Clinicopathological conference: An 11-year-old boy with recurrent infections, hypertension, skin rash, and nephritic syndrome

Keriman Tınaztepe, Şafak Güçer, Ayşın Bakkaloğlu

Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Tınaztepe K, Göçer Ş, Bakkaloğlu A. An 11-year-old boy with recurrent infections, hypertension, skin rash, and nephritic syndrome. Turk J Pediatr 2000; 42: 312-318.

In this clinicopathological conference, an 11-year old boy who presented with recurrent pyogenic infections, hypertension, malar rash, various skin lesions and nephritic syndrome since five years of age is discussed. He was hospitalized for clinical investigation with skin and renal biopsies at 10 years of age. Using clinicopathological data obtained from his last admission, a clinical diagnosis was reached, and the disorders of the complement system causing patients to show these signs or symptoms are emphasized. At the end of the discussion, a clinicopathological correlation is given for making the diagnosis.

Key words: hereditary complement deficiency, childhood, systemic lupus erythematosus, lupus nephritis.

An 11-year old boy was admitted to the hospital with the complaints of fever, rash, shortness of breath and edema. His past medical history revealed that he had been experiencing desquamative, erythematous, crusted skin lesions over the face and extremities, recurrent aphthous ulcers of oral mucosa and purulent otitis media for five years. His pyodermic skin lesions responded well to local or systemic applications of antibiotics but his malar rash and other cutaneous manifestations persisted during his follow-up. He also had a history of recurrent attacks of bronchopneumonia.

Three years after his initial admission to the hospital when he was first noted to have findings of a glomerular disease (hematuria and oliguria), he was put on oral prednisone medication. Three months later, he was hospitalized because of respiratory infection, hypervolemia and heart failure. A lesional skin biopsy revealed microvasculitis and a weak band formation with complement C3 [Lupus Band Test (LBT)] at the dermoepidermal junction, while renal biopsy showed chronic progressive sclerosing glomerulonephritis with a weak but granular staining of C3 and IgG in the glomerular basement membrane and mesangium. Cyclophosphamide and azathioprine were added to the treatment and he was discharged. Five months later, he was readmitted to the hospital with a five-day history of fever, diarrhea, shortness of breath and periodic loss of consciousness.

His parents were unrelated and healthy; no similar complaints were found in one sister (asymptomatic) and two brothers. Family investigation for serology of complement components is discussed later in the text. He was born to a first gravida mother following an uneventful pregnancy.

On physical examination, his general condition was poor. He was pale, irritable and dyspneic with a body temperature of 37 °C, regular pulse of 92/min, respiration rate of 56/min and blood pressure of 155/110 mm Hg. The femoral artery pulses were bilaterally palpable. His height was 136 cm (5^{th}-10^{th} percentile) and weight 28 kg (5^{th}-10^{th} percentile). There were small ecchymotic areas, petechia on the trunk and erythematous and pyodermic skin lesions on the face and whole body, (Fig. 1). A slight edema was noted on eyelids and lips. Fine rales were widely heard on auscultation of lungs. The liver was palpable 10 cm below the right costal margin. There was also ++ pitting edema of legs. The rest of the physical examination was unremarkable.

Laboratory investigation revealed hemoglobin (Hb) 7.5 g/dl, white blood cell (WBC) 3,000/mm^3

