Clinical Case Report

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A delayed diagnosis of X-linked hyper IgM syndrome complicated with toxoplasmic encephalitis in a child

A case report and literature review

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Abstract

Introduction: The X-linked hyper-immunoglobulin M syndrome (XHIGM) is an uncommon primary combined immunodeficiency disease caused by *CD40L* gene mutations. A delayed or missed diagnosis of XHIGM is common and concerning, owing to atypical immunoglobulin profile and phenotype of some patients, low recognition, and limited knowledge of clinicians on XHIGM in some underdeveloped areas. Opportunistic infections are a prominent clinical feature of XHIGM. However, toxoplasma encephalitis occurs sporadically and is extremely rare in patients with XHIGM.

Diagnostic and therapeutic procedure: A 2 years and 10 months' old male suffered from 3 times of serious infection since 1 year and 4 months of age. Although with history of recurrent respiratory infections, protracted diarrhea, persistent or intermittent neutropenia companioned with oral ulcer, and a typical immunoglobulin profile during his second disease attack, the consideration of XHIGM was still completely ignored because of our low recognition and limited knowledge of this disorder. The diagnosis of XHIGM was ultimately confirmed by detection of elevated serum IgM concentration, decreased serum IgG and IgE concentration, and identification of a mutation c.654C>A (p.C218X) in *CD40L* gene. Given clinical manifestation of lethargy, uncontrollable somnolence and ataxia, a cat/dog exposure history, positive serum *Toxoplasma gondii* (*T gondii*) IgM, positive cerebrospinal fluid *T gondii* PCR results, and typical characteristics of brain magnetic resonance imaging as multiple rings liked nodules lesions in bilateral cerebral hemisphere cortex, bilateral basal ganglia, and dorsal thalamus, the diagnosis of toxoplasmic encephalitis was considered during his third disease attack. Thereafter, oral administration of sulfadiazine and azithromycin, intravenous immunoglobulin, and subcutaneous injection of G-CSF were initiated. Regrettably, the patient abandoned the treatment because of economic factor and died 3 months after discharge.

Conclusions: A more thorough clinical history and some features like recurrent respiratory infections, protracted diarrhea, and persistent or intermittent neutropenia companioned with oral ulcer could increase clinical suspicion of XHIGM. Cerebral toxoplasmosis is rare in patients with XHIGM, but still should be considered. The present study firstly reported a delayed diagnosed case of XHIGM with *CD40L* gene c.654C>A (p.C218X) mutant complicated with toxoplasma encephalitis in Chinese population, which highlighted the importance of CD40-CD40L interaction in cell-mediated immunity against *T gondii*.

Abbreviations: CD40L = CD40 ligand, CNS = central nervous system, CRP = C reaction protein, G-CSF = granulocyte colony-stimulating factor, HCT = hematopoietic cell transplantation, HIGM = hyper-immunoglobulin M syndrome, *P carinii* = *Pneumocystis carinii*, *T gondii* = *Toxoplasma gondii*, XHIGM = X-linked hyper-immunoglobulin M syndrome.

Keywords: CD40 ligand, cerebral toxoplasmosis, child, delayed diagnosis, X-linked hyper-IgM syndrome

Editor: N/A.

The authors disclose no conflicts of interest.

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Medicine (2017) 96:49(e8989)

Received: 20 October 2017 / Received in final form: 5 November 2017 / Accepted: 8 November 2017

