP: lymphocytic & plasmacell. Infiltrates (P)	Steroids	n.d.
15	F	56	12	1 (right upper lobe)	0	0	0	Granuloma & T cell infiltrates (P)	Steroids	*PI3KCD*
16	M	32	0	2 (bilateral upper lobes)	0	0	0	n.d.	None	Neg.
17	F	55	0	2 (left lingula and lower lobe)	+	++	0	n.d.	Steroids	Neg.
18	F	33	15	1 (multiple nodules bilateral)	++	++	1 (CD4/8 ratio: 4,0)	EAA (P)	Steroids	Neg.
19	M	34	192	2, 3, 4 (bilateral)	+	+	1 (CD4/8 ratio: 1,5)	Langerhans cell histiocytosis: infiltrates of lymphocytes, plamacells, eosinophils (P)	Steroids, Vin, Cyt	*CTLA-4*

Aza Azathioprine, *BALF* bronchoalveolar lavage fluid, *COP* cryptogenic organizing pneumonia, *Cycloph.* cyclophosphamide, *Cyt* cytarabine, *EAA* exogenous allergic alveolitis, *n.d.* not done, *Neg.* negative, *NSIP* non-specific interstitial pneumonia, *RTX* rituximab, *TNFa* TNF alpha inhibition, *Vin* vinblastine

Results of the most recent pulmonary function testing showed mild restriction (TLC 60–79%) in 5/19 patients and moderate restriction (TLC 40–59%) in 2/19 patients (any restriction in 7/19 patients or 37%). Diffusion capacity was mildly reduced (KCO 60–75%) in 5/19 patients, and a moderate reduction (KCO 40–59%) was found in 5/19 patients (any impairment of diffusion capacity: 10/19 or 53%). The extent of limitation in pulmonary function testing in our patients was similar to other published CVID-ILD cohorts [4]. Our data support the measuring of diffusion capacity as an early screening marker for ILD in patients with CVID. However, in symptomatic patients, normal pulmonary function testing cannot replace the diagnostic role of CT scans.

Radiomorphological features on CT scan were diverse and included nodular changes (47%), ground-glass opacities (53%), reticular changes (37%), and honeycombing (16%). Data on differential cytology in BALF was available from 17/19 patients. With regard to differential cell counts in BALF, there are conflicting results with reports on elevated, normal, and reduced CD4/CD8-ratios [1]. In our cohort, the most frequent finding was an increase in lymphocytes (lymphocytes in BALF > 20%), which was detected in eleven patients (65%). Analysis of CD4/CD8-ratio was available in 10/11 patients, showing an increased ratio (CD4/CD8-ratio > 3.5) in four patients (40%). Histopathology was analyzed in eight pulmonary specimens and three lymph nodes. Major histopathological changes were lymphocytic infiltrates (*n*:4), sarcoid-like changes (*n*:4), and other granulomatous lesions (*n*: 3). In recent years, a number of disease-causing monogenetic disorders were discovered, including the identification of CTLA-4 deficiency, LRBA deficiency, or APDS (activated phosphoinositide 3-kinase delta syndrome), which are associated with CVID and lung disease [1]. Genetic testing using whole-exome sequencing was conducted in 16/19 patients, revealing known disease-causing mutations in four patients in *NFKB1*, *NFKB2*, *PI3KCD*, and *CTLA4* (*n*:1 each). Twelve patients are on immunosuppressive treatment, mostly using steroids (see Table 1). One patient requires supplemental oxygen therapy (see Table 1).

Most studies on ILD in CVID patients focused on possible risk factors for developing non-infectious pulmonary complications and how ILD affects the clinical course in these patients. Interestingly, in the largest clinically detailed cohort, it was reported that ILD developed on average 8 years after diagnosis of the underlying primary immunodeficiency [4]. In contrast to this observation, 53% of our patients with ILD presented initially at the pulmonologist with non-infectious pulmonary symptoms and on average 36 months before CVID was recognized. Looking at the clinical findings of our patients, it is not surprising that sarcoidosis was the most frequent pulmonary (mis)diagnosis, since lymphocytic alveolitis and sarcoid-like lesions in the biopsy are typical findings in sarcoidosis.

However, most of all, our observations show that it is important to create awareness for interstitial lung disease also as an early presenting clinical aspect of patients with CVID. Our findings advocate for the routine assessment of immunoglobulin levels in patients with ILD, allowing an early identification and initiation of treatment in these cases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Kellner ES, Fuleihan R, Cunningham-Rundles C. USIDNET Consortium, Wechsler JB. Cellular defects in CVID patients with chronic lung disease in the USIDNET registry. J Clin Immunol. 2019;39(6):569–76.
2. Mannina A, Chung JH, Swigris JJ, Solomon JJ, Huie TJ, Yunt ZX, et al. Clinical predictors of a diagnosis of common variable immunodeficiency-related granulomatous-lymphocytic interstitial lung disease. Ann Am Thorac Soc. 2016 Jul;13(7):1042–9.
3. Rao N, Mackinnon AC, Routes JM. Granulomatous and lymphocytic interstitial lung disease: a spectrum of pulmonary histopathologic lesions in common variable immunodeficiency – histologic and immunohistochemical analyses of 16 cases. Hum Pathol. 2015;46:1306–14.
4. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol. 2004;114:415–21.
5. Wang J, Cunningham-Rundles C. Treatment and outcome of autoimmune hematologic disease in common variable immunodeficiency (CVID). J Autoimmun. 2005;25:57–62.