Received: 19 February 2022 | Accepted: 25 April 2022

DOI: 10.1002/ppul.25950

CLINICAL CORRESPONDENCE

WILEY

Elevated serum TARC/CCL17 levels associated with childhood interstitial lung disease with *SFTPC* gene mutation

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To the Editor,

Childhood interstitial lung disease (ILD) is a serious and often life-threatening disease that causes interstitial lung lesion formation. Several causative genes of childhood ILD, such as *SFTPC*, *SFTPB*, and *ABCA3*, have been identified in some children. The pathogenesis of ILD caused by *SFTPC* mutations may involve the accumulation of misfolded surfactant protein C (SP-C) in vesicles, inhibition of pulmonary surfactant reuptake, and decreased expression of SP-C. However, this pathogenesis remains to be confirmed.[1]

Thymus and activation-regulated chemokine/C-C motif chemokine ligand 17 (TARC/CCL17) is a known disease marker for atopic dermatitis. Recently, it has been reported that plasma TARC/CCL17 levels were upregulated in patients with idiopathic pulmonary fibrosis compared with those in normal controls.[2] However, to date, there has been no report on the association between childhood ILD and TARC/CCL17.

Herein, we report our experience with a case of childhood ILD with *SFTPC* mutation and elevated TARC/CCL17 levels at disease onset that decreased after patient improvement with treatment. In children with *SFTPC* mutation, elevated TARC/CCL17 levels may be associated with ILD, which is different from the pathogenesis of atopic dermatitis. Moreover, it was suggested that TARC/CCL17 levels could be used as a biomarker for ILD in patients with *SFTPC* mutation.

An otherwise healthy 15-month-old girl was admitted to our hospital for fever, breathing difficulty, and poor oral intake. Nine days before admission, nasal discharge and cough appeared and gradually worsened; subsequently, poor oral intake appeared. No fine crackles were heard. The patient required supplemental oxygen and was admitted to the hospital. She had no history of respiratory impairment at birth. However, the patient had a family history of ILD in her maternal grandmother. Informed consent was obtained from the patient's guardians for the publication of this case report.

Laboratory test results showed white blood cell count, 941×10^9/L; neutrophil count, 58%; C-reactive protein level, 0.01 mg/dl; lactate dehydrogenase level, 929 IU/L; Krebs von den Lungen-6 (KL-6) level, 909 U/ml (normal range < 500 U/ml); surfactant protein A level, 319 ng/ml (normal < 43.8 ng/ml); and surfactant protein D level, 2770 ng/ml (normal < 110 ng/ml), which were suspicious findings for ILD (Table 1). ß-D-glucan level was 7.9 pg/ml (normal < 20 pg/ml) and both IgG and IgM were negative for cytomegalovirus. Chest radiography showed bilateral diffuse ground-glass opacities (Figure 1). Chest computed tomography scan showed bilateral diffuse frosted shadows (Figure 2), leading to ILD diagnosis.

Although prednisolone was started on Day 2 after admission, the patient's respiratory status did not sufficiently improve, and supplemental oxygen therapy was required. Therefore, methylprednisolone (30 mg/kg/day) was administered two times for 3 consecutive days on Days 13–15 and 19–21. However, the patient's respiratory status remained poor. Hydroxychloroquine (10 mg/kg/day) was then started on Day 21, and azithromycin (10 mg/kg/day) three times a week was started on Day 56. Thereafter, her respiratory status gradually improved. Although posthospitalization treatment improved her hypercapnia and labored breathing, the child was still in need for oxygen therapy administration and could not be weaned off it. On Day 66 after hospitalization, the patient was discharged with home-based oxygen. Chest X-rays showed little improvement in imaging findings between admission and discharge (Figure 3). Respiratory status, oxygenation, and laboratory data of ILD markers such as KL-6 gradually improved after discharge (Table 1).

Genetic analysis of *SFTPB*, *SFTPC*, *ABCA3*, *CSF2RA*, and *CSF2RB* showed *SFTPC* mutation and p.I73T (c.218T>C). Therefore, ILD was determined to be caused by this *SFTPC* mutation. The parents and grandparents of the patient did not wish to undergo genetic testing.

TABLE 1 Patient biochemical analysis results since the first visit.

