

## Deficit in Complement C4 Fraction Associated with Autoimmune Manifestations and Vertebral Osteolytic Lesions

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### Abstract

### Case Report

The C4 protein is part of the classical complement pathway which plays an important role in innate immunity and in the maintenance of immune complexes in the soluble phase. We report the observation of a 35 year old patient admitted to the respiratory diseases department for etiological assessment of diffuse bronchial dilatation foci (DDB) complicating repeated respiratory infections. After eliminating an acquired immunodeficiency, a balance of primary immune deficiency carried out, allowing to retain the diagnosis of a deficit in complement fraction C4 associated with a systemic lupus erythematosus. Complete C4 deficiency is very rare, can be revealed in adulthood by bacterial infections with encapsulated germs and predisposes to diseases with deposits of immune complexes. Requiring a diagnosis and an early management in order to avoid complications sometimes frightening, as was the case of our patient.

**Keywords:** C4 protein, immunity, (DDB), infections.

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## INTRODUCTION

The complement system is a set of proteins synthesized in the liver in an inactive form, most of which have an enzymatic activity. It is involved both in the fight against infections, in particular in bacteria encapsulated via the membrane attack complex, the elimination of immune complexes and also in the modulation of specific immune response. It also has non-immune functions such as lipid metabolism, maturation of synapses and blood clotting [1]. Complement protein C4 is an essential component of the classical pathway that is initiated by attachment of the C1 complex to immunoglobulins. This complex will be able to cleave C4 and C2 to form the classic C3 convertase (C4b2a) essential for the formation of the membrane attack complex.

## OBSERVATION

Mr K.W aged 35, from a 1st degree consanguineous marriage. Having as a family history, two sisters who died one at the age of 21 by meningoencephalitis and the other at the age of 39 in an acute respiratory failure table following a bacterial superinfection of foci of dilation of the bronchi. Our patient presented since the age of 11 years with recurrent bronchopneumonia complicated by foci of dilation of the bronchi. Followed from the age of 17

years for an autoimmune hemolytic anemia splenectomized after failure of corticotherapy, had presented an abscessed appendicular chest plate 14 years ago, a pulmonary tuberculosis probable 13 years ago, a pneumococcal meningitis 11 years ago and who had alopecia plaques for 10 years. Admitted to the respiratory diseases department for a bacterial superinfection of foci of dilation of the diffuse bronchi. The clinical examination at admission found moderate digital hippocratism and toes, cervical hyperlordosis and dorsal kyphosis. Chest imaging had shown focal areas of bilateral cylindrical bronchi with associated mediastinal lymphadenopathy and lyric vertebral lesions of suspicious appearance with a nibbled appearance of the cervico-dorsal vertebrae and compacted pancake of the D5.

After treating the episode of bacterial superinfection of DDB foci. An assessment made to eliminate a malignant origin of vertebral lesions, in particular multiple myeloma or bone metastases from thyroid or renal cancer was negative. CT of the spine showed confluent osteolytic lesions of the vertebral bodies from D2 to D9 with peripheral osteosclerosis and wedge packing of D5. A bone biopsy was proposed but not done due to the absence of active vertebral lesions detectable on MRI. Regarding the etiological assessment of DDB foci, a serology of the human

immunodeficiency virus (HIV) was negative, a sweat test and an alpha1 antitrypsin test were normal. Also an electrophoresis of plasma proteins, a weight assay of serum immunoglobulins (IgG, IgM, IgA and the IgG subclasses) and a lymphocyte phenotyping were without particularity.

However, the activity of the total hemolytic complements (CH50) as well as the rate of the C4 fraction were collapsed. In contrast, the level of the other fractions of the complement C2, C3, C5, C7, C8 and C9 was normal. Bronchoscopy showed a diffuse inflammatory state with thickening of the spurs, bronchial biopsies done in favor of an inflammatory change. In addition, the blood count showed a normochromic macrocytic anemia. The Haptoglobin level was collapsed, the LDH level was normal and the Coombs test was positive (Ig G C3d). To eliminate cryoglobulinemia, the search for cold agglutinins.

As part of the systemic lupus erythematosus assessment, the immunological assessment performed was negative except the anti RNP antibodies were positive. The abdominal ultrasound showed a portal vein thrombosis with the appearance of a portal cavernoma. At the hepatic assessment, there was a slight cytolysis with cholestasis. Viral hepatitis B and C serologies were negative. Digestive fibroscopy found an aspect of ulcerative and polypoid duodenitis, biopsies was in favor of nodular lymphoid hyperplasia without signs of malignancy. An immunological assessment in the context of autoimmune As part of the systemic lupus erythematosus assessment, the immunological assessment performed was negative except the anti RNP antibodies were positive.

