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Letter to the Editor

Adult-Onset Chronic Granulomatous Disease and CD10-Negativity in Neutrophils

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TO THE EDITOR

On August 8, 2003, a 23-year-old male was referred to our hospital because of an abnormal shadow in the right lung. He had no family members affected with immunodeficiency disorders. He was diagnosed as having pneumonia. On August 1, 2005, he was admitted again because of pneumonia. Serum IgG, IgA, and IgM levels were normal. An anti-human immunodeficiency virus test was negative. An abdominal computed tomographic scan showed multiple low-density lesions in the spleen, which led to the suspicion of fungal infection. On September 30, 2005, analysis of the peripheral blood lymphocytes showed normal T-cell subsets and a normal CD4/CD8 ratio. He developed intractable skin inflammatory lesions due to methicillin-sensitive *Staphylococcus aureus*.

On December 14, 2010, the patient was referred to the Division of Hematology to determine a diagnosis for the repeated infections. He had low-grade fever. Peripheral blood neutrophils were morphologically normal without abnormal cytoplasmic granules. The serum CRP level was 6.33 mg/dl. The patient's clinical course was strongly suggestive of disorders related to neutrophil dysfunction. Phenotypes of the peripheral blood neutrophils were $CD11b^+$, $CD13^+$, $CD15^+$, $CD33^+$, and phosphatidyl $glucoside^+$ as well as $CD10^-$, $CD14^-$, $CD34^-$, $CD36^-$, and $HLA\text{-}DR^-$ (Fig. 1). These phenotypes were consistent with phenotypes of neutrophils, except for CD10. Superoxide production from neutrophils stimulated by phorbol 12-myristate 13-acetate was measured by flow cytometry using dihydrorhodamine 123 :[1] superoxide production from the patient's neutrophils slightly decreased compared with that from a healthy volunteer's neutrophils (Fig. 2B). The analysis of an extracellular epitope on heme-binding membrane glycoprotein gp91phox by flow cytometry using the monoclonal antibody 7D5, which specifically binds to the epitope of the neutrophils, showed slightly decreased expression in the patient's neutrophils (Fig. 2D).[2] Cytochrome b subunit β (CYBB) gene analysis of the patient's leukocytes did not show mutations (data not shown).[3] The patient was diagnosed with chronic granulomatous disease (CGD) without CYBB gene mutation. One of the mechanisms of CGD in our patient is suggested to be decreased expression of the CYBB gene, leading to relatively mild CGD. There are two novelties in our patient : one is the adult onset of CGD and the other is CD10-negativity in neutrophils. According to the Primary Immunodeficiency Database in Japan, adult onset of CGD occurred in only 1.1% of cases (2 out of 187 patients).[4] There are several reports on the late onset of CGD.[5-7] Recurrent and intractable bacterial or fungal infections led to the suspicion of CGD in these patients. Although CGD usually occurs in children, this disorder should be considered for adults with recurrent and intractable infections. CD10, a neutral endopeptidase, is expressed on lymphocyte precursors, a subset of B cells and neutrophils under normal conditions.[8] CD10 hydrolyzes biologically active peptides, leading to neutrophil inflammatory responses via the migration and aggregation of cells.[9] In severe infections such as those in burn and sepsis, CD10 expression on neutrophils decreases transiently, suggesting either active bone marrow release of the cells or a response to inflammatory challenge to the cells, or both.[10,11] An injection of lipopolysaccharide from Escherichia coli to healthy volunteers causes reduced CD10 expression on neutrophils with

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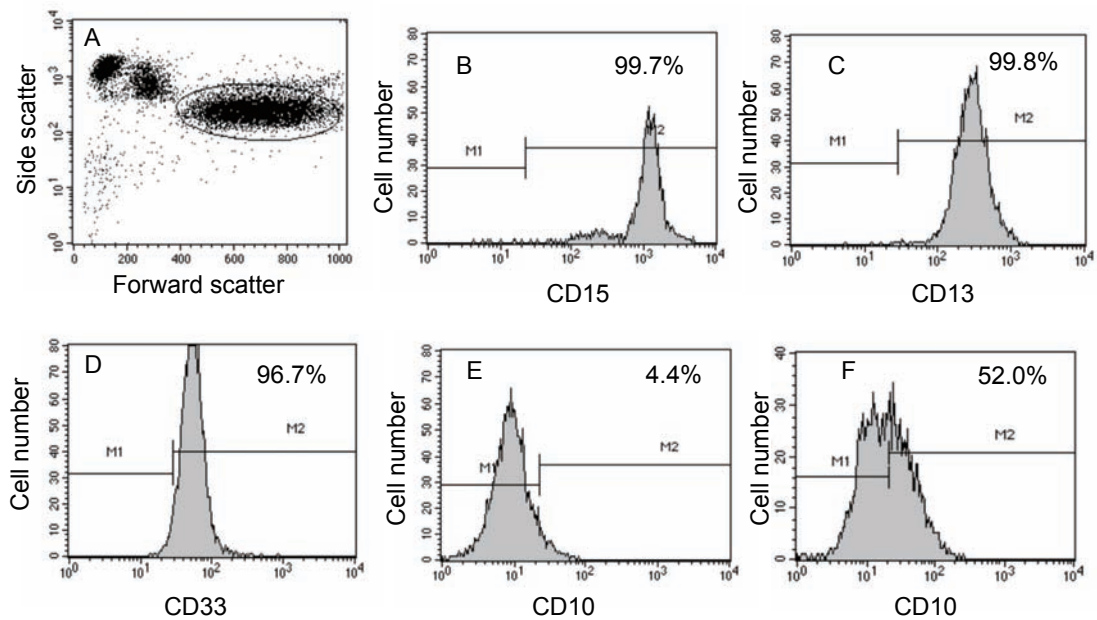

