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BRIEF REPORT

# X-linked hyper-IgM syndrome complicated with interstitial pneumonia and liver injury: a new mutation locus in the CD40LG gene

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## Introduction

X-linked hyper-IgM syndrome (HIGM1) is a rare primary immunodeficiency syndrome caused by mutations in the *CD40L* gene. The major clinical feature of the disease is repeated opportunistic infections; however, in rare cases, presentation is with interstitial lung lesions complicated with liver injury. Herein, we present a case of a 5-month-old child presented with a prolonged cough with difficulty breathing. The clinical presentation of the child included progressive pulmonary interstitial changes and liver damage. Testing revealed a lack of IgA and a decrease in IgM level. Whole-exome sequencing revealed that there was a homozygous mutation in exon 5 of the *CD40LG* gene (c.685T>C, F229L). The child's mother carried a heterozygous mutation at this locus. The child was diagnosed with HIGM1, and the mutation locus is chrX:135741473, a novel mutation site in *CD40LG*. The onset of this disease is occult, but it progresses rapidly. It is rare to report lung interstitial changes combined with liver damage. Gene testing is the gold standard for diagnosis. Hematopoietic stem cell transplantation is currently the most effective treatment.

## Case presentation

A 5-month-old boy was admitted to Jiaxing Second Hospital, Zhejiang, China, on March 29, 2018, after coughing for 3 weeks and difficulty breathing. The child had a 5-year old brother with a history of asthma, and his father had a history of allergic rhinitis. The boy did not show abnormalities when he was born. His temperature was 36.9 °C and pulse was 150/min; he took 60 breaths per minute; his weight was 10 kg; and his $SPO_2$ level was 84%. The patient was irritable and showed mild three-concave sign. The patient also had mild cyanosis around the mouth and pharyngeal congestion. Moist rales were not heard. His heart rhythm was normal and no obvious heart murmur was detected. His abdomen was slightly bulging and liver and spleen were not felt under the ribs. Bowel sounds could be heard. CRT was 3 s. In a routine blood examination, his white blood cell level was $5.85 \times 10^9$/L, neutrophil percentage was 14.7%, hemoglobin was 123 g/L, platelet level was $347 \times 10^9$/L, C reaction protein was 0.66 mg/L, ESR was 2.30 mm/h, and procalcitonin was 0.5 ng/mL. In a blood gas analysis, we found his blood pH to be 7.32, $pCO_2$ was 45.3 mmHg, and $pO_2$ was 36 mmHg. In terms of liver function, his aspartate aminotransferase level was 41.7 U/L, alanine aminotransferase was 45.5 U/L, and alkaline phosphatase was 141 U/L. His immune index showed an IgM level of 0.25 g/L, IgG of 4.6 g/L, IgA of 0.04 g/L, CD3 of 48.61%, CD4 of 34.81%, CD8 of 11.77%, and CD19 level of 37.52%. *Mycobacterium tuberculosis* antibody was negative. Coagulation function, electrolytes, kidney function, and calcium, magnesium, phosphate, and iron levels were normal. Hepatitis B was negative. No abnormalities were found in myocardial enzymes, blood culture, TORCH, and Widal tests.

On the first day of admission, the patient was given nasal catheter oxygen therapy, ECG monitoring, injection of ceftazidime, intravenous infusion of azithromycin, oseltamivir for anti-virus, and 2 mg/kg methylprednisolone for anti-inflammation. On the second day after admission, the patient's dyspnea was exacerbated, and $SpO_2$ was below 90%. The oxygen supply was changed to CPAP supplemental positive pressure ventilation immediately; other treatments included 10 mg/kg

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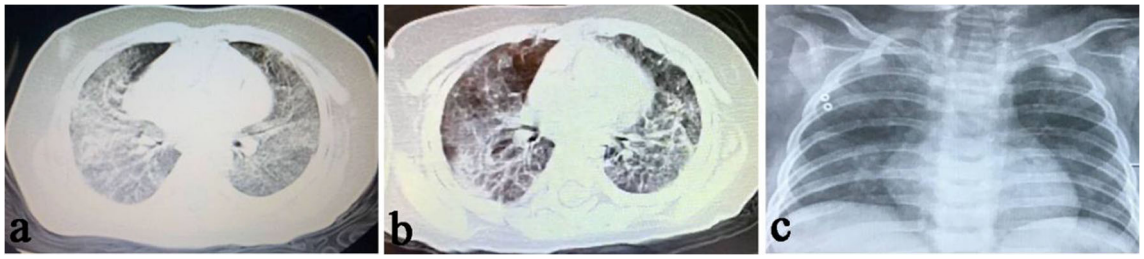