with abundant thrombocytes, and no toxic granulation or hypochromia. Urinalysis demonstrated 1012 of specific gravity, 3 (+) proteinuria, no glucose, abundant erythrocytes and 8-10 WBC per high power field in the sediment. Blood urea nitrogen (BUN) was 98 mg /dl (creatinine 8.6 mg/dl, Na 137 mEq/L, K 6 mEq/L, Cl 100 mEq/L, total albumin 4.2 g/dl, albumin 2.2 g/dl, calcium 7.4 mg/dl, phosphorus 4.0 mg/dl, ALT 14 U/L, AST 21 U/L, uric acid 3.5 mg/dl, and creatinine clearance 17 ml/min/ 1.73 m^2. Tests for ASO, CRP, cellular and humoral immunity (blastogenesis, skin tests, T-cell markers, immunoglobulins) were all in normal ranges. Serum total hemolytic activity (CH50) was zero. Complement C3 and C4 levels were normal. Direct Coombs test, LE cell, cryoglobulins, Latex test, HBsAg and antiHBs were negative. Initial antinuclear, anti-DNA, anti-extractable nuclear antigens (anti-ENA), anti-mitochondrial and anti-smooth muscle antibodies were negative. However, anti-DNA antibody became positive during his follow-up. Serum immune complex assays remained persistently elevated.

The patient was treated for lung infection, hypervolemia and hypertension. Fresh frozen plasma given on two occasions was of no benefit. Renal functions progressively deteriorated and a peritoneal dialysis was performed. However, it was ineffective and the patient died of renal failure six days after hospital admission.

CLINICAL DISCUSSION

Based on the medical history, and physical and laboratory findings, it was clearly understood that this patient had experienced recurrent and chronic infections of various organs and systems since early childhood. He also had additional signs and symptoms indicating renal involvement for three years. In childhood,

a) a history of systemic bacterial infections on two or more occasions.
b) three episodes of severe respiratory infection or bacterial infection like cellulitis, or purulent otitis media documented by cultures.
c) development of an infection in unusual sites like liver or brain abscess.
d) development of an infection with uncommon pathogens, i.e. Aspergillus infection and,
e) presence of more severe infections than expected by common pathogens.

indicate a necessity for a thorough investigation of the immune system[1]. In this context, this patient should first have been thought to have an immune deficiency state because of the recurrent infections occurring in the respiratory system, ears and skin.

The initial step to work-up the immunodeficiency disorders is routine screening for complete blood count (CBC), peripheral blood smear and erythrocyte sedimentation rate (ESR), with tests for B and T cell functions and CH50 for the complement system. Afterwards, more sophisticated molecular, biologic and other specific tests may be needed in light of obtained data[1]. The present case showed nearly normal results for T and B cell functions for his age. On the other hand, it was a notable finding that the value of CH50 was zero, while serum levels of complement C3 and C4 were normal. Therefore, a functional and quantitative measurement of other components of the complement system, particularly the early ones like C1q and C2, should be determined.

This case revealed capillaritis, a weakly positive lupus band test (LBT), anemia, leukopenia, and biochemical data and urinary findings, such as proteinuria, hematuria and granular casts in the sediment, suggesting a renal involvement. Renal biopsy performed six months prior to his death also confirmed the latter, yielding a diagnosis of chronic sclerosing progressive glomerulonephritis (GN). In view of the combined data, a systemic disease, particularly systemic lupus erythematosus (SLE), should be strongly suspected[2,3]. LBT is known to be positive in 90 percent of lesional skin in cases with SLE[4]. It is also detected in 60 percent of non-lesional skin in these cases, providing a rather specific and diagnostic finding in making the diagnosis of SLE. On the other hand, an initially negative anti-DNA antibody test became positive during the course of the disease with simultaneous deterioration of renal functions. Though a small percentage of patients with SLE may show a negative ANA test, especially in the state of antigen excess, it is wellknown that ANA and anti-DNA antibody may be completely undetectable in cases with SLE or SLE-like illnesses associated with primary deficiency of the complement components[2]. The present case could be considered deficient for the early components of the complement system since he had undetectable CH50 with all these findings and in view of results of family

investigation on serum complement levels. Deficiency of early complement components should be remembered because our patient was a male child with clinical findings and serology mimicking SLE, and with an elevated level of circulating immune complexes, and his initial complaints started in the preschool period. Development of SLE is unusual in a male child of this age. Therefore, SLE accompanying a hereditary deficiency of early complement components is most likely. This underlines the value of evaluation of age and gender in these conditions.

