Early-onset Systemic Lupus Erythematosus: A Case Series

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Abstract

Early-onset Systemic lupus erythematosus (SLE) is a heterogeneous disease with more variable symptoms than other types of SLE. It can begin as early as 12 months after birth, and the clinical process appears to be more severe. The common clinical manifestations of early-onset SLE are skin and mucosal lesions, renal involvement, central nervous system diseases and hematological system abnormalities. Although the disease is well described in the literature, diagnosis is often difficult due to its insidious onset, early onset, and atypical symptoms. Here, we present four cases of early-onset SLE. Next-generation sequencing were performed and detected mutations were confirmed by Sanger sequencing in all four cases. In addition, glucocorticoid, propyl, cyclophosphamide, and other drugs were significantly improved after treatment.

Conclusion: To our knowledge, this is the first case study in China describing early-onset SLE. With the research progress and knowledge integration of basic disciplines such as genomics, epigenetics and immunology, the pathogenesis of early-onset SLE and other rheumatoid immune diseases will be revealed, which will bring more hope for the diagnosis and treatment of early-onset SLE.

What Is Known

Early onset systemic lupus erythematosus (SLE) is a rare multi-system autoimmune disease. The disease is linked to mutations in a single gene.

What Is New

Four cases of early-onset SLE were documented in this study, which is the first case series reported in China. The mutated genes in these cases were C1s, C3, ITGAM and TREX1. Except for C1s, mutation sites of other genes have not been reported.

Introduction

SLE is a chronic autoimmune disease that invades the connective tissue of the whole body and involves multiple organs [1]. Early-onset SLE is a rare manifestation of the disease. Children are in a special stage of growth and development, and need to experience the development of immune system and the arrival of puberty [2]. The condition of early-onset SLE is more serious than that of adult SLE, which belongs to difficult and miscellaneous diseases in clinical practice [3]. The occurrence of early-onset SLE is related to many factors, including genetic, immune dysfunction and environmental factors. The common clinical manifestations of early-onset SLE are cutaneous mucosal lesions, renal involvement, central nervous system diseases, and hematological abnormalities. Children with this disease often go to many medical institutions for treatment [4]. The treatment after diagnosis belongs to the management category of typical chronic diseases. With the research progress and knowledge integration of basic disciplines such as genomics, epigenetics and immunology, the disclosure of the pathogenesis of various rheumatic

immune diseases such as early-onset SLE will bring more hope for the diagnosis and treatment of early-onset SLE.

This report describes three rare cases of early-onset SLE. To our knowledge, this is the first case study in China describing early-onset SLE. We also reviewed the genetic and clinical manifestations of more early-onset SLE cases reported in the literature to better understand the disease, help clinicians make early diagnosis and promote the treatment and management of the disease.

Case Report

Case 1

In 2018, a 2-year-old male presented with intermittent low fever, accompanied by pale red papules, facial edema, and night snoring. He was hospitalized in a local hospital and received cefazoxime without improvement. Later, the patient was transferred to the Children's Hospital affiliated to Fudan University due to fever. The results showed that ALT was 120 IU/L and AST was 284 IU/L. Epstein-Barr virus IgG, ANA and anti-nucleosome antibody was positive. The patient was diagnosed as "abnormal liver function and erythema multitype". Body temperature was normal after 3 days of methylprednisolone impact therapy. Medrol 4-12mg was taken after discharge. A month later, high fever occurred again, with a temperature of 39.4℃, accompanied by convulsions, two eyes up, weakness of limbs, and foaming at the mouth, which resolved spontaneously about 5 minutes later. A large amount of facial rash followed by facial edema, red and dry lips, conjunctival congestion, left neck mass, and oral ulcer. EEG diagnosis at the local hospital showed moderate abnormalities, no epileptic discharge. After 3 days of treatment with methylprednisolone 12mg/d and clindamycin 0.15g twice a day, the patient still had fever. The patient was referred to our facility. At admission, he still had a low fever and a rash scattered on both inner thighs.

Physical examination was found that pharyngeal mucosa was congested and bilateral tonsils were II degree swollen. The lips were dry red and chapped, the oral mucosa was ulcerated, and the conjunctiva of both eyes was congested. The face was swollen, and a large number of red spots could be seen on the face, which were partially fused and higher than the skin (Figure 1A). Several soybean sized lymph nodes could be touched under the right armpit, with medium quality and moderate activity.

Serology demonstrated high titer anti-nuclear antibodies (ANA; Hep2 titer 1280), anti-double-stranded deoxyribonucleic acid (anti-dsDNA; titer 10). antimitochondrial antibody (AMA) M2, Ro-52 and anti-nucleosome antibody were positive. The level of ferritin was high (704.2ng/ml). Plain computed tomography (CT) scan of chest showed pneumonia with a small amount of pleural effusion on both sides (Fig. 2). Brain magnetic resonance imaging (MRI) showed Flaky FLAIR high signal in the posterior portion of bilateral lateral ventricles with widening of sulci in hemispheres and significant sulci in cerebellum (Fig. 3). Neck skin biopsy light microscope examination showed consistent with the pathological changes of erythema multiforme. Small pieces of skin were examined and the epidermis was found to be focal atrophy and thinning, with a small amount of bad dead corner prion cells, focal

basal cells liquefied degeneration, and a small number of lymphocytes and histocytes at the epidermal dermal junction. Immunohistochemical results were $CD3^+$, $CD68^+$, and $Ki\text{-}67^+$. Gene detection showed mutations in integrin subunit alpha M (ITGAM) (c.1592A > G, p.N531S; c.3213G > C, p.E1071D) and complement component 1 (C1)s (c.217-5T > G, splicing).

After hospitalization, he was given ertapenem for anti-infection and Compound Ammonium Glycyrrhizinate for liver protection. Intravenous immunoglobulin (IVIG) was given 2g/kg, actually 5g for 5 days. After adding methylprednisolone 2mg/kg/d, the thermal peak decreased. On the 7th day of admission, ertapenem was stopped and changed to cefamandole 0.5g, twice a day for anti-infection treatment. Then the child developed intermittent fever, the blood routine three systems decreased and the transaminase increased. It is considered that there may be early macrophage activation syndrome. The patient was treated with methylprednisolone 0.36g (27mg/kg), IVIG 5g, cyclosporine 50mg via intravenous drip. After 5 days of treatment, the overall situation of the children was significantly improved compared with that before admission. The patient can eat from his mouth and pull out his stomach tube. Then the patient was given prednisone acetate tablets 2mg /kg/d actually 27.5mg/d orally. Tofacitinib was given 2.5mg, 2 times a day. After one week of treatment, the body temperature was normal and the rash was significantly relieved (Fig. 1B). In addition, the inflammatory indicators were improved, and the lesions on chest radiographs were less than before. Tofacitinib was then used for about a year, and was switched to belimumab combined with IVIG and glucocorticoid. His condition has been stable for nearly a year without fever or rash.

Case 2

In 2019, a 2-year-old female was hospitalized with a rash and recurrent fever. At 6 months after birth, the child developed a round red skin rash on the face, alopecia, and subsequent leg pain. 3 months before admission, rash appeared all over the body, accompanied by fever, once a day. Physical examination showed scattered irregular red rash on the face and hands, and old brown rash on the trunk and limbs. The lower extremities were slightly stiff, the knees and ankles were swollen without tenderness, and the right dorsum was edema. Both lower limbs movement is limited, cannot squat. Unsteady walking, walking on tiptoes.

