Drug-induced thrombocytopenia in a patient with colorectal cancer: A case report

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Received February 13, 2023; Accepted June 12, 2023

DOI: 10.3892/ol.2023.13984

Abstract. Drug-induced thrombocytopenia is an adverse reaction characterized by accelerated platelet destruction. The present study described a case of thrombocytopenia that occurred during treatment with panitumumab. A female patient aged 49 years with metastatic rectal adenocarcinoma was treated with 9 out of 12 cycles of therapy with the standard of care, 5-fluorouacil (5-FU), oxaliplatin and folic acid, in association with panitumumab. During cycle 10, the patient developed severe thrombocytopenia, so the therapy was adjusted to a lower dosage; however, during cycle 11, after administration of panitumumab and before administration of 5-FU or oxaliplatin, the patient again presented with severe thrombocytopenia, with a platelet count <$2x10^9$/l. Immunology test results were negative apart from anti-nucleus antibodies (titration, 1:160). Naranjo's algorithm was used to establish the relationship between the use of panitumumab and thrombocytopenia onset and a score of 6 ('probable') was found. The temporal link between the onset of symptoms and administration of therapy, the relapse of thrombocytopenia after re-administration of the drug during cycle 11 (positive rechallenge) and Naranjo score of 6 ('probable') are crucial elements for establishing the causal relationship and the probability that thrombocytopenia was related to the administration of panitumumab. The patient then underwent two cycles of therapy with 5-FU, folic acid and irinotecan, in association with bevacizumab, experiencing again the same adverse event. Treatment with monoclonal antibodies was suspended altogether in favor of a switch to trifluridine/tipiracil. No other serious adverse events were reported.

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Key words: colorectal cancer, panitumumab, bevacizumab, thrombocytopenia, adverse drug reaction

Introduction

Chemotherapy-induced thrombocytopenia is a relatively common adverse drug reaction (ADR) in the oncological setting; the effects of chemotherapy drugs such as oxaliplatin or fluoropyrimidines on bone marrow functionality are well known (1). Oxaliplatin is a third-generation platin compound frequently used for colorectal cancer; thrombocytopenia is a common adverse reaction during treatment, occurring in up to 70% of patients (2,3). Drug-induced thrombocytopenia is an ADR characterized by accelerated platelet destruction or interference with regular bone marrow function, resulting in impaired platelet growth (4). It is characterized by a severe and rapid reduction of the platelet count, usually <$50x10^9$/l, which may lead to clinically relevant conditions such as purpura, spontaneous bleeding or even haemorrhage, requiring blood transfusion in certain cases. Once identified, the causative agent must be immediately suspended and further re-exposure should be avoided, as it may lead to relapse of the disorder (positive rechallenge) (5). The present case report described the occurrence of acute thrombocytopenia, probably triggered by panitumumab, a human anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (mAb), in an oncology patient.

Case report

The patient was a female aged 49 years who was diagnosed with rectal adenocarcinoma in June 2018 at the Medical Oncology Unit of E.O. Ospedali Galliera (Genoa, Italy). There, from 2018 to 2020, the patient was administered chemotherapy with 5-fluorouracil (5-FU), Oxaliplatin, L-leucovorin (FOLFOX4 regimen). Afterwards, the patient was treated with Radiotherapy in combination with Capecitabine up until 2021, when metastatic progression was reported (pT3, N2b, M1). Therefore, at the end of June 2021, the patient started therapy with FOLFOX6, a chemotherapeutic regimen composed of 5-FU, oxaliplatin and folic acid, in association with panitumumab, a human mAb (IgG2 subtype). The intravenous (IV) dosage was as follows: Oxaliplatin 135 mg IV infusion over 2 h, 5-FU 600 mg IV bolus injection + 4,000 mg IV 48 h infusion (corrected for body surface area), L-leucovorin

Table I. Laboratory findings from day 0 to day 7 after administration of panitumumab (cycle 11).

