IMMUNE THROMBOCYTOPENIA DURING INTERFERON-ALFA THERAPY FOR RENAL CELL CARCINOMA

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Immune thrombocytopenia is a rare complication of interferon-alfa (IFN-α). A patient with renal cell carcinoma developed severe thrombocytopenia during therapy with purified IFN-α. The patient's exposure to IFN, exclusion of other causes, and bone marrow biopsy were consistent with drug-induced immune thrombocytopenia. Cessation of IFN and corticosteroid administration resulted in the prompt recovery of platelets. The patient was re-challenged with recombinant IFN-α-2b under careful observation ; there was no occurrence of severe thrombocytopenia. It was suggested that the difference of the subtypes composing IFN-α resulted in the lack of cross reactivity.

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Key words : Renal cell carcinoma, Interferon- alpha, Autoimmune thrombocytopenia

INTRODUCTION

Interferon-alpha (IFN-α) has anti-tumor activity against renal cell carcinoma. While mild reversible bone marrow suppression is a common side effect of IFN-α, severe thrombocytopenia is extremely rare. We report a case of drug-induced immune thrombocytopenia in a patient treated with purified IFN-α. Re-challenge with a recombinant IFN-α-2b did not induce severe thrombocytopenia.

CASE REPORT

A 55-year-old man presented with hematuria and left flank pain lasting for two months. Ultrasonography revealed a left renal tumor ; computed tomography (CT) and magnetic resonance imaging (MRI) showed a 11×11×20 cm left renal tumor penetrating the Gerota's fascia. A chest x-ray demonstrated multiple nodules in the lung field, and the left thorax was filled with pleural effusion.

After a chest tube was fitted, left radical nephrectomy was attempted ; however, diffuse peritoneal dissemination and invasion to the descending colon was confirmed during surgery, and the operation was discontinued. A biopsy of the tumor was performed, and it was determined a renal cell carcinoma, clear cell type, grade 2. Transarterial embolization (TAE) of the tumor was performed post operatively for local disease control. Low-grade fever, lumbago and mild elevation of C-reactive protein, alkaline phosphatase, and lactate dehydrogenase was observed for a few days after TAE.

One week after TAE, administration of a purified

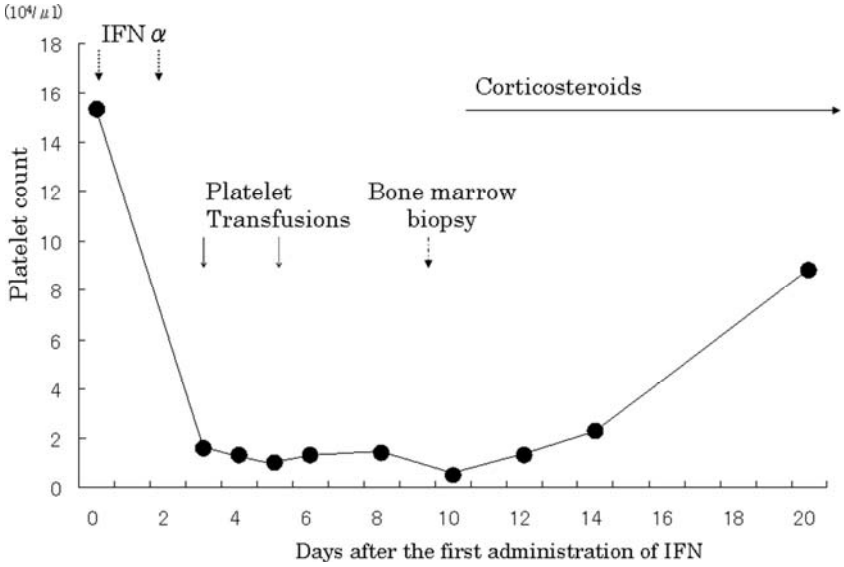

Fig. 1. A diagram showing the platelet count after administration of IFN α. Platelet count declines to as low as $0.5\times10^4/\mu$l. Note that the platelet count recovers quickly after corticosteroid administration.

IFN-α (human lymphoblastoid interferon, Sumiferon®) was commenced subcutaneously every other day. After two injections, the platelet count acutely fell to $1.6\times10^4/\mu l$. Other laboratory data were unremarkable. There was no physical sign of bleeding, and the patient's general condition was stable. The only other medication taken was loxoprofen sodium for fever. The platelet count remained low despite the transfusion of platelets. A bone marrow biopsy showed normocellular marrow with increased megakaryocytes and mild thrombocythemia, consistent with the reaction of marrow to immune thrombocytopenia. Drug-induced immune thrombocytopenia was suspected. Interferon was stopped, and corticosteroid was orally administered. The platelet count recovered promptly after corticosteroid administration (Fig. 1).

After the recovery of the platelets, the administration of corticosteroid was stopped and the patient was re-challenged with loxoprofen sodium; however, thrombocytopenia was not observed. Three months later, recombinant IFN-α-2b (Intron A®) was carefully administered intramuscularly every other day. Mild thrombocytopenia was observed but the platelet count did not severely decline (Fig. 2). IFN-α-2b administration was safely continued three times weekly. However, one month later, the patient's condition deteriorated rapidly due to tumor growth, and IFN-α-2b was discontinued. The patient died of disease two months after discontinuation of IFN-α-2b.