Fig. 1. Flow cytometric analysis of the patient's neutrophils. The circle indicates a region of neutrophils. (*1A*) to (*1E*), the patient ; (*1F*), a healthy volunteer.

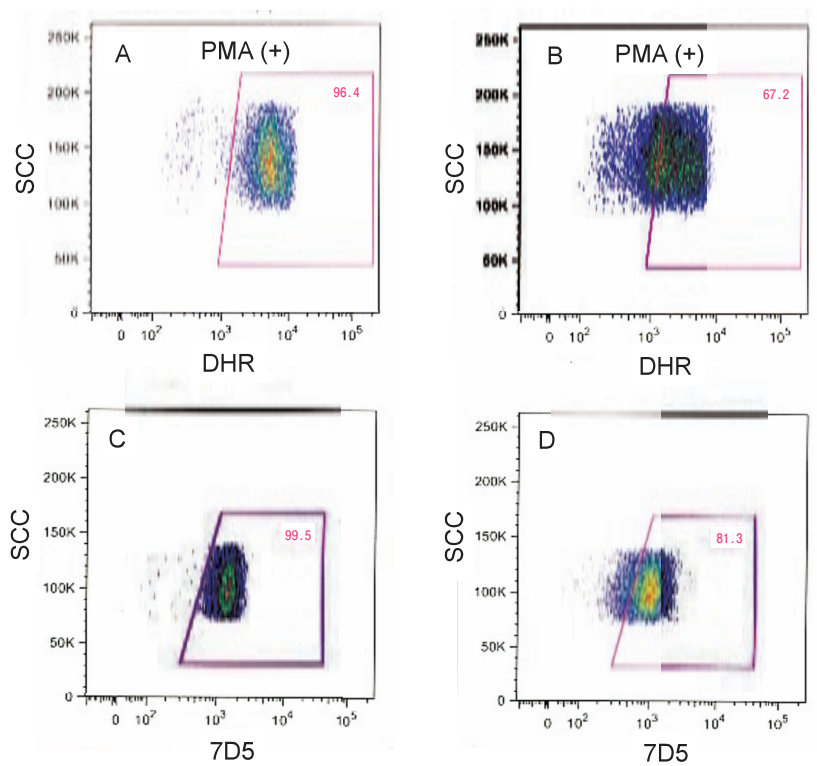

Fig. 2. Superoxide production and expression of gp91phox. (***2A***) and (***2B***), superoxide production from neutrophils using dihydrorhodamine 123 ; (***2C***) and (***2D***), gp91phox expression in neutrophils using the monoclonal antibody 7D5. (*2A*) and (*2C*), a healthy volunteer ; (*2B*) and (*2D*), the patient. PMA, phorbol 12-myristate 13-acetate ; DHR, dihydrorhodamine 123 ; SCC, side scatter

chill, nausea, fever, and myalgia, peaking at 2 to 8 hours after the injection.[12] These reports indicate that CD10 expression on neutrophils of healthy subjects decreases in response to various inflammatory stimuli. Interestingly, HIV patients reportedly showed decreased CD10 expression on bone marrow neutrophils, although the patients' condition was not described.[13] This report suggests that immunodeficient conditions may be associated with the decreased expression of CD10 on neutrophils. Because infections are common in CGD, the CD10-negativity in neutrophils of our patient may solely reflect the infectious conditions. Alternatively, CD10 expression on neutrophils may be associated with superoxide production from the cells. It is not known whether slight infections may induce CD10-negativity in neutrophils of healthy subjects and immunodeficient patients including CGD patients. Further studies are needed to examine the relationship between CD10 expression on neutrophils and immunodeficiency disorders including CGD.

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