

Morphine induced thrombocytopenia: A case report

Ayman Rasmy, Mohammed Rahal, Masood Kisana,
Shakeel Ahmad, Ahmed Salah

ABSTRACT

Introduction: Thrombocytopenia is defined as a platelet count below the 2.5th lower percentile of the normal platelet count distribution. The results of the third US National Health and Nutrition Examination Survey support the traditional value of 150 μL as the lower limit of normal. However, platelet counts between 100 μL and 150 μL , do not necessarily indicate disease if they have been stable for more than six months, and the adoption of a cut-off value of 100 μL may be more appropriate to identify a pathologic condition. **Case Report:** A 57-year-old male patient known diabetic and hypertensive who has metastatic rectosigmoid cancer to the liver that was treated with chemotherapy FOLOFX for 12 cycles with disease progression and uncontrolled severe lower abdominal pain that was not controlled on oral morphine, so started to receive morphine infusion by PCA pump with development of severe thrombocytopenia, which reach Less than 5000 μL . Urgent platelet transfusion was given for life-saving and by investigations, there was

no definite primary pathological cause for this unexplained severe thrombocytopenia, and it was most probably drug –induced secondary to morphine because the depth of thrombocytopenia was increased with the increasing dose of morphine. The diagnosis of morphine induced thrombocytopenia in this case was confirmed by positive anti-platelet antibody and increasing the platelet to 76000 μL one week after stopping the morphine. **Conclusion:** Although it is very rare worldwide, morphine induced thrombocytopenia can happen and may be life threatening if not diagnosed and treated probably.

Keywords: Chemotherapy, Metastatic rectosigmoid cancer, Morphine, Thrombocytopenia

How to cite this article

Rasmy A, Rahal M, Kisana M, Ahmad S, Salah A. Morphine induced thrombocytopenia: A case report. J Case Rep Images Oncology 2015;1:15–19.

Article ID: 100004Z10AR2015

doi:10.5348/Z10-2015-4-CR-4

Ayman Rasmy^{1,3}, Mohammed Rahal¹, Masood Kisana², Shakeel Ahmad², Ahmed Salah²

Affiliations: ¹Adult Oncology Department- King Fahad Specialist Hospital – Dammam-KSA; ²Palliative Department - King Fahad Specialist Hospital – Dammam-KSA; ³Medical Oncology Department- Zagazig University Egypt.

Corresponding Author: Dr. Ayman Ahmed Rasmy, Adult Oncology Department, Oncology Center, King Fahad Specialist Hospital (KFSH-D), Al Murekbat Area, Omar Bin Thabet Street, Dammam, Saudi Arabia; Postal Code Box: 15215, ZIP Code: 31444; Ph: 00966541899333, Fax: 0096638442222 (Ext. 6854); Email: ay_rasmy@yahoo.com

Received: 01 July 2015
Accepted: 14 September 2015
Published: 22 December 2015

INTRODUCTION

Thrombocytopenia separates three stages. Mild: 100,000–150,000 microliter (μL), Moderate: 50,000–100,000 μL . Severe: <50,000 μL . However, thrombocytopenia is not usually detected clinically until the platelet count has fallen to levels below 100,000 μL . Severe thrombocytopenia with intracerebral and intra-

abdominal bleeding may be life-threatening, so the treatment immediately can save the life [1].

There are three main reasons of thrombocytopenia, (a) decreasing platelet production, (b) increasing of platelet destruction, and (c) changing of distribution platelet.

Drugs are a common cause of thrombocytopenia [2]. When evaluating a patient with thrombocytopenia, a medication history (including over-the-counter medications) should be carefully elicited and any recently initiated drug should be suspected.

Most other drugs cause thrombocytopenia by immune mechanisms [1]. The immune thrombocytopenia depends on drugs occurred by forming antibody when the drug is taken for the first time. This antibody, when the drug is taken second time, form complex with drug, this complex connecting platelet membrane and causing platelets lysis. Heparin is one of medication that cause thrombocytopenia by creating a complex with platelet fact 4 (TF4) which is formed from the platelet alpha granule is a cationic protein. [3]. Also morphine, one of the drug that was mentioned to induce immune thrombocytopenia by the same mechanism [4].

To standardize the reporting of adverse reactions in clinical trials, NCI has developed common terminology criteria for adverse events (NCI-CTCAE). The NCI-CTCAE was most recently updated in June 2010 (version 4.03) (Table 1).