Days after visit	1	7	13	18	26	40	47	61	75	83	103	131
TARC/CCL17 (pg/ml)	–	–	10,270	–	–	–	10,630	–	–	7046	2962	2122
LDH (IU/L)	929	621	671	651	737	580	600	497	463	477	471	420
KL-6 (U/ml)	909	–	1003	942	1107	1011	1040	1001	925	935	890	769
SP-A (ng/ml)	–	319	–	244	493	462	–	300	300	–	241	209
SP-D (ng/ml)	–	2770	–	2580	3080	2220	–	1770	2000	–	1950	1000

Abbreviations: KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; SP-A, surfactant protein A; SP-D, surfactant protein D; TARC/CCL17, thymus and activation-regulated chemokine/C-C motif chemokine ligand 17; –, no data.

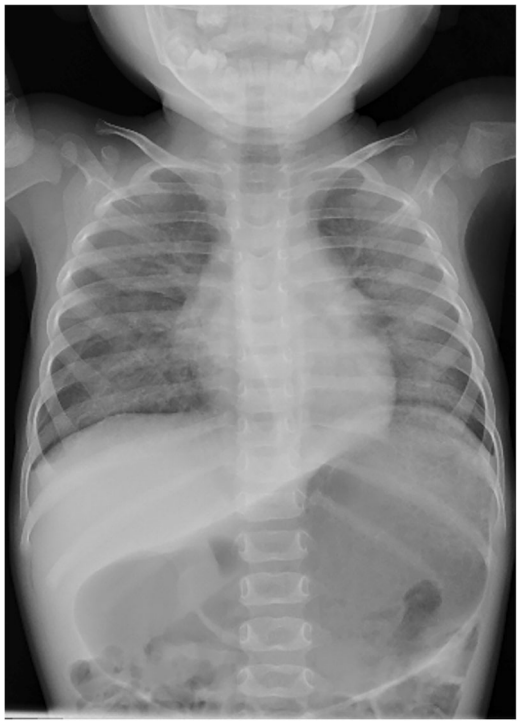

FIGURE 1 Chest X-ray revealing uniform ground-glass opacities at bilateral lung fields.

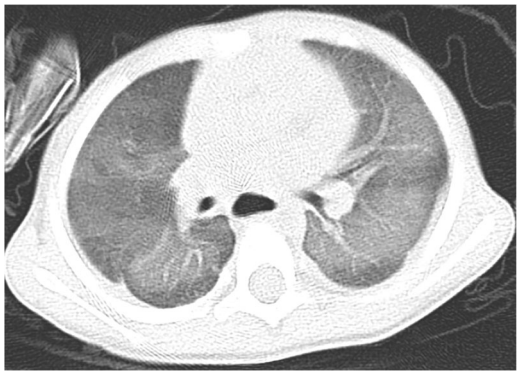

FIGURE 2 Chest computed tomography revealing bilateral diffuse ground-glass opacities.

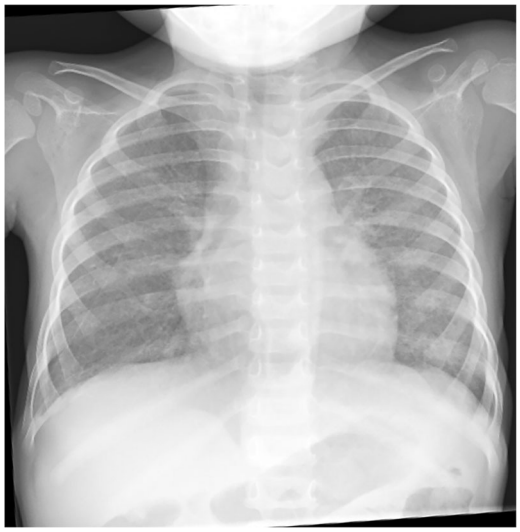

FIGURE 3 Chest X-ray at discharge showing remaining uniform ground-glass opacities at bilateral lung fields.

