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【 CASE REPORT 】

Thrombocytopenia Caused by Dexamethasone in a Patient with Colorectal Cancer

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Abstract:

Drug-induced immune thrombocytopenia (DITP) is an important cause of thrombocytopenia. A 73-year-old man with relapsed rectal carcinoma received S-1, oxaliplatin and bevacizumab combination therapy (SOX+Bev). Dexamethasone was administered as an antiemetic prophylaxis. On day 2 of the first cycle, thrombocytopenia (8,000/μL) was observed. We sequentially omitted any drugs suspected to possibly induce thrombocytopenia and confirmed dexamethasone as the cause of thrombocytopenia. DITP induced by synthetic corticosteroids is very rare and this is the first case report of DITP induced by dexamethasone. Although rare, DITP due to synthetic corticosteroids including dexamethasone should be a differential diagnosis among patients receiving synthetic corticosteroids with thrombocytopenia.

Key words: drug-induced immune thrombocytopenia, dexamethasone

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Introduction

Drug-induced immune thrombocytopenia (DITP) is relatively common, but it can be easily overlooked (1). This condition sometimes causes massive bleeding and can sometimes become fatal, and early detection is thus important. The pathogenesis is mainly due to specific immune responses mediated by immunoglobulin (Ig)G, at least 100 drugs have been reported to be causative agents (2) and the incidence is 10 cases per 1,000,000 population per year (3). The diagnostic criteria reported by George, et al. is the most widely used (4). If symptoms occur, platelets can be recovered if the drug is discontinued promptly. However, due to the rarity of this condition, the diagnosis is usually delayed. As for synthetic corticosteroids, prednisolone and methylprednisolone have been reported as causative drugs (5, 6), but no reports have described DITP attributed to dexamethasone. We herein report a rare case of drug-induced thrombocytopenia due to dexamethasone.

Case Report

A 73-year-old man diagnosed with rectal cancer cT2N0M0 Stage I (UICC-TNM Classification, 8th edition) underwent laparoscopic-assisted abdominal-perineal transrectal amputation plus D3 lymph node dissection plus sigmoid colostomy in April 20XX. The postoperative diagnosis was pT2N1cM0, stage IIIA, and well- to moderately differentiated adenocarcinoma; the RAS status was mutant (KRAS G12V). Oral tegafur/uracil (UFT) plus oral leucovorin (LV) was continued for half a year as adjuvant chemotherapy after June 20XX. CT in October 20XX+1 revealed multiple lung metastases, and a relapse of rectal cancer was diagnosed. In January 20XX+2, he started oxaliplatin, 5-fluorouracil, leucovorin and bevacizumab combination therapy (mFOLFOX6

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Table 1. mFOLFOX6+Bev Regimen and SOX+Bev Regimen.

Table 1a				
mFOLFOX6+Bev (repeated every 2 weeks)				
Rp.1	Palonosetron	iv	0.75 mg	15 min
	Dexart® injection		6.6 mg	
	Sarine		50 mL	
Rp.2	Bevacizumab	iv	5 mg/kg	90 min
	Sarine		100 mL	(after the second time 60 min→30 min)
Rp.3-1	Leucovorin	iv	200 mg/m^2	120 min
	5% glucose solution		250 mL	
Rp.3-2	Oxaliplatin	iv	85 mg/m^2	120 min (co-administration with l-levofolinate)
	5% glucose solution		250 mL	
Rp.4	Fluorouracil	bolus	400 mg/m^2	bolus
	Sarine		50 mL	
Rp.5	Fluorouracil	civ	2,400 mg/m^2	46 h
	Sarine		total 230 mL	

Table 1b				
SOX+Bev (repeated every 3 weeks)				
Rp.1	Palonosetron	iv	0.75 mg	15 min
	Dexart® injection		6.6 mg	
	Sarine		50 mL	
Rp.2	Bevacizumab	iv	7.5 mg/kg	90 min
	Sarine		100 mL	(after the second time 60 min→30 min)
Rp.3	Oxaliplatin	iv	130 mg/m^2	120 min
	5% glucose solution		250 mL	
Rp.4	Sarine	iv	50 mL	15 min
oral cytotoxic agents	S-1	po	40-60 mg according to body surface area	twice daily for 2 weeks

iv: intravenous injection, bolus: bolus injection, civ: continuous intravenous injection, po: per os

