Cardiac infiltration in early-onset sarcoidosis associated with a novel heterozygous mutation, G481D, in CARD15

Sin, Early-onset sarcoidosis (EOS) and Blau syndrome (BS) are rare multi-organ granulomatous inflammatory disorders clinically characterized by the distinct triad of skin, joint and eye lesions without any apparent cardio-pulmonary involvement [1]. Gain-of-function mutations in CARD15 (NM_022162) cause EOS and/or BS (EOS/BS) [2–4], but not the development of adult-type sarcoidosis [5, 6]. We identified a novel heterozygous gain-of-function mutation, G481D, in CARD15 from a patient with EOS, who was suffering from recurrent episodes of congestive heart failure. Cardiac infiltration is a common clinical manifestation in adult-type sarcoidosis, but is rare and atypical in EOS/BS. Notably, the cardiac manifestations of this patient are quite similar to those in adult sarcoidosis. This is the first report demonstrating the precise manifestations of cardiac infiltration of sarcoidosis in a patient with a CARD15 mutation.

The patient was an 18-year-old female. At 3 months of age she developed a miliaria-like skin rash. Thereafter, she presented various manifestations, such as uveitis, joint involvement, hepatosplenomegaly, arterial hypertension and congestive heart failure. A lymph node biopsy showed fresh-looking multiple granulomas, indicating a diagnosis of EOS. The administration of glucocorticoids improved her symptoms. However, extended treatments were required because of recurrent episodes of congestive heart failure accompanied with the activation of an autoinflammatory reaction. Echocardiography showed intraventricular septum thickness [Fig. 1A (a, b)]. A histopathological examination of the right ventricle endocardium revealed inflammatory cell infiltration, ballooning of myocardium and mild fibrosis (Fig. 1B). The histopathological findings were similar to those of cardiac sarcoidosis in adults. Other immunosuppressive treatments, e.g. NSAIDs, MTX, AZA and/or CSA, did not sufficiently improve her symptoms. The administration of TNF-α inhibitor, infliximab, in combination with MTX effectively inhibited the autoinflammation, thus resulting in an improvement of the intraventricular septum thickness [Fig. 1A (c, d)].

Under approval by the Ethics Committee/Internal Review Board of Hiroshima University and informed patient consent, we analysed the nucleotide sequence of CARD15, and found a novel heterozygous single base-pair substitution, 1442G>C (G481D), in exon 4. This mutation was located within the nucleotide-binding domain. NF-κB reporter assay revealed that MDP-independent NF-κB transactivation in the G481D, C495Y and H496L mutants in CARD15 showed significantly higher levels than that in wild-type (WT) (Fig. 1C), thus suggesting the G481D mutation to be a gain-of-function mutation [3].

Cardiac infiltration is a rare and atypical manifestation among the patients with EOS/BS. Only one report has shown cardiac infiltration among the patients with CARD15 mutations [4]. The patient suffered from severe multi-organ involvement, arterial hypertension and myocardial hypertrophy, and was identified as being a heterozygous C495Y mutation. The C495Y mutation displayed the highest level of MDP-independent NF-κB transactivation (Fig. 1C), and notably the G481D mutation also demonstrated a relatively higher level of activity. Although no genotype-phenotype correlation in EOS/BS could be proven in the previous study, cardiac infiltration may therefore be associated with higher levels of MDP-independent NF-κB activation [3].

Fig. 1. (A) Echocardiography findings (parasternal long-axis view) before (a, b) and after (c, d) sufficient anti-inflammatory treatments. The systolic (a, c) and diastolic (b, d) image. (B) Histopathological findings of endocardium [(a) HE×200, (b) Azan×100]. (C) The MDP-independent (open columns) and MDP-dependent (filled columns) NF-κB transactivation. Values represent the mean of the normalized data (mock without MDP = 1) of triplicate cultures, and error bars indicate the s.o. Both C495Y and H496L are previously reported mutations in patients with EOS [3, 4].
Cardiac infiltration in adult-type sarcoidosis has shown a variety of manifestations, such as a conduction disorder, ventricular arrhythmias, congestive heart failure and sudden cardiac death. Matsumori et al. [7] reported that echocardiography revealed cardiac abnormalities in 6 of 82 patients with adult-type sarcoidosis. Four of six patients presented intraventricular septum thickness with mild to moderate myocardial cellular infiltration and fibrosis. The clinico-pathological findings in the current case resembled cardiac sarcoidosis in adults.

Recently, TNF-α inhibitors or IL-1 inhibitors have been tried on refractory cases, and were shown to improve the clinical manifestations [4, 8]. The efficacy of TNF-α inhibitors against cardiac sarcoidosis in adults has been also reported [9]. The administration of infliximab resulted in the reduction of the daily dose of prednisolone without disease progression. Furthermore, her cardiac manifestation was also improved clinically and morphologically in response to sufficient anti-inflammatory treatment. The intraventricular septum thickness was a reversible change, similar to a previous report in cardiac sarcoidosis in adults [10].

In this report, we identified a novel heterozygous gain-of-function mutation, G481D, in CARD15 in a patient with EOS, suffering from cardiac infiltration of sarcoidosis. The clinical manifestation of cardiac sarcoidosis accompanied with EOS/BS is similar to that in observed in adults. Cardiac infiltration is an important manifestation in not only adult-type sarcoidosis, but also in patients with EOS/BS.

**Rheumatology key message**

- Cardiac infiltrations in an EOS patient associated with a novel gain-of-function CARD15 mutation.

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