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Transient Acquired Hemophilia Associated with *Mycoplasma Pneumoniae* Pneumonia

Acquired hemophilia is a rare disorder caused by autoantibodies to factor VIII (FVIII) (also referred to as factor VIII inhibitors or anti-FVIII) and may be associated with pregnancy, underlying malignancy, or autoimmune disorders. A 33-month-old girl who presented with hematochezia and ecchymotic skin lesions was diagnosed with *Mycoplasma pneumoniae* pneumonia by serology and polymerase chain reaction. Hematologic studies showed a prolonged activated partial thromboplastin time (aPTT), partially corrected mixing test for aPTT, reduced levels of FVIII, and the presence of antibodies against FVIII. She was treated conservatively with prednisone and intravenous immunoglobulin (IVIG) without FVIII transfusion and recovered without sequelae. This report provides the first description of acquired hemophilia due to anti-FVIII in association with *M. pneumoniae* in Korea. We discuss this case in the context of the current literature on acquired hemophilia in children.

Key Words : *Acquired Hemophilia; Anti-FVIII; Factor VIII inhibitor; Mycoplasma Pneumoniae Pneumonia; Autoantibodies*

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INTRODUCTION

Acquired hemophilia (AH) is a rare and potentially life-threatening coagulation disorder caused by spontaneous development of antibodies to clotting factor VIII (FVIII) in non-hemophilic children (1). AH has been described in association with the postpartum period as well as autoimmune, dermatologic, infectious and oncologic diseases, and selected drugs (2, 3). AH in non-hemophilic children is usually non-specific, transient, and not associated with clinical bleeding, but severe cases with catastrophic consequences have been reported (4). In severe cases, bleeding may be prolonged due to poor clinical response to FVIII replacement therapy in the continued presence of anti-FVIII (1).

M. pneumoniae is a common cause of pneumonia especially in young children and adults and may give rise to protean extrapulmonary manifestations including hematologic (e.g., thrombocytopenia, splenomegaly, disseminated intravascular coagulation, and hemolytic anemia), dermatologic (e.g., Stevens-Johnson syndrome), gastrointestinal (e.g., vomiting, diarrhea, and pancreatitis), renal (e.g., interstitial nephritis and glomerulonephritis), cardiac (e.g., pericarditis, myocarditis, and pericardial effusion) and central nervous system (e.g. meningitis, transverse myelitis, polyradiculopathy, cerebellar ataxia, and sensorineural hearing loss) conditions (5). The underlying causes of *M. pneumoniae*-associated extrapulmonary manifestations are unknown. While transient acquired factor II deficiency has been described in association with *M. pneumoniae*, there are no reports of AH and anti-FVIII with *M. pneumoniae* (6). In this report, we describe a 33-month-old girl with serologically and polymerase chain reaction (PCR)-confirmed infection with *M. pneumonia* and AH, who was successfully treated with prednisone and intravenous immunoglobulin (IVIG) therapy.

CASE REPORT

A previously healthy 33-month-old girl presented to an outlying hospital with a 10-day history of high fever, sore throat, and non-productive cough. Because of worsening lower respiratory tract symptoms including severe cough, acute onset hematochezia, and numerous ecchymoses, she was transferred to our facility for further treatment. The girl's parents reported no prior illness or history of bleeding problems in the child, siblings, or other family members. At the time of admission following transfer, she appeared febrile with diminished breath sounds and rales over the left lower lung field. Multiple ecchymotic skin lesions were visible over the upper and lower extremities. No evidence of hemarthroses or soft tissue hematomas

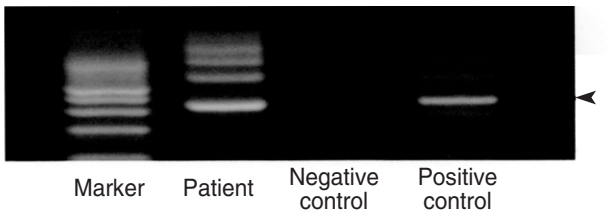

Fig. 1. Detection of *Mycoplasma pneumoniae* DNA amplification in a patient throat swab specimen by polymerase chain reaction.

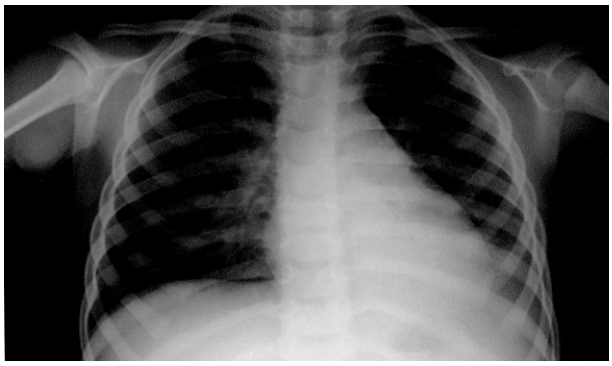

Fig. 2. Radiologic finding on admission. Chest radiograph shows consolidation in left lower lung field and blunting of the costophrenic angle.