Parameter	Day 0	Day 1	Day 3	Day 7	Reference range
Hb, g/l	14	13.2	12.9	13.3	12.5-15.5
WBC, x10^9/l	5.99	9.32	10.52	6.36	4.19-9.35
Neutrophil count, x10^9/l	3.52	7.72	9.06	4.06	1.81-6.74
PLT, x10^9/l	130	2	55	123	169-359
CRP, mg/dl	0.06	0.08	-	-	0.00-0.05
Fibrinogen, mg/dl	260	282	-	-	180-450
d-dimer, ng/ml	1,293	-	-	-	<500
IgG, mg/dl	-	-	2,296	-	700-1600
IgA, mg/dl	-	-	104	-	70-400
IgE, mg/dl	-	-	100	-	40-230
C3, mg/dl	-	-	121.3	-	90.0-180.0
ANA	-	-	1:160	-	Titration <1:160
ANCA	-	-	1:5	-	Titration <1:10
Sm-Ab	-		Negative	-	Not applicable
Anti-RNP	-		Negative	-	Not applicable
Anti-SS-A/Ro	-		Negative	-	Not applicable
Anti-SS-B/La	-		Negative	-	Not applicable
Anti-Scl-70	-		Negative	-	Not applicable
Anti-Jo-1	-		Negative	-	Not applicable
Anti-PF-4	-		Negative	-	Not applicable

HB, haemoglobin; WBC, white blood cells; PLT, platelet count; CRP, C-reactive protein; Ig, immunoglobulin; C, complement; ANA, antinuclear antibodies; ANCA, anti-neutrophil antibodies; Sm-Ab, anti-Smith antibodies; anti-SSA, anti-Ro/Sjögren's-syndrome-related antigen A; anti-SSB, anti-La/Sjögren's syndrome-related antigen B; anti-PF-4, anti-platelet factor 4 antibodies; anti-RNP, antinuclear ribonucleoprotein.

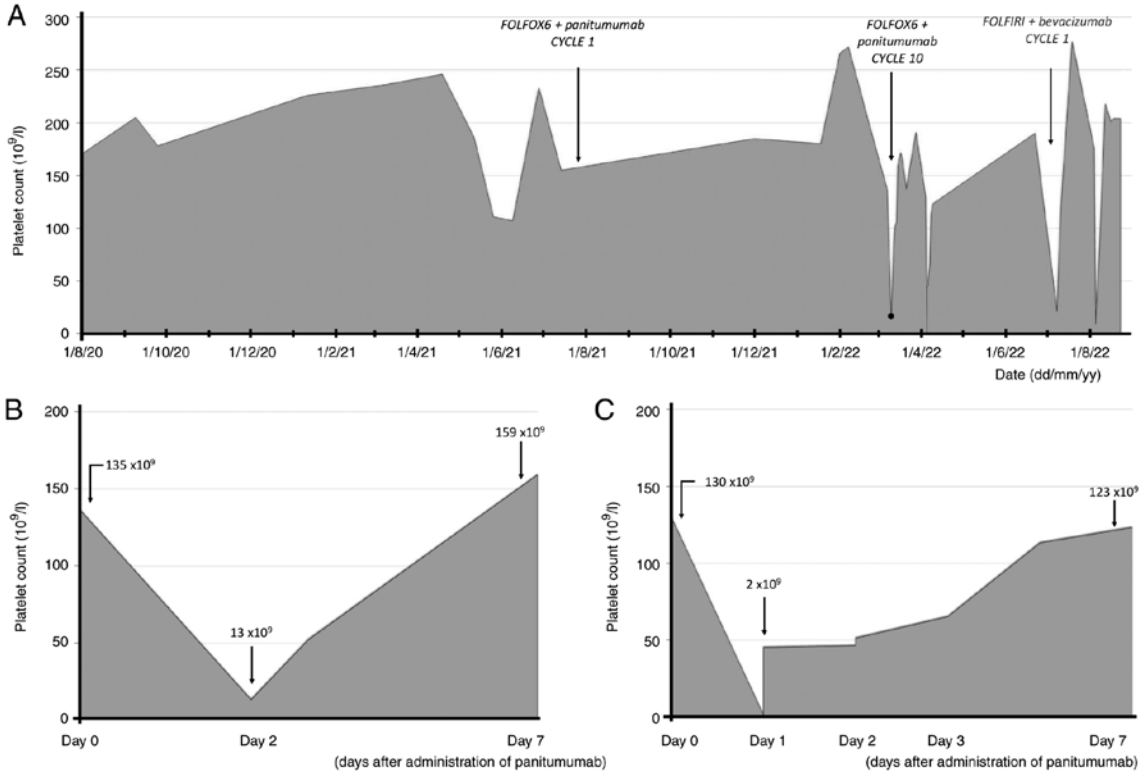

Figure 1. Graphs of platelet count during different periods of time. (A) Platelet count of the patient over a 24-month period; the day of first administration of FOLFOX6 + panitumumab and FOLFIRI + bevacizumab was highlighted. (B) Platelet count during cycle 10 of FOLFOX6 + panitumumab. Dates are expressed from day 0 to day 7 after administration of the drug. (C) Platelet count during cycle 11 of FOLFOX6 + panitumumab. Dates are expressed from day 0 to day 7 after administration of the drug