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The presence of hemolytic anemia and thrombosis of the portal vein should suggest a paroxysmal nocturnal hemoglobinuria (PNH), an analysis of symmetry of dependent GPI markers (CD14 CD55 CD66b) on monocytes and PNN did not show from clone HPN. For skin lesions, the skin biopsy was in favor of nonspecific scar alopecia. The lip biopsy performed showed a granuloma without caseous necrosis. The diagnosis was made of a deficit in complement C4 fraction associated with systemic lupus

erythematosus according to the diagnostic criteria of ACR with cutaneous and hematological manifestations.

The impact report showed type 1 respiratory failure with severe hypoxia and pulmonary hypertension with a chronic pulmonary heart appearance on cardiac ultrasound. The patient has always been followed up for 4 years, the general condition is still preserved. He is currently on long-term oxygen therapy, diuretics, respiratory physiotherapy, antibiotic prophylaxis and vitamin D supplementation.

## DISCUSSION

The C4 fraction is part of the classical complement route. It is encoded by two genes, C4A and C4B located in the class III region of the major histocompatibility complex MHC on the short arm of chromosome 6 (MIM +120810 and\* 120820, respectively) [3, 4]. The presence of non-functional C4A or C4B genes is responsible for a complete deficiency in C4A or C4B, called the homozygous C4 deficiency. The presence of a C4A or C4B gene is called partial or heterozygous C4A or C4B deficiency [5].

Complement protein deficits can be acquired or inherited. Acquired deficits are relatively common and can result either from a decrease in protein synthesis, especially in patients followed for hepatic cirrhosis, an excessive loss during a nephrotic syndrome or an increased consumption often linked to a disease. with immune complexes, notably LES and therefore the dosage of complement fractions constitutes a biomarker of disease activity. However, hereditary C4 deficits are relatively rare. May be partial what is common in the general or a complete population (neither the functional C4A nor functional C4B genes), the latter remains exceptional and to date only 28 patients have been described in the literature [6-8].

Homozygous C4A and C4B deficiencies differ in their clinical characteristics and their associations with disease. Our patient presented with recurrent respiratory infections complicated by diffuse bronchitis' and autoimmune manifestations. Unfortunately the diagnosis was late in the stage of chronic respiratory failure and chronic pulmonary heart, the interest of an early diagnosis, especially in the presence of a family history of immune deficiencies.

The data in the literature on the predisposition to infections during C4 deficiency are controversial [22]. A study in Finland has shown that C4 deficiency is responsible for recurrent respiratory infections in children and adolescents [21] and studies have shown that C4B deficiency is associated with an increased risk of infections, in particular with invasive germs [24, 9, 22-23]. Also, other studies have demonstrated the association of this deficit with the development of pulmonary tuberculosis [9] and others have shown that

patients with non-tuberculous mycobacterial pulmonary infections often have a deficiency in C4 compared to control subjects [2].

In addition to infectious complications, homozygous C4A deficiency is linked to systemic autoimmune diseases characterized by the production of autoantibodies, most often it is systemic lupus erythematosus [17-20, 15, 25, 26]. On the other hand, the C4B deficiency does not seem to be more frequent in the patients followed for lupus, but the latter deficit would predispose to insulin-dependent diabetes, coronary artery disease [11] or glomerular disease [12, 13]. Thus other autoimmune manifestations linked to C4 deficiency have been reported in the literature such as autoimmune rheumatic diseases, celiac disease, Henoch-Schönlein purpura, juvenile idiopathic arthritis and rheumatoid arthritis [5, 7, 9, 14].

The age at onset of symptoms and the severity of the disease vary considerably from one subject to another, probably in relation to other genetic and / or environmental factors that play a role in the development and pathogenesis of the disease.

It is likely to be assumed that in the event of complete or partial C4 deficiency, the infection can contribute to autoimmunity through mechanisms involving molecular mimicry.

C4 deficiency is also associated with other complications such as the development of lymphoma, sarcoidosis or capillary leak syndrome during cardiopulmonary bypass surgery in children. However, the number of cases reported in the literature remains very low [10, 15, 16].

Our patient had on the lip biopsy, a granuloma without caseous necrosis, bronchial biopsies performed did not find granulomatous lesions. Regarding the bone lesions we could not retain an etiological diagnosis remains most likely of autoimmune origin without being able to confirm this.

## CONCLUSION

The complete hereditary deficit in C4 remains exceptional. Repetitive infections, in particular with encapsulated germs, the presence of autoimmune manifestations and a family history of immune deficiency should lead to the search for a primitive immune deficiency, in particular a deficiency in complement.

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