

Significance of precipitins and asymptomatic lymphocytic alveolitis: a 20-yr follow-up

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ABSTRACT: What is the significance of serum precipitins and lymphocytic alveolitis in a healthy subject exposed to antigens responsible for hypersensitivity pneumonitis (HP)? This study was done to evaluate the 20-yr outcome of asymptomatic dairy farmers with or without precipitins or lymphocytic alveolitis in their bronchoalveolar lavage (BAL).

Twenty-seven of the initial 43 farmers were restudied. Of the missing 16, 11 refused the follow-up, three had died and two could not be located. The restudied farmers had a clinical evaluation, lung function tests and a high resolution computed tomography (HRCT).

Only one subject, an asthmatic, had dyspnoea, none described present or past symptoms suggestive of HP. Of those who were no longer on the farm, none had quit because of respiratory problems. Lung function changes were as expected with aging. The only difference was that farmers with positive precipitins had a statistically significant greater decrease in their forced expiratory volume in one second than the sero-negative farmers. Four HRCTs showed signs of minimal parenchymal abnormalities; these were not more prevalent for subjects with or without precipitins or BAL lymphocytosis.

Serum precipitins and asymptomatic lymphocytic alveolitis in an asymptomatic, exposed dairy farmer have no clinically meaningful long-term consequences.

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Dairy farmers in humid regions, such as the province of Quebec in Eastern Canada, are exposed to large quantities of bacteria and moulds that can lead to farmer's lung, a classical form of hypersensitivity pneumonitis (HP) [1]. Although only a small number of these farmers are ever diagnosed as having HP (estimated three in 1,000 in Quebec), a much higher proportion have specific antibodies (precipitins) to the responsible antigens. The prevalence of positive precipitins in Quebec dairy farmers varies between 8 and 10%, with significant fluctuation over time in those who are positive [2, 3].

The significance of positive precipitins has always been controversial. Although most cases of farmer's lung or other forms of HP have a positive serology to the responsible antigen, it remains unclear if these antibodies are simply a reflection of exposure or if they contribute to the disease pathogenesis [4]. The role of serum antibodies in an exposed but asymptomatic individual is even more uncertain. Are these subjects more at risk of developing HP than those who are sero-negative? Do these subjects have low-grade, clinically silent and indolent HP activity that could eventually lead to pulmonary scarring or destruction? Twenty years ago (1981–1982), in an attempt to shed some light on these issues, the current authors studied asymptomatic dairy farmers, some of whom were sero-positive [5, 6]. All these volunteers had a clinical evaluation, lung function tests, a chest radiograph and a bronchoalveolar lavage (BAL). At that time, all had normal physical examination, lung functions

and chest radiography. However, a significant proportion, especially those who had positive precipitins, had a lymphocytic alveolitis defined as >20% lymphocytes in their BAL fluid [7]. A similar finding has been reported in asymptomatic sero-positive pigeon breeders and peat moss factory workers [8, 9]. The long-term significance of asymptomatic lymphocytic alveolitis is unknown. A 5-yr follow-up of the farmers with a lymphocytic alveolitis failed to show a higher prevalence of HP in those who had a lymphocytic alveolitis, as compared to those with a previously normal BAL [10]. In addition, the changes in lung function over that period were not different between the two groups. Since the follow-up was relatively short and since the evaluation at that time did not include high resolution computed tomography (HRCT), the authors could not rule out the possibility that subjects with lymphocytic alveolitis had a low-grade HP, which could eventually lead to respiratory health disturbances. Therefore, in reality, the studies did not solve the problem but actually provided additional controversy on the meaning of so-called asymptomatic alveolitis.

The purpose of the current study was to evaluate, after 20 yrs, the outcome of these subjects. The aim was to see if serum precipitins against farmer's lung antigen and/or an asymptomatic lymphocytic alveolitis would predict an adverse outcome in their respiratory health. The reasoning was that if serum precipitins and/or lymphocytic alveolitis were associated with a low-grade disease, any adverse effects would become apparent over that time frame.

