Morphine induced thrombocytopenia: A case report

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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

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 (Bevziumab 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/μL.

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.

### 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/mm3 | Neutrophils <1,500 to 1,000/mm3 | Neutrophils <1,000 to 500/mm3 | Neutrophils <500/mm3 | N/A |
| Thrombocytopenia | Platelets <LLN to 75,000/mm3 | <75,000 to 50,000/mm3 | <50,000 to 25,000/mm3 | <25,000/mm3 | N/A |

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

For clinical and radiological assessment of the liver and
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 GPIb/Ix 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 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

| Day before infusion pump/SC | Day before infusion pump | SC morphine (mg) Regular | SC morphine (mg) on pain | Pain assessment |
|----------------------------|------------------------|--------------------------|-------------------------|----------------|
| 60                         | 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         |                |

**Table 2: Morphine Doses**

| Day before infusion pump/SC | Day before infusion pump | SC morphine (mg) Regular | SC morphine (mg) on pain | Platelet count (μL) |
|----------------------------|------------------------|--------------------------|-------------------------|----------------------|
| 60                         | 60                     | 10                       | Pain uncontrolled       | 311                  |
| First day of infusion pump | 20                     | 45                       | Moderate pain           | 302                  |
| 2nd day                    | Stopped                | 55                       | Mild pain               | 44                   |
| 3rd day                    | Stopped                | 80                       | Pain controlled*        | 50                   |
| 4th day                    | 120                    | 10                       | Pain controlled         | 50                   |
| 5th day*                   | 120                    | 5                        | 11*                    |
| 6th day*                   | 120                    | 0                        | 7*                     |
| 7th day*                   | 120                    | 0                        | 16*                    |

**Table 3: Platelet Level/ Morphin Doses**

| Day before infusion pump/SC | Day before infusion pump | SC morphine (mg) Regular | SC morphine (mg) on pain | Platelet count (μL) |
|----------------------------|-------------------------|--------------------------|-------------------------|----------------------|
| 60                         | 60                      | 10                       | Pain uncontrolled       | 311                  |
| First day of infusion pump | 20                      | 45                       | Moderate pain           | 302                  |
| 2nd day                    | Stopped                 | 55                       | Mild pain               | 44                   |
| 3rd day                    | Stopped                 | 80                       | Pain controlled*        | 50                   |
| 4th day                    | 120                     | 10                       | Pain controlled         | 50                   |
| 5th day*                   | 120                     | 5                        | 11*                    |
| 6th day*                   | 120                     | 0                        | 7*                     |
| 7th day*                   | 120                     | 0                        | 16*                    |

**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 |

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.

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

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.

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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
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Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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