A novel PRKDC mutation caused B lymphocytes V(D)J rearrangement disorder in the SLE-DAH like symptoms patient

Hongwei Li¹², Yawen Zhang¹², Biyun Zhang¹² and Dehui Chen¹²*}

Abstract
Background Analyzed the clinical features and treatment process of the patient suffering from immunodeficiency with systemic lupus erythematosus (SLE)-like syndrome in a novel mutation of PRKDC.
Case presentation The patient had multiple positive auto-antibodies, chest CT and bronchoscopy showed Diffuse alveolar hemorrhage (DAH), and psychiatric symptoms showed brain atrophy by magnetic resonance imaging (MRI). Whole exome sequencing showed that novel complex heterozygous mutations of PRKDC gene (C. 1777 − 710_1777-709insA (IVS16/IC16), C.1337T > A(p.Phe446Tyr). The mature B cell (CD19 + CD27 + CD38 dimIgD IgM-) were absent. The treatment of high-dose methylprednisolone (MP) and cyclophosphamide (CTX) can quickly relieve the symptoms of the patient.
Conclusion We described the case of an infant immunodeficiency with SLE like-syndrome, which may cause by PRKDC mutation, treated successfully with high-dose MP and CTX.

Keywords PRKDC, Mutation, Systemic lupus erythematosus, Immunodeficiency

Introduction
Childhood systemic lupus erythematosus (cSLE) has been a common autoimmune disease in children, mainly characterized by multi-system chronic lesions, including skin, joint, kidney, nerve, cardiovascular, and lung damage, accompanied by extensive auto-antibody formation [1, 2]. Diffuse alveolar hemorrhage (DAH) syndrome is a very serious and fatal interstitial lung disease with an average mortality of 50%, caused by autoimmune diseases, especially SLE [3–5].

SLE has been mainly related to the immune dysfunction of B cells. Abnormal activation of B cells can generate multiple auto-antibodies, leading to the formation of immune complexes [6]. PRKDC encodes DNA-dependent protein kinase (DNA-PK), which is abundantly expressed in almost mammalian cells [7, 8]. Studies show that PRKDC mutation influenced production T/B cells and V(D)J rearrangement, which act as major triggers of auto-antibodies and autoimmune disease production [9, 10]. PRKDC mutation is seldom reported on autoimmune diseases and no related studies on SLE, especially for the treatment and prognosis of SLE with this gene mutation.

Here, we found a novel compound heterozygous mutation of PRKDC in a male cSLE for the performances of...
severe acute diffuse alveolar hemorrhage, multiple positive auto-antibodies, psychiatric abnormalities and multiple pathogen infections. Both parents were found to be heterozygous for the mutation. Aggressive plasma exchange, high-dose methylprednisolone pulse combined with cyclophosphamide (CTX) immunosuppression therapy significantly improved the clinical symptoms of the children. These results suggested that PRKDC mutations may induce T/B cell dysfunction and immune leakage, promoted the formation of auto-antibodies, which caused severe SLE with DAH symptoms.

**Case presentation**
An 8-month-old male child was admitted to the hospital because of cough and hemoptyses for more than one month with butterfly erythema and hepatomegaly. An episode of acute onset of alveolar hemorrhage (hemoglobin 8 g/L, Fib 0.5 g/L), pulmonary infection (Enterobacter cholaera, Pseudomonas Aeruginosa, Enterobacter cloacae, Mycoplasma pneumoniae, Parainfluenza virus. Acinetobacter and oligoxomonas maltophilia were detected in alveolar lavage fluid with Next Generation Sequencing(NGS), hypoxemia and psychosis were presented. Personal history: The patient was a full-term natural birth baby, and had retarded psychomotor development manifested as dysphasia and poor active grip with regular rehabilitation treatment at the age of 4 months old. Family history: His father worked in the administrative department of electronic components waste recycling. The parents and the sister were in good health. His father’s antinuclear antibody spectrum showed suspicious positive anti-SM antibody and weak positive anti-RNP/Smith antibody. The mother and the sister were negative in routine of auto-antibodies, immunity and hematuria detecting. Past history: He had been hospitalized twice for broncopneumonia and moderate anemia. Laboratory test of autobiographies showed, positive antinuclear antibody (ANA) (nuclear
granular + cytosolic) 1:640, anti-double, stranded DNA (dsDNA) and others were detect in the patient.