Material and methods

Study population

A total of 43 asymptomatic dairy farmers participated in the 1981–1982 studies. All these subjects were solicited for the present study. Initially, 23 had serum precipitins against *Saccharopolyspora rectivirgula*, the bacteria most frequently responsible for farmer's lung. In 1981–1982 all subjects had a clinical evaluation, lung function measurements, a standard postero/anterior and a lateral chest radiograph, and a fibroscopic bronchoscopy with BAL. At that time, all were asymptomatic (by definition), and had normal physical examination, lung functions and chest radiography. Nineteen had a lymphocytic alveolitis (>20% lymphocytes in their BAL fluid). The lymphocytic alveolitis was most frequent in subjects with positive precipitins (14 versus five). For the current study (2002), the authors were able to re-evaluate 27 out of the initial 43 subjects. Three had died (one of lymphoma, one of multiple myeloma and one of prostate cancer), two could not be located and 11 refused. Those who refused the current evaluation agreed to answer a few questions on their current and past respiratory health status. All subjects signed an inform consent form approved by the current authors' institution's ethics committee.

Evaluations

Each re-evaluated subject had a clinical, lung function (volumes, flows and carbon monoxide diffusion capacity (DLCO)) and HRCT assessment. All films were read by an experienced radiologist (L. Létourneau), who was aware that he was looking for signs of hypersensitivity pneumonitis, either active disease or its sequelae, but was blinded to the results of precipitin antibodies or BAL lymphocytosis at the time of the initial study. All films were read and scored using a previously published method [11]. In summary, the lungs were divided into six sections (five lobes and the lingula). Each section was graded on a score of 0 (none) to 3 for decreased attenuation/mosaic perfusion, air trapping, ground glass, micronodules, reticular pattern/honeycombing and emphysema. The maximal total score for each pattern was, therefore, 18 (grade 3 in all six regions). The presence of lymphadenopathy (short axis >10 mm) was also noted.

Statistical analyses

Results of representative measures were expressed using mean±SD for continuous variables. Categorical variables were expressed using the count of the observed event. The Fisher's exact test was performed to compare groups. To analyse lung function changes and cell counts between farmers with and without precipitins, a repeated-measures analysis of variance (ANOVA) was performed. The Brown-Foresythe test was used to verify the homogeneity of variances. A similar approach was used to compare farmers with or without BAL lymphocytosis. The univariate normality assumption was verified with the Shapiro-Wilk test and multivariate normality was verified with Mardia tests [12]. All assumptions were fulfilled. The results were considered significant if p-values were ≤0.05.

Results

Characteristics of the patients who were or not restudied were similar in terms of age, years since retirement, lung

Table 1.—Current number of subjects with abnormal signs, symptoms or high resolution computed tomography (HRCT) according to the precipitin and bronchoalveolar lavage lymphocytosis status in 1981–1982

	Precipitins		Lymphocytosis	
	+	-	+	-
Cough	2	2	3	1
Dyspnoea	1	0	0	1
Crackles	1	2	1	2
Abnormal HRCT	0	4	1	3

functions and BAL at the initial study. None of those not restudied had had or currently had respiratory symptoms, and thus none had ceased farming because of respiratory ailments. The population in the current study included 24 males and three females, now aged 39–82 yrs.

Subjects not restudied tended to be older and subsequently had retired earlier, but these differences were not statistically different. For the 27 farmers restudied, their mean duration of exposure to the farm since the initial evaluation was 15.1 yrs. Fifteen subjects were no longer in contact with the farm environment (either retired or changed profession), the 12 others were still actively farming. Of those who had quit farming, none had done so because of respiratory problems.

Since the purpose of this study was to verify the outcome of these farmers in relation to the presence of serum precipitins or of a lymphocytic alveolitis in their BAL, the results are presented with the subjects divided into two groups based on these variables.