Physical examination: scattered old brown rash could be seen on the trunk and limbs. Bilateral muscle strength was normal. Double knee and double ankle joints were swelling, the right foot dorsum was edema. Babinski signs and ankle clonus were positive with hyperreflexia of tendon.

Laboratory inspection: hemoglobin was 101g/L and platelet was 264×10^9/L. Inflammatory marker displayed that blood sedimentation and ferritin were high (29 mm/h and 116.3ng/ml, respectively). Antinuclear antibody was 1:1000. anti-U1 small nuclear ribonucleoprotein (anti-U1-nRNP), Anti-Sm (anti-Sm), anti-Sjgren's-syndrome-related antigen A (anti-SSA), anti-Ro-52, anti-ribosomal P-protein (anti-rRNP) antibodies were all expressed strong positive. Renal pathological examination showed mild mesangial proliferative glomerulopathy. Skin pathological examination showed hyperkeratosis with incomplete keratosis and incontinence of pigment in the papillary layer. Vascular endothelial cells swell. Gene tests

showed C1s gene (c.849G > A, p.W283X) mutation. Gene tests also found that her father also had the mutation, but her mother did not. This indicates that the mutation was inherited from the father (Fig. 5).

After hospitalization, the child was diagnosed as early-onset SLE. The patient was given IVIG 400mg/kg/d, 5g/d for 4 days of immune support, methylprednisolone 280mg/d shock therapy for 3 days, and ertapenem for anti-infection. Three days later, methylprednisolone was stopped and methylprednisolone 8mg was given orally twice a day. The blood routine examination showed a decrease in three levels, which was considered to be combined with macrophage activation syndrome. The patient was then given IVIG 2.5g for 3 days, cyclosporine 0.2ml, 2 times a day, 25mg thalidomide and 0.25g mycophenolate mofetil (MMF) once a day orally. One week later, the child's temperature returned to normal without fever, and the rash subsided significantly without new rash. After discharge, the patient continued to receive prednisone acetate 15mg once daily, thalidomide 25mg once daily, and MMF 0.25g once daily. Two year later, the patient's condition did not occur repeatedly.

Case 3

In 2019, a 4-year-old boy was hospitalized with foamy urine and abdominal enlargement. Four months before admission, abdominal distension appeared, followed by fever, with the highest temperature of 40.0℃, 2–3 thermal peaks every day, scattered red papules on the limbs and trunk. After the child urine foam increased, mouth ulcer. Physical examination showed scattered red papules on the limbs and trunk. The skin is dry and scaly. Abdominal examination showed abdominal distension, with abdominal circumference 58cm. There was concave edema in both lower limbs.

The patient's hemoglobin and albumin were lower than normal (79g/L, 28.1g/L, respectively). C-reactive protein (CRP) was 44.36mg/L. Routine urine examination showed urinary protein and occult blood 2+, white cells and tubular type in urine. The 24-hour proteinuria was 1.803g. CT scan of the lungs showed bronchopneumonia, right interlobar effusion, and little stromal change in the left lung. There were unbalanced nucleoplasm development and unclassified cells in sternal bone puncture. Anti - nuclear antibody, anti-dsDNA and anti-rRNP were positive. Abdominal ultrasound showed large liver and spleen. Positron emission tomography-computed tomography (PET-CT) showed an enlarged spleen and increased fluorodeoxyglucose metabolism in the bone marrow cavity of sternum, spine and pelvis. Genetic tests revealed a mutation in the complement component 3 (C3) gene (c.1508C > T, p.A503V).

After admission, the children were given oral prednisone acetate tablet 10mg, once a day, hydroxychloroquine sulfate tablet 25mg, three times a day to suppress the immune response. Captopril tablet was given 6.25mg, three times a day to reduce urinary protein. IVIG was given 400mg/kg/d, 7.5g continuous for 3 days to regulate immunity. Fresh frozen plasma was given 100ml for 5 days to supplement coagulation factors to prevent hypercoagulability. And dipyridamole 25mg, three times a day was taken orally to prevent platelet aggregation and micro thrombosis. Due to the lung was infected, azithromycin was given orally for 5 days to clear the infection. After 14 days of treatment, there was no fever, foam reduction in urine, edema of lower limbs and abdominal distension. The skin of the whole body is slightly dry, no rash observed. No ulceration of oral mucosa. After discharge, prednisone was

given 40mg, once a day; MMF 0.25g, three times a day; captopril 6.25mg, three times a day; dipyridamole 25mg, three times a day. Two years after discharge, regular outpatient visits were made, and the disease did not worsen again.

Case 4

In 2022, a four-year-old girl developed a skin rash of patchy red macules on the left and right inner corners of her eyes 2 years ago. One month later, she developed a rash on the edge of both outer auricles. The rash was reduced after her parents applied prednisone ointment on their own. Subsequently, she developed a patchy red rash on both sides of his cheeks, accompanied by oral ulcers and bleeding spots on the palate. She was treated with tacrolimus and elloxone and relieved after topical application in Capital Institute of Pediatrics. One year ago, she was admitted to the dermatology clinic of Beijing Children's Hospital and was given topical application of tachlimus and cicyotal. Later, skin pathology revealed lupus erythematosus, and prednisone was taken 27.5mg/d orally. Two weeks ago, complement C3 was 0.74g/L, complement component 4 (C4) was 0.08g/L, and anti-dsDNA test showed positive, titer 1:320.

Physical examination: slightly dry lips, scattered dark red old sunken scars on the face(Fig. 6A-D).

Auxiliary examination: Positive chest X-ray showed increased and blurred texture in the right lung. Ultrasonography of knee joint showed a little effusion in bilateral knee cavity, synovial membrane slightly thick, left side. The results of dynamic electrocardiogram suggested sinus rhythm, sinus arrhythmia, partial sinus tachycardia, single premature ventricular beat, partial triad, ST segment elevation, QTC value greater than 0.46. Ophthalmologic examination showed dark spot above left visual field and poor reliability of binocular examination. Parotid gland ultrasound showed uneven echo in bilateral parotid gland parenchyma. Enhanced CT of the right thigh indicated that the distal great saphenous vein was not uniform in thickness and the wall was slightly thick locally, which was considered great saphenous vein thrombosis. The dermatologic examination was consistent with cutaneous lupus erythematosus. Genetic testing revealed a mutation in the three prime repair exonuclease 1 (TREX1) gene (c.861_864delinsATT, p. L287Lfs).

After hospitalization, prednisone acetate tablets 15mg were given once a day in the morning. Calcium carbonate D3 particles 0.5mg, once a day. As the ECG showed myocardial damage, coenzyme Q10 10mg, twice a day was given to nourish the myocardium. Aspirin 25mg once a day orally was used for anticoagulant therapy. After 2 weeks of treatment, the child's temperature was normal and the rash disappeared completely (Fig. 6E).

