

Acquired Factor VIII Deficiency Associated With a Novel Primary Immunodeficiency Suggestive of Autosomal Recessive Hyper IgE Syndrome

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Summary: Primary immunodeficiency diseases (PID) are associated with various autoimmune complications and several manifestations of autoimmunity can be seen in the disorders of T cells, B cells, phagocytes, and complement components. Acquired hemophilia is a rare entity in childhood. Although autoantibodies may develop in various forms of PID, Factor VIII (FVIII) inhibitors have not been described before. Herein, we present a case of acquired hemophilia resulting from FVIII inhibitors who had underlying undefined PID features suggestive of autosomal recessive hyper IgE syndrome. Our patient responded to corticosteroid treatment rather well and quickly, with an increased FVIII level and decreased FVIII inhibitors. However, FVIII inhibitor reappeared 7 months later, and disappeared spontaneously 4 months ago. Long-term and close follow-up is needed to observe the long-term prognosis in this child.

Key Words: factor VIII inhibitor, acquired hemophilia, hyper IgE syndrome, T-cell immunodeficiency

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Inhibitors directed to Factor VIII (FVIII) may be either alloantibodies produced against infused FVIII or autoantibodies produced against an individual's own FVIII, which is referred to as acquired hemophilia A.¹ Autoantibodies occur primarily in older individuals^{2,3} and these inhibitors are usually IgG and polyclonal in nature. In only about half of affected patients, there is an associated underlying medical condition like malignancy, pregnancy, autoimmune disease, and lymphoproliferative disorders, or drug use, mostly penicillin.^{4,5} Acquired hemophilia is a rare entity in children. To date, 15 children have been reported to have acquired FVIII inhibitors without an underlying genetic deficiency of FVIII.^{1,6} In 4 cases, the underlying etiologic factor was penicillin or penicillinlike drugs, whereas in all but one

of the remaining 11 cases, the underlying diseases were juvenile rheumatoid arthritis, Goodpasture disease, and infections.¹

Primary immunodeficiency diseases (PID) are associated with autoimmune complications and several manifestations of autoimmunity can be seen in the disorders of T cells, B cells, phagocytes, and complement components. PID associated with acquired FVIII deficiency has not been previously reported.^{7,8} Herein, we present a case of acquired hemophilia that had underlying, undefined PID features suggestive of autosomal recessive hyper IgE syndrome (AR-HIES).

CASE REPORT

The patient was a 7.5-year-old boy referred to our department with complaints of recurrent, painful oral aphthous lesions since 7 months of age. Occasionally fever accompanied these lesions, which usually lasted few weeks and were resistant to therapy. He also had several attacks of lower and upper respiratory tract infections during the previous 4 years. When he was 2.5 years old, he had peripheral facial paralysis, without any defined etiology, which resolved spontaneously. At 3 years of age, he was hospitalized with severe varicella infection. On one occasion, he developed an inguinal abscess following a trauma, which required drainage; however, the infectious agent was not recorded. He had no history of allergic disorders including atopic dermatitis. His parents are first-degree relatives and he has a healthy 13-year-old sister.

Physical examination revealed vesiculopapular lesions on the lips and bilateral fine rales by lung auscultation. His laboratory tests and immunologic work-up are shown in Table 1 and Figure 1. He had persistent leukopenia and lymphopenia, decreased CD4⁺ T-cell population. He had elevated IgE together with elevated IgA and IgM levels, whereas the IgG level was within normal limits. In vitro lymphocyte responses to mitogens, phorbol myristate acetate and ionomycin were low upon initial evaluation, but progressively increased to normal levels during follow-up. His polio antibody response was positive. Maternal engraftment was ruled out. Thorax tomography was consistent with diffuse cylindrical bronchiectasis. He was put on trimethoprim-sulfamethoxazole and fluconazole prophylaxis.

Eight months later, he developed a subcutaneous hematoma on the right thigh following trauma. Partial thromboplastin time was prolonged despite normal prothrombin time values. Factor analysis revealed low levels of FVIII owing to elevated FVIII inhibitor levels. He had not been given any FVIII concentrate or fresh frozen plasma. Antinuclear antibody (1/80+) was also present.