In fact, SLE or SLE-like illnesses may develop in hereditary complement deficiency states, particularly of the early components like C1q, C2, C3 or C4[5-10]. These patients have an increased risk of autoimmunity and of serious bacterial infections, particularly with pneumococcus. Deficiencies of terminal components are associated with a high incidence of Neisseria infections. SLE or other collagen vascular diseases may also be seen in these cases, though to a lesser extent (Table I)[5]. In addition to SLE, recurrent skin lesions, discoid lupus or SLE-like illnesses, patients with C1q deficiency have been reported in association with various types of glomerular diseases such as lupus GN, membranoproliferative GN, mesangioproliferative GN and IgA nephropathy[7-10]. Renal biopsy done six months before death in our case revealed a diagnosis of chronic progressive sclerosing glomerulonephritis. However, the needle biopsy could reflect only this aspect of lupus nephritis with a highly pleomorphic nature varying from one glomerulus to another. Immunohistology revealed evidence of an immune complex-mediated disease. The demonstration of granular deposition of immune reactants in glomeruli with LBT positivity in skin by immunofluorescence microscopy confirmed the diagnosis of SLE. Additionally, both glomeruli and skin revealed C3 deposition but no C1q, suggesting a disorder of complement system components especially when the CH50 value was found to be zero. These immunohistological findings also indicated the progressive nature of the chronic sclerosing glomerulonephritis. The persistence of high levels of circulating immune complexes indirectly supported this. Hypertension is considered as a natural consequence of chronic

Table I. Primary Deficiencies of Complement Components and Associated Clinical Findings

Deficient component	Infection type	Renal and/or rheumatologic findings
Classical pathway		
C1q, r, s	Pneumococcal sepsis, meningitis, other pyogenic	SLE*, GN, cutaneous vasculitis
C4	Other pyogenic	SLE, GN, collagen tissue disease
C2	Other pyogenic, pneumococcal sepsis, meningitis, meningococcal meningitis	SLE, GN, collagen tissue disease cutaneous vasculitis, discoid lupus
C3	Other pyogenic, pneumococcal sepsis, meningitis, meningococcal meningitis	GN, cutaneous vasculitis, SLE, discoid lupus
C5-9	Meningococcal, gonococcal infections	SLE, GN, collagen tissue disease
Alternative pathway		
Factor D	Rarely gonococcal infections	
Factor B	Frequent meningococcal infections	
Control proteins		
C1 esterase INH	Hereditatry angioedema	
Factor I	Other pyogenic meningococcal, meningococcal meningitis	
Factor H	Meningococcal meningitis, Other pyogenic	GN, cutaneous vasculitis, SLE, discoid lupus, membranoproliferative GN type 11, hemolytic, uremic syndrome
Properdin	Meningococcal meningitis Pneumococcal sepsis	Cutaneous vasculitis, discoid lupus Collagen tissue disease excluding SLE

SLE: systemic lupus erythematosus; GN: glomerulonephritis.

parenchymatous disease leading to chronic renal failure.

In conclusion, a primary deficiency of one of the early complement components (C1q or C2) in our case was likely and SLE and/or SLE-like disease might develop with this genetic background. The manifestations associated with renal involvement may reflect morphologically the lupus nephritis since all types of GN with immune complex deposition may be encountered in patients with SLE.

Clinical Diagnoses

I. Primary (hereditary) complement deficiency
   a) Deficiency of early components, C1q or C2?
   b) SLE or SLE-like disease
      1. Lupus nephritis (renal biopsy diagnosis) (Class IV WHO classification)
         Chronic progressive sclerosing glomerulonephritis
         (with granular immune complex deposition)
      2. A weak LBT positivity (lesional skin)
      3. Malar rash, oral and nasal mucosal ulcers and various types of skin lesions
      4. A history of frequent chronic active suppurative infections such as bronchopneumonia, otitis and bacterial dermatitis