**Fig. 1** Chest CT and X-ray examination. **a** On the second day after admission, a chest CT showed diffuse lung lesions on both sides; interstitial changes were predominant. **b** On the 7th day after admission, a chest CT showed bilateral pulmonary diffuse inflammatory lesions, although the condition had improved. **c** On the 13th day after admission, a chest X-ray showed that the bilateral pneumonia had clearly absorbed

methylprednisolone pulse administration and intravenous injection of immunoglobulin (IVIG). A chest CT revealed bilateral diffuse lung lesions with predominant interstitial changes (Fig. 1a). On the third day after admission, the patient developed dyspnea again and SpO2 decreased to 86.2%. Ventilator-assisted breathing was administered immediately. On the fourth day after admission, Sulperazon (Cefoperazone Sodium and Sulbactam Sodium for Injection) was administered for anti-infection supplemented by intermittent prolapse ventilation. On the 7th day after admission, the patient's coarse rales reduced and a re-check of the chest CT indicated bilateral diffuse pulmonary inflammatory lesions, which had improved (Fig. 1b). Treatment with Sulperazon continued, and assisted ventilation was withdrawn. On the 13th day after admission, the child had no obvious shortness of breath or dyspnea. A chest X-ray showed that the inflammation of the lungs had clearly improved (Fig. 1c); the patient was then discharged. Atomization therapy and oral anti-infection therapy were continued. A follow-up visit 1 month later showed that the patient had no cough. A routine blood check showed a neutrophil ratio of 0%. A bone marrow puncture suggested a significant decrease in the proliferation, maturation, and release of myeloid cells. Treatment with granulocyte colony-stimulating factor (G-CSF) was given, and the child's condition improved. A genetic test found that there was a homozygous mutation in exon 5 of the *CD40LG* gene (chrX:135741473, c.685T>C, F229L), and his mother carried a heterozygous mutation at this locus. The patient was diagnosed with HIGM1 (Table 1). Two months after discharge, the child was hospitalized again due to fever and oral skin infection for 2 days. After 1 week of anti-infection treatment with vancomycin + ceftriaxone, the condition of the patient improved, and the patient was discharged. Afterward, the patient still had repeated fevers and skin infections and was hospitalized for symptomatic treatment (Fig. 2).

## Discussion

HIGM1 is a rare primary immunodeficiency disease. The most recent large-scale study in the USA showed that its incidence was about 1/1,000,000. The main clinical manifestations are repeated bacterial infections complicated with low or absent serum IgG and IgA levels, and an elevated or normal IgM level. The disease is occult but progresses rapidly. The median survival time after diagnosis is about 25 years [1]. Reports of interstitial lung lesions accompanied by liver injury are rare.

The pathogenesis of HIGM involves antibody class switch recombination (CSR) dysfunction, with or without somatic hypermutation (SHM) defects. B cells normally express IgM in the late developmental stages, and then produce IgG and IgA through CSR and SHM mechanisms. Any factors interfering with these processes can cause HIGM, for example, an abnormal interaction between T cells and B cells, abnormal alteration of the NF-κB signaling pathway, or dysregulation of DNA cleavage, repair, and ligation [2]. HIGM can be categorized into 7 subtypes according to different genetic defects; among them, type I is the most common, accounting for 70% of total cases. HIGM1 has X-linked recessive inheritance, so it is also called X-linked HIGM. A common cause of HIGM1 is mutations in the *CD40L* (*CD154*) gene, which is located on the X chromosome. In the developmental history of B cells, IgM is expressed earlier than other antibodies. CD40 is expressed on the surface of early B, pre-B, and mature B cells. CD40 binds to the CD40 receptor on the surface of activated CD4 cells, which provides signals for the proliferation and differentiation of B cells. At the same time, CD40 participates in the secretion and CSR of immunoglobulins [3–6]. In HIGM1 patients, due to mutations in *CD40L*, CD40 cannot bind to CD40L, resulting in defects in the production and secretion of other immunoglobulins. On the other hand, IgM

**Table 1** DNA variation found in the patient

| Chromosome | Gene | Mutation | Source of variation | Nucleotide change |
|---|---|---|---|---|
| chrX:135741473 | *CD40LG* | Hemizygote | Mother | NM_000074:exon5:c.685T>C:p.F229L |