CASE REPORT

A 57-years-old male known diabetic and hypertensive who had metastatic rectosigmoid cancer to the liver that was treated with chemotherapy FOLOFX as 48 hr continue infusion every two weeks for 12 cycles, initial assessment post six cycles showed a partial response, so the patient was continued on chemotherapy for total 12 cycles as per a standard guideline (Bevzumab target therapy was not given to avoid bleeding because he had a rectal stent).

Regarding the history of morphine received by this patient before, he was started to receive 3 mg subcutaneous injection (SC) every six hours when he was admitted for chemotherapy and 3 mg syrup as oral (every four hours when he was at home) for about four months and the dose was changed to 10 mg tablets /oral/ twice per day for two months after that. The complete blood pictures (CBC) for this patient never showed any thrombocytopenia, anemia or leucopenia when he received chemotherapy or morphine before as the lowest platelet level was 176,000/ μ L.

Unfortunately, the radiological evaluation post cycle-12 showed he had disease progression, so our decision was to switch him to 2nd line FOLFIRI/Cetuximab but we cannot start at that time because he had severe lower abdominal pain that was not controlled on his home pain medication, so the patient was admitted to be seen by palliative team.

Once the patient was admitted, the palliative team started to give him morphine orally on a regular basis and subcutaneous injection every 2 hours on needed for pain (PRN), but the pain not controlled even with increasing doses up to 60 mg oral/ twice per day for about 3 days, so the decision at that time is to start subcutaneous morphine infusion by PCA pump (the doses of morphine given to him is summarized in Table 2).

Daily laboratory assessment of this patient showed significant decreases in his platelet count, which reach critical levels as given in Table 3.

At these time, urgent six units of platelet transfusion for life-saving was given and we started to investigate for the cause of this unexplained severe thrombocytopenia and as he did not start any chemotherapy yet, and last chemotherapy was given more than one month before and his platelets did not show any decrease before, so chemotherapy-induced thrombocytopenia was excluded.

Regarding other medication the patient was received, he did not receive any medications that commonly induced this thrombocytopenia as showed in Table 4. For clinical and radiological assessment of the liver and

Table 1: NCI-CTCAE* (Version 4).

Adverse reaction	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hb <LLN to 10.0 g/dL	Hb <10.0 g/dL to 8.0 g/dL	Hb <8.0 g/dL; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Neutropenia	Neutrophils <LLN to 1,500/mm ³	Neutrophils <1,500 to 1,000/mm ³	Neutrophils <1,000 to 500/mm ³	Neutrophils <500/mm ³	N/A
Thrombocytopenia	Platelets <LLN to 75,000/mm ³	<75,000 to 50,000/mm ³	<50,000 to 25,000/mm ³	<25,000/mm ³	N/A

Abbreviations: *NCI-CTCAE:- National Cancer Institue-Common Terminology Criteria for Adverse Events . Version 4.0 (Published: May 28, 2009) - V4.03: June 14, 2010) LLN; Lowe Limit of Normal.

Table 2: Morphine Doses

	Oral morphine (mg) Regular	SC morphine (mg) on pain	Pain assessment
Day before infusion pump/SC	60	10	Pain uncontrolled
First day of infusion pump	20	45	Moderate pain
2nd day	Stopped	55	Mild pain
3rd day	Stopped	80	Pain controlled*
4th day	120	10	Pain controlled
5th day	120	5	Pain controlled
6th day	120	0	Pain controlled

Abbreviations: SC: Subcutaneous
NB: once pain was controlled on 3rd day, the oral morphine was resumed on 4th day aiming to stop infusion pump and switch the patient to oral only.

spleen, this patient did not have splenomegaly and the liver showed mets same metastatic lesion as before.

So, by exclusion, morphine was highlighted as the cause of this thrombocytopenia because the depth of thrombocytopenia was increased with the increasing the dose of morphine as given in Table 4, and because of this, both of the oral and infusion morphine were stopped and another opioid (Hydromorphone) was started. After platelet transfusion, his platelet count showed transient increasing then decrease again even with frequent platelet transfusion (six Units every time) which raise suspicion of immune destruction, so we request further studies including anti-platelet antibody which came as positive for GPIIb/IIIa and also positive for IgG/IgM/IgA (Anti-Platelet Ab reactivity).

