Clinical Case Report

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A mutation in *PIK3CD* gene causing pediatric systemic lupus erythematosus

A case report

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Abstract

Rationale: Gain of function (GOF) mutations in *PIK3CD* gene encoding PI3K p110δ were recently associated with a novel combined immune deficiency characterized by recurrent sinopulmonary infections, CD_4^+ lymphopenia, reduced class-switched memory B cells, lymphadenopathy, cytomegalovirus and/or epstein-Barr virus (EBV) viremia, and EBV-related lymphoma. A subset of affected patients also had elevated serum IgM.

Patient concerns: We report a patient who was diagnosed with systemic lupus erythematosus (SLE) at a young age and was recently found to carry heterozygous mutations in *PIK3CD*. The patient not only presented with recurrent sinopulmonary infections, CD_4^+ lymphopenia, lymphadenopathy, EBV viremia, and elevated serum IgM, but also met classification criteria of SLE based on persistent proteinuria and hematuria, leukopenia and anemia, low level of serum complement, and positive autoantibody for antinuclear antibodies.

Diagnoses: Activated PI3Kδ syndrome.

Interventions: Oral prednisolone and hydroxychloroquine combined with mycophenolate mofetil was given to the patient. He was currently receiving intravenous immunoglobulin per month in association with hydroxychloroquine, low-dose prednisolone, and mycophenolate mofetil.

Outcomes: At present, the level of complement restored to normal, hematuria and proteinuria disappeared, and liver function returned to normal.

Lessons: SLE may be a novel phenotype of GOF mutation in *PI3CKD* gene (GOF PIK3CD).

Abbreviations: ANA = antinuclear antibodies, APDS = activated PI3Kδ syndrome, GOF = gain of function, PASLI = p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency, PI3K = phosphoinositide 3-kinase, SLE = systemic lupus erythematosus.

Keywords: *PI3CKD* gene, primary immunodeficiency, systemic lupus erythematosus

1. Introduction

Human cells express three classes of phosphoinositide 3-kinase (PI3K) (I, II, and III).[1] There are three class IA PI3Ks in mammalian cells, α, β, and δ, that catalyze the phosphorylation of PtdIns (4,5)P2 to generate PtdIns (3,4,5)P3 (PIP3).[2] Each class IA PI3K is composed of a catalytic subunit, p110α, p110β, or p110δ (encoded by genes *PIK3CA*, *PIK3CB*, and *PIK3CD*, respectively), and one of the five regulatory subunits: p85α, p55α, p50α (all encoded by different transcripts of the *PIK3R1* gene), p85β (encoded by the *PIK3R2* gene), or p55γ (encoded by the *PIK3R3* gene).[3] Gain of function (GOF) PIK3CD and PIK3R1 that cause a combined immunodeficiency syndrome referred to as activated PI3Kδ syndrome (APDS) or p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency (PASLI).[4–6] APDS is characterized by recurrent sinopulmonary infections with associated lung damage, lymphadenopathy, reduced class-switched memory B cells, epstein-Barr virus (EBV) and cytomegalovirus viremia, as well as EBV and non-EBV-driven malignancies.[6,7] We describe a child with GOF PIK3CD. The child not only presented with recurrent sinopulmonary infections, CD_4^+ lymphopenia, lymphadenopathy, EBV viremia, and elevated serum IgM, but also met classification criteria of systemic lupus erythematosus (SLE) based on persistent proteinuria and hematuria, leukopenia and anemia, low level of serum complement, and positive autoantibody for antinuclear antibodies (ANA).

2. Case reports

The patient, a 15-year-old Chinese boy, presented with respiratory tract infections at the age of 9. He was referred to our hospital for evaluation because of recurrent sinopulmonary infections, neck lymphadenopathy, and splenomegaly at the

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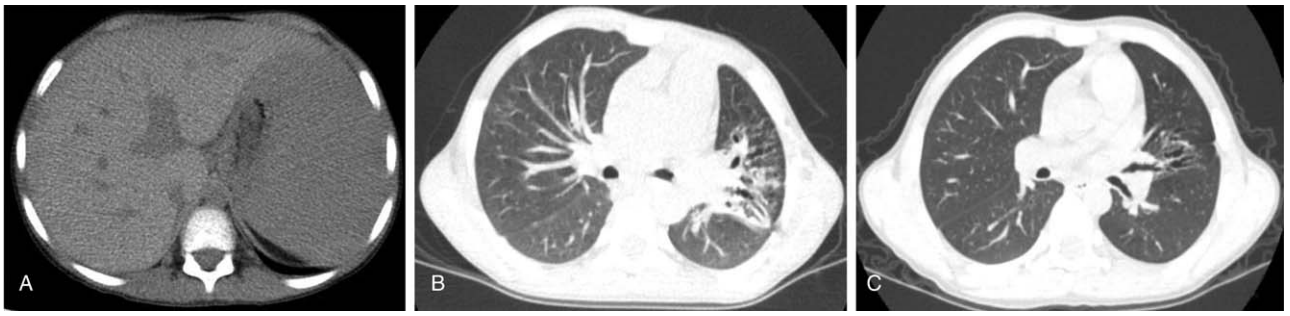