Additional examination revealed elevated TARC/CCL17 level at 10,270 pg/ml. However, IgE (24.2 IU/ml, normal < 173 IU/ml) and IL-4 (2.7 pg/ml, normal < 6 pg/ml) levels were not elevated in the early stages of treatment. TARC/CCL17 level decreased to 2122 pg/ml on Day 131 after admission. Granulocyte-macrophage colony-stimulating factor (GM-CSF) level was measured two times on Days 11 and 83 and on both days, its level was under 5 pg/ml without significant elevation. Anti-GM-CSF antibody (0.3 U/ml, normal < 1.7 U/ml) was negative.

Although it has been hypothesized that many of these effector cell populations, such as macrophages and lymphocytes, are recruited by TARC/CCL17 and act profibrogenically, the details remain largely unknown.[3] *SFTPC* mutations increase the number of abnormal alveolar type 2 epithelial cells (AT2) due to impaired metabolism of SP-C. A knock-in mouse model capable of regulating the expression of an isoleucine-to-threonine substitution at codon 73 (p.I73T) in SFTPC, at the same site as in the present case, showed persistently elevated TARC/CCL17 level in the bronchoalveolar lavage fluid (BALF). Furthermore, the same study also reported that TARC/CCL17 was specifically released by AT2.[3] In ILD caused by *SFTPC* mutations,

its pathogenesis involves AT2 hyperplasia. The reduction in TARC/CCL17 level in our patient suggests that either AT2 itself or TARC/CCL17 produced by AT2 decreased with treatment. In this case, we report, for the first time, elevated serum TARC/CCL17 level in a patient with *SFTPC* mutation, which decreased with treatment.

Our patient showed no symptoms of atopic dermatitis. Furthermore, she had neither skin condition nor elevation of IgE and IL-4 levels. In the *SFTPC* p.I73T mouse model mentioned above, no significant level of IL-4 or IL-13 was detected in BALF. Moreover, no involvement of the antigen-specific Th2 response was observed.

This high TARC/CCL17 level was not considered to be a result of the GM-CSF cascade. TARC/CCL17 is released from macrophages as a product of the GM-CSF cascade.[4] GM-CSF is also known to be produced by AT2.[5] However, in this case, serum GM-CSF levels were within normal range, both at the beginning of treatment and after improvement.

The limitation to this case report is that bronchoalveolar lavage was not performed. Therefore, the evaluation was based on serum levels rather than on local lung findings.

Normal serum values of TARC/CCL17 in children have not been established yet. Cut-off values of TARC/CCL17 for the diagnosis of atopic dermatitis have been found to be different among various age groups. A previous study reported measured serum TARC/CCL17 values in 45 children with atopic dermatitis and 52 non-atopic controls. It showed that serum TARC/CCL17 cutoff values to establish AD diagnosis were: 1431 pg/ml in the 0–1 year group, 803 pg/ml in the 2–5 year group, and 510 pg/ml in the 6-year and older group. Within the same literature, they also reported significantly higher normal TARC/CCL17 values in the 0- to 1-year-old group.[6] Compared with the cutoff values in that report, TARC/CCL17 level was elevated in our present case.

TARC/CCL17 may be associated with ILD and could potentially be used as a biomarker for detecting childhood ILD in patients with *SFTPC* mutations. Further elucidation of the chemokine and receptor signaling cascade may lead to targeting some stages for therapy, which may be an important issue for establishing future medical treatment. Therefore, elucidation of this pathogenesis is required.

AUTHOR CONTRIBUTIONS

Yuto Otsubo: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); visualization (equal); writing–original draft (equal); writing–review and editing (equal). **Yuji Fujita**: Writing–review and editing (supporting). **Yusuke Ando**: Writing–review and editing (supporting). **George Imataka**: Writing–review and editing (supporting). **Shigemi Yoshihara**: Writing–review and editing (supporting).

ACKNOWLEDGMENTS

The authors would like to thank Editage (www.editage.com) for English language editing. The authors thank Dr. Goro Koinuma, Division of Pulmonology, National Center for Child Health and Development, Tokyo, Japan, for his invaluable expert opinion regarding the diagnosis and treatment of the patients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Otsubo Y, Fujita Y, Ando Y, Imataka G, Yoshihara S. Elevated serum TARC/CCL17 levels associated with childhood interstitial lung disease with *SFTPC* gene mutation. *Pediatric Pulmonology*. 2022;1-3. doi:10.1002/ppul.25950