Close monitoring of this patient clinically and laboratory showed no evidence of purpura or bleeding and his platelet started to increase without any further transfusion, reaching 76000 µL on 9th day post stopping morphine.

From this patient laboratory and radiological assessment as well as his medical history, including chemotherapy, we can conclude that this patient had morphine induced thrombocytopenia which is an interesting case as it is very rare worldwide.

DISCUSSION

As per literature, there was one interested case report was published with sudden thrombocytopenia that was

Table 3: Platelet Level/ Morphine Doses

	Oral morphine (mg) Regular	SC morphine (mg) on pain	Platelet count (µL)
Day before infusion pump	60	10	311
Start Morphine Infusion Pump			
1st day	20	45	302
2nd day	0	55	44
3rd day	0	80	50
4th day	120	10	50
5th day*	120	5	11* 5* 14*
6th day*	120	0	7* 16*
7th day* (morning)	Stop all Morphine (oral and Infusion Pump) due to sever thrombocytopenia (6000 which was corrected to 25000 after platelet transfusion) and patient switched to another analgesic		
1st day after	0	0	6* 25*
2nd day after	0	0	17
3rd day after	0	0	11
4th day after	0	0	21
5th day after	0	0	15
9th day after	0	0	76

Abbreviations: *In these days patient received platelet transfusion and platelet re-checked again post transfusion, so several readings was were documented in that day

Table 4: Medication Received

Medication	Dose
Insulin	20 SQ/BID
Bisoprolol	5 mg/PO/OD
Pantoprazole	40 PO/QD
Metochlopramide	10mg/IV/8hrs-PRN- Vomiting
Morphine	Oral and PCA pump

temporally related to the administration of morphine sulfate developed in a 23-year-old female. A morphine-dependent platelet antibody was found in her serum by chronic chloride Cr 51 platelet lysis. The antibody was complemented dependent, present in the IgG immunoglobulin fraction, and its drug-dependent platelet lytic activity was demonstrable with several narcotic

analgesics in addition to morphine. The antibody activity declined over an eight-month period following recovery from thrombocytopenia. To our knowledge, morphine-induced immune thrombocytopenia has not previously been described [5].

From eHealthMe study [6], from the FDA reports published On January, 26, 2015: There were 48,666 people reported to have side effects when taking morphine. Among them, 156 people (0.32%) have Heparin-induced Thrombocytopenia.

From this report, 100% of this incident was happened in 1st month of receiving morphine, which means it is an early effect with no documented delay effect.

Regarding sex affected, 57.86% of this patient were men and 42.14% were female and regarding the age of the patient, there was 0% effect on patient less than 20 years old and the incidence increasing gradually from 1.31% in age from 20-29 years old to reach highest incidence which is 67.32 at the age above 60.

CONCLUSION

Although, it has a very low incidence worldwide, morphine induced thrombocytopenia can occur in some patients especially with higher doses.

Author Contributions

Ayman Rasmy – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Mohammed Rahal – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Masood Kisana – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Shakeel Ahmad – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Ahmed Salah – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

Copyright

© 2015 Ayman Rasmy et al. This article is distributed under the terms of Creative Commons Attribution License which permits unrestricted use, distribution

and reproduction in any medium provided the original author(s) and original publisher are properly credited. Please see the copyright policy on the journal website for more information.

REFERENCES

1. Sekhon SS, Roy V. Thrombocytopenia in adults: A practical approach to evaluation and management. *South Med J* 2006 May;99(5):491–8.
2. George JN, Raskob GE, Shah SR, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998 Dec 1;129(11):886–90.
3. George JN, Rizvi MA. Thrombocytopenia. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn A eds. *Williams Hematology*. 6ed. New York: McGraw-Hill Co; 2001. p. 1495–1539.
4. Mehmet A, Emin K, Ilhami B, et al. Thrombocytopenia in Adults: Review Article. *Journal of Hematology* 2012 June;1(2-3):44–53.
5. Cimo PL, Hammond JJ, Moake JL. Morphine-induced immune thrombocytopenia. *Arch Intern Med* 1982 Apr;142(4):832–4.
6. eHealthMe Study from FDA and social media reports. eHealthMe 2015. [Available at: <http://www.ehealthme.com>]

Access full text article on
other devices



Access PDF of article on
other devices