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TABLE 1. Immunologic Features of the Patient

	Patient	Normal Values
White blood cell count (/mm ³)	2600-6800	(4500-10000)
Absolute neutrophil count (/mm ³)	1232-3470	(> 1500)
Absolute lymphocyte count (/mm ³)	520-1648	(1100-5900)
Eosinophils count (/mm ³)	344-468	(< 300)
Lymphocyte subsets (/mm ³)		
CD3	449-996	(700-420)
CD4	288-326	(300-2000)
CD8	398-735	(300-1800)
CD19	202-569	(200-1600)
CD16-56	178-277	(90-900)
IgG (mg/dL)	890-1310	(760-2134)
IgM (mg/dL)	160-1270	(69-387)
IgA (mg/dL)	205-521	(70-303)
IgE (IU/mL)	203-440	(< 100)
Antibody titers to poliovirus		
Type 1	1/8	
Type 2	< 1/4	
Type 3	1/16	
In vitro lymphocyte proliferation		
PHA* (cpm × 10 ⁻³)	7, 7, 67, 138, 26	124 ± 44
ConA* (cpm × 10 ⁻³)	7, 15, 51, 96, 32	87 ± 40
PMA + I* (cpm × 10 ⁻³)	NT, NT, 81, 64, 30	48 ± 21
Antinuclear antibody titer	1/80	

*The numbers represent measurements of 6, 6.5, 7, 8, 9 years in chronologic order.

ConA indicates concanavalin A; I, ionomycin; NT, not tested; PHA, phytohemagglutinin; PMA, phorbol myristate acetate.

Prednisolone (2 mg/kg, per oral) was started, which resulted in a rapid improvement, both in FVIII level and bleeding. FVIII inhibitory level became undetectable 6 weeks later; however, FVIII inhibitor level changed over time (Fig. 1). Seven months after the cessation of steroid therapy, the FVIII level began to decrease, whereas FVIII inhibitor increased and he was given another course of steroid treatment, which was stopped due to varicella zoster infection. One and a half years after the diagnosis of acquired hemophilia, he is doing well with a normalized FVIII level and absence of FVIII inhibitor.

DISCUSSION

Severe hemophilia A patients treated with FVIII may develop antibodies (Ab) that block FVIII function (inhibitors), but autoimmune inhibitors may also develop in subjects without congenital hemophilia and cause acquired hemophilia.

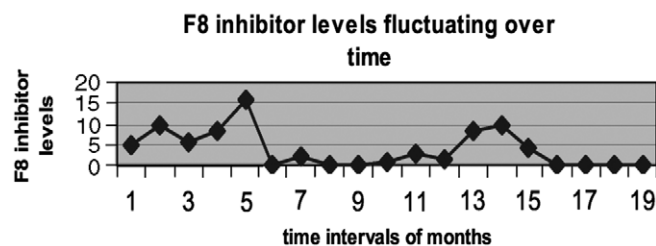


FIGURE 1. Factor VIII inhibitor (F8 inh/Bethesda unit) levels during 18 months after the diagnosis of acquired hemophilia.

PIDs are associated with various autoimmune complications and several manifestations of autoimmunity can be seen in the disorders of T cells, B cells, phagocytes, and complement components. It has been suggested that autoimmunity associated with PID is not simply a breakdown of tolerance to self-antigens; rather, it is the inability of an inherently defective immune system to completely eradicate microbial pathogens and their antigens through the usual immune pathways. The result is an exaggerated and chronic inflammatory response by less effective alternative immune pathways, which damage not only infected cells, but also surrounding tissue.⁷ Although autoantibodies may develop in various forms of PID, antibodies to FVIII, that is, FVIII inhibitors have not been described before. Our patient's clinical and laboratory features were suggestive of AR-HIES namely a T-cell deficiency with high IgE level.

