

B형 인플루엔자 감염에서 나타난 특발성 혈소판 감소성 자색반증

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A Case of Acute Idiopathic Thrombocytopenic Purpura Following Influenza B Virus Infection

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Virus-associated immune thrombocytopenic purpura (ITP) can occur following common viruses, but cases of ITP associated with influenza infection has seldom been reported. In this report we describe a previously healthy 5-year-old boy who admitted with fever, flu-like symptoms and a few bruises on both legs. Severe thrombocytopenia were found. Bone marrow aspirates and biopsy showed no abnormalities and results of coagulation tests were all in normal limit. Real-time polymerase chain reaction was positive for influenza B infection. The patient fully recovered with intravenous immunoglobulins and steroid therapy.

Key Words: Idiopathic thrombocytopenic purpura, Influenza

Introduction

Recent viral illness proceeds in 50-65% of acute idiopathic thrombocytopenic purpura (ITP)¹⁾. Virus-associated ITP can occur following common viruses: Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV)²⁾. Influenza viruses are known to seldom be associated with ITP. There have been a few cases of ITP induced by influenza vaccination,

But as far as we know, there has been one only single report of acute ITP following influenza viral infection in English literature³⁾. In this report, we describe a patient who developed acute ITP while he was suffering from influenza B infection.

Case Report

A 5-year-old boy arrived at our hospital with a history of 5 days of fever up to 39.5°C, cough, rhinorrhea, sore throat and myalgia. He was previously healthy with no special medical past history. He had not got influenza vaccine this year and his older brother had been diagnosed as influenza B infection with similar symptoms 1 week prior, and had recovered from the illness. On admission he appeared well. His body tem-

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perature was 38.5°C, pulse rate was 118 beats/min, and respiratory rate was 22 breaths/min. He had slightly injected pharynx without exudate. No petechiae or bleeding was seen in oral cavity. A few greenish bruises were present on both legs. The rest of his physical examination was unremarkable. No enlarged lymph nodes or palpable organomegaly were found. Complete blood count revealed WBC of 3.56×10^9 cells/L (segmented neutrophil 21.4%, lymphocyte 64.0%, monocyte 12.9%, eosinophil 1.1%, basophil 0.6%), hemoglobin of 12.1 g/dL and platelet count of 13×10^9 cells/L. Morphology of RBCs and WBCs appeared normal on smeared blood film, without any features of microangiopathy. The platelets were normal in size, and not aggregated. C-reactive protein was 0.01 mg/dL. Liver and renal functions tests, electrolytes, prothrombin and activated partial thrombin time coagulation tests were all within normal limits. Anti-platelet antibody and platelet associated antibody were negative. Serologic tests against common viruses associated with ITP (EBV, CMV, hepatitis virus) were all negative for acute infection. A chest X-ray demonstrated no active lung lesions. The rapid immunofluorescence antigen test with a nasal swab revealed the presence of positive reaction to influenza B virus antigen. As a confirmatory test, his nasal secretion aspirates were tested with influenza A/B real time PCR, and influenza B virus was identified.

Diagnosis of influenza B virus infection and acute ITP were made. The treatment was initiated with the first dose of intravenous immunoglobulins (IVIG) 1.0 g/kg and oral oseltamivir 45 mg twice daily. On the second hospitalized day, the platelet counts were 15×10^9 cells/L. As there was no response to the first dose of IVIG, methylprednisolone of 15 mg/kg/day combined with second dose of IVIG 1.0 g/kg were given. On the third day he became afebrile. His pharyngeal soreness and myalgia regressed. His platelet count rose to 48×10^9 cells/L and WBC count reached nadir of 2.03×10^9 cells/L. IVIG therapy ceased and methylprednisolone administration in the same dosages were kept. The bone marrow aspirates revealed normal cellularity with slightly increased numbers of megakaryocytes, consistent with acute ITP. Marrow cells of all three lineages

revealed normal morphology. Malignant cells or active hemophagocytes were not found. On the fourth day, his platelet count returned to 113×10^9 cells/L and he was discharged without any other complication or clinical symptoms. Oral prednisone of 1 mg/kg/day had been prescribed as a discharge medication. Oseltamivir was stopped completing whole 5-day course. A week after he was discharged, the platelet count had increased to 770×10^9 cells/L and oral prednisone was stopped. And on his third week after admission, platelet counts had normalized to 210×10^9 cells/L.

