Severe Immune Thrombocytopenia Possibly Elicited by the Anti-influenza Viral Agent Peramivir


Abstract

A 44-year-old man whose platelet count had been at the lower limit of the normal range for years visited the urgent care department of our hospital for treatment of a high fever and severe fatigue. The influenza A virus was detected, and the patient therefore received the intravenous antiviral agent, peramivir. One week later, he developed systemic petechial rashes. A peripheral blood examination showed a markedly decreased platelet count (3.0×10^9 cells/L), and the bone marrow findings were compatible with a diagnosis of immune thrombocytopenia (ITP). Furthermore, a drug-induced lymphocyte-stimulating test was positive for peramivir. The thrombocytopenia slowly responded to treatment with oral prednisolone. This case suggests that neuraminidase inhibitors, including peramivir, can elicit or worsen ITP.

Key words: influenza virus, peramivir, neuraminidase inhibitor, immune thrombocytopenia (ITP)


Introduction

Peramivir is a novel intravenous neuraminidase inhibitor drug approved for use as an Emergency Use Authorization (EUA) agent by the US Food and Drug Administration (FDA) in 2009 to treat pandemic outbreaks of the influenza virus worldwide (1). The Japanese Ministry of Health, Labour and Welfare also approved its application in 2009 (2). In 2013, China decided to approve the use of peramivir due to the threat of increasing human transmission viral infections (3), including the novel influenza virus H7N9 (4). Although some investigators have reported that peramivir has significant efficacy in treating serious infections with the influenza virus (5-7), the safety of this drug remains controversial (8-10). We herein report the case of a patient with severe immune thrombocytopenia (ITP) that was possibly triggered by peramivir.

Case Report

A 44-year-old man visited the urgent care department of our hospital due to a high fever and severe fatigue in early 2013. He had a history of well-controlled hypertension, hyperuricemia and hyperlipidemia, and his platelet count had been below the lower limit of the normal range, although his peripheral blood cell count had been examined only a few times, for the past five years. The antigen of the influenza A virus was detected and the patient had exhibited dehydration with severe nausea, vomiting and coughing; therefore, he was administered the neuraminidase inhibitor drug, peramivir (300 mg/body), intravenously by an urgent care specialist, due to the difficulty in administering the drug either orally or via inhalation. At that point, the patient’s peripheral blood was not examined; however, no signs of bleeding were observed. After treatment, the fever and nausea promptly disappeared.

One week later, the patient developed systemic petechial
showed severe thrombocytopenia (3.0×10^9/L), and he was thus referred to our department. A bone marrow examination showed increased megakaryocytes lacking the production of platelets. Neither myelodysplasia nor chromosomal abnormalities were detected in the bone marrow, and, indeed, the peripheral blood leukocyte count (7.1×10^9/L) and hemoglobin concentration (15.8 g/dL) were normal. Blood coagulation parameters, including the international normalized ratio of prothrombin time (0.94), activated partial thromboplastin time (25.2 seconds) and plasma fibrinogen (273 mg/dL) and D-dimer (0.8 μg/mL) levels, were within the normal range. Furthermore, the platelet-associated immunoglobulin G (PAIgG) value was elevated (223 ng/10^9/L) and broad anti-platelet autoantibodies to human platelet antigens (11) were detected, although other autoantibodies, including antinuclear antibodies and anti-phospholipid antibodies, were negative. Based on these findings, the patient was diagnosed with ITP. To rule out the possibility of secondary ITP, we conducted drug-induced lymphocyte-stimulating tests (DLSTs) for some of the drugs that he had been given. Among them, peramivir was positive on the DLST (stimulation index, 220%; n<180). We also attempted to examine whether peramivir enhanced the reaction of autoantibodies on flow cytometry (12). The mean fluorescence intensity (MFI) of fluorescein isothiocyanate-conjugated IgG reactive to the patient’s autologous platelets was 2.4- or 3.0-fold higher than that of the MFI of healthy volunteers in the absence or presence of peramivir, respectively. Although the patient received peramivir only once, severe thrombocytopenia was sustained for over two weeks. Therefore, treatment with 60 mg/day of prednisolone (PSL) was started; however, no other drugs were stopped. As shown in Figure, the thrombocytopenia slowly but steadily improved, although the patient continues to exhibit mild thrombocytopenia 11 months after the start of the PSL therapy.

Discussion

We herein documented a case of severe thrombocytopenia that was likely elicited by treatment with peramivir, although we cannot rule out the contribution of the influenza A virus infection itself. In fact, influenza viruses, especially influenza B, sometimes induce mild thrombocytopenia (13). It is also difficult to determine whether the thrombocytopenia occurred as an acute crisis of mild chronic ITP or a form of peramivir-induced acute ITP. Moreover, thrombocytopenia may occur after both natural influenza infection and influenza vaccination (14). In this case, an acute crisis of chronic ITP caused by peramivir therapy may be likely according to the positive DLST results for this drug and the patient’s history of chronic mild thrombocytopenia. His platelet count was slightly higher than the threshold for a diagnosis of ITP (100×10^9/L) (15), although it was examined only a few times, and we therefore cannot confirm a diagnosis of chronic ITP in this case. Since the patient’s titer of anti-platelet autoantibodies was strongly positive, even in the absence of peramivir, we investigated whether peramivir enhanced these antibodies. On flow cytometry, the MFI of IgG for autologous platelets was higher in the present patient, even in the absence of peramivir, and was slightly, but certainly, increased by the addition of peramivir therapy. This finding potentially supports the hypothesis that treatment with peramivir induced an acute crisis of chronic ITP in this case. On the other hand, lymphocyte transformation tests, such as DLST, may reflect reactions mediated by helper T cells in cases of chronic (16, 17) and drug-induced (18) ITP. It has also been reported that helper T cells derived from ITP patients, including both those with and without anti-platelet antibodies, react to glycoproteins on platelets upon stimulation (16). Therefore, the positive DLST finding for peramivir observed in the present case may reflect the effects of reactions of helper T cells elicited by this drug against some antigens on platelets, although there is no direct evidence of reactions of helper T cells against platelet membrane antigens.

A few studies have shown the significant efficacy of peramivir therapy for some types of influenza viruses associated with mild temporal side reactions, such as diarrhea, pneumonia and oral herpes infection, rather than life-threatening or long-term adverse events (5-7). With regard to hematological side effects, 3-21% of patients have been reported to exhibit leukocytopenia, although severe thrombocytopenia requiring interventional treatments, such as steroids, has not been mentioned. Therefore, intravenous peramivir may be usually effective and safe in patients with influenza viruses, including novel viruses such as H7N9. In contrast, the present case certainly suggests that peramivir therapy may trigger the development of ITP. Therefore, when administering peramivir, especially in those with a low platelet count, it is necessary to anticipate the potential for thrombocytopenia. Furthermore, future research should fur-
ther investigate the frequency and clinical significance of thrombocytopenia caused by neuraminidase inhibitor drugs in larger populations.

The authors state that they have no Conflict of Interest (COI).

References


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