Respiratory symptoms, crackles and HRCT abnormalities are shown in table 1. These were infrequent, mild and not more prevalent in subjects who had precipitins or a lymphocytic alveolitis as compared to those who had not. For example, the HRCT scores out of the four subjects with abnormalities were as follows: 1, 2, 4 and 6, out of a maximal possible score of 18 had the abnormalities been diffuse and intense. No subject had significant lymphadenopathy. Results of the forced expiratory volume in one second (FEV1) for the 1982 and 2002 evaluations are given in table 2. Note that, as expected with aging, FEV1 significantly decreased between the two studies (p=0.001). The changes in FEV1 were significantly larger in farmers with precipitins than in the initially sero-negative group (p=0.03). The difference between the two groups was, however, small and, therefore, not clinically meaningful, since in both groups the decline was within normal decline with aging [13]. The FEV1 changes were not different in subjects with BAL lymphocytosis than those with a normal BAL. The forced vital capacity (FVC) in 1982 was similar for subjects with or without precipitins (4.95±0.62 versus 4.74±0.75) or lymphocytosis (4.74±0.82 versus 4.82±0.61), and changes over the 20-yr follow-up paralleled those of the FEV1. FVC decreased to 4.18±0.53 for the precipitin-positive group and to 4.26±0.78 for the sero-negatives. For the subjects with BAL lymphocytosis, the 2002 FVC was 4.18±0.98 while it was 4.26±0.43 for those with normal BAL. Total lung capacity and DLCO did not change significantly in either group. In addition, there was no correlation between the intensity of the lymphocytic alveolitis and changes of lung functions over time (data not shown).

Discussion

The results presented here show no evidence of a clinically meaningful unfavourable respiratory outcome in dairy farmers

Table 2. – Forced expiratory volume in one second at both study periods for subjects who were sero-positive (precipitins +) or sero-negative (precipitins -) for farmer's lung antigens in 1982 or had a lymphocytic alveolitis in their 1982 bronchoalveolar lavage (lymphocytes +) or not (lymphocytes -)

Precipitins				Lymphocytes			
+		-		+		-	
1982	2002	1982	2002	1982	2002	1982	2002
3.80	3.15	4.30	3.43	3.62	2.99	3.80	3.15
4.47	3.76	3.83	3.28	3.64	3.90	4.30	3.43
3.31	2.45	3.62	2.99	4.67	4.07	3.83	3.28
3.52	2.51	4.00	3.47	3.31	2.45	4.00	3.47
3.40	2.70	3.71	3.50	3.52	2.51	3.71	3.50
3.57	3.10	3.64	3.90	3.40	2.70	3.62	2.98
4.00	2.96	3.62	2.98	3.57	3.10	4.47	3.76
3.94	3.17	4.67	4.07	4.94	4.51	3.85	3.27
3.72	3.16	3.85	3.27	2.35	2.27	5.01	3.70
4.33	3.31	5.01	3.70	4.33	3.31	2.62	2.27
		2.62	2.27			4.00	2.96
		4.18	3.57			4.18	3.57
		2.20	1.98			2.20	1.98
		4.94	4.51			3.94	3.17
		2.35	2.27			3.72	3.16
3.81±0.38	3.03±0.39	3.77±0.85	3.28±0.70	3.74±0.74	3.18±0.76	3.82±0.68	3.18±0.49

Data are presented as individual data or mean±SD.

whether they had or did not have serum precipitins against farmer's lung antigen or a lymphocytic alveolitis 20 yrs earlier. Lung biopsies were not performed in the subjects in this study, neither in 2002 or at the original work-up. Transbronchial biopsies are of questionable value in the diagnosis of HP [14] and open lung biopsies could not be justified in these asymptomatic subjects. However, it is likely that lung biopsy in a subject with a lymphocytic alveolitis on BAL would show some abnormality, at least an increase of inflammatory cells in the alveolar spaces [15]. BAL was not repeated for the current study. The objective was not to study the outcome of the alveolitis itself but its clinical significance. As many of the subjects had ceased their contact with the farm environment >2 yrs previously, it is probable that their lymphocytosis would have cleared [16].

Although the number of subjects restudied is relatively small, none of the 11 subjects not restudied had symptoms suggestive of respiratory health problems and the three who had died had not died of respiratory problems. This study supports the concept that lymphocytic alveolitis in asymptomatic farmers is not a predictor of lung abnormalities. In addition, since the 11 subjects who were not re-evaluated were similar to those who were, in terms of precipitins and BAL, it is reasonable to assume that the 27 subjects restudied are representative of the initial cohort of farmers.

In conclusion, this study demonstrates that asymptomatic dairy farmers who have specific serum antibodies to farmer's lung antigens or a lymphocytic alveolitis are not at higher risk of developing abnormal respiratory outcomes than farmers who have no sensitisation to the antigens or lymphocytosis in their bronchoalveolar fluid.

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