

# Acyclovir-Induced Immune Thrombocytopenia in a Patient with Herpes Zoster of the Trigeminal Nerve

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Acyclovir has been widely used as an antiviral agent for the treatment of infections caused by herpes simplex and varicella-zoster viruses. The drug is usually well tolerated; however, rarely, adverse effects may be severe, including neuropsychiatric reactions, gastrointestinal disturbances, skin lesions, renal disorders, and dyscrasias. We describe a 20-year-old man who was treated with intravenous acyclovir 5 mg/kg every 8 hours for a herpes zoster infection (shingles) that involved painful vesicular lesions and skin eruptions along the third branch of trigeminal nerve. Despite favorable improvement of his cutaneous lesions, the patient developed severe thrombocytopenia within 5 days of starting acyclovir. The drug was discontinued, and the patient's condition improved by using a supportive therapeutic approach. An extensive workup for detection of acyclovir-dependent platelet antibodies indicated positive results, implicating acyclovir as a cause of thrombocytopenia. In addition, the temporal relationship between the start of acyclovir and the onset of thrombocytopenia, along with the exclusion of the other most frequently occurring known causes of thrombocytopenia, established a definitive diagnosis of acyclovir-induced immune thrombocytopenia. To our knowledge, this is the first well-documented report of isolated severe immune thrombocytopenia induced by acyclovir. Clinicians should be aware of this rare potential adverse reaction, as prompt diagnosis is the cornerstone of appropriate management.

**Key Words:** acyclovir, herpes zoster, varicella-zoster virus, thrombocytopenia, trigeminal nerve.

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Acyclovir is a synthetic acyclic purine nucleoside analogue with potent antiviral activity. The drug is indicated for the treatment of a variety of infections caused by herpes simplex (types 1 and 2) and varicella-zoster viruses.<sup>1,2</sup> It is considered a safe and well-tolerated antiherpetic agent when given in the usual therapeutic doses. However, severe gastrointestinal, neuropsychiatric, cutaneous, and renal adverse effects have been reported, mainly emanating from high-dose intravenous infusions.<sup>3–6</sup> Furthermore, only a

few reports of bone marrow depression attributed to acyclovir use, given either intravenously or orally, have been published.<sup>7–10</sup> We describe what we believe to be the first case report of acyclovir-induced severe isolated thrombocytopenia in a young man who received the drug for trigeminal herpes zoster.

## Case Report

A 20-year-old man was admitted to our service because of a painful and erythematous maculopapular rash on his left chin and zygomal area that evolved rapidly to vesicular lesions. His pain was burning and constant, and he developed a pruritic skin eruption along the distribution of the trigeminal nerve. He also reported minimal

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photophobia and left eye pain. Constitutional symptoms, such as headache, low-grade fever, and malaise were also reported by the patient. Examination of his left eye showed slight conjunctival and circumcorneal hyperemia without attenuation of visual acuity. The rest of his clinical evaluation was unremarkable. Before this admission, the patient had been in good health; he took no drug therapy, including over-the-counter and herbal products.

The patient's clinical features were compatible with a herpes zoster infection (shingles) affecting the branches of the left trigeminal nerve. In addition, immunoglobulin (Ig)M and IgG antibodies to varicella-zoster virus were detectable in high titers in the patient's serum, confirming the diagnosis. A complete blood count showed a hematocrit of 43.5% (normal range 40–52%); white blood cell count  $7.5 \times 10^3/\text{mm}^3$  ( $4.6\text{--}10.2 \times 10^3/\text{mm}^3$ ) with 62% neutrophils (38–68%), 34% lymphocytes (20–45%), and 4% monocytes (2–10%); and platelet count  $215 \times 10^3/\text{mm}^3$  ( $140\text{--}450 \times 10^3/\text{mm}^3$ ). Results of a serum biochemistry test panel were also within the normal range. Standard-dose intravenous acyclovir was started at 5 mg/kg every 8 hours, to be administered over next 7 days. Gradual improvement in the patient's clinical condition was noted.

Two days later (hospital day 3), scattered small ecchymoses became visible over the patient's trunk and extremities. A complete blood count was promptly performed, revealing isolated mild thrombocytopenia (platelet count  $115 \times 10^3/\text{mm}^3$ ). Because of the patient's satisfactory clinical picture, acyclovir was continued. Three days later (hospital day 6), however, multiple petechiae were noted, more extensively disseminated than the former skin lesions, as well as spontaneous epistaxis. A repeat complete blood count showed profound severe thrombocytopenia, with the platelet count dropping precipitously to a nadir of  $1 \times 10^3/\text{mm}^3$  (Figure 1). Acyclovir was immediately discontinued, and given the clinical setting, transfusion was attempted with 10 units of platelet concentrate. Before administering the platelet transfusion, however, further laboratory investigations were performed, including platelet count measured in a blood sample containing sodium citrate, peripheral blood smear, fibrinogen level, D-dimer level, fibrin degradation products, prothrombin time, international normalized ratio, activated partial thromboplastin time, and lactate dehydrogenase, bilirubin, and haptoglobin levels; no abnormal findings were demonstrated.