II. Chronic renal failure and its related hypertension

III. Failure to thrive

Additional Tests for Evaluation of the Complement System

These studies were performed by Berkel et al.[8] Immunohistochemical and functional tests of all complement components were within normal values except for C1q. The alternative pathway activity was normal. A sister was found to be asymptomatic with undetectable CH50 and no C1q activity, suggesting a hereditary, (primary) complement deficiency. The father had a normal CH50 and the mother had intermediate values of CH50. A retrospective study was initiated to find any known mutations for the genes of C1q in the family members. Unfortunately, no specimen was available to extract chromosomal DNA of the present case. However, a point mutation at amino acid position 186 in the C1q A chain gene was identified in the asymptomatic sister with C1q deficiency by polymerase chain reaction of amplified C1q A chain gene and restriction with endonuclease PvuII. This finding confirmed the diagnosis of a hereditary deficiency of C1q.

Pathological Findings and Clinicopathological Correlation

Histopathological and Immunohistological Findings: Renal and skin biopsies together with micronecropsies of right whole kidney, skin, muscle, liver and small intestine were examined. On light microscopy, when comparing the renal biopsy done six months prior to death, glomeruli and interstitial tissue revealed more severe involvement. There were various types of injury in almost all glomeruli. (Fig. 2). Mesangial proliferation, mesangial matrix increment, basement membrane thickening (as wire-loop lesions in some areas), segmental or global sclerosis in some glomeruli, subepithelial spikes and focal membranous changes resembling chain-like structures, double-contour appearance and focal extracapillary proliferation were noted (Figs. 3-6). Additionally, polymorphonuclear leukocyte infiltration, karyorrhexis, focal areas of necrosis and intraluminal thrombosis in some glomeruli were also observed (active lesions). Tubuli showed prominent atrophy with hyalin and cellular casts in their lumina (Fig. 2). Vessels seemed to be unaffected while the interstitial tissue revealed focal areas of fibrosis, minute calcifications and mononuclear cell infiltration. All these chronic and acute pleomorphic findings were compatible with lupus nephritis. On immunohistology, a weak granular staining with C3, C4, IgG, and IgM was demonstrated in the glomerular basement membrane zone (BMZ), but no C1q deposition. A diagnosis of "diffuse active, segmentally proliferative, focal membranous and sclerosing and extracapillary proliferative lupus glomerulonephritis" (WHO Class IV) was made. Lesional skin biopsy revealed microvasculitis and a weakly positive LBT. Liver necropsy revealed congestion and non-specific triaditis. There were no remarkable findings on histological examination of skin, muscle or small intestine micronecropsies.

Final Pathologic Diagnoses

1. Pimary C1q deficiency(clinicopathological diagnosis)
   SLE or SLE-like illness (Clinicopathological correlative diagnosis)

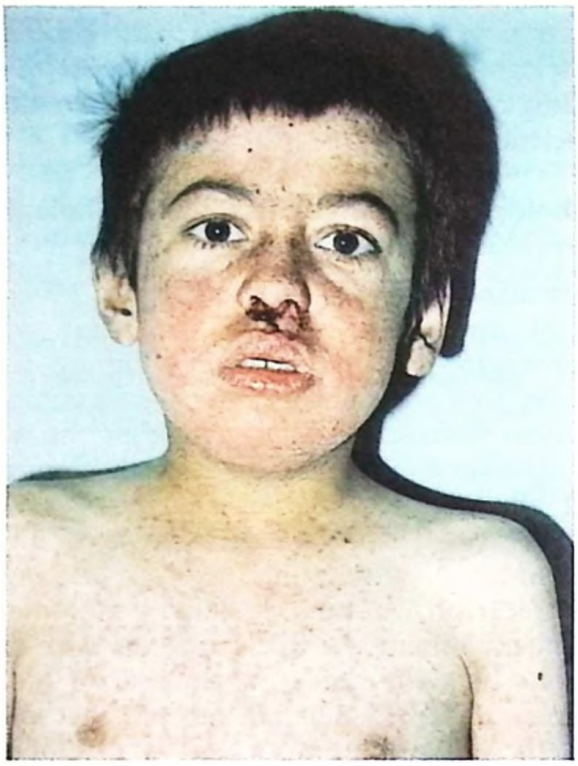

Fig. 1. Butterfly rash on the face, maculopapular lesions covering whole face and upper part of the trunk, and epistaxis (recalling ulcerative lesions of nasal mucosa).