Discussion

SLE is a chronic, multisystemic autoimmune connective tissue disease with various clinical phenotypes [5]. Approximately 20% of SLE develops in childhood and is clinically diagnosed [6]. The mortality of children with early-onset SLE was higher than that of adults with SLE. Typical early-onset SLE patients

are easy to be clinically diagnosed, but for patients with occult onset, early onset and atypical symptoms, it is often difficult to clinically diagnose them [7]. There are multiple autoantibodies and other immunological changes in early-onset SLE. Early detection and early treatment are one of the important principles of clinical treatment of early-onset SLE [8]. In recent years, with the rapid development of molecular biology and gene diagnosis, the early diagnosis, pathogenesis and prognosis evaluation of early-onset SLE have undergone profound changes [9].

pathogenesis

The early-onset SLE is closely related to genetic susceptible allele mutations, which explains why the severity of this disease is higher than that in adults from the perspective of pathogenesis [10]. The early emergence of multi-system autoimmune diseases requires vigilance against the possibility of rare single-gene diseases [11]. Functional mutations of immune deficiency genes were found in all four children in this study, suggesting that childhood onset lupus-like syndrome caused by immune deficiency gene mutations [12]. The functional effects of mono-gene SLE mainly include complement deficiency, abnormal expression of type I interferon, and abnormal tolerance of T/B cells according to their genetic mutations. Mutations in genes related to primary immunodeficiency disease led to the body's clearance of immune complexes, DNA fragments and apoptotic cells, abnormal cells and DNA fragments as autoantigens to stimulate the body to produce autoantibodies to activate the immune response, and abnormal activation of complement, leading to lupus-like syndrome [13]. The related genes reported at present include ITGAM, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PIK3CD), C1q, C1r, C1s, C4, TREX1, etc., accounting for 1–4% of pediatric lupus cases [14].

The mutated genes in this study were C1s, C3, ITGAM and TREX1. To our knowledge, except for C1s, mutation sites of other genes have not been previously reported. The mutant gene in case 1 were ITGAM and C1s. ITGAM, like integrin Mac-1 or complement receptor 3, is an encoding ITGAM that is involved in clearance of immune complexes, leukocyte activation, and endothelial cell adhesion by interacting with a variety of ligands, such as intercellular adhesion molecule-1, glycoproteins, and fibrinogen [15]. ITGAM plays a key role in the pathogenesis of SLE, especially in vascular endothelial injury of SLE [16]. Case 2 also had C1s gene mutation. The gene of C1s is a complement related gene. C1r and C1s are tetramer proenzymes that form C1 complex with C1q in the presence of Ca^{2+}. In the absence of C1 complex, which is essential for the initiation of the classical complement pathway, the body cannot effectively clear the immune complex and apoptotic cell debris through conditioning, and the accumulated autoantigens continuously activate the immune response [17]. Patients with C1s deficiency have severe skin lesions [18]. The case 2 in this study had skin lesions at onset of SLE.

Case 3 has a C3 gene defect, resulting in loss of C3 function in vivo. Patients with C3 deficiency are hindered in their opsonization of pathogens, resulting in impaired phagocytosis of Complement Component 5 (C5)a and the lysis of cells by membrane-attacking complexes, leading to suppurative infections [18]. Lupus is rare in patients with hereditary C3 deficiency, the main clinical features of which

are membranous proliferative glomerulonephritis, hematuria and proteinuria [19]. Case 3 presented with urinary protein and lower limb edema.

The nuclease activity expressed by TREX1 plays an important role in maintaining the immune tolerance of the innate immune system to recognize its own DNA, which avoids the excessive activation of innate immunity and the production of autoantibodies caused by the continuous accumulation of some free DNA in the cytoplasm. Case 4 has the mutation of this gene. Lupus like chilblain and intracranial calcification are more common after the gene mutation, and this case has lupus like chilblain.

Clinical manifestations and laboratory tests

Fever is the most common first manifestation in children with early-onset SLE, which often involves the kidney, blood and nervous system [20]. Compared with the classic manifestations of lupus, the clinical symptoms of children with early-onset SLE are not typical, and they are prone to complicated infection, repeated and severe activity, and persistent hypo complement, which are easy to be misdiagnosed [21]. Musculoskeletal involvement is similar to other forms of SLE. Skin involvement appears to be more common in early-onset SLE and is usually manifested as inflammatory and degenerative changes at the epidermal to dermal junction. Immunofluorescence showed banded deposition of granular IgG and complement [22]. In addition to the common manifestations of fever, joint symptoms and edema, a few children with SLE start with parotid gland swelling, chest pain and cough. Pericarditis is the most common cardiac involvement in children with SLE, while myocarditis, abnormal heart valve and arrhythmia are relatively rare [23]. Some children may have abnormal thyroid function, menstrual disorder, growth retardation and other manifestations of endocrine system damage in the course of the disease [24]. Early onset SLE is prone to renal involvement, manifested as edema or abnormal urine test. Most children with SLE can have neurological symptoms after onset, among which headache is the most common. It can also be manifested as convulsions, disturbance of consciousness and so on [25]. The clinical features at the onset of each case are summarized as follows.

Table 1
Clinical features at the onset of early-onset SLE in 4 cases

Cases	Case 1	Case 2	Case 3	Case 4
Gender	Male	Female	Male	Female
Age of onset	2 years	6 months	4 years	2 years
Fever	+	+	+	+
Rash	+	+	+	+
Alopecia	-	+	-	-
Dental ulcer	+	-	+	-
Xerochilia	-	-	-	+
Arthralgia	-	+	-	-
Foam urine	-	-	+	-
Edema	+	+	+	-
Conjunctival hyperemia	+	-	-	-
Gum swelling	+	-	-	-
Pharyngeal hyperemia	+	-	-	-
Tonsil enlargement	+	-	-	-
Abdominal distension	-	-	+	-
Lymphadenectasis	+	+	+	-
Convulsions	+	-	-	-

Early-onset SLE is more common than adult SLE [26]. The abnormal blood system of early-onset SLE is mainly manifested by the decrease of white blood cells, red blood cells, platelets and lymphocytes in peripheral blood [27]. This may be related to excessive production of autoantibodies or deposition of immune complexes in peripheral blood circulation in early-onset SLE patients [28]. ANA antibody is one of the most sensitive markers of early-onset SLE [29]. Anti-dsDNA antibody is highly specific for early-onset SLE and is closely related to the activity of the disease [30]. The positive rate of ENA antibody spectrum is not high, which can be used as a supplement to ANA antibody and anti dsDNA antibody to a certain extent [31]. Previous studies have found that anti-dsDNA antibody is related to the occurrence of lupus nephritis, and anti-Sm antibody is related to oral ulcer, Reynolds's phenomenon and leukopenia [32]. However, there was no significant correlation in this study. It can be seen that the significance of immunological indicators is still limited. The laboratory tests for each case are as follows.