http://dx.doi.org/10.1097/MD.0000000000008989

1. Introduction

The X-linked hyper-immunoglobulin M syndrome (XHIGM; HIGM1; OMIM: 308230) is an uncommon primary combined immunodeficiency disease caused by the mutations of *CD40* ligand (*CD40L*) gene. With a frequency of about 2:1,000,000, it accounts for 65%~70% of all forms HIGM[1] and results from defective CD40-CD40L signaling pathway characterized as normal or elevated serum levels of IgM, low serum levels of IgG, IgA, and IgE, and defective T-cell function.[2] Overall, the prognosis of patients with XHIGM was relatively poor, with an average of 20% survival by age 25 years. However, with early diagnosis and subsequent supportive treatment (e.g., regular treatment with intravenous immunoglobulin, prevention of opportunistic infections such as Pneumocystis with trimethroprim-sulfamethoxazole) and even corrective therapy (hematopoietic cell transplantation), those patients have a much better chance to survive.[3,4] Unfortunately, owing to atypical immunoglobulin profile and phenotype of some patients in early disease stage, low recognition and limited knowledge of clinicians on XHIGM in some underdeveloped areas, a delayed or missed diagnosis of XHIGM is common and concerning, even for those with positive family history, which might lead to recurrent opportunistic infections, malignancy occurrence, and even death.[4–6]

Pneumonia was the most common infection in patients with XHIGM, followed by recurrent sinusitis, otitis, oral ulcer, and protracted diarrhea. Central nervous system (CNS) infection was relatively uncommon, with an incidence of 5% to 10% in different case series.[3,4,7] Opportunistic infections were a prominent clinical manifestation of XHIGM. CNS infections with *Histoplasma capsulatum*, *Cryptococcmneo-formans*, cytomegalovirus, echovirus, and *Mycobacterium bovis* have been reported in patients with XHIGM.[4] However, toxoplasma encephalitis, predominantly in those with AIDS and in cardiac transplants patients,[8,9] occurs sporadically and is extremely rare in patients with XHIGM. Here, we reported a delayed diagnosed case of XHIGM with *CD40L* gene c.654C>A (p.C218X) mutant, who had recurrent severe infections for almost 3 times before and finally died of toxoplasma encephalitis, aiming to share some experience and improve the recognition and prompt diagnosis of XHIGM for pediatric clinicians, and highlight the importance of the CD40-CD40L system in the defense against toxoplasmic infection.

2. Case report

The patient was a 2 years and 10 months' old male. He was firstly admitted into local hospital because of diarrhea and lethargy 1 month before transferring to our hospital. With fluid therapy for 1 week, the symptoms of diarrhea remarkably relieved. However, his mental status became worse and onset with fever and hypologia. Even worse, those situations did not turn better and abnormal gait and ataxia gradually occurred to him 2 weeks later. Then, he was transferred to our hospital because several patch-shaped hypointense lesions with surrounding edema in bilateral basal ganglia and frontal lobe were noted on the brain CT scan. On arrival, he was lethargic, afebrile, had no bradycardia, no irregular breath, and no hypoxia. Abnormal gait was noted and the Romberg sign was positive. Meningeal irritation sign and Babinski sign were negative. No other positive findings were identified by physical examination. Any history of drugs or poisons taken and abnormal growth or mental retardation before symptoms onset was denied by his parents. However, a history of recurrent infections was recorded and he has been hospitalized in our hospital for 2 times because of serious infections (Table 1). He was admitted for the first attack because of prolonged fever, recurrent oral ulcer, otitis media, protracted diarrhea, and peritonitis at the age of 16 months. For the second attack, his symptom was more serious and had been admitted into our pediatric intense care unit (PICU) because of diarrhea, severe pneumonia, and acute respiratory distress syndrome, and was aged 23 months.

