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CASE REPORT

Autoimmune Manifestations in Heterozygote Type I Complement 2 Deficiency: A Child Eventually Diagnosed With Systemic Lupus Erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disorder resulting in a broad spectrum of manifestations in several organs, mainly skin and kidney. SLE occurs with interaction of genetic and environmental factors. The most remarkable genetic predisposition to SLE is deficiency of early components of the classical complement pathway. A five-year-old, previously healthy female patient was admitted to our hospital with headache, fever, focal partial seizure, diagnosed and treated as encephalitis. She was re-admitted to our hospital at six years of age with fever, fatigue, alopecia and oral aphthous ulcers and necrotizing vasculitis on extremities. Significant hypocomplementemia, anemia, proteinuria and positive autoantibodies and coombs test led to the diagnosis of SLE. Due to early disease onset and distinct autoimmune manifestations, we diagnosed our patient with type I complement 2 (C2) deficiency with a frameshift mutation in C2 gene and a serum C2 level of <0.2 mg/dL. To our knowledge, this is the first case of genetically confirmed and successfully treated hereditary C2 deficient SLE patient diagnosed with necrotizing vasculitis. We wish to highlight that distinctive autoimmune manifestations should guide physicians to research on monogenic lupus, particularly C2 deficiency, even in the absence of coexisting recurrent pyogenic infections.

Keywords: Child, complement 2, cutaneous vasculitis, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is an autoimmune disorder associated with interaction of genetic and environmental factors and a broad spectrum of manifestations in several organs, mainly skin and kidney.[1] Childhood SLE represents 15-20% of all SLE patients and its course is more severe with higher incidence of nephritis and hematologic disorders.[2]

Complement system activation by presence of immune complexes is known to be the leading cause of inflammation in SLE. It is not surprising that the most remarkable genetic predispositions to SLE are deficiencies of early components of classical complement pathway.[1] In this article, we report a pediatric patient who presented with autoimmune manifestations, met SLE criteria over time and was finally diagnosed with heterozygote type I complement 2 deficiency (C2D).

CASE REPORT

A five-year-old female patient was admitted to our hospital with headache and fever for the last five days. Brain magnetic resonance imaging showed bilateral focal lesions but particularly in right hippocampal gyrus and basal ganglions

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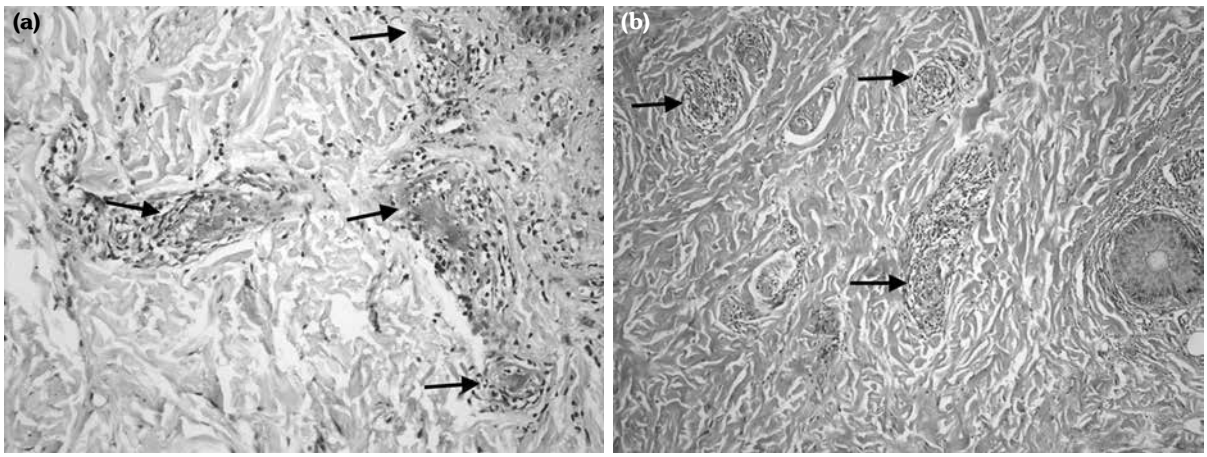

Figure 1. Pathological features of skin in our patient with systemic lupus erythematosus, revealing cutaneous necrotizing vasculitis. **(a)** Fibrinoid necrosis of vessel wall (periodic acid-Schiff stain ×200). **(b)** Neutrophil and lymphocyte infiltration in vessel wall (H-E×20).

compatible with encephalitis. With partial benefit from treatment with vancomycin, meropenem and acyclovir, the patient had developed focal partial seizure lasting 10 minutes on the right side of her face and right hemiparesis on the 12th day of hospitalization. Electroencephalogram showed epileptiform activity originating from left hemicortex and the patient was successfully treated with phenytoin, phenobarbital and carbamazepine subsequently. Neurological manifestations clinically improved and hemiparesis almost disappeared at second month after discharge.