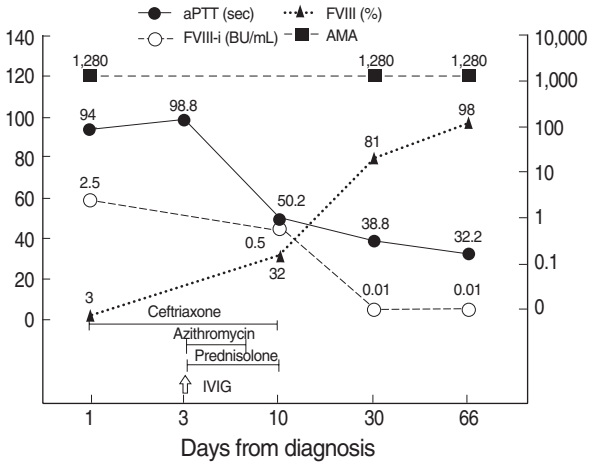

Fig. 3. The changes of aPTT, FVIII, factor VIII inhibitor during treatment. aPTT, activated partial thromboplastin time; F VIII, factor VIII; F VIII-I, factor VIII inhibitor; IVIG, intravenous immunoglobulin; AMA, anti-mycoplasma antibody.

was found. No hepatosplenomegaly or sensorimotor deficits were observed and her cardiac examination was unremarkable.

The initial laboratory studies showed normal red and white blood cell counts, liver and renal function studies, urinalysis and Widal test, and anti-streptolysin O titer. Fecal occult blood testing was positive, but there was no evidence of stool leukocytes. The latex agglutination test for rotavirus was negative. Her C-reactive protein level was elevated at 8.3 mg/L (reference range, <5 mg/L). On the day of admission to our hospital, her IgM antibody titer to *M. pneumoniae* was 1:1,280 and, on her 4th hospital day, an oropharyngeal swab was collected and tested positive for *M. pneumoniae* by PCR (Fig. 1).

Coagulation studies revealed a normal prothrombin time (PT) of 12.7 sec (reference range, 11.7 to 13.7 sec), and a prolonged activated partial thromboplastin time (aPTT) of 94.0 sec (reference range, 29.8 to 41.8 sec). Plasma mixing studies with normal control failed to correct the aPTT (77.3 sec) and raised our suspicion regarding the presence of an inhibitor. The patient's bleeding time was normal, FVIII activity was 3% (reference range: 60 to 140%, STA Compact, Diagnostica Stago, France), factor IX activity was 61% (reference range, 60 to 140%), von Willebrand factor antigen was 146.2% (reference range, >50%), ristocetin cofactor activity was 110.1% (reference range, 45 to 160%), and FVIII inhibitor was 2.5 Bethesda Units (BU)/mL (reference range, <0.01 BU/mL), confirming the presence of anti-FVIII. Additional tests showed no evidence of disseminated intravascular coagulopathy, and her fibrinogen, fibrin degradation products, and anti-thrombin 3 levels were normal. Tests of anti-nuclear, anti-phospholipid, lupus anticoagulant, and anti-smooth muscle cell antibodies were all negative. On admission, her chest radiograph showed an area of ill-defined consolidation in the left lower lobe with blunting of left costophrenic angle (Fig. 2). Based on these clinical and laboratory findings, we established the diagnosis of AH.

Because of her stable condition on admission and the absence of complications such as intracranial and intramuscular hematomas, she was treated with daily oral prednisone (2 mg/kg/day) and a single dose of IVIG (2 g/kg) without FVIII concentrate. For the treatment of her underlying *Mycoplasma*-associated pneumonia, she received ceftriaxone (50 mg/kg/day) given twice daily for 7 days and azithromycin (10 mg/kg/day) given once daily for 3 days. The titer of FVIII inhibitor rapidly declined without additional immunosuppressive therapy. Total disappearance of autoantibodies to FVIII was achieved four weeks after admission (Fig. 3).

DISCUSSION

AH is the most common acquired clotting factor disorder and may involve a deficiency of factors VII, VIII, or IX (7). AH has been observed in non-hemophilic patients with a frequency of 1 to 5 cases per million persons and 50% of cases occur in healthy persons with no underlying medical condition (8). It is notable that AH is typically a disease of adults with most cases reported in patients aged 50 yr and older and sometimes in younger women of child-bearing age who experience postpartum bleeding. Cases of AH due to anti-FVIII have only rarely been reported in the literature and AH has not been described in the context of *M. pneumoniae* infections among Asian children (9).