For the auxiliary examination, neutropenia (0.16×10^9 cells/L) was detected in blood routine test. However, C reaction protein (CRP), erythrocyte sedimentation rate, procalcitonin, liver function, renal function, blood creatase levels, blood gas analysis, blood glucose, blood ammonia, blood fat, autoantibody, anti-neutrophil cytoplasmic antibodies, and thyroid function were unremarkable. Cerebrospinal fluid (CSF) examination was also normal. CMV-IgM, HSV-IgM, RV-IgM, EBV-IgM, JEV-IgM, EV71 antigen, coxsackie virus antigen, mycoplasma IgM, TPPA, T-spot, PPD skin test, fungal G test, and GM test were negative. Notably, a positive serum *Toxoplasma gondii* (*T gondii*) IgM was found. Brain vascular magnetic resonance imaging (MRI) did not reveal any abnormal findings. However, multiple rings liked nodules lesions in bilateral cerebral hemisphere cortex, bilateral basal ganglia, and dorsal thalamus were detected on brain MRI with enhancement (Fig. 1). Given the characteristic features of the brain MRI, positive serum *T gondii* IgM and a cat/dog exposure history, the diagnosis of toxoplasmic encephalitis was suspected. Furthermore, PCR amplification of *T gondii* in the CSF was performed. Encouragingly, the result was positive and confirmed our diagnosis. Ophthalmic examination was done thereafter and no positive findings were revealed.

Given the diagnosis of toxoplasmic encephalitis and the history of recurrent infection, an increased clinical suspicion of

Table 1

Clinical manifestations of this patient for 3 times attack.

	Age, mo	Duration of the attack, days	Pathogen	Clinical Presentation	Treatment
1st	16	30	None	Oral ulcer, otitis media, diarrhea, peritonitis, sepsis, URI	Meropenem, G-CSF
2ed	23	40	*S pneumoniae,* IFVB	Diarrhea, Sever pneumonia, respiratory failure	Mechanical assisted ventilation, Meropenem, Vancomycin, Micafungin, IVIG
3rd	34	13	*Toxoplasma gondii*	Lethargy, diarrhea, hypologia, ataxia, Cerebral toxoplasmosis	SMZ, Azithromycin, G-CSF, IVIG

G-CSF = granulocyte colony-stimulating factor, IFVB = influenza B virus, IVIG = intravenous immunoglobulin, *S pneumoniae* = *Streptococcus pneumonia*, SMZ = sulfamethoxazole, URI = upper respiratory infection.