In addition, due to the patient's exposure to heparin flushes for maintaining catheter patency, laboratory testing for heparin–platelet factor 4 (PF4 complex) antibodies was performed, which yielded negative results. A bone marrow aspirate revealed an increased number of megakaryocytes, whereas erythroid and myeloid precursors were found to be normal in terms of morphology and numbers. Platelet transfusion led to a minor response of the patient's hematologic parameters; hence, corticosteroids in conjunction with intravenous immune globulin were administered. Complete rebound of the platelet count and clinical response were noted within the next week.

Additional workup for detection of acyclovir-dependent platelet antibodies indicated positive results. In particular, using the enzyme-linked immunospecific assay, high levels of IgG acyclovir-dependent, platelet-reactive antibodies were identified when the patient's serum was incubated with normal platelets in the presence of acyclovir, whereas no immunoglobulin was detected when patient's serum was incubated with intact platelets in the absence of acyclovir. These findings, taken together with the temporal relationship between the putative drug (acyclovir) and the onset of thrombocytopenia, along with the exclusion of the other most frequently occurring known causes of thrombocytopenia, established a definitive diagnosis of acyclovir-induced immune thrombocytopenia.

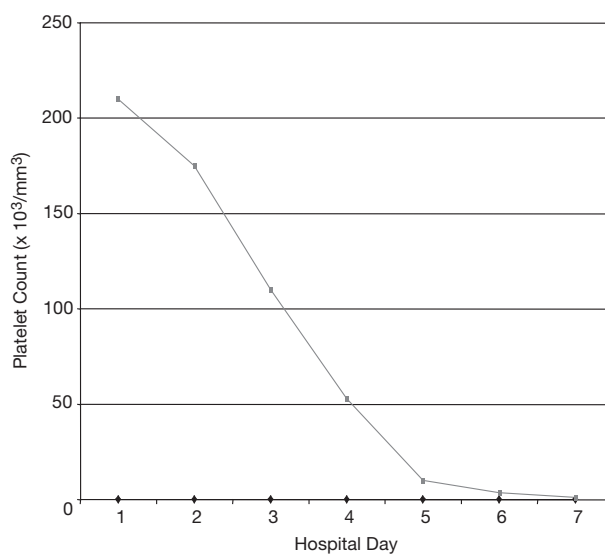


Figure 1. Time course of the patient's platelet count after starting treatment with intravenous acyclovir on hospital day 1.

The patient was discharged 3 weeks after admission, without any major complications. One month later, there was no recurrence of thrombocytopenia or the shingles lesions. Due to the presence of specific antibodies and our patient's previous severe reaction, the patient was not rechallenged with acyclovir.

## Discussion

Acyclovir has been licensed as an antiviral agent for nearly 30 years in clinical medicine. It has effective antiviral activity that is essentially confined to the herpes viruses and is particularly active against the herpes simplex and varicella-zoster viruses.<sup>1, 2, 11-13</sup> The drug is incorporated into viral DNA and eliminates its synthesis through phosphorylation by virus-produced thymidine kinase.<sup>14</sup> Since the drug is only absorbed by the cells that are infected with the virus, acyclovir has minimal untoward effects.<sup>15</sup>

Drug-induced thrombocytopenia is a progressively common cause of isolated thrombocytopenia, given the ever-growing pharmacopeia nowadays.<sup>16</sup> Drug-induced thrombocytopenia can be the corollary of decreased platelet production (bone marrow suppression) or accelerated platelet destruction (usually immune-mediated destruction). The immune-mediated form of drug-induced thrombocytopenia is a relatively common and occasionally serious condition characterized by the presence of drug-dependent antibodies that bind tightly to the surface of platelets, causing their destruction. Several mechanisms of drug-dependent antibody formation have been suggested, including hapten-induced antibody, drug-glycoprotein complex antibody formation, autoantibody creation, ligand-induced binding site formation, drug-specific antibody production, and immune complex-mediated antibody formation.<sup>17, 18</sup> Numerous drugs have been implicated in its development, but the most frequently associated with immune thrombocytopenia are quinine, quinidine, heparin, anticonvulsants, nonsteroidal antiinflammatory drugs, diuretics, oxaliplatin, antibiotics (e.g., sulfamethoxazole, vancomycin, rifampin), platelet inhibitors, gold salts, antiarrhythmics, and sedatives.<sup>19-21</sup>

The diagnosis of drug-induced thrombocytopenia is mainly established by the exclusion of all recognized causes of thrombocytopenia and the temporal association between the administration of the culpable drug and the development of thrombocytopenia. In addition, clinical criteria

**Table 1. Clinical Criteria and Levels of Evidence for Diagnosis of Drug-Induced Thrombocytopenia**

Variable	Definition
Clinical criteria	<ol style="list-style-type: none"> <li>1. Drug administration preceded thrombocytopenia; recovery from thrombocytopenia was complete and sustained after drug discontinuation</li> <li>2. Other drugs administered before thrombocytopenia were continued or reintroduced after discontinuation of the suspected drug</li> <li>3. Other etiologies of thrombocytopenia were excluded</li> <li>4. Reexposure to the drug resulted in recurrent thrombocytopenia</li> </ol>
Levels of evidence	
Definite	Criteria 1-4 met
Probable	Criteria 1-3 met
Possible	Only criterion 1 met
Unlikely	Criterion 1 not met