+Bev) (the regimen is shown in Table 1a) as first-line chemotherapy. The lung metastases shrank and he achieved a partial response (PR) according to the Response Evaluation Criteria In Solid Tumors (RECIST) after 10 cycles. In June 20XX+3, while he underwent the 32nd course of mFOLFOX6+Bev therapy, mild allergic symptoms (rash, forehead discomfort) appeared during the co-administration of oxaliplatin and LV, We firstly suspected oxaliplatin to be the cause, but allergic symptoms appeared even after omitting oxaliplatin administration. We sequentially omitted any suspicious drugs. LV was finally considered to be the cause of allergic reaction. Accordingly, we decided to change the regimen to S-1, oxaliplatin and bevacizumab combination therapy (SOX+BV; regimen is shown in Table 1b), which does not contain LV. In September, SOX + Bev was administered on admission and no allergic reactions were seen. However, thrombocytopenia (8,000/μL) was observed at the next day of the administration (day 2) (Figure). The white blood cell count, red blood cell count and coagulation parameters (PT and APTT) were normal (Table 2). Thrombocytopenia as a marker of bone marrow suppression resulting from chemotherapy was ruled out based on the timing. Pseudo-thrombocytopenia was excluded because of no platelet aggregation in peripheral blood smears and thrombocytopenia was finally confirmed by a blood test using a heparin blood collection tube. Heparin-induced thrombocytopenia (HIT) was excluded because thrombocytopenia occurred without the use of heparin. Furthermore, idiopathic thrombocytopenic purpura (ITP) was excluded because the administration of suspected drugs causes repeated thrombocytopenia, and the discontinuation of suspected drugs promptly restored platelet counts although the platelet-associated-IgG (196.2 ng/107 cells) level was elevated. According to these situations and the diagnostic criteria (4), DITP was considered. Suspicious drugs were S-1, oxaliplatin, bevacizumab, palonosetron and dexamethasone sodium phosphate injection (Dexart®, Fuji Pharma, Tokyo, Japan). The re-administration of S-1 did not cause thrombocytopenia. Because no nausea was present, palonosetron was first discontinued, and only oxaliplatin, bevacizumab and dexamethasone sodium phosphate injection were administered, but the platelet count decreased to 3,000/μL the next day. Next, after the recovery of platelets, bevacizumab and dexamethasone sodium phosphate injection were administered. However, the platelet count decreased to 9,000/μL the next day. Finally, dexamethasone sodium phosphate alone was administered. Surprisingly, platelets decreased to 6,000/μL and mild nasal bleeding was observed, thus indicating dexamethasone so-

