A novel hypomorphic ζ-chain-associated protein tyrosine kinase 70 kDa mutation with normal CD8+ T cells count

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To the Editor: The ζ-chain-associated protein tyrosine kinase 70 kDa (ZAP70) deficiency is a rare autosomal recessive primary immunodeficiency characterized by absent CD8+ T cells and non-functional CD4+ T cells.[1] According to current reports, approximately 18 pathogenic ZAP70 mutations have been identified in less than 30 patients.[1-4] ZAP70 deficiency always results in recurrent bacterial, viral, and opportunistic infections, diarrhea, and autoimmune diseases. Distinctively, ZAP70 hypomorphic mutations appear to have observable clinical heterogeneity, such as Epstein-Barr virus-associated lymphoproliferative disorder/lymphoma, late-onset immunodeficiency,[3] and silent brain infarcts.[5] Hence, next-generation sequencing technology might be the predominant diagnostic approach.

Here, we introduce a 16-month-old girl with heterozygous ZAP70 mutations. After birth, the patient was given a Bacillus Calmette-Guerin vaccination, and then the vaccination site became purulent 2 months later. When she was 5 months old, she was diagnosed with severe fungal and bacterial pneumonia (a left armpit lump with pus showed acid-fast bacillus positive, and plasma and sputum showed cytomegalovirus [CMV]-deoxyribonucleic acid positive). Ultrasound results revealed multiple enlarged left axillary and inguinal lymph nodes, as well as hepatosplenomegaly. In addition, extensive lesions were observed in her fundus oculi due to CMV infection. When she was 11 months old, she suffered from continuous liver dysfunction. The ultrasound results showed small nodules in the liver and multiple small lymph nodes in the hepatic hilar and pancreatic head. Currently, oral candidiasis (thrush) has also been observed in this patient. All clinical symptoms correspond with the ZAP70 deficiency.

The immunologic investigations are summarized in Table 1. The patient did not show an observable decrease in CD8+ T cells. Autoantibodies were also tested in this patient, but all the results were negative. Roifman *et al* previously described that the CD8+ T cell count increased with time,[6] suggesting that the thymus might participate in residual functions of CD8+ T cell maturation. This patient revealed that the absence of normal CD8+ T cells cannot be the exclusion criterion to diagnose ZAP70 mutation, which makes it more difficult to identify this mutation early.

The patient is from a non-consanguineous family and she has a healthy old sister. Next-generation sequencing technology was used to identify the disease-causing gene, and two heterozygous ZAP70 mutations (c.703-1G>A and c.1523C>A [p. P508H]) were found in the patient. The mutation c.703-1G>A was inherited from her father, which led to a splice variant lacking exon 6, and the mutation c.1523C>A was from her mother, which has not been reported previously. The predicted functional effects of this variant (c.1523C>A) were determined using SIFT (Sorting Intolerant From Tolerant) (http://sift.jcvi.org, Pauline Ng, Computational and Systems Biology, Genome Institute of Singapore, Singapore), PolyPhen2 (http://genetics.bwh.harvard.edu/pph2, Division of Genetics, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA), and MutationTaster (http://www.mutationtaster.org/, Charité-Universitätsmedizin Berlin, Berlin, Germany). PolyPhen-2 predicted the probably damaging to the protein with a score of 1.000, MutationTaster predicted disease-causing with a probability of 0.9999, and SIFT predicted damaging on protein function with a score of 0.00 (<0.05).

Currently, the patient's family is searching for a suitable unrelated hematopoietic stem cell donor. Hematopoietic stem cell transplantation (HSCT) is a life-saving therapy for ZAP70 deficiency, providing excellent long-term

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Table 1: Laboratory parameters of the patient in different ages.

Laboratory parameters	Age				Normal reference range[7,8]
	5 months	8 months	12 months	14 months	
NK (%)	18.09↑	13.85	20.39	17.54↑	4.84–15.47
CD3+ (%)	64.80	65.96	58.20	63.15	60.15–72.29
CD3+CD4+ (%)	52.57↑	48.35	31.41	39.70	35.23–51.41
CD3+CD8+ (%)	11.66	15.86	25.60	22.31	14.11–27.77
CD3-CD19+ (%)	16.08	19.34	20.72	18.20	16.57–27.65
CD4/CD8	4.51↑	3.05↑	1.23	1.78	1.28–3.40
NK (cells/μL)	836.90	971.31	1464.19	647.75	306–896
CD3+ (cells/μL)	2998.00	4626.63	4178.84	2332.39	2488–5422
CD3+CD4+ (cells/μL)	2432.38	3391.55	2255.18	1466.09	1433–3874
CD3+CD8+ (cells/μL)	539.56	1112.10	1837.88	823.84	710–1843
CD3-CD19+ (cells/μL)	744.07	1356.27	1487.46	672.12	807.44–1803.72
CD45+ (cells/μL)	4626.90	7013.90	7179.92	3693.14	2488–5422
IgG (g/L)	17.30↑	8.72	10.70	11.60	3.15–11.41
IgA (g/L)	0.39	0.09↓	0.90	0.43	0.23–1.14
IgM (g/L)	5.56	0.51	0.35↓	1.51	0.32–1.88
Total IgE (U/mL)	83.87	<4.34	<17.20	<4.34	<60
WBC ($\times10^9$/L)	9.40	15.32↑	9.91	3.14	4.0–15.0
NEC ($\times10^9$/L)	1.10↓	2.20↓	1.91↓	0.68↓	2.4–4.0
LYM ($\times10^9$/L)	7.71↑	12.04↑	6.29↑	2.04	1.2–3.4
MON ($\times10^9$/L)	0.20	0.92↑	1.30↑	0.33	0.1–0.6
EOS ($\times10^9$/L)	0.06	0.15	0.40↑	0.08	0.05–0.30
Hb (g/L)	97↓	120	101↓	119	110–160
PLT ($\times10^9$/L)	457	494	475	299	100–550

↓: lower than the reference; ↑: higher than the reference. NK: Natural killer; Ig: immunoglobin; WBC: White blood cell; NEC: Neutrophils; LYM: Lymphocytes; MON: Mononuclear cell; EOS: Eosinophils; Hb: Hemoglobin; PLT: Platelets.

immune function, but more cases should be included in clinical investigations to prove the effects of HSCT on the heterogeneity of ZAP70 mutations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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