SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2014; 31; 364-367

Seasonal variation of serum KL-6 and SP-D levels in bird-related hypersensitivity pneumonitis

Tsukasa Okamoto, Toshiharu Tsutsui, Kozo Suhara, Haruhiko Furusawa, Yasunari Miyazaki, Naohiko Inase

Department of Respiratory Medicine, Tokyo Medical and Dental University, Tokyo, Japan

Dear Editor

Bird-related hypersensitivity pneumonitis (HP) is an immunologically mediated lung disease induced by inhalation of bird dropping extracts and antigens in feathers (1). Environmental assessment and removal of the avian antigen are crucial in the management of bird-related HP. Measurement of serum Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) is widely accepted in Japan, as a diagnostic test for interstitial lung diseases (ILDs) and as a marker of disease activity (2, 3). In our experience of patients with summer-type HP, serum KL-6 and SP-D levels increase together with disease activity in hot and humid times of year, when *Trichosporon Asahii* and other causative molds grow best (4). Conversely, patients with bird-related HP seem to present with higher serum levels of KL-6 and SP-D in winter. To our knowledge, no earlier reports have described seasonal differences of serum KL-6 and SP-D levels in patients with ILDs. We therefore decided to investigate the seasonal variations of serum KL-6 and SP-D levels in patients with bird-related HP.

Received: 31 March 2014
Accepted after revision: 15 April 2014
Correspondence: Tsukasa Okamoto
1-5-45 Yushima, Bunkyo-ku,
Tokyo 113-8519, Japan
Phone: +81-3-5803-5954
Fax: +81-3-5803-0260
E-mail address: tokamoto.pulm@tmd.ac.jp

We collected data about serum KL-6 and SP-D levels retrospectively in patients with bird-related HP and idiopathic pulmonary fibrosis (IPF) diagnosed between 2002 and 2012 in our institution. The bird-related HP was diagnosed by inhalation provocation test using avian antigen (5) and IPF was diagnosed based on a multidisciplinary review according to established criteria (6). Twenty-five patients with bird-related HP and 28 patients with IPF were enrolled. No treatments were administered during the period between the first patient visit and enrollment in the study more than 1 year later, and serum KL-6 and SP-D were measured at least once every season in every patient. The serum cut-off levels were 500 U/ml (KL-6) and 110 ng/ml (SP-D). All statistical analyses were performed using Prism 6 (GraphPad Software, Inc., San Diego, CA, USA). The significance of differences among frequency data was evaluated using the chi-square test. Intergroup comparisons were assessed using the Mann-Whitney U test. The Wilcoxon matched-pairs test was used to compare serum KL-6 and SP-D levels from season to season. Significance was defined as $p < 0.05$. This study conformed to the Declaration of Helsinki and was approved by the institutional review board (approval number: 1677).

Patient's characteristics are shown in Table 1. Of the patients with bird-related HP, 14 had histories of bird breeding and 23 had used duvets, jackets, or other products insulated with bird feathers mainly in winter. All cases of HP were chronic forms. Histologically, all 8 of the patients who underwent