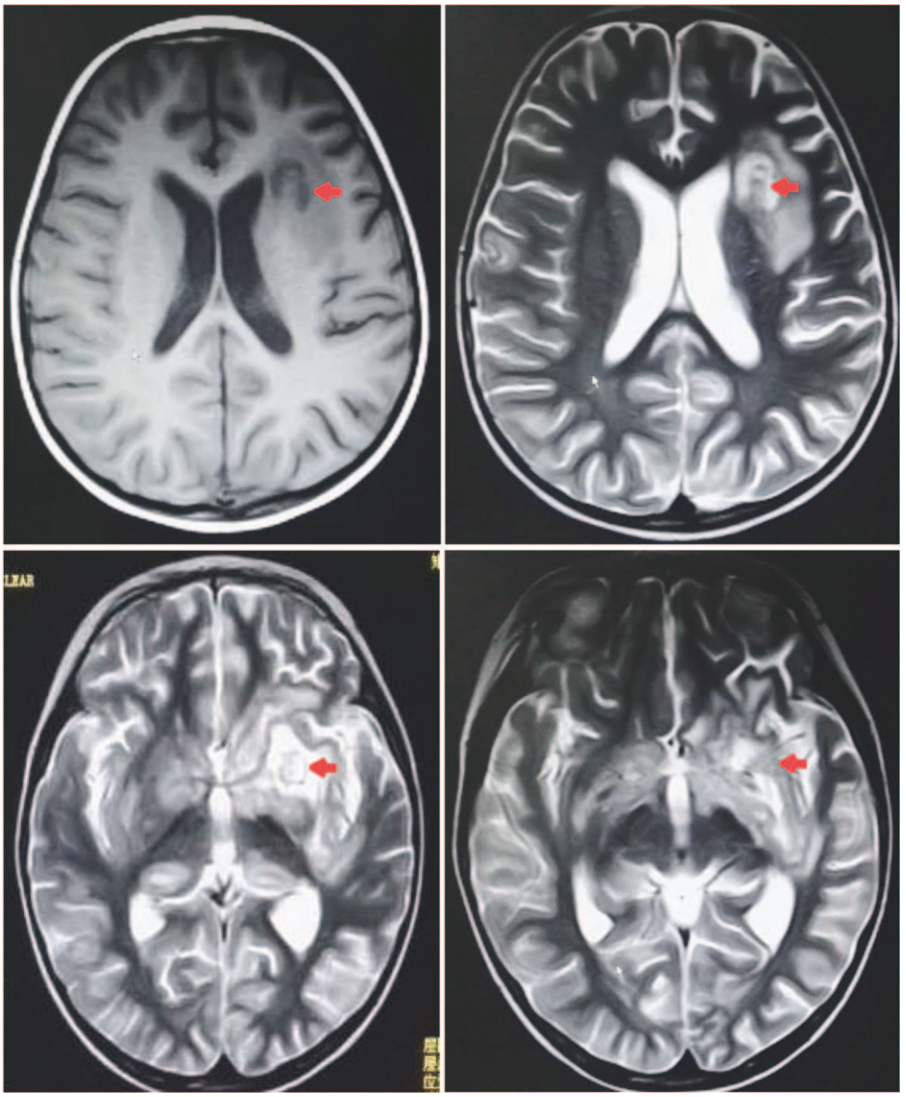

Figure 1. Brain magnetic resonance imaging scans showing multiple nodules associating with ring-enhancing lesion in bilateral cerebral hemisphere cortex, bilateral basal ganglia, dorsal thalamus. The white matter near left side of deep island lobe, temporal lobe, and frontal lobe shows demylination lesions (red Arrow).

immunodeficiency was initiated. Negative serum HIV antibody ruled out the possibility of HIV infection. Immediately, examinations regarding humoral and cellular immunity were done and elevated serum IgM concentration (1.78 g/L, normal range:0.43–1.63 g/L), decreased serum IgG concentration (1.05 g/L, normal range: 3.41–19.6 g/L) and IgE concentration (<165IU/ml), but normal serum IgA level (1.24 g/L, normal range:0.19–2.2 g/L) were found. The lymphocyte counts and the percentage of different lymphocyte subsets including CD3/CD4/CD8/CD19 were generally normal, but with a reduced ratio of CD4/CD8 (0.6, normal range: 1.5–2.0). In light of those findings, the diagnosis of HIGM was highly suspected. Thereafter, we reviewed the results regarding humoral and cellular immunity during his previous 2 times of hospitalization (Table 2). His high IgM with normal IgG and IgA concentrations, detected during his first attack, were not characteristics for HIGM. However, with a typical immunoglobulin profile during his second severe attack, the possibility of HIGM was still completely ignored, which arose from our low recognition and limited knowledge of this disorder.

To confirm our suspicion, the whole-genome sequencing was suggested for his parents this time. The blood sample of his parents and himself was obtained with informed consent. Encouragingly, a mutation c.654C>A (p.C218X) in *CD40L* gene was identified, which has been reported in previous 2 studies,[6,10] whereas his mother was heterozygous and his father was wild type (Fig. 2). The mutation c.654C>A (p.C218X) could result in premature termination of CD40L synthesis. Based on the sequence analysis and elimination of the possibility of hyper-immunoglobulin M secondary to congenital rubella syndrome, the use of phenytoin, T cell leukemia, or lymphomas, the diagnosis of XHIGM was ultimately confirmed genetically up to 2 years later since the symptom onset at the young age of 16 months. Thereafter, oral administration of sulfadiazine (20 mg/kg/day bid for 10 days) and azithromycin (10 mg/kg/day qd for 10 days), intravenous immunoglobulin (IVIG,1 g/kg once per month), and subcutaneous injection of G-CSF were immediately initiated, and the hematopoietic cell transplantation (HCT) was suggested. Regrettably, the patient abandoned the treatment because of economic factor and died 3 months after discharge.

Table 2

The results with respect to humoral and cellular immunity during this patient's 3 times disease attack.