Figure 1. Imaging features of abdomen and lung in a patient. (A) Abdominal contrast-enhanced CT revealed hepatosplenomegaly. (B) Lung CT scan showed partial consolidation of left upper lung with bronchiectasis and left upper bronchial stenosis (prior treatment). (C) Lung CT scan showed partial consolidation of left upper lung with bronchiectasis and left upper bronchial stenosis (post-treatment).

age of 10. Physical examination disclosed short stature (−2.6 standard deviation), neck lymphadenopathy, splenomegaly, and verruca plana all over the body. Other physical findings were unremarkable. Laboratory testing revealed leukopenia, anemia, thrombocytopenia, hematuria, proteinuria, low level of complement and high levels of erythrocyte sedimentation rate, and C-reactive protein. Coombs test was positive. Autoantibody was positive for ANA (1:640) and peripheral anti-neutrophil cytoplasmic antibodies (1:100), and the others are negative. Serum level of complements was low, such as C3, C4, and CH50. Serum level of IgM and IgE was elevated, but IgG and IgA was normal. Lymphocyte subsets by flow cytometry revealed CD_4^+ lymphopenia. Abdominal contrast-enhanced MRI revealed splenomegaly (Fig. 1A). Lung CT scan showed partial consolidation of left upper lung with bronchiectasis and left upper bronchial stenosis (Fig. 1B and C). The clinical and laboratory data met four criteria of SLE of the Systemic Lupus International Collaborating Clinics (renal and hematological disorder, low level of complement, and positive ANA). Therefore, the patient was diagnosed of SLE, lupus nephritis, and recurrent sinopulmonary infections. Renal biopsy was also done because of persistent hematuria and proteinuria, and it displayed moderately increased mesangial matrix and mesangial hypercellularity under the light microscope; subepithelial deposits was noted, and some mesangial changes may be present as seen in electron microscopy. Immunofluorescence was positive for C1q, C3, IgG, IgM, and Fb (Fig. 2). The patient was given oral prednisolone and hydroxychloroquine combined with mycophenolate mofetil. Six months later, the level of complement was restored to normal, hematuria and proteinuria disappeared, and liver function returned to normal. He was currently receiving intravenous immunoglobulin in association with hydroxychloroquine, low-dose prednisolone, and mycophenolate mofetil, with a good efficacy. Family history revealed that his mother died of gastric cancer. Whole exome sequencing was performed in patient and in his father, when he was at the age of 15 and the *PI3KCD* gene was found to exhibit good coverage. Sanger sequencing of *PIK3CD* gene confirmed a known and *de novo* GOF heterozygous mutation c.3061G>A (p.E1021K) in patient (Fig. 3). Informed written consent was obtained from the patient's father for publication of this case report and accompanying images. Ethics board approval and consent was obtained for this work from the Ethics Committee at the Children's Hospital of Fudan University, Shanghai, China (ekyy-2015–28).

3. Discussion

Our patient presented with recurrent sinopulmonary infections, CD_4^+ lymphopenia, lymphadenopathy, EBV viremia, and elevated serum IgM. Lung CT scan showed lung damage, such