Table 2
Laboratory examination at the onset of early-onset SLE in 4 cases

Cases	Case 1	Case 2	Case 3	Case 4
Peripheral blood routine				
Red blood cell count ($\times 10^{12}$/L)	4.18	4.23	3.14	4.59
Hemoglobin (g/L)	113	99	79	130
White blood cell count ($\times 10^{9}$/L)	3.76	7.28	8.43	5.42
Percentage of neutrophils (%)	50	50.3	61.1	34.4
Platelet ($\times 10^{9}$/L)	194	191	124	267
urinalysis				
24h urine protein quantification (mg/24h)	205	35	1803	98
Microscopic red blood cells (/HPF)	Little	-	-	-
Inflammatory cytokines				
CRP (mg/L)	1	< 8	44.3	7
ESR (mm/h)	12	29	44	< 8
SAA (mg/L)	-	-	-	5.4
Biochemical examination				
Serum albumin (g/L)	38.9	36.1	28.1	43
BUN (mmol/L)	3.75	3.68	2.89	5.13
Cr(μmol/L)	26.8	23.1	20.3	23.8
ALT(U/L)	32.9	14.6	17	12.7
AST(U/L)	27	59.7	38.4	23.2
Immunological examination				
C3 (g/L)	0.64	1.21	0.86	0.82
C4 (g/L)	0.131	0.339	0.18	0.1

Abbreviations: ALT, alanine aminotransferase; ANA, antinuclear antibody; Anti-U1-nRNP, anti-U1 small nuclear ribonucleoprotein; Anti-dsDNA, anti-double-stranded deoxyribonucleic acid; Anti-rRNP, anti-ribosomal P-protein; Anti-Sm, anti-Smith; Anti-SSA, anti-Sjgren's-syndrome-related antigen A; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C3, complement component 3; C4, complement component 4; Cr, creatinine; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; HPF, high power field; MRI, magnetic resonance imaging; RAAS, renin-angiotensin-aldosterone system; RF, rheumatoid factor; SAA, Serum amyloid A

Cases	Case 1	Case 2	Case 3	Case 4
RF(IU/ml)	24.5	217	< 20	< 20
ANA	+	+	+	+
Anti-dsDNA antibody	+	+	+	-
U1-nRNP antibody	-	+	-	-
Anti-Sm antibody	-	+	-	-
Anti-SSA antibody	-	+	-	-
Anti-rRNP antibody	-	+	+	-
Anti-nucleosome antibody	-	-	-	-
Antiphospholipid antibody	+	-	+	-
System function evaluation				
RAAS system inspection	+	+	+	-
Urinary ultrasound	-	+	-	-
Abnormal renal biopsy	+	+	-	-
Lung CT abnormal	+	+	+	+
Head MRI	+	+	+	-

Abbreviations: ALT, alanine aminotransferase; ANA, antinuclear antibody; Anti-U1-nRNP, anti-U1 small nuclear ribonucleoprotein; Anti-dsDNA, anti-double-stranded deoxyribonucleic acid; Anti-rRNP, anti-ribosomal P-protein; Anti-Sm, anti-Smith; Anti-SSA, anti-Sjgren's-syndrome-related antigen A; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C3, complement component 3; C4, complement component 4; Cr, creatinine; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; HPF, high power field; MRI, magnetic resonance imaging; RAAS, renin-angiotensin-aldosterone system; RF, rheumatoid factor; SAA, Serum amyloid A

Treatment

The clinical purpose of the treatment of early-onset SLE is to inhibit the autoimmune response and non-specific inflammation in children in a short period of time, eliminate and relieve the injury of relevant organs, control infection and/or control the causes of aggravating the disease, and maintain the balance of the body's internal environment and immune function [33]. In the treatment of early-onset SLE, it is necessary to consider the potential influence of drugs on the growth and development of children and reproductive function in the future, which requires multidisciplinary combination therapy [34]. Before the use of cytotoxic drugs, the guardians of early-onset SLE should be informed in detail of the possible short-term and long-term adverse reactions caused by drugs [35]. Although treatment options for early-

onset SLE vary from country to country, corticosteroids and immunosuppressants are used in the vast majority of treatments, with the primary goal of reducing the activity of early-onset SLE [36].

Specific medication should be individualized according to the degree of disease, organ involvement and severity [37]. The main role of non-steroidal anti-inflammatory drugs (NSAIDs) is in pain management and the treatment of musculoskeletal disorders such as myalgia, arthralgia and arthritis [38]. Glucocorticoids are the main treatment for lupus [39]. After laboratory tests are generally normal, low-dose maintenance therapy is switched to for several years [40]. Immunosuppressants such as cyclophosphamide, MMF, and methotrexate are certain to control SLE activity, and early use in combination with hormones is key to reducing mortality and improving quality of life [41]. Cyclophosphamide pulse therapy in severe cases may fleetly relieve the inflammatory response, and maintenance therapy with MMF can be switched to after stable improvement [42]. In addition, severe cases can be treated with IVIG, plasma replacement or stem cell transplantation [43].

In this study, all the 4 cases received glucocorticoid as first-line anti-inflammatory drugs, and the oral dose of prednisone was 1-2mg/kg/d, with the maximum dose of 60mg/d. Case 1 and case 2 were treated with high-dose methylprednisolone (20mg/kg/d). IVIG were given for 3 cases (total dose 1-2g/kg). 2 cases were given cyclophosphamide (400-600mg/m^2), 2 MMF (10-30mg/kg/d), 2 cyclosporine (1-5mg/kg/d), 1 tofacitinib, and 1 hydroxychloroquine (5-6mg/kg/d).

Conclusion

Early-onset SLE is more serious than adult SLE and is a difficult disease in clinical practice. Early onset is usually caused by homozygous or heterozygous mutations in a single gene. Complement deficiency related genes are more common among mutated genes, and lupus-like phenotypes such as fever, rash, nephritis and arthritis can be seen clinically. Children with this disease often go to many medical institutions for treatment, and the treatment after diagnosis belongs to the category of typical chronic disease management. In the treatment of early onset SLE, autoimmune response and non-specific inflammation should be inhibited for a short period of time to reduce the activity of this disease.

Abbreviations

ALT	Alanine aminotransferase
ANA	antinuclear antibody
Anti-U1-nRNP	Anti-U1 small nuclear ribonucleoprotein
Anti-dsDNA	Anti-double-stranded deoxyribonucleic acid
Anti-rRNP	Anti-ribosomal P-protein
Anti-Sm	Anti-Smith
Anti-SSA	Anti-Sjogren's-syndrome-related antigen A
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
C1	Complement component 1
C3	Complement component 3
C4	Complement component 4
C5	Complement component 5
Cr	Creatinine
CRP	C-reactive protein
CT	Computed tomography
ESR	Erythrocyte sedimentation rate
HPF	High power field
ITGAM	Integrin subunit alpha M
IVIG	Intravenous immunoglobulin
MMF	Mycophenolate mofetil
MRI	Magnetic resonance imaging
PET-CT	Positron emission tomography-computed tomography
PIK3CD	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
RAAS	Renin-angiotensin-aldosterone system
RF	Rheumatoid factor
SAA	Serum amyloid A
SLE	Systemic lupus erythematosus
TREX1	Three prime repair exonuclease 1

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Li Cai-Feng, Deng Jiang-Hong and Kuang Wei-Ying. The first draft of the manuscript was written by Zhao Wen-Jia, Tan Xiao-Hua, and Zhang Jun-Mei. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical approval

This report has been approved by institutional review board (2022-E-055-R). The study was performed in accordance with the 1964 Helsinki declaration and its later amendments.

Informed consent

Informed written consents to publish the cases have been obtained from the patients' parents.

Consent to participate

Written informed consent was obtained from the parents.