	Age, mo	IgM, g/L	IgG, g/L	IgA, g/L	IgE, IU/mL	C3, g/L	C4, g/L	CD3 (%)	CD4 (%)	CD8 (%)	CD19 (%)	NK (%)	CD4/CD8	Lowest NEUT ($\times 10^9$ cells/L)	LYMPH ($\times 10^9$ cells/L)
1st	16	3.84	9.53	0.51	<5	1.42	0.08	89.5	53	38.3	—	2.4	1.4	0.05	2.25
2ed	23	2.32	<0.33	0.36	<5	0.84	0.04	74.7	38	34.5	22.3	0.4	1.1	0.03	1.99
3rd	34	1.78	1.05	1.24	<5	0.86	0.10	85.5	29.6	50.7	10.2	2.2	0.6	0.16	2.18

Reference value: NEUT: 0.72–4.8 $\times 10^9$ cells/L, LYMPH: 1.44–7.98 $\times 10^9$ cells/L, CD3: 39%–73%, CD4: 25%–50%, CD8: 11%–32%, CD19: 17%–41%, CD4/CD8: 1.5–2.0, NK: 3%–16%, IgG: 3.41–19.6 g/L, IgA: 0.19–2.2 g/L, IgM: 0.43–1.63 g/L, IgE: <165 IU/mL, C3: 0.70–2.06 g/L, C4: 0.11–0.61 g/L.

3. Disscusion

The XHIGM is an uncommon primary immunodeficiency disease caused by mutations in the gene for CD40L, which affects approximately 2:1,000,000 males and accounts for 65%~70% of all forms HIGM.[1] The importance of CD40-CD40L interaction for the biology of B cells (proliferation of B cells, Ig synthesis, isotype switch, and germinal center formation) is well established.[11] More recent data indicate that CD40L is also central to the maturation of antigen-presenting cells, in stimulating effector functions of macrophages, and in antigen priming of T lymphocytes. Therefore, those patients with XHIGM not only exhibit impaired humoral immunity, but also suffer from infections associated with defects in T cell-mediated immunity. Pneumonia is the most common infection, followed by sinusitis, recurrent otitis, and recurrent/protracted diarrhea, which is consistent with the conditions for our patient during his previous 2 disease courses. However, CNS infections, particularly for CNS toxoplasmosis, are extremely rare in patients with XHIGM. As shown in Table 3, just 3 cases of cerebral toxoplasmosis in children were reported until now.[5,12,13] According to our knowledge, this is the first case with XHIGM complicated with toxoplasmic encephalitis reported in Chinese population and it highlights the importance of CD40-CD40L interaction in cell-mediated immunity against *T gondii*.

The susceptibility of patients with XHIGM to toxoplasmosis is probably multifactorial. Peripheral blood mononuclear cells from patients with XHIGM are identified to defect in interleukin-12 and interferon-γ production in response to *T gondii* that is reverted when these cells are incubated with recombinant CD40.[14] Additionally, T cells from a XHIGM patient with a previous history of toxoplasmic encephalitis lacked evidence of priming against the pathogen in vivo. These findings are consistent with the central role of the CD40-CD40L pathway for T cell priming. Finally, the toxoplasmacidal activity acquired by macrophages stimulated through CD40 together with the evidence that such a response is accompanied by in vivo restriction of parasite proliferation, which suggested that impaired macrophage effector functions may also contribute to susceptibility to toxoplasmosis in these patients.

Overall, the prognosis of patients with XHIGM is still guarded, with an average of 20% survival by age 25 years.[4] In 2016, Mt et al[3] reported a retrospective analysis of 176 patients with XHIGM that the median survival post diagnosis was 25 years.