The patient was re-admitted to our hospital at six years of age with fever, fatigue and alopecia. Physical examination revealed multiple oral aphthous ulcers and necrotic ulcers on the left arm and leg. In laboratory tests, acute phase reactants were markedly increased, significant hypocomplementemia, anemia and 0.4 g/day proteinuria were present. Antinuclear antibody was positive at 1/100 titer in immunofluorescence assay. Additionally, direct Coombs, anti-Smith antibody and anti-double stranded deoxyribonucleic acid were positive. Skin biopsy showed cutaneous necrotizing vasculitis (Figure 1). SLE was diagnosed according to American College of Rheumatology classification criteria for SLE.[3] Renal biopsy was planned but delayed due to the anticoagulant medications and possible vasculitic process. In the studies for hypercoagulability, serum homocysteine was slightly elevated while anti-thrombin 3 was mildly reduced and protein C and free protein S levels were markedly reduced. Anticardiolipin immunoglobulin G was positive, while immunoglobulin M was negative. Furthermore, genetic analysis revealed homozygote MTHFR A1298C mutation. After five doses of intravenous pulse metilprednisolone, plasmapheresis and prophylaxis with low molecular weight heparin, remission was maintained with six pulses of monthly intravenous cyclophosphamide, consequent mycophenolate sodium treatment and systemic steroids. Low molecular weight heparin was discontinued after three months; serum C4 and C3 returned to normal range within two months and remained normal at six years of follow-up. She suffered from mild upper respiratory tract infections only four times a year. Due to discrete autoimmune manifestations including encephalitis, necrotizing vasculitis and SLE, we investigated our patient for early complement deficiencies. With new generation sequencing system, we detected c.2170-2170delC (p.P724Rfs*16) frameshift mutation causing premature stop codon. Immunochemical quantitation of C2 antigen by radial immunodiffusion confirmed the presence of type I C2D with a serum C2 level of <0.2 mg/dL. Table 1 summarizes the laboratory results of the patient. A written informed consent was obtained from the parents.

DISCUSSION

Systemic lupus erythematosus is a multi-systemic autoimmune disease demonstrating complement

Table 1. Laboratory results of patient with C2 deficiency and systemic lupus erythematosus

Parameters	At diagnosis	At the 6th month of treatment	7 years after the diagnosis
Hemoglobin (gr/dL)	8.3	13.3	13.4
Leukocytes (/mm^3)	4,920	6,010	5,180
Neutrophil (/mm^3)	2,120	3,060	2,100
Lymphocytes (/mm^3)	2,340	1,682	2,600
Thrombocytes (/mm^3)	169,000	309,000	326,000
ESR (mm/h)	26	22	15
CRP (mg/dL)	1.06	2.5	0.4
C3 (mg/dL)	33	110	112
C4 (mg/dL)	7.1	22	25.1
ANA (titer, IFA)	1/100	Not-determined	Not-determined
ANA (U/mL, ELISA)	54.9	75.1	Negative
Anti-DNA (U/mL, ELISA)	20	Negative	55
Anti-Sm (U/mL, ELISA)	194.8	Not-determined	10.4
Urine protein (g/d urine)	0.4	0.2	Not-determined
Direct coombs	Positive (+3)	Not-determined	Negative
LDH (mg/dL)	673	199	175
Anticardiolipin IgG	Positive	Positive	Negative
Anticardiolipin IgM	Negative	Negative	Negative
Anti-β2 glycoprotein I antibodies	Negative	Negative	Negative
Protein C (70-130%)	52	21	70.2
Free protein S (60-125 %)	51	16.9	100.6
Antithrombin 3 (79-125%)	74	118.4	72.4

C: Complement; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: Antinuclear antibody; IFA: Immunofluorescence assay; Anti-DNA: Antibody to double-stranded deoxyribonucleic acid; ELISA: Enzyme-linked immunosorbent assay; Anti-Sm: Anti-Smith antibody; LDH: Lactate dehydrogenase; IgG: Immunoglobulin G; IgM: Immunoglobulin M; Normal values for autoantibodies evaluated with enzyme-linked immunosorbent assay are as follows: <40 U/mL for antinuclear antibody, <20 for anti-deoxyribonucleic acid, <15 for anti-Smith.