Consent to publish

The parents signed informed consent regarding publishing patients' data and photographs.

References

1. Aljohani R, Gladman DD, Su J, Urowitz MB (2017) Disease evolution in late-onset and early-onset systemic lupus erythematosus. Lupus 26(11):1190–1196. https://doi.org/10.1177/0961203317696593
2. Demirkaya E, Sahin S, Romano M, Zhou Q, Aksentijevich I (2020) New Horizons in the Genetic Etiology of Systemic Lupus Erythematosus and Lupus-Like Disease: Monogenic Lupus and Beyond. J Clin Med 9(3):712. https://doi.org/10.3390/jcm9030712

3. Batu ED, Koşukcu C, Taşkıran E, et al (2018) Whole Exome Sequencing in Early-onset Systemic Lupus Erythematosus. J Rheumatol 45(12):1671–1679. https://doi.org/10.3899/jrheum.171358
4. Kwon OC, Park JH, Lee SW, Song JJ, Park YB, Park MC (2020) Worse Renal Presentation and Prognosis in Initial-Onset Lupus Nephritis than Early-Onset Lupus Nephritis. Yonsei Med J 61(11):951–957. https://doi.org/10.3349/ymj.2020.61.11.951
5. Nanthapisal S, Omoyinmi E, Murphy C, Standing A, Eisenhut M, Eleftheriou D, Brogan PA (2017) Early-Onset Juvenile SLE Associated With a Novel Mutation in Protein Kinase C δ. Pediatrics 139(1):e20160781. https://doi.org/10.1542/peds.2016-0781
6. Wang W, Zhou Y, Zhong L, Wang L, Tang X, Ma M, Li J, Song H (2019) RAS-associated Autoimmune Leukoproliferative disease (RALD) manifested with early-onset SLE-like syndrome: a case series of RALD in Chinese children. Pediatr Rheumatol Online J 17(1):55. https://doi.org/10.1186/s12969-019-0346-1
7. Delfino J, Dos Santos TAFG, Skare TL (2020) Comparison of lupus patients with early and late onset nephritis: a study in 71 patients from a single referral center. Adv Rheumatol 60(1):5. https://doi.org/10.1186/s42358-019-0105-5
8. Weill O, Decramer S, Malcus C, et al (2017) Familial and syndromic lupus share the same phenotype as other early-onset forms of lupus. Joint Bone Spine 84(5):589–593. https://doi.org/10.1016/j.jbspin.2016.12.008
9. Ichinose K, Kitamura M, Sato S, et al (2020) Comparison of complete renal response and mortality in early- and late-onset lupus nephritis: a multicenter retrospective study of a Japanese cohort. Arthritis Res Ther 22(1):175. https://doi.org/10.1186/s13075-020-02271-3
10. Hedrich CM, Smith EMD, Beresford MW (2017) Juvenile-onset systemic lupus erythematosus (jSLE) - Pathophysiological concepts and treatment options. Best Pract Res Clin Rheumatol 31(4):488–504. https://doi.org/10.1016/j.berh.2018.02.001
11. Medlin JL, Hansen KE, McCoy SS, Bartels CM (2018) Pulmonary manifestations in late versus early systemic lupus erythematosus: A systematic review and meta-analysis. Semin Arthritis Rheum 48(2):198–204. https://doi.org/10.1016/j.semarthrit.2018.01.010
12. Girardelli M, Valencic E, Moressa V, et al (2021) Genetic and immunologic findings in children with recurrent aphthous stomatitis with systemic inflammation. Pediatr Rheumatol Online J 19(1):70. https://doi.org/10.1186/s12969-021-00552-y
13. Lei L, Muhammad S, Al-Obaidi M, Sebire N, Cheng IL, Eleftheriou D, Brogan P (2018) Successful use of ofatumumab in two cases of early-onset juvenile SLE with thrombocytopenia caused by a mutation in protein kinase C δ. Pediatr Rheumatol Online J 16(1):61. https://doi.org/10.1186/s12969-018-0278-1
14. Li G, Li Y, Liu H, Shi Y, Guan W, Zhang T, Yao W, Wu B, Xu H, Sun L (2020) Genetic heterogeneity of pediatric systemic lupus erythematosus with lymphoproliferation. Medicine 99(20):e20232. https://doi.org/10.1097/MD.0000000000020232

15. Li G, Liu H, Li Y, Zhang T, Yao W, Guan W, Shi Y, Wu B, Xu H, Sun L (2021) Genetic heterogeneity in Chinese children with systemic lupus erythematosus. Clin Exp Rheumatol 39(1):214–222.
16. Pakzad B, Shirpour R, Mousavi M, Karimzadeh H, Salehi A, Kazemi M, Amini G, Akbari M, Salehi R (2020) C1QTNF4 gene p.His198Gln mutation is correlated with early-onset systemic lupus erythematosus in Iranian patients. Int J Rheum Dis 23(11):1594–1598. https://doi.org/10.1111/1756-185X.13981
17. Komici K, Faris P, Negri S, Rosti V, García-Carrasco M, Mendoza-Pinto C, Berra-Romani R, Cervera R, Guerra G, Moccia F (2020) Systemic lupus erythematosus, endothelial progenitor cells and intracellular Ca^{2+} signaling: A novel approach for an old disease. J Autoimmun 112:102486. https://doi.org/10.1016/j.jaut.2020.102486
18. Gendelman O, Tiosano S, Shoenfeld Y, Comaneshter D, Amital H, Cohen AD, Amital D (2018) High proportions of dementia among SLE patients: A big data analysis. Int J Geriatr Psychiatry 33(3):531–536. https://doi.org/10.1002/gps.4819
19. Khan WA, Zaman GS, Alouffi S, Khan MWA (2019) Depression and its related parameters increased the production of autoantibodies against 16α-hydroxyestrone-albumin complex in systemic lupus erythematosus. Int Immunopharmacol 71:215–223. https://doi.org/10.1016/j.intimp.2019.03.036
20. Schnappauf O, Heale L, Dissanayake D, et al (2021) Homozygous variant p. Arg90His in NCF1 is associated with early-onset Interferonopathy: a case report. Pediatr Rheumatol Online J 19(1):54. https://doi.org/10.1186/s12969-021-00536-y
21. Billi AC, Gharaee-Kermani M, Fullmer J, et al (2019) The female-biased factor VGLL3 drives cutaneous and systemic autoimmunity. JCI Insight 4(8):e127291. https://doi.org/10.1172/jci.insight.127291
22. Mayer-Pickel K, Stern C, Eberhard K, Lang U, Obermayer-Pietsch B, Cervar-Zivkovic M (2018) Angiogenic factors in pregnancies of women with antiphospholipid syndrome and systemic lupus erythematosus. J Reprod Immunol 127:19–23. https://doi.org/10.1016/j.jri.2018.04.002
23. Al-Mayouf SM, Alreefi HA, Alsinan TA, AlSalmi G, AlRowais A, Al-Herz W, Alazami AM, Alsonbul A, Al-Mousa H (2021) Lupus manifestations in children with primary immunodeficiency diseases: Comprehensive phenotypic and genetic features and outcome. Mod Rheumatol 31(6):1171–1178. https://doi.org/10.1080/14397595.2021.1886627
24. Kim HY, Song JY, Kim WI, Ko HC, Park SE, Jang JH, Kim SH (2020) The First Case of an Infant with Familial A20 Haploinsufficiency in Korea. J Korean Med Sci 35(30):e252. https://doi.org/10.3346/jkms.2020.35.e252
25. Kisla Ekinci RM, Balci S, Ozcan D, Atmis B, Bisgin A (2021) Monogenic lupus due to DNASE1L3 deficiency in a pediatric patient with urticarial rash, hypocomplementemia, pulmonary hemorrhage, and immune-complex glomerulonephritis. Eur J Med Genet 64(9):104262. https://doi.org/10.1016/j.ejmg.2021.104262
26. Seo E, Lee BH, Lee JH, Park YS, Im HJ, Lee J (2021) Hematopoietic stem cell transplantation in an infant with dedicator of cytokinesis 8 (DOCK8) deficiency associated with systemic lupus

erythematosus: A case report. Medicine 100(13):e20866. https://doi.org/10.1097/MD.0000000000020866