Adapted from reference 19.

have been devised to support the causal relationship of individual drugs with thrombocytopenia.<sup>20, 22</sup> Although these criteria (Table 1) are helpful in determining which agents can produce thrombocytopenia, they do not provide a definite way of establishing the causative agent in an individual when a diagnostic challenge with the offending drug is not performed after recovery from the thrombocytopenia. Moreover, the detection of drug-dependent antiplatelet antibodies can substantiate the diagnosis of drug-induced thrombocytopenia.<sup>23</sup> This testing, however, is time consuming to perform, and receipt of assay results requires several days to weeks, which hinders the decision on whether to withdraw a potentially implicated drug. Results can also be negative in patients with definite or probable drug-induced thrombocytopenia because assays may be inadequately sensitive to detect antibodies; several drugs are insoluble in water, and in vitro tests are thus difficult to perform; and a drug metabolite produced in vivo can be the culprit agent for thrombocytopenia. Nevertheless, in vitro detection of platelet-bound antibodies, in the presence of the candidate drug, provides strong evidence that the tested drug is responsible for causing thrombocytopenia. A diagnostic challenge with the culprit agent after recovery from the thrombocytopenia can be performed in special situations when the drug-dependent antibody test is negative and the offending drug is indispensable to a patient's care.

The diagnosis in our patient was established by

ruling out all known causes of nondrug isolated thrombocytopenia after a thorough workup. Of interest, varicella-zoster virus infection could itself have been the cause of severe thrombocytopenia<sup>24</sup>; however, this was unlikely given our patient's normal platelet count before acyclovir treatment was started. Moreover, the diagnosis of acyclovir-induced immune thrombocytopenia was supported by clinical criteria (Table 1), as well as the identification of specific acyclovir-dependent platelet antibodies. The fact that our patient received no other drugs besides acyclovir facilitated the diagnosis to a large extent. However, if the patient had been receiving several concomitant drugs, the identification of the offending agent would be more difficult, since each drug should be evaluated, one at a time, by its withdrawal or substitution with another drug, if possible. This diagnostic approach, however, can be risky in cases of severe thrombocytopenia because the culprit drug may not directly be withdrawn.

Although decreases in hematologic indexes are described as adverse effects in acyclovir's package insert, grave isolated immune thrombocytopenia after intravenous acyclovir infusion is not mentioned.<sup>25</sup> There is also a paucity of published literature pertaining to marrow-suppressive adverse effects with acyclovir use. In particular, a few published case studies describe patients who experienced leukopenia and/or thrombocytopenia while receiving acyclovir.<sup>26, 27</sup> However, those patients suffered from immunosuppressive conditions (e.g., lymphomas, acquired immunodeficiency syndrome, bone marrow transplantation, use of antineoplastic drugs) and were infected concomitantly with herpes viruses, thus mystifying the cause of blood cell count derangement.

One case report describes an infant with severe herpes simplex encephalitis whose neutropenia was completely restored when acyclovir was discontinued and then recurred when the drug was reintroduced, thus demonstrating that the neutropenia was due to acyclovir administration.<sup>7</sup> In another case report, anemia and mild leukopenia developed in a child with severe herpes zoster who was treated with intravenous acyclovir.<sup>8</sup> A bone marrow aspiration revealed decreased erythroblasts as well as increased promyelocytes and myelocytes, suggesting a possible mechanism for acyclovir-induced myelotoxicity by inhibiting maturation of red and white blood cell precursors.

Acyclovir use in neonates infected with herpes

simplex virus was demonstrated to be well tolerated, aside from reversible neutropenia in a small group (21% of patients).<sup>28</sup> However, in a randomized controlled trial that investigated the efficacy of intravenous acyclovir in infants with neonatal herpes simplex virus, leukopenia was not observed but mild thrombocytopenia developed in a few of the infants.<sup>10</sup>

Neutropenia (absolute neutrophil count 987 cells/mm<sup>3</sup>) and mild thrombocytopenia (platelet count 122 x 10<sup>3</sup>/mm<sup>3</sup>) was reported in a boy treated with oral acyclovir as "preemptive" therapy for herpes labialis recurrence.<sup>9</sup> On further questioning, it was disclosed that the child had received oral acyclovir 200 mg twice/day for 5 months, as prescribed by his pediatrician. The diagnosis of acyclovir-associated neutropenia and thrombocytopenia was mainly based on the authors' clinical observation that discontinuation of the acyclovir led to rapid resolution of hematologic abnormalities.

## Conclusion

This case report highlights that acyclovir could be a cause of severe isolated immune thrombocytopenia and that clinicians should be aware of this potential adverse reaction. The diagnosis of acyclovir-induced thrombocytopenia is made by using clinical criteria and is supported by positive testing for acyclovir-dependent antiplatelet antibodies. Prompt diagnosis of this serious condition is the cornerstone of appropriate management.

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