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SUPPORTING INFORMATION

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Drug (vaccine)-induced thrombocytopenia 2021: Diversity of pathogenesis and clinical features

To the Editor:

Drug-induced thrombocytopenia (DITP), caused by drug-dependent, platelet-reactive antibodies (DDAbs), is commonly described as unexpected, sudden, and severe. Thrombocytopenia typically occurs 1 week after beginning a new daily drug or occurs suddenly following

ingestion of a drug taken intermittently. Severe thrombocytopenia persists if the drug is continued but resolves promptly when the drug no longer remains in the circulation. DDAbs remain in the circulation but they have low affinity for their target platelet antigen unless the antigen structure is altered by binding to a drug.[1] Based on these observations, we established clinical criteria in 1998 to define the probability of a drug as the cause of thrombocytopenia.[2] Our criteria define a drug as the definite cause of thrombocytopenia if other drugs or etiologies have been excluded and re-exposure results in recurrent severe thrombocytopenia.[3] We also define a drug as the definite cause of thrombocytopenia if DDAbs are identified by the Versiti Blood Center of Wisconsin. Using these criteria, we have updated our website every 3 years to list drugs that can cause DITP, documented by data from published reports or by identification of DDAbs.

Four recent observations have expanded the scope of DITP. [1] Drugs developed for long-term sustained release may cause prolonged, severe, and refractory thrombocytopenia after the drug is discontinued. [2] Some drugs may cause sustained, moderate thrombocytopenia while the drug is continued, indicating that the clinical course of DITP may not always be severe. [3] Sudden and severe thrombocytopena with clinical characteristics of autoimmune thrombocytopenia (ITP) may occur following COVID-19 vaccination. [4] Immune checkpoint inhibitors commonly cause sustained thrombocytopenia, also with clinical characteristics of ITP.

In this report, we first describe the results of our current systematic literature review searching for reports of DITP, December 2018 through September 2021, using our previously established criteria for assessing the evidence that a drug caused thrombocytopenia.[3] We also report the experience of the Versiti Blood Center of Wisconsin, 2018–2021, identifying previously unreported DDAbs causing DITP. Then we address the four recent observations and discuss their relevance to our understanding of DITP.

Current systematic literature review: By searching six databases (Ovid, Embase, CINAHL, PubMed, Web of Science, and IPA Database), we identified 57 articles (excluding reports of COVID-19 vaccine and immune checkpoint inhibitors) describing 48 drugs in 67 patients with suspected DITP (Table S1). Using our previously established criteria, we identified five drugs (aspirin, ethosuximide, exenatide, filgrastim, and linezolid) with definite evidence for causing thrombocytopenia that had not previously been reported with definite evidence (Table 1).

It is surprising that aspirin is now reported for the first time with definite evidence for causing thrombocytopenia since it has been available without a prescription for more than 100 years and is the most commonly used drug world-wide. The authors described a patient with multiple acute episodes of severe thrombocytopenia that continued for 4 years until they recognized association with aspirin. Subsequently, with no aspirin exposure, he maintained a normal platelet count for 2 years. They did not report testing for aspirin-dependent, platelet reactive antibodies. In previous unpublished patients with suspected aspirin-induced thrombocytoenia, aspirin-depdendent, platelet-reactive antibodies have been identified by the Versiti Blood Center of Wisconsin.[3]

TABLE 1 Drug-induced thrombocytopenia: 2018–2021

Drugs not previously reported with definite evidence for a causal association with thrombocytopenia in published case reports[a]	
Aspirin[b]	Ethosuximide[b]
Exenatide[b]	Filgastrim (G-CSF)
Linezolid	
Drugs not previously reported with drug-dependent, platelet-reactive antibodies documented by the Versiti Blood Center of Wisconsin	
Cetirizine	Diazoxide[c]
Diclofenac[c]	Diltiazem
Fluorouracil	Oseltamivir
Palonosetrone	Sulbactam
Tratuzumab[c]	
COVID-19 vaccines reported to cause thrombocytopenia[d]	
Pfizer–BioNTech	Moderna
Oxford–AstraZeneca	Johnson & Johnson
Immune checkpoint inhibitors reported to cause thrombocytopenia	
Nivolumab (16)[e]	Atezolizumab (1)
Pembrolizumab (9)	Nivolumab/Ipilimumab (6)
Ipilimumab (2)	Nivolumab/Pembrolizumab (1)
Durvalumab (2)	

[a]Citations for the reports of these five drugs are in Table S1.
[b]Previously reported with drug-dependent, platelet-reactive antibodies causing drug-induced thrombocytopenia (DITP).
[c]Previously reported with definite clinical evidence for causing DITP.
[d]Additional data describing thrombocytopenia attributed to COVID-19 vaccines and infection are presented in Table S2.
[e]Numbers in parentheses are the number of patients or patient groups reported with thrombocytopenia.

Ethosuximide has been used for 60 years to treat absence (*petit mal*) seizures. The authors described a child who developed severe thrombocytopenia 1 week after beginning ethosuximide; the Versiti Blood Center of Wisconsin identifed ethosuximide-dependent, platelet-reactive antibodies.

Exenatide extended-release (biodegradable microspheres) is used as a weekly subcutaneous injection to treat type 2 diabetes. Detectable levels may remain in the plasma for 10 weeks. The authors described a patient who presented with severe thrombocytopenia after 11 weeks of treatment. ITP was suspected but he did not respond to dexamethasone, IVIg, and splenectomy on day 10. Then the Versiti Blood Center of Wisconsin identified exenatide-dependent, platelet-reactive antibodies. Severe thrombocytopenia persisted for 4 more weeks in spite of continued treatment with dexamethasone, IVIg, rituximab, and romiplostim. His platelet count gradually returned to normal.