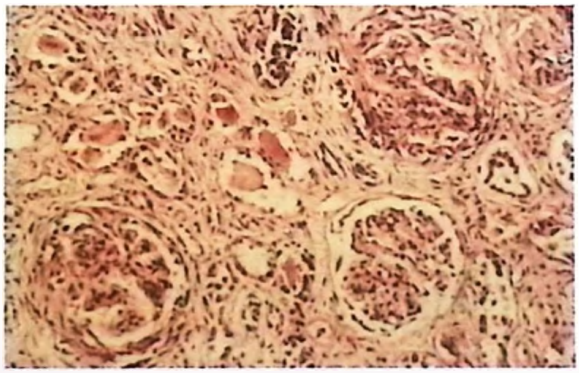

Fig. 2. Renal necropsy under lower magnification. Glomerular lesions (diffuse proliferative, crescentic, lobular) varying from one glomerulus to another, even from one segment to another in a single glomerulus. Variable tubular atrophy, interstitial and periglomerular fibrosis, are also seen. (HE x 200).

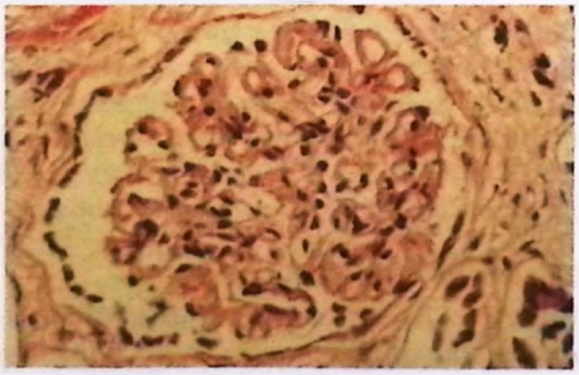

Fig. 3. A glomerulus with focal endocapillary proliferation and basement membrane thickening are seen, (HE x 400).

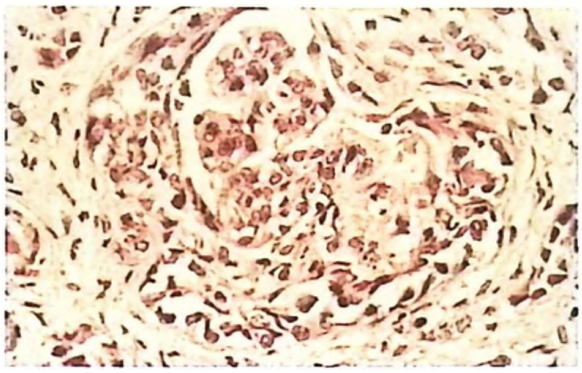

Fig. 4. This microphoto depicts a glomerulus with endo- and extracapillary proliferation. The crescent is mostly epithelial covering two-thirds of the glomerular thuft. (HE x 400).

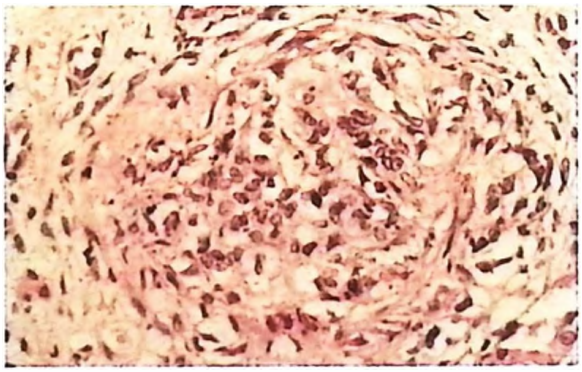

Fig. 5. Bowman's capsule space in a glomerulus is completely obliterated by crescent consisting of mostly fibrous and a few cellular components. Endocapillary proliferation is still prominent in the middle of the glomerulus (chronic active) (HE x 320).