consumption and type I interferon signaling. There is also an imbalance in apoptosis and apoptotic material removal, which results in break in tolerance and antibody production against self-antigens. In recent years, description of monogenic lupus-like disorders has improved our understanding of SLE.[1]

Deficiencies of early components of complement system were the first defined monogenic causes of lupus. Autoimmunity may occur due to altered opsonization, immune complex removal from the circulation, clearance of apoptotic debris, and lack of normal B cell tolerance, overwhelming production of autoantibodies in C2D.[4]

Systemic lupus erythematosus or lupus-like manifestations prevalence among early complement deficiencies is reported in 10% of C2D. Severe recurrent infections associated with high mortality may be occasionally present in homozygote complement deficiencies.[5] On the other hand, our patient had only suffered from recurrent mild pharyngitis.

While the frequency of heterozygous C2D is 1-2% in Caucasian populations, its prevalence is higher in SLE patients with 2.4-5.8%.[1,5] C2 deficient SLE patients typically present with renal disease, arthritis, malar rash, discoid rash and photosensitivity.[1,6] Our patient clinically differed from the patients in the literature

with the presence of oral aphthous, cutaneous vasculitis, hematological and neurological findings and the absence of arthritis or other skin findings.

Immunological analysis of C2D patients with SLE has shown low titer positive antinuclear antibody and a distinctive profile of negative anti-deoxyribonucleic acid and positive anti-Sjögren's syndrome A and anti-ribonucleoprotein. Despite the absence of antiphospholipid syndrome, patients with C2D tended to have positive anti-cardiolipin antibodies.[5,6] Similarly, our patient had transiently positive anti-cardiolipin antibody without clinical antiphospholipid syndrome. She was transiently positive for antinuclear antibodies and anti-Smith antibodies with high titers, in contrast to the literature. Although our patient did not have any thrombotic event, she had multiple hereditary and acquired factors for hypercoagulation such as homozygote MTHFR A1298C mutation, transiently reduced levels of protein C and S. To our knowledge, these additional factors do not seem to increase thrombotic risk in SLE patients.[7]

Regarding genotype; type I C2D, usually caused by a deletion and generation of a stop codon in C2 gene, results in the absence of detectable serum C2. Type II C2D leads to reduced plasma levels of C2 caused by particularly a point mutation.[1] Our case was diagnosed as SLE and type I C2D with a novel c.2170-2170 delC (p.P724Rfs*16) frameshift mutation causing premature stop codon and undetectable serum levels of serum C2.

Since necrotic skin ulcers and vasculitis are unusual in SLE course and C2D, the most distinctive finding was cutaneous necrotizing vasculitis in our patient.[8,9] To the best of our knowledge, this is the first case of genetically confirmed and successfully treated hereditary C2 deficient SLE patient diagnosed with necrotizing vasculitis. We wish to highlight that early disease onset or distinctive autoimmune manifestations should guide physicians to research on monogenic lupus, particularly C2D, even in the absence of coexisting recurrent pyogenic infections.

Declaration of conflicting interests

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REFERENCES

1. Macedo AC, Isaac L. Systemic lupus erythematosus and deficiencies of early components of the complement classical pathway. Front Immunol 2016;7:55.
2. Papadimitraki ED, Isenberg DA. Childhood- and adult-onset lupus: an update of similarities and differences. Expert Rev Clin Immunol 2009;5:391-403.
3. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
4. Truedsson L, Bengtsson AA, Sturfelt G. Complement deficiencies and systemic lupus erythematosus. Autoimmunity 2007;40:560-6.
5. Kallel-Sellami M, Laadhar L, Zerzeri Y, Makni S. Complement deficiency and systemic lupus erythematosus: consensus and dilemma. Expert Rev Clin Immunol 2008;4:629-37.
6. Lipsker DM, Schreckenberg-Gilliot C, Uring-Lambert B, Meyer A, Hartmann D, Grosshans EM, et al. Lupus erythematosus associated with genetically determined deficiency of the second component of the complement. Arch Dermatol 2000;136:1508-14.
7. Sallai KK, Nagy E, Bodó I, Mohl A, Gergely P. Thrombosis risk in systemic lupus erythematosus: the role of thrombophilic risk factors. Scand J Rheumatol 2007;36:198-205.
8. Gheita TA, Abaza NM, Sayed S, El-Azkalany GS, Fishawy HS, Eissa AH. Cutaneous vasculitis in systemic lupus erythematosus patients: potential key players and implications. Lupus 2017:961203317739134.
9. Bennett RE, Clough JD, Calabrese LH. Fulminating vasculitis in a homozygous C2-deficient patient. Cleve Clin Q 1985;52:213-5.