The Whole-exome showed novel compound heterozygous mutation of PRKDC was detect in the patient (Fig. 1), which had been reported to be pathogenic for this variant to involve in the pathogenesis of immuno-deficiency type 26 [9]. The CD19 + CD27 + CD38dim IgD/IgM of classical immunoglobulin class conversion B lymphocytes decreased significantly which be converted from IgM to IgG, IgA, IgE, etc. [11] (Table 1). The polymorphism of B-cell receptor (BCR) and T-cell receptor (TCR) were limited in patients with PRKDC mutations (Fig. 2). Above the result present the patient had the deficiency in the VDJ rearrangement with secondary immune disorder.

The treatment was given MP combined with CTX immunosuppression, and the dose was adjusted according to the ratio of T/B/NK cell subsets (Fig. 3), supplemented with plasma exchange three times to remove auto-antibodies and inflammatory mediators, and anti-infection treatment were performed with cefoperazone sodium and sulbactam sodium, teicoplanin, azithromycin and voriconazole according to the etiological examination. Finally, the patient’s blood oxygen and hemoglobin were stable, and pulmonary exudation was improved obviously in assessment of high-resolution chest CT (Fig. 4). Chest High-resolution CT showed the imaging changes of DAH (Fig. 5). Bronchoscope record: hemorrhagic diffuse alveolar in left and right side of the bronchial (Fig. 6).

Discussion and conclusions

SLE was proved to be a typical autoimmune disease and the damage to B cell tolerance checkpoints may be the main reason for the production of auto-antibodies. Antibodies, as secretory Immunoglobulin (Ig), are produced by B lymphocytes and are Y-type protein complexes composed of IgH and IgL pairs connected by disulfide bonds. IgH and IgL have variable and constant regions, respectively, in which the variable region specifically recognizes and binds antigens. Variable region coding genes are produced by V(D)J recombination. In this case, we found

**Table 1** Detailed immune function analysis of the patient with PRKDC mutation

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Cell phenotype</th>
<th>Value</th>
<th>Reference value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B lymphocytes</td>
<td>CD19+CD3-</td>
<td>16.13</td>
<td>3.80–21.50</td>
</tr>
<tr>
<td>Transitional B lymphocytes</td>
<td>CD19+CD27+CD38high IgM+CD24+</td>
<td>0.09</td>
<td>0.10–6.30</td>
</tr>
<tr>
<td>Primary B lymphocytes</td>
<td>CD19+CD27-IgD+</td>
<td>92.03</td>
<td>17.90–75.10</td>
</tr>
<tr>
<td>Marginal zone B lymphocytes</td>
<td>CD19+CD27+IgD+</td>
<td>3.04</td>
<td>3.80–35.60</td>
</tr>
<tr>
<td>Memory B cells</td>
<td>CD19+CD27+CD38dim</td>
<td>3.23</td>
<td>11.00-46.60</td>
</tr>
<tr>
<td>Classic immunoglobulin class conversion B cell</td>
<td>CD19+CD27+CD38dimIgD-IgM-</td>
<td>0.00</td>
<td>4.60–35.50</td>
</tr>
<tr>
<td>Non-immunoglobulin class conversion B cell</td>
<td>CD19+CD27+CD38dimIgD+</td>
<td>2.28</td>
<td>1.90–23.70</td>
</tr>
<tr>
<td>Plasmoblast</td>
<td>CD19+CD27highCD38highIgL-IgM-</td>
<td>0.19</td>
<td>0.30–7.80</td>
</tr>
<tr>
<td>CD21low B lymphocytes</td>
<td>CD19+CD38lowCD21low B cells</td>
<td>2.47</td>
<td>1.90–19.30</td>
</tr>
</tbody>
</table>

**Fig. 2** B-cell receptor oligoclonal repertoire in PBMC of the patient with PRKDC mutation. Quantitative analysis of immunoglobulin polymorphism (heavy chain of BCR) of the patient, overrepresentation in IgD mono-clone and the quantification data.
the DAH as the first episode symptom of cSLE with genetic compound heterozygous mutation in PRKDC gene. PKCDC regulated apoptosis and proliferation of B cells and it had been reported that mutation of PRKDC can cause type 26 immune deficiency (Table 2), mainly manifested by impaired differentiation of T and B cells, due to DNA-PKCs deficiency and V(D)J rearrangement obstruction [12].