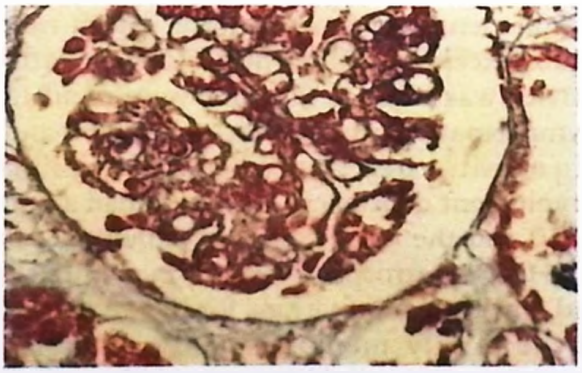

Fig. 6. Focal 'wire-looping' appearance due to thickening of the glomerular basement membrane. On close examination, reddish immune complexes can be seen in the thickened segments of the glomerular basement membrane, (thrichrome stain x 400).

1. Lupus nephritis (Class IV)

   Diffuse proliferative chronic progressive lupus glomerulonephritis (WHO Class IV)
2. LBT positivity (lesional skin)
3. Dermal vasculitis, lupus dermatitis (clinicopathological diagnosis)

Clinicopathological Correlation

Glomerular lesions in this 10-year-old boy were both histopathologically and immunohistologically consistent with diffuse lupus nephritis. Lupus nephritis develops in two-thirds of patients with SLE[2,3], and the diffuse type indicates a poor prognosis. Systemic lupus erythematosus is a rare disease in childhood and is seen mostly in adolescent girls. Male:female ratio is 1:9 in this age group and reduces to 1:3 below 10 years of age. It is notable that the patient was male and that his complaints started before the age of 10. In such a case, primary complement deficiency should be kept in mind when SLE or an SLE-like disease is encountered[7-9].

The complement system is one of the most important components of humoral immunity[5]. This biomolecular system plays a role in virus neutralization, opsonization, release of histamine and, other mediators and most importantly, solubilization of immune complexes. The complement system describes early components of classical (C1423) and alternative (C3, Factors B and D) activation pathways, the membrane attack complex (C5b-9), seven serum and five membrane regulatory proteins, one serosal regulatory protein and eight membrane receptor binding components and their fragments. These 20 components are all proteins and make up 10 percent of the serum globulin fraction. They are made mainly in the liver but are also produced by monocytes and adipose tissue. Complement components interact like a cascade which is known to be activated in two different pathways, the classical and alternate pathways (Fig. 7). In the classical pathway, the sequence of interaction of complements is antigen-antibody-C142356789, and in the alternate pathway, activator (antibody)-C3BD-C356789.

