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Sodium-glucose cotransporter-2 inhibitor-associated thrombocytopenia

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Letter to the Editor

Dear Editor,

Recent studies have revealed that sodium-glucose cotransporter-2 (SGLT2) inhibitors, including empagliflozin, decrease the risk of heart failure in patients with type 2 diabetes mellitus and reduce the risk of major cardiovascular events in patients with heart failure. SGLT2 inhibitors have been widely prescribed for cardiac, renal, and other diseases, in addition to diabetes mellitus. Antiplatelet therapy and other therapies are also sometimes used, especially in patients at risk for developing cardiovascular events. In such cases, attention should be paid to drugs that can induce hemorrhage because they may aggravate bleeding tendency.

The patient was a 53-year-old woman with a history of systemic lupus erythematosus (SLE), diabetes mellitus, and Graves' disease (GD). She received 3 mg of prednisolone, 1000 mg of metformin, and 5 mg of thiamazole daily. Her SLE symptoms and thyroid status were well controlled for several years. Her glycemic status was also generally stable, with her glycated hemoglobin maintained at approximately 6%. She had had proteinuria due to SLE for several years; therefore, 10 mg of empagliflozin was initiated to preserve renal function.

Surprisingly, a rapid drop in her platelet count to 60,000/ μ L was observed at the first scheduled visit 28 days after initiation of empagliflozin, although no bleeding tendency was observed. We changed the anticoagulant used for blood collection from ethylenediaminetetraacetic acid (EDTA) to heparin sodium, but the platelet count remained unchanged, which ruled out EDTA-dependent pseudothrombocytopenia. The patient's platelet-associated immunoglobulin G (IgG) test results were negative. Empagliflozin was promptly discontinued and platelet counts increased after 4 days (102,000/ μ L), recovering almost to pre-empagliflozin levels within 1 month of discontinuation (Fig. 1). During the

process of platelet count decrease and recovery, no changes were observed in white or red blood cells, SLE disease severity, or thyroid function. These results suggested that empagliflozin was the underlying cause of the thrombocytopenia.

Although the frequency of SGLT2 inhibitor-induced thrombocytopenia appears to be low, caution should be exercised when SGLT2 inhibitors are used in patients at high risk for bleeding. The bleeding risk would increase if SGLT2 inhibitors were administered to patients on antiplatelet agents and thrombocytopenia were to occur. However, we are not aware of previous reports of thrombocytopenia associated with SGLT2 inhibitors.

The mechanism of empagliflozin-induced thrombocytopenia in this patient is not clear. Idiosyncratic immune-mediated reactions are known to cause drug-induced immune thrombocytopenia [1]. Drug-dependent antibodies bind to specific epitopes on platelet surface glycoproteins only in the presence of sensitizing drugs. On the other hand, the patient has various autoimmune diseases, such as SLE and GD, and some autoimmune mechanisms might be involved in the SGLT2 inhibitor-induced thrombocytopenia. In addition, medications can have direct cytotoxic effects on megakaryocytes and/or platelets, resulting in nonimmune drug-induced thrombocytopenia [2]. It is thus evident that the mechanisms by which empagliflozin causes thrombocytopenia should be clarified, including the issue of whether thrombocytopenia is a class effect of SGLT2 inhibitors.

Recent basic research revealed that empagliflozin affected the differentiation of CD4⁺ T-cell subsets by inhibiting T helper type 1 (Th1) and Th17 cell populations while increasing regulatory T-cells; it additionally proposed that empagliflozin could have potential for the treatment of immune thrombocytopenia by modulating metabolic reprogramming in CD4⁺ T

cells [3]. The platelet trends in our cases ran opposite to the research results described above, which may constitute a cautionary indication for not using empagliflozin in treating immune thrombocytopenia.

The number of patients taking SGLT2 inhibitors is expected to increase in any case. Despite the seeming rarity of thrombocytopenia by SGLT2 inhibitors, the global increase in the use of these drugs may see a rise in this adverse effect. The frequency of this event is also a subject for future study. It might be preferable to evaluate platelet counts after initiating SGLT2 inhibitors. Clinicians should keep this in mind.

Compliance with Ethical Standards

- Conflict of Interest: The author declares no conflict of interest related to this manuscript.
- Ethical Approval: N/A
- Informed Consent: Written informed consent was obtained from the patient for case presentation.

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Figure legend

Fig. 1. Changes in the patient's platelet count

Platelet counts decreased with empagliflozin initiation and improved immediately after discontinuation.

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Figure 1