At the early stage of the disease, we found that the patient presented with nervous system lesions such as
dysphoria, irritability, hypertonia and other neurological manifestations which was indicated as brain atrophy by MRI. After treatment with MP and cyclophosphamide, the above symptoms disappeared and brain atrophy resumed. In this patient, Brain atrophy may be associated with the development of symptoms of lupus of the nervous system. A Kalinowska-Lyszczarz reported that the same classifiers were identified in a subgroup analysis that included patients with a short disease duration. In SLE brain atrophy was the main determinant of brain volume. Different correlation patterns between volumetric and clinical data may suggest that is mostly associated with age in SLE.

DNA PKcs-the key partners of autoimmune regulator play an important role in regulating human autoimmune responses, especially in systemic lupus erythematosus. Anne-laure Mathieu found that PRKDC mutation reduced the level of DNA-PKcs, causing autoimmune diseases [9]. In addition, the accumulation of anti-Ku and DNA-PKcs antibodies related to the non-homologous DNA end-joining pathway were detected in SLE patients with PRKDC polymorphism [13–15]. Above all, we suggested the PRKDC mutation can causes the occurrence of SLE.

Conclusions
Here we described the case of an infant immunodeficiency with SLE like-syndrome, which cause by PRKDC mutation, treated successfully with high-dose MP and CTX. The novel compound heterozygous mutation of PRKDC may be relate to dysregulates B-cell proliferation, promotes auto-antibody formation.
Acknowledgements
Not applicable.

Authors' contributions
LHW and ZYW analyzed clinical and FC data analysis of patient immune function; LHW offered the T and B cell receptor sequencing to detect the V(D)J rearrangement of the patient; ZBY and summarized clinical data and interpretation; DHC was responsible for writing articles; All authors read and approved the final manuscript.

Funding
This work was supported by the Basic and applied basic research foundation of guangdong province enterprise mutual funds on the project, (grant number 2021A1515220043) and Zhongnanshan Medical Foundation of Guangdong Province (grant number 202102010343) and the Science and Technology Program of Guangzhou (grant number 202102010276).

Data Availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Patient consent for publication
The research proposal for human menstrual blood collection was approved by the Ethics Committee of The first hospital affiliated to Guangzhou Medical University (approval no.20220514). All volunteers participating in the experiment signed the informed consent.

Ethics approval and consent to participate
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

Received: 19 February 2023 / Accepted: 5 June 2023
Published online: 14 August 2023

Table 2  Clinical characteristics and genetic analysis in our study and the reported cases with PRDDC mutation

<table>
<thead>
<tr>
<th>Num</th>
<th>DATA</th>
<th>Gender</th>
<th>Age of onset</th>
<th>family history</th>
<th>Gene</th>
<th>Nucleotide changes</th>
<th>Amino acid change</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Our study</td>
<td>Male</td>
<td>p.G51S05</td>
<td>Father dsDNA(+)</td>
<td>PRDCC</td>
<td>1. c.1777-710_1777-709 insA; 2. c.1337T&gt;A</td>
<td>p.IVS16/C16</td>
<td>DAH, mental disorder, severe infection positive antibodies dsDNA, ANAs, low C3 and C4 alopecia, rash, photosensitive malar rash, positive antibodies dsDNA, ANAs</td>
</tr>
<tr>
<td>2</td>
<td>Sira2017</td>
<td>Female</td>
<td>12M</td>
<td>Sister SLE symptom</td>
<td>PRDCC</td>
<td>c.1294G&gt;T, homozygous</td>
<td>Gly342Trp</td>
<td>Skin involvement, autoimmune anemia, thrombocytopenia, antiphospholipid, CNS vasculitis, dsDNA antibodies, ANAs, low C3 and C4</td>
</tr>
<tr>
<td>3</td>
<td>Belot A2013</td>
<td>Female</td>
<td>8y</td>
<td>SLE family</td>
<td>PRDCC</td>
<td>c.1528G&gt;A, homozygous</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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8. Kurosawa A. Autophosphorylation and Self-Activation of DNA-Dependent protein Kinase[Genes (Basel), 2021,12(7).]

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