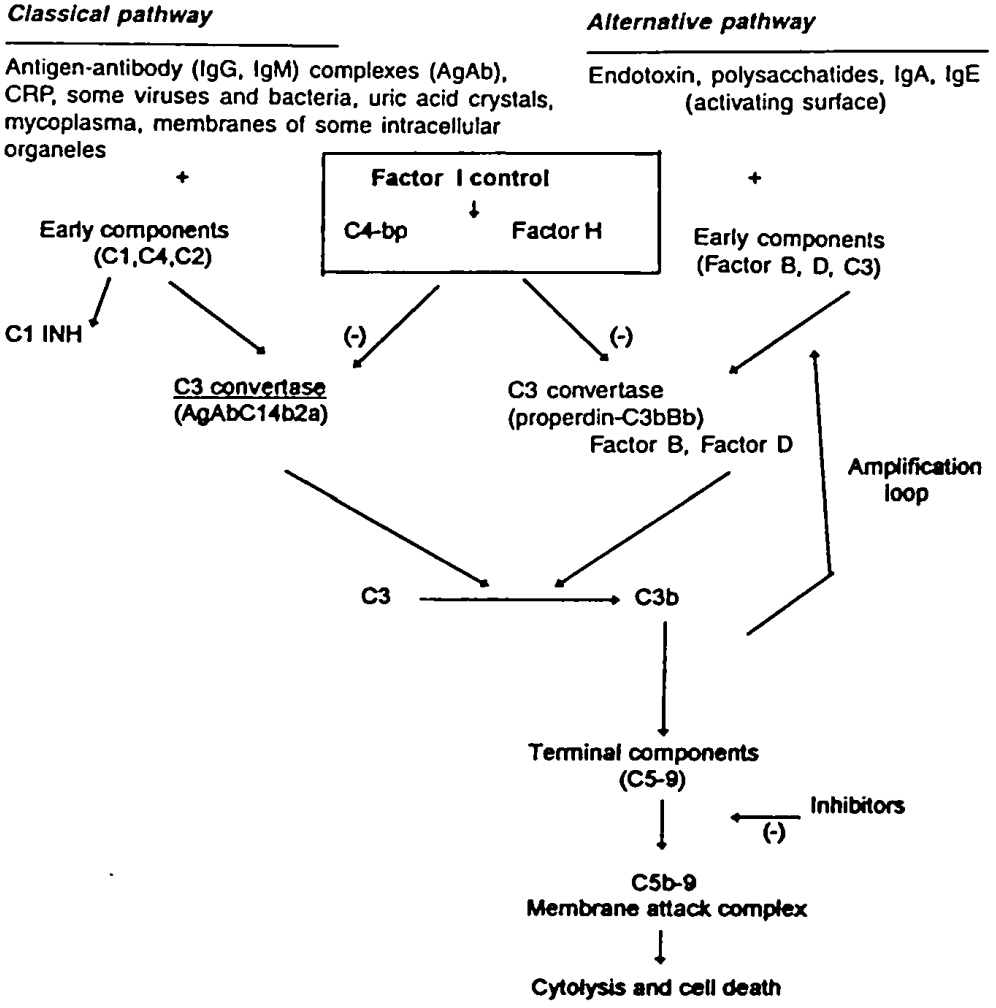

Fig. 7. Complement system and its activation cascade.

Patients with hereditary complement deficiencies have an increased risk of autoimmunity and of development of life-threatening infections such as sepsis or meningitis[5]. This is because of defective clearance of immune complexes by the mononuclear phagocytic system due to failure of their opsonization caused by the complement deficiency. These insoluble immune complexes can aggregate in the tissues resulting in initiation of the inflammatory reaction and the release of autoantibodies[5,6]. Studies on C1q deficiency suggest that C1q-C1q receptor interactions may play an important part in cleaning the apoptotic cells. In deficiency states, this residual apoptotic material may trigger the autoimmune response[9,11].

Clinical and laboratory findings of patients with SLE associated with primary complement deficiencies differ somewhat from those of cases without primary complement deficiency. For instance, renal disease might not be evident and could be identified only by biopsy (Lupus nephritis Class I, WHO classification). In addition, tests for ANA and anti-DNA antibody can be negative or appear weakly positive later in most of the patients, as in the present case.

C1q deficiency is a rare complement deficiency[10,11]. The disease is usually associated with recurrent pyogenic skin and mucosal lesions, glomerulonephritis accompanying SLE or SLE-like diseases (Fig. 1). The number of cases with C1q deficiency reported so far is now over 40. Many cases with complete C1q deficiency (both functionally and antigenically) may present with SLE-like disease, infectious complications and mesangioproliferative GN, whereas those with only functionally deficient C1q may show severe SLE and lupus nephritis[8].

In conclusion, this rare complement defect should be insistently investigated in male patients who are under 10 years of age presenting with SLE or SLE-like diseases with recurrent infections, erythematous desquamative skin lesions, malar rash, and oral and nasal aphthous lesions.

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