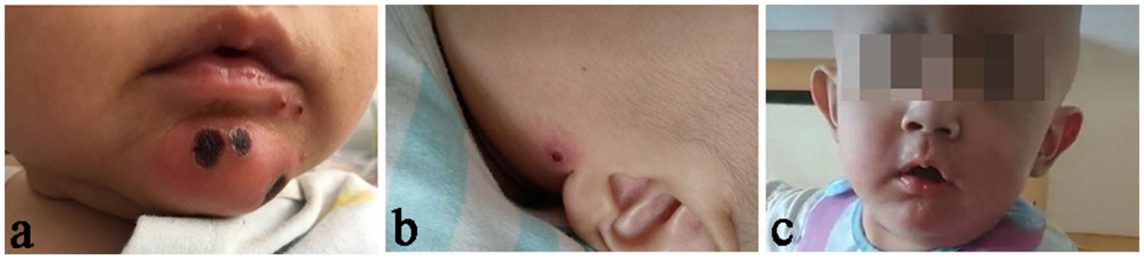


**Fig. 2** Skin infections of the patient. **a** Perioral and mandibular skin infections. **b** Skin infection near the earlobe. **c** The infections improved after treatment

can be secreted in the absence of CD154, thus leading to high IgM levels.

HIGM1 is an occult disease and has diverse clinical manifestations often accompanied by infections, organ injury, neutropenia, autoimmune disease, lymphatic hyperplasia, and neoplasms [3, 7–9]. The present pediatric patient had the following characteristics: (1) Lung interstitial inflammatory lesions: Due to decreased immune antibodies, abnormal T lymphocyte function, and secondary hypogammaglobulinemia, patients with HIGM1 are susceptible to bacterial, protozoan, and fungal infections [6]. However, interstitial pneumonia is not common in HIGM1 [9]. It has been reported that *CD40L* mutations can lead to dysfunction of macrophage activation, resulting in excessive accumulation of surfactants in the alveolar cavity and airways, causing pulmonary alveolar proteinosis (PAP), which is probably the pathological basis of interstitial pneumonia [7, 9]. Other studies have reported that deficiencies of IgG and memory B cells involved in CSR may induce pulmonary fibrosis, while it has been confirmed that there exist deficiencies of IgG and memory B cells in HIGM1 [10]. In the present case, the patient developed bilateral diffuse pathological changes in the lung on the second day after admission. However, there was no evidence of bacterial or viral infections detected by pathogen tests. The lung lesions in this child were considered to be associated with HIGM1. The condition of the patient improved after anti-inflammatory, anti-viral, and hormonal pulse therapy. When a child has rapidly progressing pulmonary interstitial lesions, in addition to looking for infectious pathogen evidence, the evaluation of the child's immune status, as well as genetic tests, should be taken into account so that rare hereditary diseases can be detected early and treated. (2) Neutropenia: About two-thirds of children with HIGM1 develop neutropenia in the late stages of the disease, which may be associated with abnormal autoantibodies and *CD40L* mutations [11], or dysregulated granulopoiesis mediated by the CD40 signaling pathway in the inflammatory microenvironment [12]. However, the etiology of neutropenia in HIGM1 still needs to be further clarified. Neutropenia did occur in this child, and his neutrophil count was below the detection limit (Table 2). His condition improved after treatment with G-CSF. (3) Liver damage: One study [13] showed that liver damage occurred in 50% of HIGM1 patients and is the main cause of death in these patients. As the disease progresses, liver damage can evolve into sclerosing cholangitis, even cholangiocarcinoma. Some studies [3] have shown that the liver plays an important role in the regulation of immune balance. Autoimmune liver disease may be a manifestation of immunodeficiency, although the associated mechanism remains unclear. If a patient is positive for the migration inhibition test (MIT) and is anti-mitochondrial antibody (AMA)-positive, this may be helpful for the diagnosis of HIGM1-associated cholangitis. A study by Lleo et al. [14] suggested that in patients with primary biliary cirrhosis, while serum IgM was elevated, CD40LG was often expressed at a low level due to DNA methylation of the promoter, and the two factors showed a negative correlation. Early diagnosis, active anti-infection treatment, and control of the inflammatory response are key for the treatment of HIGM1-associated liver damage. In the present patient, liver injury developed during the progression of the primary disease, and liver