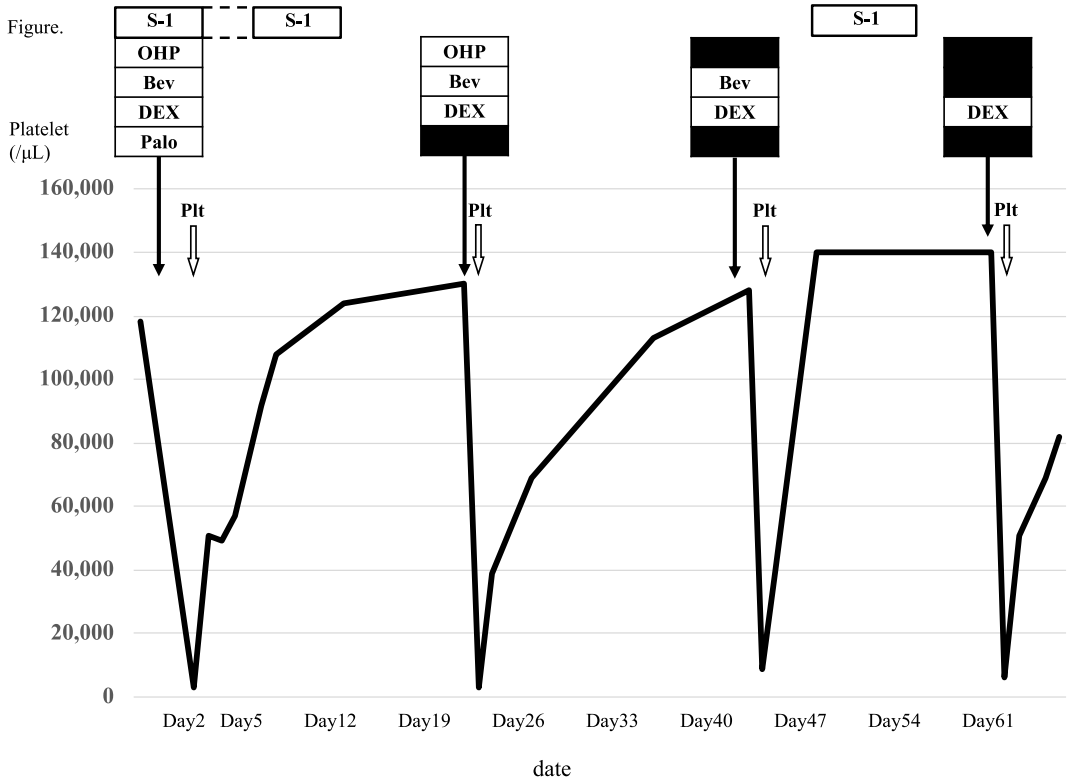

Figure. **The time course of platelet count. Upper boxes show administrated drugs. OHP: oxaliplatin, Bev: bevacizumab, DEX: dexamethasone (Dexart®), Palo: palonosetron, Plt: platelet transfusion**

Table 2. **Blood Test Data before and after Administration of Dexamethasone.**

	Reference	Baseline (Day-3)	The day after dexamethasone was administered (Day2)
WBC count (/μL)	3,330-8,600	4,430	10,440
Hemoglobin (g/dL)	13.7-16.8	12.7	13.2
Platelets count (/μL)	158,000-348,000	118,000	8,000
PT-INR	0.9-1.1	ND	1.05
APTT (s)	26-41	ND	27.9
Fibrinogen (mg/dL)	200-400	318	279
FDP (μg/mL)	<5.0	2.5	3.4
D-dimers (μg/mL)	<1.0	0.5	1.3
Total bilirubin (mg/dL)	0.4-1.5	0.7	1.1
AST (U/L)	13-30	31	32
ALT (U/L)	10-42	16	24
Creatinine (mg/dL)	0.65-1.07	0.57	0.65
CRP	<0.14	0.04	0.16

WBC: white blood cells, PT-INR: prothrombin time international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, ND: not determined

dium phosphate injection as the cause of DITP. Dexamethasone sodium phosphate injection was subsequently changed to oral dexamethasone (Decadron®). No platelet counts were measured on the day of oral dexamethasone administration, but the platelet count dropped to 45,000/μL the next day after oral dexamethasone administration in April 20XX+4. The last platelet count (110,000/μL) was made before 19 days from the administration of dexamethasone. No common additives were identified between Dexart® injection and Decadron® (Table 3). The effects of the additives were thus excluded, and we concluded that dexamethasone itself had resulted in thrombocytopenia. Since then, chemotherapy has been continued with the omission of dexamethasone, and no relapse of thrombocytopenia has been observed.

Table 3. Ingredients of Dexart® Injection and Decadron® Tablet.

Dexart® injection	Dexamethasone sodium phosphate, Dibasic sodium phosphate hydrate, Sodium citrate hydrate, Sodium hydrogen sulfite, Sodium chloride, Sodium hydroxide
Decadron® tablet	Dexamethasone, Lactate, Calcium hydrogen phosphate, Corn starch, Magnesium stearate, Red ferric oxide

Inactive ingredients of Decadron tablet do not include those of Dexart injection.

Discussion

Drugs can cause thrombocytopenia through three mechanisms: bone marrow suppression as seen in chemotherapy; the suppression of platelet production in a dose-dependent manner such as with linezolid; and specific immune responses, defined as DITP. DITP often exhibits severe thrombocytopenia, and it may sometimes induce severe symptoms such as gastrointestinal bleeding and alveolar bleeding, so an early diagnosis is important. As far as we know, this appears to be the first report of DITP caused by dexamethasone.

The annual incidence of DITP is estimated to be about 10 per million population and it may be higher in certain populations, such as hospitalized patients and the elderly, according to several epidemiological studies in the United States and Europe (7). However, this frequency may be underestimated, as DITP is often overlooked (8). Exceptionally few drugs (abciximab and gold salts) cause thrombocytopenia in about 1% of patients (9). At least 100 causative drugs have been reported, and approximately 40 of those drugs that meet the clinical diagnostic criteria (4), which is the most widely used, fall under the category of definite. The present case also meets these criteria. In an article that reviewed the detection of antiplatelet antibodies with the criteria for in vitro reproducibility, 16 drugs showed the highest evidence level, met the clinical diagnostic criteria and displayed in vitro reproducibility (10). DITP caused by steroids is very rare. However, prednisolone and methylprednisolone have been reported to cause DITP (5, 6).