Hyperimmunoglobulin E (IgE) syndromes (HIES) are very rare primary immunodeficiencies. Most cases are sporadic, but both autosomal dominant forms of HIES (AD-HIES) and AR-HIES have been described.⁸⁻¹⁰ AD forms are characterized by staphylococcal skin abscesses, pneumonia with pneumatocele formation, and skeletal symptoms such as hyperextensibility of joints, scoliosis, osteoporosis, and retained primary teeth.¹⁰ AR-HIES characterized by severe recurrent viral infections, recurrent or severe infection of *Staphylococcus aureus*, *Haemophilus influenzae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Cryptococcus*, severe chronic refractory *Molluscum contagiosum* infections, eosinophilia, and neurologic complications, but without skeletal or dental abnormalities, has recently been described.⁸ The presence of recurrent aphthous lesions, recurrent herpes infections of lips, neurologic symptom (facial paralysis), severe varicella infection which required hospitalization, abscess formation, recurrent upper and lower respiratory tract infections, varicella zoster infection, increased serum IgE levels, development anti FVIII autoantibody, were all suggestive for AR-HIES in our patient. However, this patient did not experience dermatitis and recurrent abscesses defined in HIES and the eosinophil count and total IgE were, although elevated, below the range expected for AR-HIES. Although the decreased numbers of CD4 and subnormal in vitro T lymphocyte responses are not classic features of AR-HIES, both were present in 1 out of 6 patients as described by Renner et al.⁸ High IgA and IgM levels were also present in patients described in some of these patients as in our patient.⁸

Several of the symptoms of HIES are also features of other well-defined T-cell deficiencies; for example, Wiskott-Aldrich syndrome and Omenn syndrome. Lack of specific blood tests other than elevation of IgE levels, and eosinophilia, or specific immunologic or molecular markers, makes the diagnosis of HIES difficult, especially in young patients and atypical, less severe cases (HIES-variants).⁹⁻¹¹ A scoring system was developed at the National Institutes of Health to assist linkage studies in

families with multiple cases of HIES.⁹ According to this system, our patient scores 15, a borderline score, which can be compatible with a diagnosis of AR-HIES. However, this scoring system is mostly informative for diagnosis of patient with an autosomal dominant pattern since most of the criteria are suggestive for the dominant form.

The clinical course of acquired hemophilia is variable and sometimes causes significant morbidity and mortality. Replacement therapy with porcine FVIII or prothrombin complex concentrates, and recombinant FVIIa are used for management of bleeding; however, immunosuppressive regimens, steroids alone, or in combination with cytotoxic drugs, are targeted to clear autoantibodies. In adults whose inhibitor persists, response to treatment is slow and mortality is high, up to 20%.

Despite the absence of a standardized treatment regimen in children, it seems to be easier to eliminate inhibitors in children than adults.¹ Although our patient responded to corticosteroid treatment rather well and quickly, FVIII inhibitor reappeared. Long-term and close follow-up is needed to observe the long-term prognosis in this child who has an associated immunodeficiency.

REFERENCES

1. Moraca RJ, Ragni MV. Acquired anti-F8 inhibitors in children. *Hemophilia*. 2002;8:28–32.
2. Kessler CM, Ludlam CA., for the International Acquired Hemophilia Study Group. The treatment of acquired factor VIII inhibitors: worldwide experience with porcine factor VIII concentrates. *Semin Hematol*. 1993;30(suppl 1):22–27.
3. Gren D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to factor VIII. *Thromb Haemost*. 1981;45:200–203.
4. Hay CR, Baglin TP, Collins PW, et al. The diagnosis and management of factor VIII and factor XI inhibitors: a guide from the UK Haemophilia Centre Doctors' Organization (UKHCDO). *Br J Haematol*. 2000;111:78–90.
5. Saxena R, Mishra DK, Kashyap R, et al. Acquired haemophilia—a study of ten cases. *Haemophilia*. 2000;6:78–83.
6. Klukowska A, Laguna P, Obitko-Pludowska A, et al. Acquired factor VIII inhibitor in a non-hemophilic boy. *Haemophilia*. 2003;9:642–645.
7. Arkwright P, Abinun M, Cant A. Autoimmunity in human primary immunodeficiency diseases. *Blood*. 2002;99:2694–2702.
8. Renner ED, Puck JM, Holland SM, et al. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. *J Pediatr*. 2004;144:93–99.
9. Grimbacher B, Schaffer AA, Holland SM, et al. Genetic linkage of hyper IgE syndrome to chromosome 4. *Am J Hum Genet*. 1999;65:735–744.
10. Grimbacher B, Holland SM, Gallin JI, et al. Hyper IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Eng J Med*. 1999;340:692–702.
11. Grimbacher B, Belohradsky BH, Holland SM. Immunoglobulin E in primary immunodeficiency diseases. *Allergy*. 2002;57:995–1007.