**Table 2** Changes in white blood cell index during treatment

| Items | 03/29/2018 | 03/31/2018 | 04/01/2018 | 04/22/2018 | 05/14/2018 | 05/17/2018 | 05/20/2018 | 05/23/2018 | 06/08/2018 | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| White blood cell count ($10^9$/L) | 9.5 | 5.85 | 5.43 | 4.84 | 4.68 | 9.4 | 5.9 | 4.7 | 5.1 | 4–10 |
| Neutrophil percentage (%) | 22.5 | 14.7 | 10.3 | 0.6 | 0 | 1 | 20.5 | 23.6 | 65 | 45–77 |
| Neutrophil count ($10^9$/L) | 2.14 | 0.86 | 0.56 | 0.03 | 0 | — | — | — | 5.3 | 2–7.7 |
| Eosinophil percentage (%) | — | 0 | 0.5 | — | — | 1 | 3 | 2.6 | 3.4 | 0.5–5 |
| Lymphocyte percentage (%) | — | 53.3 | 63.9 | — | — | 51 | 57.6 | 54.7 | 32 | 20–40 |
| Monocyte percentage (%) | — | 31.8 | 25.8 | — | — | 41 | 18.9 | 18.9 | 5.2 | 3–8 |

**Table 3** Changes in liver function indicators during treatment

| Items | 04/01/2018 | 04/03/2018 | 04/08/2018 | 04/22/2018 | 04/25/2018 | 05/14/2018 | 08/31/2018 | Reference |
|---|---|---|---|---|---|---|---|---|
| Aspartate aminotransferase (U/L) | 41.7 | 33.7 | 78.2 | 72.2 | 102 | 204 | 24.8 | 0–40 |
| Alanine aminotransferase (U/L) | 45.5 | 33.4 | 109.6 | 86.6 | 106 | 174 | 36.8 | 0–40 |
| Alkaline phosphatase (U/L) | 141 | 102 | 64 | 134 | 155 | 204 | 233 | 40–136 |
| Glutamyltranspeptidase (U/L) | 22.7 | 23.5 | 50.1 | 22.4 | 19 | — | 10 | 0–50 |
| Total protein (g/L) | 65.7 | 59.7 | 57.1 | 56 | 63 | — | 53.4 | 62–82 |
| Albumin (g/L) | 28.8 | 33.7 | 35.6 | 40.7 | 38.7 | — | 42.9 | 34–55 |

enzymes were elevated accordingly (Table 3). Liver function recovered to normal after anti-inflammation, anti-infection, and liver treatment. (3) Changes in immunological phenotype: Mutation in the *CD40L* gene in HIGM1 interferes with the process of SHM and CSR, leading to the deficiency of IgG and IgA, and elevated or normal IgM, which is the reason for the decrease in immunity and repeated infections [15]. HIGM1 in the present patient was confirmed to be due to a mutation in the *CD40L* gene. A significant deficiency of IgA is consistent with the pathology of the disease; IgG levels could not be assessed in the patient because of the infusion of gamma globulin. However, the decreased IgM level in this patient seems to conflict with the typical clinical manifestation of HIGM1 (Table 4). An immune protein test was only taken once during the disease course in this patient; therefore, we were unable to assess whether there were dynamic changes in IgM. In addition, it has been reported that about 6.4% of HIGM1 patients have decreased IgM serum levels, and only 62.5% of HIGM1 patients have an increase in IgM at diagnosis, which may be associated with different phenotypic features [16, 17]. An elevated serum IgM level has both low sensitivity and specificity as a screening marker for the HIGM syndrome; hence, Some researchers believe that the name "HIGM" may lead to the misdiagnosis of some patients with low IgM. It seems more reasonable to include HIGM1 in the group "B-cell switch defect diseases" [18].

HIGM1 has a high mortality. Severe infection and liver disease are the main causes of death in children with HIGM1 [5, 13]. The diagnosis of the disease is based on clinical manifestations, immunological phenotype, family history, and CD40L protein detection. Genetic testing is the gold standard for diagnosis. In recent years, next-generation sequencing (NGS) has become more and more widely used in clinical molecular diagnosis, which greatly reduces the cost of sequencing while achieving high throughput. Whole-exome sequencing can quickly identify disease-causing genes and mutation sites, and has obvious advantages in the screening of monogenic diseases. A recent study successfully diagnosed a 5-month old HIGM child with alveolar proteinosis by whole-exome sequencing [9]. Lopez-Herrera et al. [19] reported an HIGM1 case with a deletion in *CD40LG* and normal CD40L protein, suggesting that the variation did not affect CD40L expression and stability; therefore, normal CD40L protein does not necessarily exclude the possibility of HIGM1, and a genetic test is still required. As for the present patient, there was a homozygous mutation in exon 5 of the *CD40LG* gene detected by whole-exome sequencing; by searching the PubMed, ExAC, ClinVar, OMIM, and GeneCards databases, we did not find a record of this mutation site. It is considered to be a novel mutation site in *CD40LG*, which is of significance for the diagnosis of HIGM1.