DISCUSSION

Autoimmune thrombocytopenia can be induced by a variety of medications[1], and is assumed to be the result of immune platelet destruction by drug-dependent antiplatelet antibodies. Generally, it is considered that antigens are formed on the platelet surface by the binding of the drug to a membrane receptor, creating a structural change that initiates antibody formation. The drug-dependent antibodies are highly specific for the structure of the drug, and so are sensitive to minor changes in drug structure. A diagnosis can only be confirmed by recurrent thrombocytopenia following a re-challenge with the drug. However, a re-challenge can be dangerous, as severe thrombocytopenia can develop rapidly. It is important to exclude all other causes of thrombocytopenia, such as myelosuppression, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and peripheral consumption of platelets due to tumor growth; as well, a bone marrow biopsy can be helpful. Measurement of platelet-associated IgG (PaIgG) can support a clinical diagnosis[2], but is not specific. Drug-induced thrombocytopenia typically produces profoundly low platelet counts. The time from starting drug administration to the occurrence of thrombocytopenia varies, but the median time is 14 days. With re-challenge, thrombocytopenia almost always occurs within 3 days[1]. Withdrawal of the causative drug is the most important therapeutic measure, and a corticosteroid is commonly given.

IFN-α has established anti-tumor activities in a number of malignancies. However, its immunomodulatory property is known to exacerbate or induce autoimmune diseases[3], though autoimmune thrombocytopenia is reported to occur in less than 1% of the patients treated with IFN[4]. IFN-α induced autoimmune thrombocytopenia can be explained either by the same mechanism described for other drugs, or by the

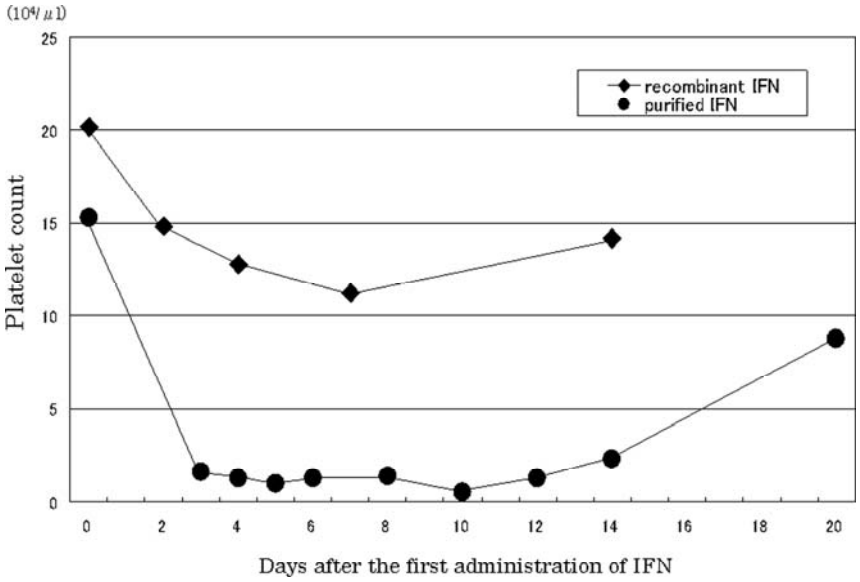

Fig. 2. A diagram showing the difference in the decline of the platelet count after administration of two kinds of IFN α. Though a slight decline of the platelet count is also observed with administration of a recombinant IFN, the severity of the decline is not comparable to that seen with a purified IFN.

immunomodulatory properties of IFN-α; however, the exact mechanism remains to be elucidated.

IFN-α can be categorized into about 20 structurally different subtypes, each having a different biologic activity[5]. Purified IFN-α (human lymphoblastoid interferon, Sumiferon®) includes all existing subtypes, as opposed to a recombinant IFN-α-2b (Intron A®), which consists of just one subtype. In our case, re-challenge with IFN-α-2b (Intron A®) did not induce immune thrombocytopenia. It is suggested that the subtypes of IFN-α not included in IFN-α-2b (Intron A®) lead to the formation of antiplatelet antibodies. The lack of cross reactivity could be attributed to the structural differences, or to the difference in the biologic activity of the IFN-α subtypes. There is no clinical evidence that administration of different subtypes of IFN-α could lead to differences in effects or side effects; however, physicians should be aware of the possibilities when using different subtypes of IFN-α.

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和文抄録

インターフェロン α 投与により免疫機序性血小板減少症をきたした腎癌の 1 例

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免疫機序性血小板減少症はインターフェロン α 投与に伴う稀な合併症である．腎癌に対し天然型インターフェロン α を投与中の患者に重度の血小板減少症を認めた．インターフェロンの投与歴，他の原因の除外，および骨髄穿刺所見より薬物起因性免疫性血小板減少症が疑われた．インターフェロンの中止とステロイドの投与により血小板数は速やかに回復した．遺伝子組み換え型インターフェロン α-2b を注意しながら再投与したところ，重度の血小板減少症は見られなかった．インターフェロン α を構成するサブタイプの違いにより交差反応が回避されたと考えられた．

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