Clinically, the bleeding pattern in AH patients is characterized by hematoma formation in fascial planes or mucosal bleeding in contrast to congenital hemophilia in whom hemarthroses are more common. Hemorrhagic manifestations may be severe including upper and lower gastrointestinal bleeding that may initially present in previously healthy individuals or following surgical procedures. AH should be suspected in patients who have no personal or family history of bleeding disorders and develop a hemorrhagic diathesis accompanied by a prolonged aPTT. The aPTT is a reliable screening test to detect anti-FVIII as it will be prolonged when FVIII activity falls below 45% of the mean normal level. In AH, mixing studies using patient plasma and normal plasma will not normalize the aPTT and the FVIII activity, whereas in cases with clotting factor deficiency, the prolonged aPTT will be corrected following the addition of normal plasma (10). Thus, mixing studies provide a critical tool to distinguish between the presence of a coagulation factor deficiency and a circulating anti-FVIII. Antibodies to FVIII may be quantified by the Bethesda assay that allows quantitation of the inhibitor strength (11). In our patient, we confirmed the diagnosis of AH by the presence of multiple ecchymotic lesions, a prolonged aPTT, normal PT, low FVIII activity, and the presence of FVIII inhibitor.

Up to 36% of patients who do not receive immunosuppressants experience a spontaneous disappearance of their autoantibodies, but the predictors of spontaneous resolution are not well-known. Thus, prompt therapy is needed when AH is confirmed (12, 13). In patients with AH, the primary goal is to achieve effective control of bleeding closely followed by elimination of the anti-FVIII using one or more factor concentrates or immunosuppressive agents. The choice of agent for hemostasis depends on the severity of bleeding and the titer of anti-FVIII. Desmopressin, human FVIII (hFVIII) or porcine FVIII (pFVIII) may raise FVIII activity. If the anti-FVIII titer is high (>5 BU) or bleeding continues despite the use of hFVIII or pFVIII infusions, other FVIII bypassing agents, such as activated prothrombin complex concentrates, recombinant factor VIIa or recombinant human activated factor VIIα may be used (13). In patients who are resistant to treatment with factor concentrates or FVIII bypassing agents, immunosuppressive therapy may be considered (13). Immunosuppressants may be called for in cases for whom bleeding is life-threatening, where factor concentrates may not be readily available, or when resolution does not occur with factor concentrates.

At present, there are neither gold standard treatments nor standardized therapeutic guidelines. However, for several years, corticosteroids and cyclophosphamide have been the mainstay of treatment in AH. The use of prednisone in AH typically results in the disappearance of anti-FVIII within 3 to 6 weeks in approximately 50% of cases. The addition of oral cyclophosphamide may double the response rate in AH patients who are resistant to steroids (10). However, other combination therapies appear to be effective in eliminating anti-FVIII, including prednisone plus azathioprine or prednisone plus cyclophosphamide and vincristine. In patients who do not respond to cyclophosphamide, azathioprine, vincristine, and cyclosporin A may be considered either alone or in combination with prednisone as a salvage therapy (13). In addition to the use of immunosuppressive agents, the use of high-dose IVIG, plasmapheresis, and plasma exchange has also proven effective for some patients with AH (14). Our patient was treated successfully with a combination of prednisone and IVIG (15), which led to a complete resolution of clinical and laboratory abnormalities after 4 weeks of treatment. The prognosis of patients with AH is quite variable. In some cases, remission may occur within a few months but, in others, anti-FVIII may persist for years.

Although the etiology of this disorder remains unclear, about 40-50% of AH cases are associated with autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus, graft-versus-host disease after allogenic bone marrow transplantation, the postpartum period, underlying malignancies, or drug administration (e.g., penicillin, sulfonamides, chloramphenicol, and others) (8). AH has also been reported in association with BCG and influenza vaccination, but the causal pathway in these cases remains unclear (16). Sixteen different Mycoplasma species have been found to colonize the upper respiratory and genitourinary tract in humans and, of these, *M. pneumoniae* is the most important pathogen in children (17). Despite several reports of the extrapulmonary manifestations associated with *M. pneumoniae* infection, the mechanism by which this injury occurs has not yet been established. Recent data suggest that several autoantibodies may be produced during infection with *Mycoplasma* including cold agglutinins and autoantibodies against pulmonary and central nervous system tissue as well as cardiolipin and smooth muscle tissue. In some cases, it is thought that this autoimmune response appears to result from molecular mimicry due to homology between mammalian structural proteins and the mycoplasmal P1 adhesin (18). These autoantibodies may inhibit binding of FVIII to von Willebrand factor or phospholipid (preventing the association of FVIII with factor IXa), block the binding of factor Xa to FVIII, or interfere with the formation of the FVIIIa-factor IXa-phospholipid (tenase) complex. Additionally, autoantibodies have also been described to catalyze the hydrolysis of FVIII (19).

While the pathogenic mechanisms of AH remain unclear, recent evidence from experimental studies of *Mycoplasma* suggests that a clonal expansion of B lymphocytes is important (20, 21). It is well known that bacterial lipopeptides (sometimes called lipid-associated membrane proteins) such as the Macrophage Activating Lipoprotein 2 (MALP2) found in *Mycoplasma* species may stimulate B lymphocytes via a pathway involving Toll-like receptor 2 (TLR2) activation of nuclear factor-kappaB (NF-kB). If TLR2 and other TLRs (e.g., TLR1 and TLR6) prove to be important in the causal pathway to AH and other autoimmune disorders, agents targeting one or

more TLRs may provide a new and effective class of immunomodulating agents.

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