300 mg IV infusion over 2 h and panitumumab 320 mg IV; panitumumab was the first drug administered, followed by oxaliplatin with leucovorin, followed by 5-FU. The therapy was well tolerated for 9 cycles, with three more to complete before re-evaluation of the disease. No life-threatening events of thrombocytopenia were reported nor documented in the 4 years of treatment (from diagnosis to March 2022). In March 2022, the patient was administered her 10th cycle of therapy; at 48 h after administration, the patient had developed severe thrombocytopenia, as indicated by a low platelet count ($13x10^9$/l; normal range, 169-359 $x10^9$/l) and purpura on both legs. The patient was rapidly treated with transfusion of 1 bag of blood (450 ml) and was transferred to the Internal Medicine Unit of E.O. Ospedali Galliera (Genoa, Italy), where she was monitored. After 7 days, the patient's platelet count increased to $158x10^9$ (Fig. 1A), and the patient was then discharged. According to the most recent Common Terminology Criteria for Adverse Events (AEs) v.5.0 (6), this event was classified as grade 3 thrombocytopenia. The AE was regarded as being caused by chemotherapy (CT), so at the next planned cycle of therapy (11th cycle in April 2022), the CT dosage was overall reduced as follows: Oxaliplatin 110 mg (20% reduction), 5-FU 500 mg IV bolus injection (20% reduction) + 2,800 mg (30% reduction) IV infusion for 48 h, L-leucovorin 300 mg (unchanged) and panitumumab 320 mg (unchanged). Soon after the end of panitumumab IV infusion, the patient developed acute back pain and shivering; therefore, subsequent CT was suspended altogether. The next morning, the patient had developed severe thrombocytopenia (platelet count $<2x10^9$/l, double checked) and purpura, leading once more to admission to the Internal Medicine Unit. The patient was hospitalized and treated with transfusion of 1 bag of blood and dexamethasone 6 mg IV infusion once per day. Blood tests indicated increased d-dimer (1,293 ng/ml), while activated partial thromboplastin time, prothrombin time, haemoglobin, white blood cell count, neutrophil count and fibrinogen results were normal. Immunology tests were conducted regarding anti-nucleus antibody (ANA), anti-double-strand DNA antibodies, anti-Smith antibodies, anti-ribonucleoprotein antibodies, anti-Ro/Sjögren's-syndrome-related antigen A, anti-La/Sjögren's syndrome-related antigen B, anti-platelet factor 4 antibodies, anti Jo-1 antibodies, anti SCl-70 antibodies, IgM and IgG. These autoimmunity test results were negative except for ANA (titration, 1:160) and increased levels of IgG (2,296 mg/dl). After 5 days of therapy and observation, the patient's platelet count returned to normal (Table I). No other AEs were reported. The Clinical Pharmacology Unit of E.O. Ospedali Galliera (Genoa, Italy) used Naranjo's algorithm to calculate the probability of relationship between the reported adverse event and the drug, resulting in a score of 6 (‘probable’) (7). The toxicity levels were deemed clinically unacceptable by the oncologists; thus, treatment with the FOLFOX6 regimen and panitumumab was interrupted and re-evaluation of disease was anticipated. Positron emission tomography taken in June 2022 documented progression of disease; therefore, the oncologists decided to further treat the patient with a different mAb both in terms of mechanism of action and in IgG type. Thus, CT with the FOLFIRI regimen and bevacizumab, a humanized anti-VEGF mAb (IgG1 subtype), was chosen for start in July. The dosage of the new treatment option was as follows: Irinotecan 280 mg IV infusion over 1 h, 5-FU 500 mg IV bolus injection + 2,800 mg IV 48 h infusion, L-leucovorin 300 mg IV infusion over 2 h and bevacizumab 270 mg IV; irinotecan and leucovorin are administered first, followed by bevacizumab and 5-FU. However, 48 h after administration of the new treatment, the patient experienced a similar event of thrombocytopenia (platelet count, $21x10^9$/l; Fig. 1A). Re-evaluation of the autoimmunity panel was then conducted, but once again, the results were negative except for ANA titration 1:160. After careful considerations, treatment with monoclonal antibodies was suspended altogether. The next treatment in August 2022 was conducted with only FOLFIRI. Once more, the patient manifested with sings of acute thrombocytopenia (platelet count, $12x10^9$/l). Treatment with FOLFIRI was terminated altogether. In September 2022, the patient started a new treatment with trifluridine/tipiracil, 110/45 mg/day oral tablet. The patient is currently undergoing this therapy without the occurrence of any serious AEs.