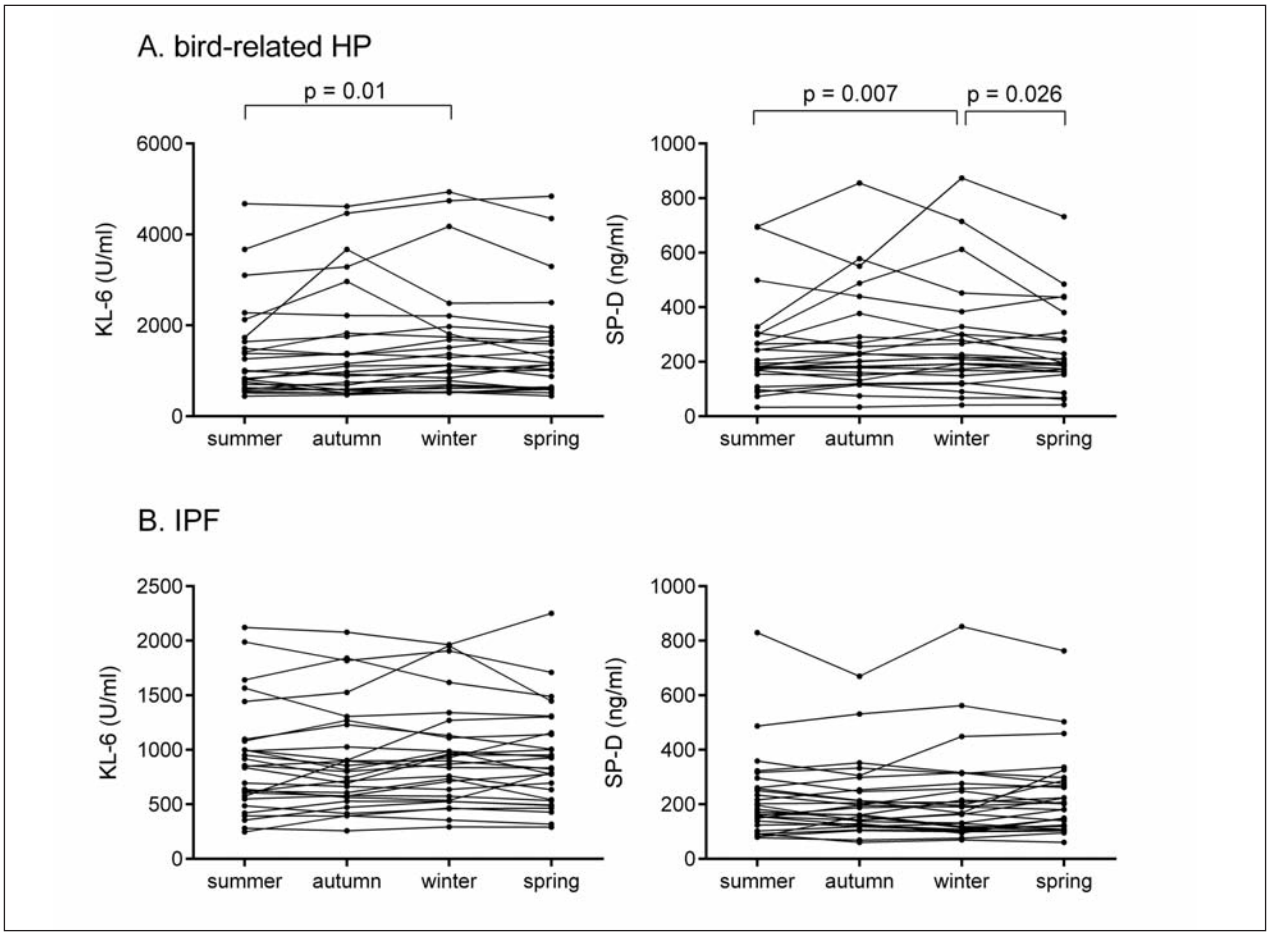

Fig. 1. The variations of serum KL-6 and SP-D levels in four seasons in the patients with bird-related HP (A) and IPF (B) were shown.

surgical lung biopsy exhibited a usual interstitial pneumonia pattern. Serum KL-6 levels were significantly higher in winter than in summer (median, 1121 U/ml vs. 990 U/ml, p = 0.01) (Fig. 1, Table 1). Similarly, serum SP-D levels were significantly higher in winter than in summer (median, 217 ng/ml vs. 182 ng/ml, p = 0.007). Serum SP-D levels were also significantly higher in winter than in spring (median, 217 ng/ml vs. 195 ng/ml, p = 0.026). There were no significant differences of KL-6 levels between spring and the other seasons, although the median KL-6 levels in spring was the highest. In patients with IPF, there were no significant inter-seasonal differences in serum KL-6 or SP-D levels. No episodes of acute exacerbation of bird-related HP or IPF occurred during the observational period.

Serum KL-6 and SP-D levels can predict the activity and prognosis of ILDs (2, 3). The clinical manifestations of HP are likely to be determined by the intensity and frequency of exposure to etiologic antigens. We speculate that the elevated serum levels of KL-6 and SP-D in winter reflect a more frequent exposure to avian antigen. Many people in Japan rely on feather-insulated products such as duvets, pillows, and jackets in winter, and by doing so may heighten their exposure to avian antigen.

The physical symptoms, radiological and pathological abnormalities, and prognosis of bird-related HP are similar to those of IPF. In fact, bird-related HP is often misdiagnosed as IPF, since most physicians are unfamiliar with the disease and have limited diagnostic means. Immunologically, bird-related

Table 1. Patient characteristics

	bird-related HP	IPF	p
Number	25	28	-
Gender (male/female)	13/12	18/10	0.365
Age	68 [58 - 74]	67 [62 - 73]	0.449
Smoking history (current/ex/never)	1/11/13	4/17/7	0.094
Clubbed fingers (+/-)	7/18	12/16	0.260
PaO_2 (Torr)	82.4 [78.4 - 93.3]	92.5 [82.3 - 96.0]	0.080
%VC (%)	78.7 [69.1 - 83.0]	93.9 [82.6 - 104.1]	< 0.001
%FVC (%)	69.7 [60.7 - 79.9]	81.7 [66.8 - 92.0]	0.033
%Dlco (%)	55.9 [40.6 - 70.2]	60.2 [38.7 - 70.5]	0.825
BALF lymphocytes (%)	17.2 [5.2 - 28.7]	9.8 [4.8 - 15.6]	0.071
BALF CD4/8	3.25 [2.06 - 7.50]	1.98 [1.22 - 3.99]	0.117

HP: hypersensitivity pneumonitis, IPF: idiopathic pulmonary fibrosis, PaO_2: partial pressure of arterial oxygen, %VC: percentage predicted vital vapacity, %FVC: percentage predicted forced vital capacity, %DLco: percentage predicted diffusing lung capacity for carbon monoxide, BALF: bronchoalveolar lavage fluid. Data were expressed as number or median [interquartile range].