27. Mishima S, Kaneko K, Okazaki Y, Kohno C, Murashima A (2021) A woman with systemic lupus erythematosus, multiple pregnancy complications, and cerebral infarction who was only positive for phosphatidylserine-dependent antiprothrombin antibodies. Mod Rheumatol Case Rep 5(1):47–51. https://doi.org/10.1080/24725625.2020.1782030
28. Contreras JL, Ladino MA, Aránguiz K, et al (2021) Immune Dysregulation Mimicking Systemic Lupus Erythematosus in a Patient With Lysinuric Protein Intolerance: Case Report and Review of the Literature. Front Pediatr 9:673957. https://doi.org/10.3389/fped.2021.673957
29. Pan L, Lu MP, Wang JH, Xu M, Yang SR (2020) Immunological pathogenesis and treatment of systemic lupus erythematosus. World J Pediatr 16(1): 19–30. https://doi.org/10.1007/s12519-019-00229-3
30. Bhattad S, Rawat A, Gupta A, Suri D, Garg R, de Boer M, Kuijpers TW, Singh S (2015) Early Complement Component Deficiency in a Single-Centre Cohort of Pediatric Onset Lupus. J Clin Immunol 35(8):777–85. https://doi.org/10.1007/s10875-015-0212-y
31. Alperin JM, Ortiz-Fernández L, Sawalha AH (2018) Monogenic Lupus: A Developing Paradigm of Disease. Front Immunol 9:2496. https://doi.org/10.3389/fimmu.2018.02496
32. Ugolini-Lopes MR, Santos LPS, Stagnaro C, Seguro LPC, Mosca M, Bonfá E (2019) Late-onset biopsy-proven lupus nephritis without other associated autoimmune diseases: severity and long-term outcome. Lupus 28(1):123–128. https://doi.org/10.1177/0961203318811603
33. Zecevic M, Minic A, Pasic S, Perovic V, Prohászka Z (2021) Case Report: Early Onset Systemic Lupus Erythematosus Due to Hereditary C1q Deficiency Treated With Fresh Frozen Plasma. Front Pediatr 9:756387. https://doi.org/10.3389/fped.2021.756387
34. Wenderfer SE, Eldin KW (2019) Lupus Nephritis. Pediatr Clin North Am 66(1): 87–99. https://doi.org/10.1016/j.pcl.2018.08.007
35. Budhoo A, Mody GM, Dubula T, Patel N, Mody PG (2017) Comparison of ethnicity, gender, age of onset and outcome in South Africans with systemic lupus erythematosus. Lupus 26(4):438–446. https://doi.org/10.1177/0961203316676380
36. Simard JF, Arkema EV, Nguyen C, Svenungsson E, Wikström AK, Palmsten K, Salmon JE (2017) Early-onset Preeclampsia in Lupus Pregnancy. Paediatr Perinat Epidemiol 31(1):29–36. https://doi.org/10.1111/ppe.12332
37. Mohamed A, Chen Y, Wu H, Liao J, Cheng B, Lu Q (2019) Therapeutic advances in the treatment of SLE. Int Immunopharmacol 72:218–223. https://doi.org/10.1016/j.intimp.2019.03.010
38. Miguel DF, Terreri MT, Pereira RMR, Bonfá E, Silva CAA, Corrente JE, Magalhaes CS; Brazilian Childhood-onset Systemic Lupus Erythematosus Group (2020) Comparison of urinary parameters, biomarkers, and outcome of childhood systemic lupus erythematosus early onset-lupus nephritis. Adv Rheumatol 60(1):10. https://doi.org/10.1186/s42358-020-0114-4

39. Shah S, Kavadichanda CG, Belani P, Ganesh RN, Negi VS (2019) Early onset neutropenia and thrombocytopenia following rituximab in lupus nephritis. Int J Rheum Dis 22(5):946–950. https://doi.org/10.1111/1756-185X.13365
40. Chang JC, Xiao R, Knight AM, Kimmel SE, Mercer-Rosa LM, Weiss PF (2020) A population-based study of risk factors for heart failure in pediatric and adult-onset systemic lupus erythematosus. Semin Arthritis Rheum 50(4):527–533. https://doi.org/10.1016/j.semarthrit.2020.03.019
41. Lopes SRM, Gormezano NWS, Gomes RC, et al (2017) Outcomes of 847 childhood-onset systemic lupus erythematosus patients in three age groups. Lupus 26(9):996–1001. https://doi.org/10.1177/0961203317690616
42. Abd Rahman R, DeKoninck P, Murthi P, Wallace EM (2018) Treatment of preeclampsia with hydroxychloroquine: a review. J Matern Fetal Neonatal Med 31(4):525–529. https://doi.org/10.1080/14767058.2017.1289511
43. Benninghoff AD, Bates MA, Chauhan PS, Wierenga KA, Gilley KN, Holian A, Harkema JR, Pestka JJ (2019) Docosahexaenoic Acid Consumption Impedes Early Interferon- and Chemokine-Related Gene Expression While Suppressing Silica-Triggered Flaring of Murine Lupus. Front Immunol 10:2851. https://doi.org/10.3389/fimmu.2019.02851