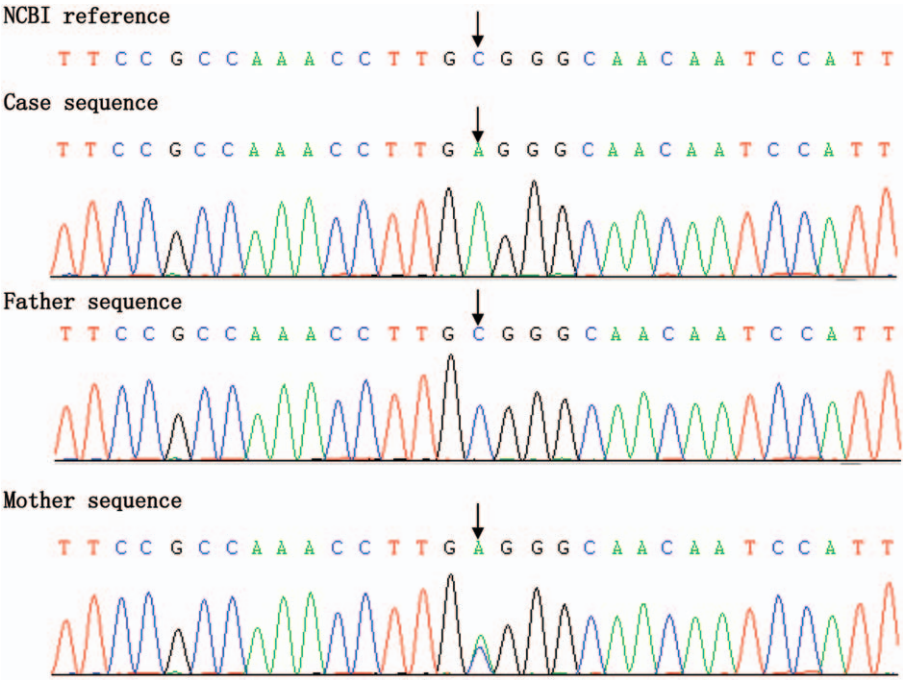

Figure 2. The results of genetic sequencing that indicate the mutation of CD40L c.654C>A (exon 5), whereas his mother was a carrier and his father was wild type.

Table 3

The literature reviews of XHIGM patients with *T gondii* infection.

Author	Onset age, y		Clinical manifestations	Immunoglobulin level, g/L					The approach to diagnosis of TE	Brain MRI imaging findings	*CD40L* gene	Treatment	Prognosis
	XHIGM	*T.gondii* infection		IgM	IgG	IgA	IgE	Neutropenia					
This report	1.4	2.8	Diarrhea, lethargy, fever, and hypologia	1.78	1.05	1.24	<5	(+)	Clinical symptoms and positive PCR amplification of *T gondii* in the CSF	Multiple nodules associating with ring-enhancing lesion in bilateral cerebral hemisphere cortex, bilateral basal ganglia, dorsal thalamus	C218X	IVIG, Sulfadiazine, azithromycin, G-CSF	Died
Leiva et al[12]	2	10	Recurrent otitis media, sinusitis	7.45	6.50	1.23	<0.085	(+)	Brain biopsy	Multiple enhancing nodules throughout the brain	N/D	Pyrimethamine, Sulfadiazine, IVIG, Dexamethasone	Live
Tsuge et al[5]	0.4	9	*P carinii* pneumonia	3.66	5.13	<7.8	N/D	N/D	Brain biopsy	The presence of new lesions in the cerebellum and pons	V237E	IVIG, dexamethasone, acyclovir, interferon α	Died
Yong et al[13]	41	41	Recurrent impetigo and chest infections	2.58	2.75	0.57	N/D	N/D	Brain biopsy	A right thalamic mass lesion with patchy enhancement and considerable peri-lesional oedema	R11X	IVIG, Sulfadiazine (a side effect of Stevens Johnson reaction), pyrimethamine, clarithromycin	Live

CSF = cerebrospinal Fluid, IVIG = intravenous immunoglobulin, N/D = not mentioned, *P carinii* = *Pneumocystis carinii*, *T gondii* = *Toxoplasma gondii*, TE = toxoplasmic encephalitis, XHIGM = X-linked hyper-immunoglobulin M syndrome.

