中文題目：持續地低第四補體蛋白與乾燥症：病例報告與文獻回顧

英文題目：Persistently low Complement 4 (C4) level and Sjogren's Syndrome: A Case Report and Review of the Literature

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Introduction: The complement system is a humoral defense mechanism that plays an important role against microorganisms, in controlling inflammatory response, and clearing immuno-complex. It is composed of a group of proteins that are activated sequentially to form enzyme cascades by three initiating pathways: the classical, alternative and mannose-binding protein pathways.

Complement activation can be assessed by measuring the serum levels of individual complement components, such as C3 and C4, and by the quantification of CH50 activity, which represents the sequential interaction of all the components of the classical and alternative pathways. The regular measurement of the serum C3, C4 level and CH50 is an important clinical tool in the management of systemic lupus erythematosus (SLE).

Classical complement pathway activation is antibody-dependent. The C4 component participates in the initial step of activation, and C4 expression is determined by 2 pairs of allotypes: C4A and C4B. Deficiencies in C4 allotypes have been associated with many diseases, such as SLE. In comparison to deficiencies of C2, complete deficiency of C4 is uncommon.

Sjogren's syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and causes persistent dryness of the mouth and eyes. There are few case reports or studies focusing on SS and low C4 level.

We report a patient with SS and persistently low C4 level.

Case report: A 38-year-old woman presented with severe dry eye and dry mouth for years. She also experienced intermittent purpura on legs and feet and chronic urticaria for half a year. On physical examination, non-palpable purpura and hyperpigmentation on legs and feet, livedo reticularis on legs and thighs, 2-phase Raynaud phenomenon on fingers and toes were found. A series of laboratory tests revealed abnormal results as following: ANA: 29.1 (normal range: <0.7); Anti-Ro (SSA): > 600 U/ml (<7); Anti-La (SSB): 41.6 (<7); C4: 0.3 mg/dL (13~35); rheumatoid activity 302IU/ml (<20); IgM: 351.1mg/dL. C3 level was in normal range (90.5mg/dL (65~135). Other negative findings included CBC/DC, liver and renal functions tests, thyroid function tests, anti-ds DNA, anti-Smith, anti-RNA, anticardiolipin antibodies, ANCA-P (MPO), ANCA-C(PR3), anti-thyroid antibodies (anti TG and anti TPO), IgG and IgA. Shirmer's test was positive.

The presence of four of the revised international classification criteria for SS in this patient confirmed the diagnosis. The patient was treated with low dose methylprednisolone (4~8mg/day), hydroxychloroquin(400mg/day), cetirizine (10mg/day), azathioprine (75mg/day). We continue to follow up the patient for more than 3 years, the C4 level were persistently low without significant fluctuation. And she still presented with intermittent purpura and had to adjust the dose of methylprednisolone and azathioprine.

Discussion: The C4 levels were persistently low and did not show any significant fluctuation during the course of her illness, suggesting a possible C4 deficiency. Complete deficiency of one of the early components (C1q, C1r/s, C4, or C2) of the classical pathway is one of the strongest genetic risk factors for systemic lupus erythematosus and may be associated with an increased risk of other autoimmune diseases. Disruption of this pathway would lead to the inappropriate handling of immune complexes, a defect in clearance of one's own apoptotic cells, impairment in the humoral immune response or in the regulation of autoreactive B cells, all of which are hypothesized to participate the pathgenetic mechanisms. In a case-control study, patients with SS and low C4 levels have a higher prevalence of cutaneous vasculitis, rheumatoid factor, peripheral neuropathy, cryoglobulins and lymphoma compared with those with normal C4 levels.

We suggest complement determination at diagnosis as a predictor of the outcome and in the clinical follow-up inpatients with SS.