Figures

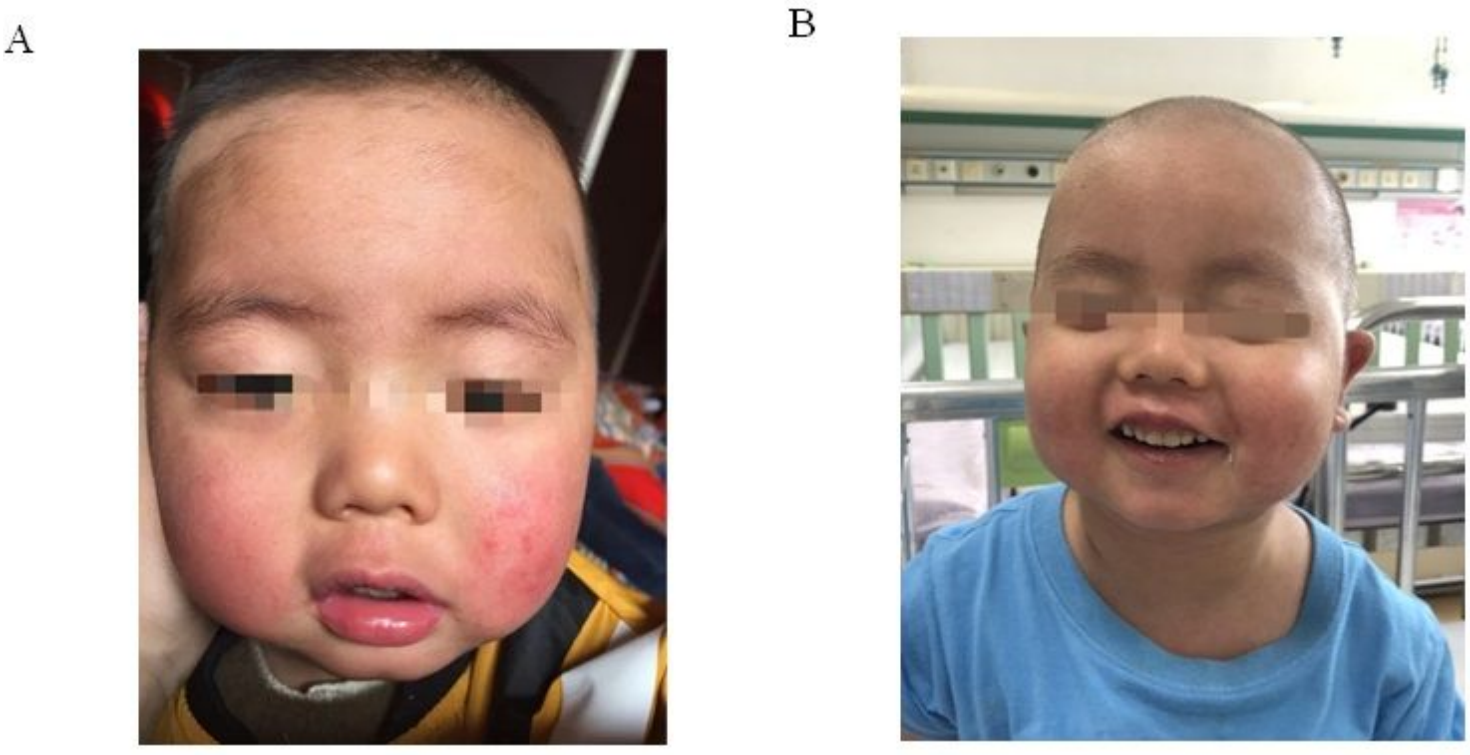

Figure 1

cold multiform erythema in Case 1 before and after treatment

(A. before treatment B. after treatment)

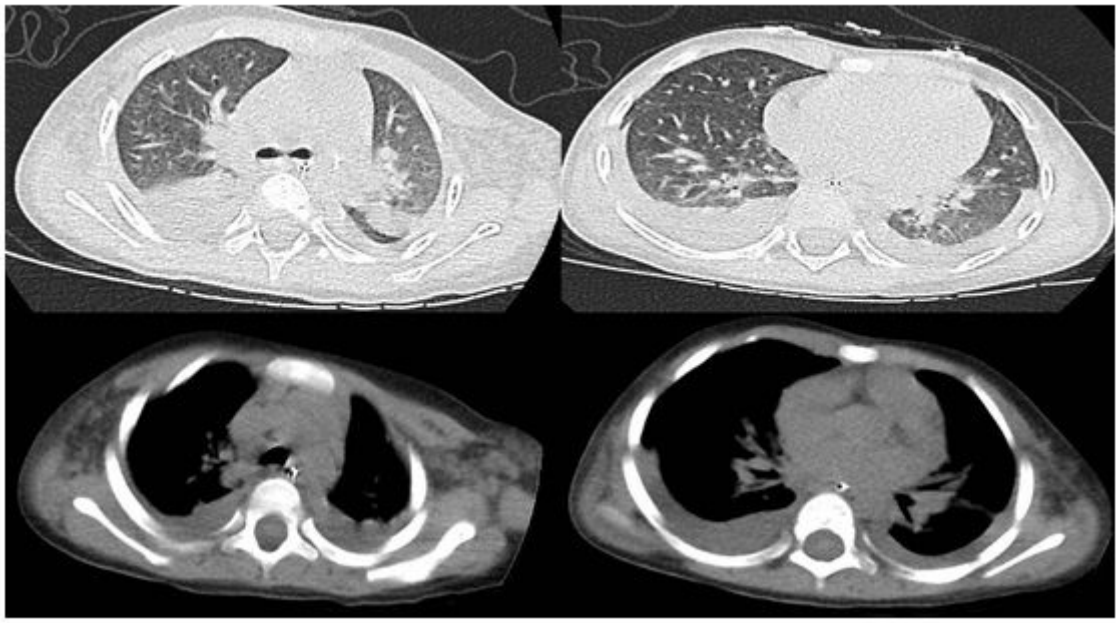

Figure 2

Case 1 lung CT showed pneumonia and pleural effusion

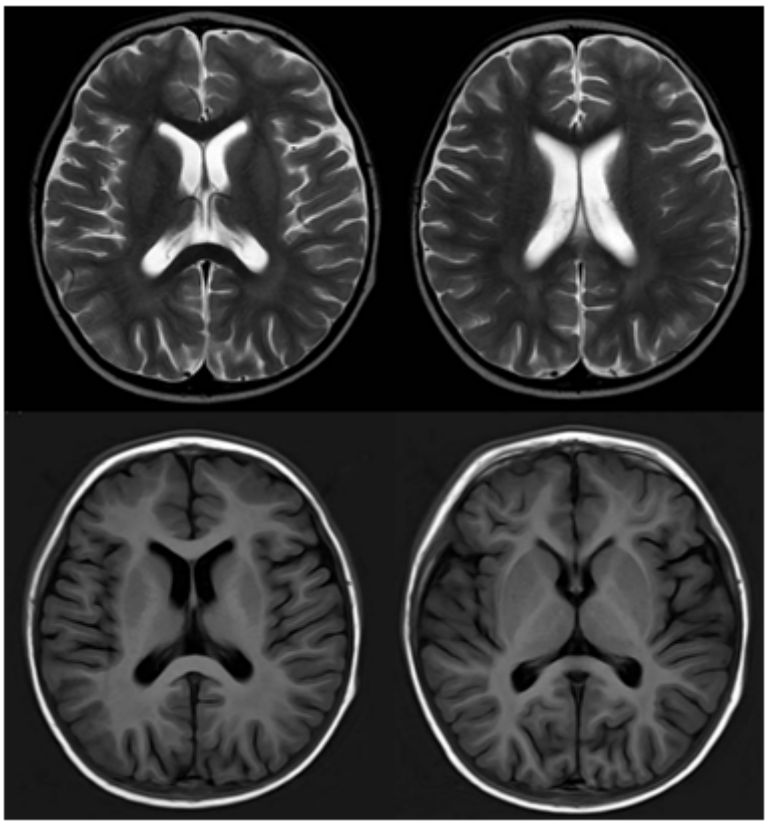

Figure 3

Brain MRI of case 1 showed FLAIR high signal in the posterior portion of bilateral lateral ventricles with widening of sulci in hemispheres