Hematopoietic stem cell transplantation (HSCT) is currently the most effective method for the treatment of HIGM1 [5]. A retrospective study in Japan [20] showed that the overall survival of children with HIGM1 undergoing HSCT was significantly higher than that of children receiving non-HSCT treatment. Moreover, the incidence of infection and organ damage in children under 5 years of age who received HSCT treatment was significantly reduced. A recent study from the University of Texas [1] also indicated that patients who received HSCT in the early stages not only achieved better prognostic benefits, but also had improved

**Table 4** Serum immunoglobulin and CD antigen in the patient

| | IgM (g/L) | IgG (g/L) | IgA (g/L) | IgE (kU/L) | C3 (g/L) | C4 (g/L) | CD3 (%) | CD4 (%) | CD8 (%) | CD19 (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 05/17/2018 | 0.25 | 4.6 | 0.04 | 5.06 | 1.48 | 0.4 | 48.61 | 34.81 | 11.77 | 37.52 |
| 01/25/2019 | 0.07 | 6.91 | | | | | 73.64 | | | |
| Reference | 0.33–1.25 | 3.7–8.3 | 0.14–0.5 | < 100 | 0.67–1.76 | 0.1–0.4 | 64–73 | 29–36 | 24–34 | 14–21 |

quality of life. However, some issues, including preventing HIGM1-associated malignancies and organ failure induced by transplant, remain to be resolved. The choice of donor and pre-treatment regimen are critical for successful transplant and re-establishment of postoperative immune function. The present patient underwent an HLA 6/10 umbilical cord blood transplantation in February 2019. The pre-treatment regimen was busulfan/cyclophosphamide/anti-thymocyte globulin and pre-treatment was performed 10 days before the transplant. Four days after the transplant, the patient developed busulfan-associated convulsion and improved after treatment. We followed up the child in October, 2019, and found that within 8 months after HSCT, the patient did not show infection. Additionally, the related immune indexes and granulocyte values were basically normal. Therefore, the therapeutic effect of HSCT is satisfactory. We will continue to follow the child's health. Studies [21, 22] suggest that with respect to unavoidable toxic side effects of busulfan and cyclophosphamide, a relatively low-dose regimen is an option. Early diagnosis and anti-infection and IVIG replacement therapy are of significance for reducing complications and acute mortality, as well as reducing infections during waiting for HSCT [6]. In this case, the disease course of the patient lasted for 21 days; the patient developed severe lung infection complicated with liver injury. The patient's condition significantly improved after active symptomatic and support treatments. Some researchers [23, 24] put forward that injection of recombinant CD40L can effectively increase T cell immune function and promote production of antibodies by B cells. However, treatment may lead to the dysfunction of other cells, and its safety requires further evaluation. The safety of gene therapy remains controversial. In gene therapy, not only the gene itself needs to be transferred but also its regulatory elements. Keeping gene expression under appropriate control is the basis for the safety of gene therapy [4, 5, 25]. Hubbard et al. [25] used an approach which combined a transcription activator-like effector nuclease-induced double-strand break and a donor template delivered by recombinant adeno-associated virus to conduct on-target, homology-directed repair (HDR) editing of the *CD40LG* locus. While maintaining the endogenous gene regulation mechanism, CD40L function was completely recovered. These results indicate that an engineered nuclease-induced gene modification can effectively restore the endogenous regulation of CD40L, and it has a promising application in HIGM1 T cell therapy. Recently, genetically modified hematopoietic stem cell transplantation has achieved initial success in mouse model experiments, which provides a theoretical basis for the treatment of HIGM1 [4]. Gene therapy is expected to become a means to cure HIGM1.

In summary, the onset of HIGM1 is occult but progresses rapidly. The disease has diverse clinical manifestations, but pulmonary interstitial changes are not common. Early diagnosis and anti-infection and IVIG replacement therapy are of significance for reducing complications and acute mortality. HSCT is currently a method used to cure HIGM1. The case we reported here is a new mutation locus in the *CD40LG* gene, which is significant for clinical and basic research of HIGM1.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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