Discussion

Panitumumab is a human monoclonal antibody authorized for the treatment of metastatic colorectal cancer. This drug is an IgG2 that binds to EGFR, inhibiting the growth of cells expressing this receptor, such as epidermal and certain tumoral cells. After the suspension of panitumumab and re-evaluation of disease, which documented a progression, the oncologists decided to treat the disease with another mAb with a different subtype and mechanism of action; thus, treatment with bevacizumab was chosen. Bevacizumab is a humanized mAb with antiangiogenic properties. It is approved for the treatment of advanced colorectal cancer, non-small cell lung cancer, breast cancer and renal cell cancer; the drug is an IgG1 antibody that binds to VEGF, inhibiting vascular growth. Drug-induced immune thrombocytopenia is a rare ADR, with an incidence of 1 case per 100,000 patients (8); it is a particular case of ADR in which certain medicines interact with platelets, accelerating their destruction through immune-mediated interactions and reducing their effective count. Among haematological AEs, the panitumumab datasheet reports anemia (very common, ≥1/10) and leucopenia (common, ≥1/100), but not thrombocytopenia (9). According to the European drug vigilance database (EudraVigilance), from 2014 up to July 2022, a total number of 138 cases of thrombocytopenia was reported; however, it is unclear whether panitumumab was the causative agent or just concurrent therapy (10). Literature describing panitumumab-related thrombocytopenia is scarce; however, it is worth noting that there is one other case report describing a similar AE after panitumumab administration (11). Bevacizumab is more frequently the cause of immune-mediated thrombocytopenia, as proven by the abundance of papers and reports that describe this type of occurrence (12-15). The reason for the more frequent immune-mediated AEs may be partially attributed to the nature of bevacizumab, a humanized mAb, compared to panitumumab, which is a fully human mAb.

In the case presented in the current study, it may be assumed that platelets were targeted by a destructive mechanism that was probably triggered by panitumumab. Several elements strongly support this assumption: i) The temporal link between the administration and the onset of clinical

manifestations; ii) the triggering of the event after re-administration of panitumumab alone, before any other therapies (such as oxaliplatin or 5-FU); iii) the absence of significant changes in immunological tests except for ANA and IgG, which may be related to the presence of panitumumab (a drug with a half-life of 7-10 days) in the patient's serum; iv) the improvement of symptoms after dechallenge with the suspected causative agent; v) the probability score of relationship between the AE and the drug (score=6), using Naranjo's algorithm (7). Albeit the mechanism of thrombocytopenia was not completely understood, it may be assumed that it is immune-related; the administration of bevacizumab, as a second-choice therapy, probably triggered the same mechanism induced by the first causative agent, a fully human mAb.

The rapid and severe clinical manifestation of thrombocytopenia suggests that more attention should be directed to the subsequent days after infusion of the mAbs; anticipating the routine complete blood count tests to identify early signs of severe thrombocytopenia would be a suggested course of action. In conclusion, the evidence presented in this case report suggests that thrombocytopenia may occur after administration of panitumumab; however, the rarity of the clinical occurrence and scarcity in the pre-existent literature makes it difficult to fully describe the event and the correct diagnostic and therapeutic approach. Physicians should be aware of this rare AE and, if possible, should gather more data to better characterize the pathophysiology and treatment of the occurrence.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available for ethical reasons as per the local guidelines but are available from the corresponding author on reasonable request.

Authors' contributions

SPa, FM, LF, MC, GA, ADC and SPi provided the necessary clinical data. GP and FM provided complementary laboratory data. SPa, MC and FM wrote the manuscript. ADC and GA also contributed to the writing of the report. MC and FM confirm the authenticity of the data. All authors contributed to the review of the manuscript and have read and approved the final version.

Ethics approval and consent to participate

The research was conducted in accordance with the ethical standards of the institutional and national research committee and with the Helsinki declaration. All data were obtained in a completely anonymized fashion to protect patient's privacy.

Patient consent for publication

Written informed consent was obtained from the patient at the time of admission to the Hospital to use the clinical data for research purposes, following the privacy policy of E.O. Ospedali Galliera (Genoa, Italy).

Competing interests

The authors declare that they have no competing interests.

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