Discussion

As in other respiratory viral infections, hematological abnormalities including transient leucopenia or mild pancytopenia have been commonly described in influenza infection^{4,5}. Transient leucopenia is commonly found in natural course of influenza infection. The mechanism of leucopenia is not fully understood, but it has been proposed that apoptosis through Fas-FasL signal plays a key role. Influenza virus induces human cytokine, increasing Fas-FasL on T cells, leading to apoptosis. Influenza virus not only induces cytokines increasing Fas-FasL on T cells, but also produces viral proteins triggering apoptosis^{6,7}. And pancytopenia can also be a result from the decreased viable B-lineage cells in bone marrow via the cell cycle arrest and apoptotic events during influenza virus infection⁸. However, isolated thrombocytopenia is very uncommon in influenza infection. Wang et al. analyzed CBC profiles of 57 culture-proven influenza B infected children. Leucopenia was found in more than half of patients, but only 1 (1.8%) showed thrombocytopenia below 100×10^9 cells/L⁹.

There have been a few case reports of acute ITP following influenza vaccination¹⁰⁻¹³. The mechanism is not yet clear. However, cross activation of immune cells through molecular mimicry is supposed to be involved in the development of autoimmune reaction including ITP¹⁴. Since the influenza vaccine which does not contain live virus produces maximal antibody response in 2 to 4 weeks, the typical period of ITP development

after influenza vaccine administration in case reports is approximately 2 weeks.

In comparison, ITP following influenza virus infection occurs during illness as in our case. The mechanism is also not fully understood. However, it has been demonstrated that neuraminidase activity of influenza virus removes surface sialic acid on platelet, and this modified platelets are rapidly cleared from circulation¹⁵⁾. And a study has reported that influenza virus hemagglutinin could bind to the platelet surface, triggering binding of viral specific antibodies and complements.

ITP associated with influenza virus infection has been rarely reported. In 1998, Rice et al. first reported a case of a 5-year old boy with isolated thrombocytopenia (92×10^9 cells/L) after an influenza A virus infection⁴⁾. However, he was not definitely diagnosed as ITP, and spontaneously recovered. To our knowledge, there have been two case reports of ITP after influenza virus infection. Lee et al. reported the case of a 14-year-old boy who developed acute ITP and was concomitantly diagnosed with influenza infection¹⁶⁾. Although it is not a case of newly developed acute ITP, Kaneko et al. reported a 41-year-old female with relapse of chronic ITP as a result of a sporadic influenza infection¹⁷⁾. Those patients achieved remission through typical dose of methylprednisolone administration. In both cases, ITP was diagnosed in patients with influenza A virus infection. There has been no case of ITP after influenza B virus infection yet.

This is the first case report of acute ITP following influenza B virus infection. As in the previous ITP cases after H1N1 influenza A virus infection, the responses to the treatments and clinical outcome of our patient were good. He was treated with IVIG and methylprednisolone, and his peripheral blood platelet counts increased to safe level on his fourth hospital day. However, his platelet counts on admission were seriously low (below 2.0×10^9 cells/L), enough to elucidate spontaneous bleeding. Also in the previous two ITP cases after influenza infection, the platelet count rapidly decreased as influenza infection symptoms increased. It is consistent with the mechanism of ITP in influenza infection mentioned above.

In conclusion, the clinician should be aware that acute ITP can occur during influenza infection, and can rapidly progress. While our patient showed dangerously low platelet count, he showed initially no sign of sickness and had no specific symptoms other than some mild bruising on his legs which could have been missed. Therefore, physical examination should be conducted with scrupulous care on influenza patient in out-patient clinic. And blood sample should be tested for complete blood count whenever the patient shows any suspicious symptoms of ITP.

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요약

인플루엔자 백신 접종에 의한 특발성 혈소판 감소증은 드물게 나타나지만, 인플루엔자 감염환자에서 병발한 혈소판 감소성 자색반증은 거의 보고된 바가 없다. 특히 병력 없던 건강한 5세 남자 환자가 고열과 독감 증상으로 내원하였으며, 혈액검사에서 심한 혈소판 감소증을 보였다. 환아는 신속항원검사, 실시간 중합효소연쇄반응을 통해 B형 인플루엔자 감염을 확진받았으며, 골수 천자 및 생검을 포함한 다른 검사상 검사상 혈소판 감소를 유발할만한 다른 원인은 보이지 않았다. 환아는 정맥 면역글로불린과 프레드니솔론 투여로 정상 혈소판 수치를 회복하였다. 본 증례는 B형 인플루엔자로 인한 혈소판 감소성 자색반증의 첫번째 증례이다. 드물지만 인플루엔자 감염에서도 이처럼 심한 혈소판 감소가 동반될 수 있으므로 외래에서 독감 의증 환자를 진찰할 때에는 멍이나 출혈 흔적 등을 놓치지 않도록 세밀하게 진찰해야 하고 의심이 될 때에는 혈액 검사가 필요할 것으로 생각된다.