Table 2. Seasonal variations of serum KL-6 and SP-D levels

	bird-related HP	IPF
KL-6 (U/ml)		
summer	990 [664 - 1687]	844 [555 - 1060]
autumn	1109 [590 - 2023]	772 [567 - 1179]
winter	1121 [675 - 1893]	883 [546 - 1125]
spring	1138 [627 - 1800]	830 [536 - 1151]
SP-D (ng/ml)		
summer	182 [162 - 283]	177 [128 - 260]
autumn	202 [141 - 334]	175 [125 - 252]
winter	217 [158 - 315]	179 [110 - 271]
spring	195 [163 - 296]	202 [120 - 285]

HP: hypersensitivity pneumonitis, IPF: idiopathic pulmonary fibrosis, KL-6: Kreb von Lungen-6, SP-D: surfactant protein D. Data were expressed as number or median [interquartile range].

HP is examined with antibodies to the avian antigen, lymphocyte proliferation test, and inhalation provocation test. Yet, only a limited number of institutions are equipped to perform these immunological examinations. We propose that elevated serum levels of KL-6 and SP-D in winter may be an important criterion for differentiating bird-related HP from IPF.

The patients with bird-related HP had a relatively modest lymphocytosis (median, 17.2%). All cases were chronic HP and the findings of BAL analysis were similar to Japanese epidemiological survey of chronic HP (median, 25%) described previously (7).

In conclusion, serum levels of KL-6 and SP-D identifiably differ between seasons in patients with bird-related HP. We propose that higher serum levels of KL-6 and SP-D in winter may relate to an increased usage of feather-insulated products.

Acknowledgements

Author contributions: Dr. Okamoto had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Okamoto: contributed to the study idea, discussion, and writing and final approval of the manuscript. Dr. Tsutsui: contributed to the data collection, discussion, and final approval of the manuscript. Dr. Suhara: contributed to the data collection, discussion, and final approval of the manuscript. Dr. Furusawa: contributed to the study idea, discussion, and final approval of the manuscript. Dr. Miyazaki: contributed to the study idea, discussion, and final approval of the manuscript. Dr. Inase: contributed to the study idea, discussion, and editing and final approval of the manuscript.

Ethics approval

This study was approved by the institutional review board of Tokyo Medical and Dental University, Tokyo. (Approval number: 1677)

Reference

1. Koschel D, Wittstruck H, Renck T, Muller-Wening D, Hoffken G. Presenting features of feather duvet lung. International archives of allergy and immunology 2010; 152: 264-270.
2. Yokoyama A, Kondo K, Nakajima M, Matsushima T, Takahashi T, Nishimura M, Bando M, Sugiyama Y, Totani Y, Ishizaki T, Ichiyasu

H, Suga M, Hamada H, Kohno N. Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis. Respirology 2006; 11: 164-168.
3. Takahashi H, Shiratori M, Kanai A, Chiba H, Kuroki Y, Abe S. Monitoring markers of disease activity for interstitial lung diseases with serum surfactant proteins A and D. Respirology 2006; 11 Suppl: S51-54.
4. Inase N, Ohtani Y, Usui Y, Miyazaki Y, Takemura T, Yoshizawa Y. Chronic summer-type hypersensitivity pneumonitis: clinical similarities to idiopathic pulmonary fibrosis. Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG / World Association of Sarcoidosis and Other Granulomatous Disorders 2007; 24: 141-147.
5. Ohtani Y, Kojima K, Sumi Y, Sawada M, Inase N, Miyake S, Yoshizawa Y. Inhalation provocation tests in chronic bird fancier's lung. Chest 2000; 118: 1382-1389.
6. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Jr., Kondoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schunemann HJ. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183: 788-824.
7. Okamoto T, Miyazaki Y, Ogura T, Chida K, Kohno N, Kohno S, Taniguchi H, Akagawa S, Mochizuki Y, Yamauchi K, Takahashi H, Johkoh T, Homma S, Kishi K, Ikushima S, Konno S, Mishima M, Ohta K, Nishioka Y, Yoshimura N, Munakata M, Watanabe K, Miyashita Y, Inase N. A nationwide epidemiological survey of chronic hypersensitivity pneumonitis in Japan. Respiratory investigation 2013; 51: 191-199.