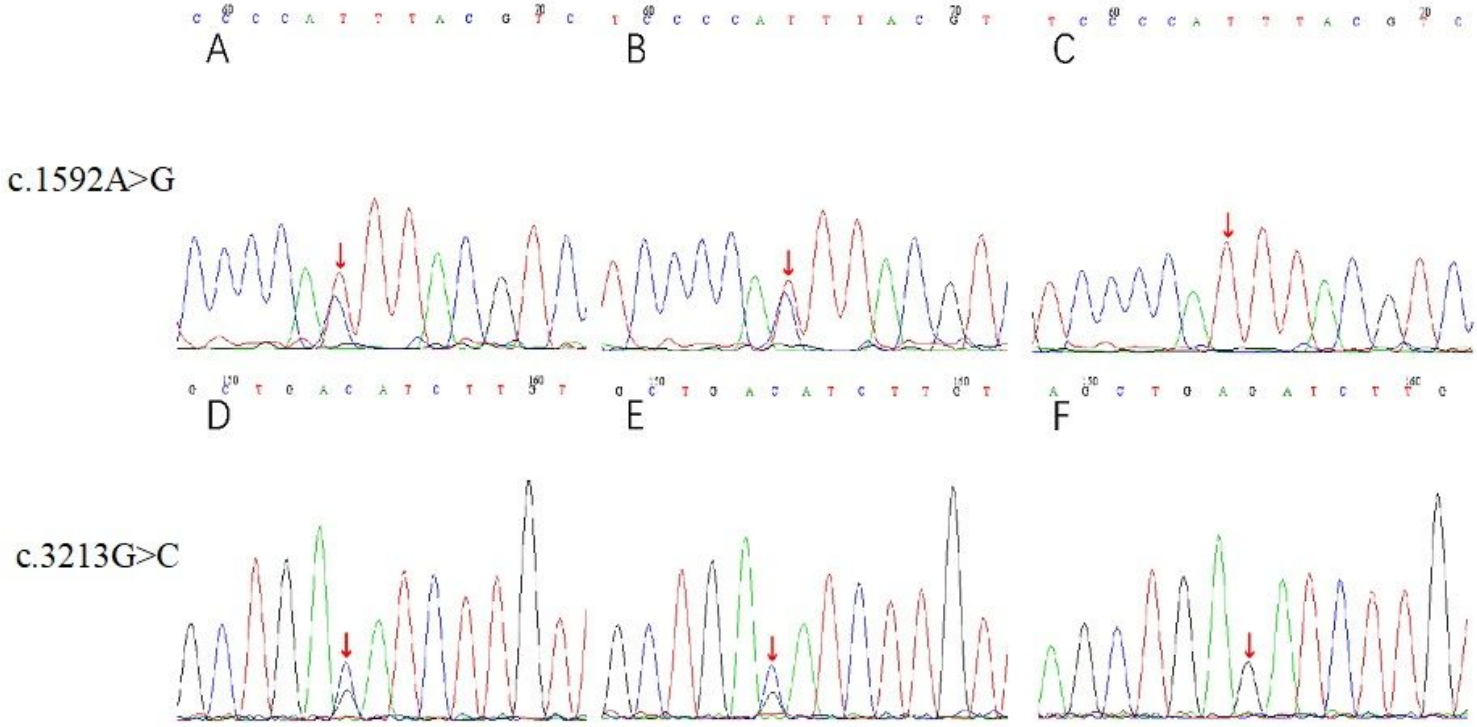

Figure 4

Mutation of ITGAM gene in case 1 and his father, his mother had no mutation

(A&D. case 1; B&E. the father of case 1; C&F. the mother of case 1)

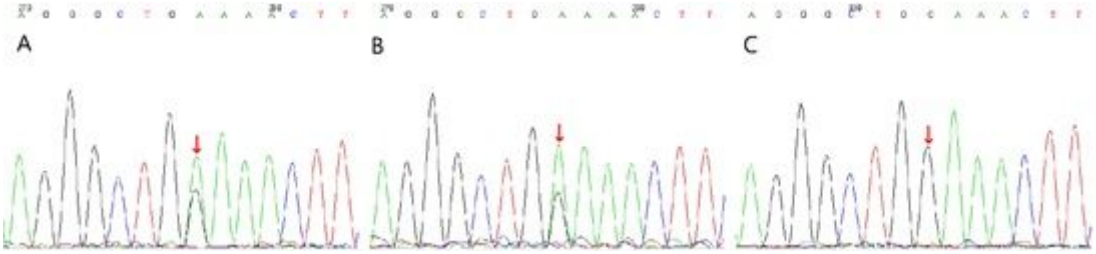

Figure 5

Mutation of C1s gene in case 2 and her father, her mother had no mutation

(A. case 2; B. the father of case 2; C. the mother of case 2)

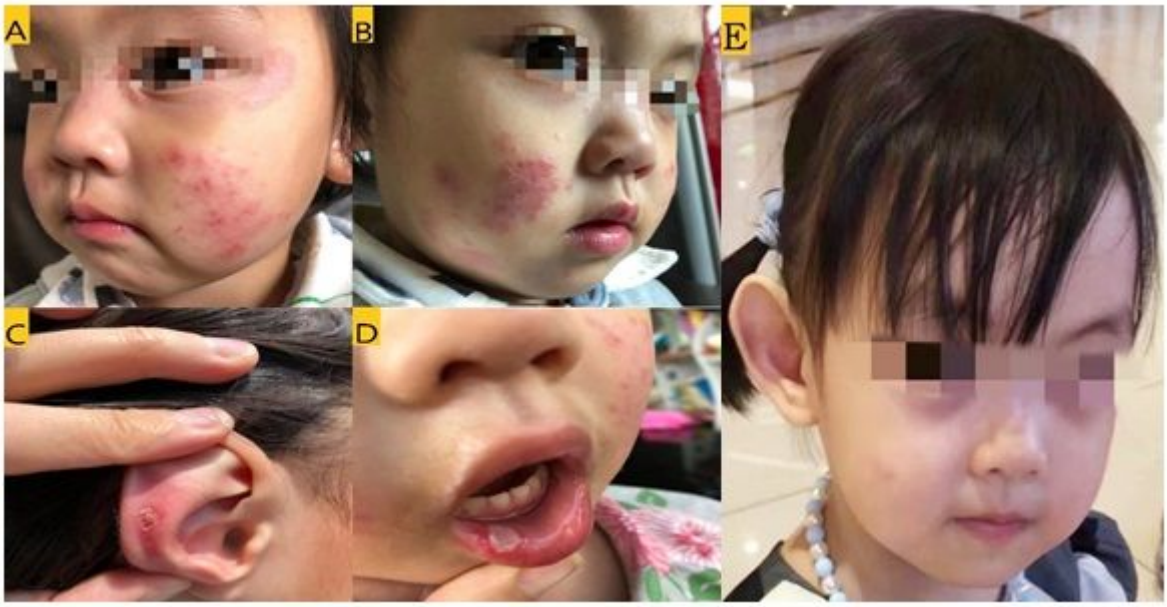

Figure 6

Case 4 with facial rash and lip ulceration (A. and B. bright red rash on both sides of the cheeks, C. red rash on the ear, D. a large ulcer on the lip, E. rash completely subsided).