However, several case series in different population have demonstrated that earlier diagnosis for this disorder and the availability of more effective therapies including regular replacement treatment of IVIG and conventional antibiotics to control infection, avoidance of transfusion-related infections with hepatitis B and C to lower the prevalence of hepatitis and cirrhosis, effective therapy with nitazoxanide to avoid cryptosporidiosis, and the development of sclerosing cholangitis/tumors of the hepatobiliary tree could offer a hope to improve outcomes and lower mortality rates. Similarly, the HCT, as the only curative option for XHIGM currently, has been proved to improve the outcomes of those patients. Nevertheless, the transplant survival was significantly influenced by year of diagnosis and age at transplantation because persistent infections and severe organ damage were frequently observed in older patients, even before 5 years or younger.[3] Recently, an international retrospective analysis of patients with XHIGM collected from Europe, North and South America, Middle East, and Australia concluded that although the median survival time was similar for patients treated with or without HCT, those patients treated with HCT had better scores that measured general well-being and activities of daily life, and early age at diagnosis/transplantation was associated with best survival.[3] Moreover, a recent study has proved the feasibility of engineered nuclease-directed gene repair to restore endogenously regulated CD40L, and the potential for its use in T-cell therapy for XHIGM syndrome.[15]

These aforementioned findings strongly strengthened the significance and importance of earlier and accurate diagnosis for XHIGM, yet it was difficult. The median age at diagnosis was 3.17 years (range, 1.5–7.75 years), with a median diagnostic delay of 2.84 years (range, 0.67–7.42 years). Moreover, a positive family history did not also contribute as prominently to the diagnosis as might have been expected. A study involving 28 children who born into a family, in which there was a previously affected member, showed that only 9, or just <33%, were diagnosed based on the presence of their positive family history alone, before clinical symptoms developed.[6] Additionally, although in the past, the immunoglobulin profile of elevated levels of IgM and decreased IgG, IgA, and IgE was considered to be characteristic of HIGM, recent data have shown variability in all these serum immunoglobulin levels, including normal levels in a substantial proportion of patients with HIGM, and dynamic changes in the immunoglobulin concentrations in different stages of disease. Our patient's immunoglobulin phenotype changed from his first evaluation at 1 year of age to his diagnosis at 3 years of age. His high IgM with normal IgG and IgA concentrations, detected during his first attack, is not characteristic for HIGM. Regrettably, with a typical immunoglobulin profile during our patient's second severe attack, a missed diagnosis of HIGM still occurred, which is resulted from limited knowledge of this disorder. Although the symptoms they developed before diagnosis were characterized usually by an increased susceptibility to infection, 2 specific clinical problems were especially prominent, *P carinii* pneumonia and neutropenia companioned with recurrent oral ulcer. Although these clinical manifestations could be found in other primary immunodeficiency diseases (e.g., *P carinii* in severe combined immunodeficiency, and neutropenia in X-linked agammaglobulinemia), the occurrence of either, or especially both, of these clinical features should prompt consideration of the diagnosis of the XHIGM syndrome. As nearly 50% of patients develop *P carinii* pneumonia before diagnosis, attention to a positive family history before symptoms develop could substantially decrease morbidity, and possibly mortality, in this disorder. Additionally, previous studies have proved that decreased CD4/CD8 ratio reflected the impaired cellular immunity and was always associated with a poor prognosis.[7] For the patient in the present study, we could notice that the CD4/CD8 ratio was gradually reduced during his 3 times disease courses, whereas the clinical symptoms were relatively more severe during his second and third attack compared with his first attack accordingly.