Although the underlying mechanism of DITP has not been completely elucidated, it is thought that DITP develops through platelet-reactive IgG and IgM in the presence of drugs which targets glycoprotein IIb/IIIa and Ib/V/IX complexes on the platelet surface (11, 12). Six types of mechanisms have been proposed: a) hapten-dependent antibody, with covalent binding of drug to platelet membrane proteins inducing an immune response; b) quinine-type drugs, with non-covalent binding of drugs to platelet glycoproteins recognized by a drug-dependent antibody only in the presence of a drug; c) fiban-type drug, with drug binding to glycoprotein (GP) IIb/IIIa inducing neoepitopes recognized by drug-dependent antibody; d) drug-specific antibody, with antibody recognizing mouse components of mouse/human chimeric Fab fragments of drug bound to platelet GPIIb/IIIa; e) autoantibody, with drug inducing production of a true platelet autoantibody; and f) immune complex, with drug binding to platelet factor 4 (PF4) and then making an IgG-drug-PF4 complex that activates platelets and results in thrombosis. The most frequent DITP is the quinine type. In a report of DITP due to methylprednisolone, anti-GP IIb/IIIa was observed only in the presence of methylprednisolone. Dexamethasone is a synthetic steroid first produced in 1958 and it is a fluorine compound that is not produced in vivo. The presence of platelet reactive antibody was not experimentally confirmed in the present report. Curtis BR et al. reported that oxaliplatin tends to induce multiple drug-dependent platelet-reactive antibodies (DDAbs) which cause DITP (13). They experimentally confirmed the presence of DDAbs specific various drugs including dexamethasone. It is possible that oxaliplatin treatment induced DDAb specific for dexamethasone, which thus led to DITP in the present case.

Sensitization to the causative drug is generally considered to be established after about 1 week of exposure or with intermittent administration for a long time. After the establishment of sensitization, DITP usually develops 1-2 days after the administration of the causative drug. Symptoms include bleeding and systemic symptoms such as headache, chills, fever and nausea. Vomiting often precedes bleeding symptoms. Thrombocytopenia is often severe, reducing the platelet count to less than 20,000/μL. After withdrawal of the drug, symptoms recover 1-2 days later and the platelet count normalizes in less than a week (9). In the present case, the platelet count decreased to less than 10,000/μL the day after dexamethasone administration, then it showed a rapid recovery after discontinuation of the suspected drug. Before SOX +Bev therapy, the patient received 36 cycles of mFOLFOX6 +Bev and dexamethasone sodium phosphate injection was also administered with each cycle. Whether thrombocytopenia occurred during mFOLFOX6+Bev is unclear, because we check the blood counts every two weeks, consistent with each cycle of mFOLFOX6+Bev. Accordingly, the timing of the onset of DITP due to dexamethasone was therefore unclear in this case.

To diagnose DITP, it is necessary to exclude other causes such as pseudo-thrombocytopenia, HIT and ITP. Pseudo-thrombocytopenia was excluded because no platelet aggregation was observed in a peripheral blood smear and a blood test using a heparin blood collection tube showed thrombocytopenia. HIT was ruled out because thrombocytopenia by dexamethasone occurred when heparin was not used. ITP was also excluded because thrombocytopenia promptly recovered within a week after the discontinuation of dexamethasone and this clinical course is not consistent with ITP. Although PA-IgG was detected in the present case, its

biological role was not evaluated, and this is a limitation of the present report. The patient sometimes manifested slight nasal bleeding and it is possible to be caused by DITP although bevacizumab, an anti-angiogenic antibody, was initially suspected as the cause because it often shows the side effect of bleeding. Considering the present case, measuring the platelet count at an early stage after administration of anticancer drugs may be warranted. The first treatment for DITP is discontinuation of the causative agent. Corticosteroids may be given empirically following treatment for idiopathic thrombocytopenic purpura or thrombotic thrombocytopenic purpura, but evidence for the efficacy of this is lacking. Gamma globulin (14) and plasma exchange (15) have been used for severe cases, but their benefits are also uncertain. In this case, other than platelet transfusion, the discontinuation of DEX was sufficient for the patient to recover from thrombocytopenia.

Dexamethasone was therefore found to cause DITP. Early measurement of the platelet count and discontinuation of suspected drugs were useful for the diagnosis. If bleeding symptoms arise, it is important to not only consider the adverse events caused by angiogenesis inhibitors, but also to conduct platelet measurements under a suspicion of DITP.

Author's disclosure of potential Conflicts of Interest (COI).
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