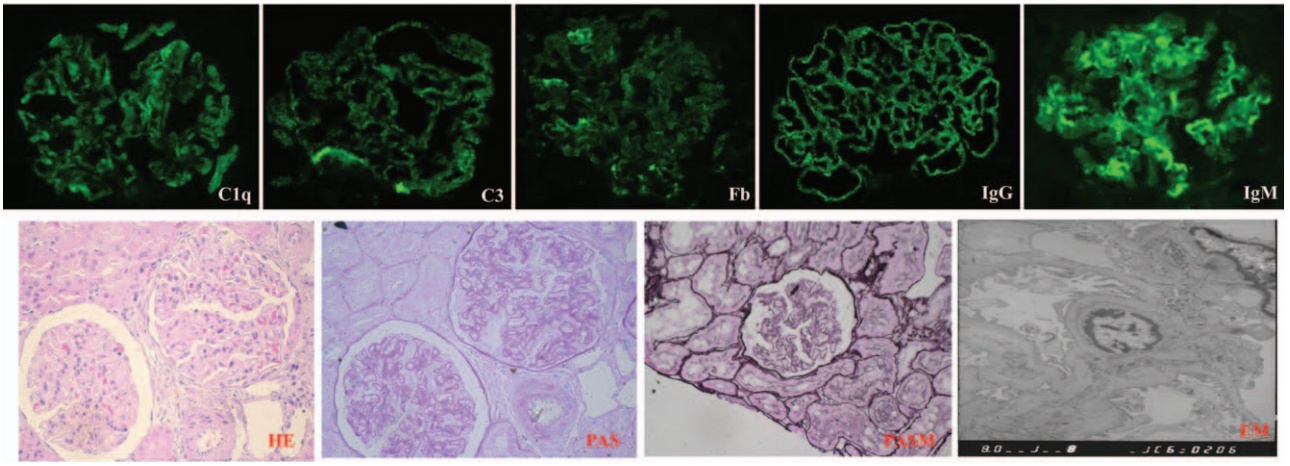

Figure 2. Renal biopsy showed lupus nephritis type IV under light (×400), electron (×11600), and immunofluorescence (×400) microscopy.

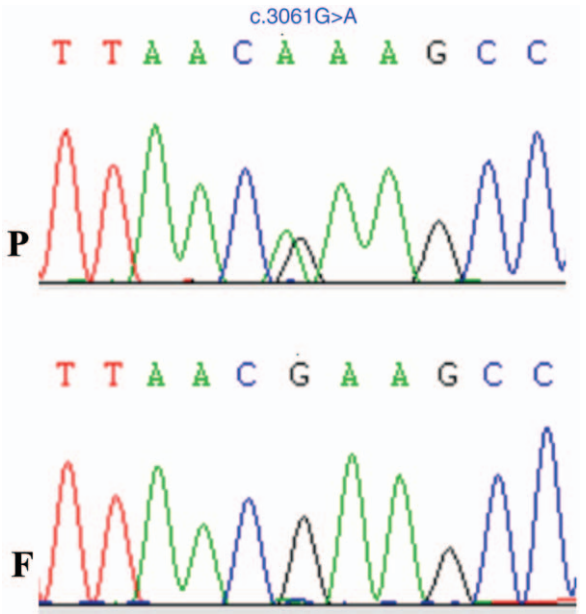

Figure 3. Mutation analysis in *PIK3CD* gene. P = patient; F = father.

as partial consolidation of left upper lung with bronchiectasis and left upper bronchial stenosis. WAS and Sanger sequencing both revealed a known GOF heterozygous mutation c3061G>A (p.E1021K) in the patient. The E1021K variant in the C-lobe of the p110δ kinase domain is by far the most frequently reported APDS mutation.[7] Therefore, the patient met diagnosis criteria of APDS, which belongs to primary immunodeficiency. Due to leukopenia, anemia, thrombocytopenia, hematuria, proteinuria, low level of complement, positive Coombs test, and ANA, he also met classification criteria of SLE, which is a prototypic, systemic, autoimmune disease.

The coexistence of immunodeficiency and autoimmunity appears paradoxical in certain types of primary immunodeficiencies, as one represents a hyperimmune state and the other a hypoimmune state.[8,9] However, this paradox may not actually be all that implausible due to the complex nature of immune cells, signaling pathways, and their interactions.[10] The most common autoimmune disorders in primary antibody deficiencies are immune thrombocytopenic purpura and autoimmune hemolytic anemia.[11] Moreover, other diseases including autoimmune thyroid disease,[12] type 1 diabetes,[13] rheumatoid arthritis,[14] SLE,[15] dermatomyositis,[16] inflammatory bowel diseases,[17] alopecia areata,[15] vitiligo,[12] and glomerulonephritis[18] are also common in primary antibody deficiencies due to the lack of self-tolerance.[19]

A study, the largest cohort to date, showed that 43% (22/53) of the cohort had clinical features suggestive of autoimmune or inflammatory disease, which included Coombs-positive hemolytic anemia (7), trilineage cytopenia (2), glomerulonephritis (3), exocrine pancreatic insufficiency (3), autoantibody-positive thyroid disease (3), cirrhosis (3), and seronegative arthritis (2).[6] No typically immunological indicators of SLE were found in these patients with autoimmune or inflammatory disease, such as ANA, anti-dsDNA, and low level of complement.[6] A few other studies around the world did not found typically immunological indicators of SLE.[2,20,21] Nonetheless, in a genetic model with enhanced activation of class IA PI3K in T cells, mice showed a greater tumor index but died of a lupus-like disease.[22] Interestingly, Suárez-Fueyo et al[23] found the potential PI3K involvement in human SLE, whose study also revealed that the PI3K pathway was frequently activated in SLE patient peripheral blood mononuclear cells and T cells (~70% of cases), more markedly in active disease phases. Our observations point to SLE as a novel phenotype of GOF mutation in *PI3CKD* gene. Phenotype of GOF mutation in *PI3CKD* gene can be the coexistence of immunodeficiency and autoimmunity.

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Author contributions

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