4. Conclusions

XHIGM is a rare combined immune deficiency. A delay to diagnosis is substantial because of the low awareness and recognition of the condition, which remains challenging to overcome in the future, particularly in developing countries. A timely and accurate diagnosis is imperative affecting its prognosis. A more thorough clinical history and some features such as recurrent respiratory infections, protracted diarrhea, and persistent or intermittent neutropenia companioned with oral ulcer could increase clinical suspicion. Decreased CD4/CD8 ratio might be associated with severe clinical symptoms and a poor prognosis. Cerebral toxoplasmosis is rare in patients with XHIGM, but still should be considered. The present study firstly reported a delayed diagnosed case of XHIGM with *CD40L* gene c.654C>A (p.C218X) mutant complicated with toxoplasma encephalitis in Chinese population, which highlighted the importance of CD40-CD40L interaction in cell-mediated immunity against *T gondii*.

References

[1] Madkaikar M, Gupta M, Chavan S, et al. X-linked hyper IgM syndrome: Clinical, immunological and molecular features in patients from India. Blood Cells Mol Dis 2014;53:99–104.

[2] Notarangelo LD, Duse M, Ugazio AG. Immunodeficiency with hyper-IgM (HIM). Immunodefic Rev 1992;3:101–21.

[3] Mt DLM, Leonard D, Torgerson TR, et al. Long term outcomes of 176 patients with X-linked hyper IgM syndrome treated with or without hematopoietic cell transplantation. J Allergy Clin Immunol 2017;139: 1282–92.

[4] Winkelstein JA, Marino MC, Ochs H, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine 2003;82:373–84.

[5] Tsuge I, Matsuoka H, Nakagawa A, et al. Necrotizing toxoplasmic encephalitis in a child with the X-linked hyper-IgM syndrome. Eur J Pediatr 1998;157:735–7.

[6] Erdos M, Alapi K, Maródi L. Retrospective diagnosis of X-linked hyper-IgM syndrome in a family with multiple deaths of affected males. Haematologica 2007;92:281–2.

[7] Mt DLM. Clinical phenotypes of hyper-IgM syndromes. J Allergy Clin Immunol Pract 2016;4:1023–36.

[8] San-Andres FJ, Rubio R, Castilla J, et al. Incidence of acquired immunodeficiency syndrome-associated opportunistic diseases and the effect of treatment on a cohort of 1115 patients infected with human immunodeficiency virus, 1989–1997. Clin Infect Dis 2003;36: 1177–85.

[9] Arora S, Jenum PA, Aukrust P, et al. Pre-transplant Toxoplasma gondii seropositivity among heart transplant recipients is associated with an increased risk of all-cause and cardiac mortality. J Am Coll Cardiol 2007;50:1967–72.

[10] Erdos M, Lakos G, Dérfalvi B, et al. Molecular genetic analysis of Hungarian patients with the hyper-immunoglobulin M syndrome. Mol Immunol 2008;45:278–82.

[11] Munroe ME. Functional roles for T cell CD40 in infection and autoimmune disease: the role of CD40 in lymphocyte homeostasis. Semin Immunol 2009;21:283–8.

[12] Leiva LE, Junprasert J, Hollenbaugh D, et al. Central nervous system toxoplasmosis with an increased proportion of circulating gamma delta T cells in a patient with hyper-IgM syndrome. J Clin Immunol 1998; 18:283–90.
[13] Yong PF, Post FA, Gilmour KC, et al. Cerebral toxoplasmosis in a middle-aged man as first presentation of primary immunodeficiency due to a hypomorphic mutation in the CD40 ligand gene. J Clin Pathol 2008;61:1220–2.
[14] Subauste CS, Wessendarp M, Sorensen RU, et al. CD40-CD40 ligand interaction is central to cell-mediated immunity against Toxoplasma gondii: patients with hyper IgM syndrome have a defective type 1 immune response that can be restored by soluble CD40 ligand trimer. J Immunol 1999;162:6690–700.
[15] Hubbard N, Hagin D, Sommer K, et al. Targeted gene editing restores regulated CD40L function in X-linked hyper-IgM syndrome. Blood 2016;127:2513.