Filgrastim (granulocyte colony-stimulating factor [G-CSF]) stimulates granulocyte production in stem cell donors. The authors described a donor whose platelet count dramatically decreased after 3 days of filgrastim. They repeated filgrastim 3 weeks later, after his platelet count had recovered to normal, and severe thrombocytopenia recurred. They did not report testing for filgrastim-dependent, platelet-reactive

antibodies; there are no previous reports of filgrastim-dependent, platelet-reactive antibodies.

In a woman treated for tuberculosis, physicans suspected that linezolid was causing severe thrombocytopenia that occurred after 10 days of treatment. After discontinuing linezolid, the platelet count recovered to normal in 2 weeks. When they began a lower daily dose of linezolid 1 week later, severe thrombocytopenia recurred after 3 days. Testing for linezolid-dependent, platelet-reactive antibodies was not reported and they have not been identified in other patients. The clinical course of this patient was characteristic of DITP.

Also in 2018–2021, the Versiti Blood Center of Wisconsin identified platelet-reactive antibodies dependent on nine drugs that had previously not been recognized to cause DITP (Table 1).

DITP with sustained, severe thrombocytopenia caused by extended-release drugs: The potential for sustained, severe DITP creates a clinical dilemma. The patient with exenatide-induced thrombocytopenia illustrated the inability of immunosuppression to alter the course of DITP. Even if a diagnosis of DITP is documented, treatment of severe thrombocytopenia ITP regimens may seem appropriate. Recognition of DITP is essential to avoid future contact with the drug.

Drug-induced sustained, moderate thrombocytopenia: Drugs such as linezolid, valproate, and daptomycin can cause sustained, moderate thrombocytopenia during weeks-months of continued treatment. We have previously excluded these reports because the clinical course was not consistent with our assumption that thrombocytopenia caused by DDAbs was always sudden and severe. We have previously identified both valproate-dependent and daptomycin-dependent, platelet-reactive antibodies.[3] Therefore, we now consider that DITP caused by DDAbs may not always be sudden and severe. Some drugs, together with DDAbs, may cause sustained, moderate thrombocytopenia by increased platelet clearance and/or decreased platelet production, similar to the pathogenesis and clinical course of ITP. Our established clinical criteria for defining the probability that a drug is the cause of thrombocytopenia are equally appropriate for these patients.

COVID-19 vaccine-induced isolated thrombocytopenia: We identified seven case reports and three case series describing thrombocytopenia following initial vaccinations. Eight of the 12 case report patients had preceding ITP or other autoimmune diseases. Most of these reports described thrombocytopenia following COVID-19 vaccine as ITP; the patients appeared to respond to treatment for ITP. A study from Scotland documented that the frequency of ITP following the forst dose of AztraZeneca vaccine, but not the Pfizer vaccine, was significantly greater than the frequency of ITP in the nonimmuinized population. The frequency of non-ITP thrombocyopenia following COVID-19 vaccines was not different from the frequency in unvaccinated adults. Two additional reports described COVID-19 vaccine-induced exacerbation of previously diagnosed ITP. Another additional report described the frequency of all-cause thrombocytopenia occurring with COVID-19 infection (without vaccination). Each of these 13 reports are described with their citation in Table S2. There are no reports of COVID-19 vaccine-dependent anti-platelet antibodies or anti-platelet antibodies dependent on any other vaccines.[3] However, we intrepreted a previous report of repeated thrombocytopenia following repeated influenza vaccine over 4 years as definite evidence for DITP.[3]

Immune checkpoint inhibitors: We identified 24 articles describing 37 patients with thrombocytopenia attributed to immune checkpoint inhibitors, an increasingly common treatment for many cancers that are refractory to initial management (Table 1). Thrombocytopenia occurred weeks-months after beginning treatment and resolved weeks-months after treatment discontinuation. The timing of the clinical course of thrombocytopenia in these patients is not consistent with our understanding of the pathogenesis of DITP caused by DDAbs.

Another article analyzed platelet counts in 202 patients who were treated with immune checkpoint inhibitors for metastatic cancer, without concurrent chemotherapy.[4] All patients had normal platelet counts when treatment began. Sixty-two (31%) patients developed thrombocytopenia; 14 had nadir platelet counts <75 000/μL. The median time to the nadir platelet count was 54 days after beginning treatment. Immune checkpoint inhibitor treatment was continued unless the platelet count was <50 000/μL. The 48 patients with nadir platelet counts of 75 000-150 000/μL had greater overall survival than the 140 patients without thrombocytopenia.

The etiology of immune checkpoint inhibitor-induced thrombocytopenia is assumed to be the development of anti-platelet autoantibodies, as in ITP. This is consistent with the occurrence of many different autoimmune disorders in patients treated with immune checkpoint inhibitors.[5] Autoimmune adverse events are a predictable result of immune checkpoint blockade, which increases activity of the immune system.[5]

Summary: Our goal for documenting the occurrence of DITP is to inform physicians about drugs that may cause unexpected sudden, severe thrombocytopenia or sustained, moderate thrombocytopenia. In some patients, multiple drugs may simultaneously cause DITP.[6] When the causative drug, or drugs, are stopped, the platelet count promptly returns to normal, unless the drug has sustained release. We have not included the reports of patients with thrombocytopenia caused by COVID-19 vaccines or by immune checkpoint inhibitors in our database of drugs that can cause DITP[3] because their presumed etiology, clinical course and management are similar to ITP.

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CONFLICT OF INTEREST

Dr. Curtis is a consultant for Argenx, Ionis, and Rallybio pharmaceuticals. The other four authors have no conflicts of interest or financial conflicts with this study.

ETHICS STATEMENT

This study involved no human or animal subjects and required no Institutional Review Board approval.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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