CASE REPORT

Opioid toxicity with underlying tumour lysis syndrome in a patient with CMML: a diagnostic and therapeutic challenge

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SUMMARY

Use of strong opioids like morphine as analgesics for painful conditions in haematological malignancies is a challenging task. We report a unique case of chronic myelomonocytic leukaemia presenting with opioid toxicity overlapping with tumour lysis syndrome. The patient was on hydroxyurea-based chemotherapy for the primary disease. She was receiving oral morphine for abdominal pain due to splenomegaly. She was brought to the emergency in unresponsive state with pinpoint pupils. Opioid overdose leading to unconsciousness was suspected as the first diagnosis. Further workup revealed a final diagnosis of tumour lysis syndrome overlapping with opioid overdose. The patient was ventilated and started on naloxone infusion, and supportive measures for managing tumour lysis were added. The patient gradually improved and was extubated on the fifth day of ventilation. This case presents several learning points for the treating physician. Haematological malignancies have a dynamic course of disease with waxing and waning tumour burden during the course of chemotherapy. This fact should be kept in mind when prescribing strong opioids like morphine on outpatient basis to these patients. Massive tumour cell lysis during the course of chemotherapy may precipitate tumour lysis syndrome and may lead to renal dysfunction which makes the patient susceptible to morphine-related adverse effects. Pain physician should keep a watch for therapy-related adverse effects to avoid diagnostic and therapeutic dilemma associated with coexisting features of these two fatal conditions.

BACKGROUND

Pain in a patient with cancer presents as a complex challenge to the treating physician. Patients with haematological malignancies often present with pain at the onset of disease or during the course of treatment. In most of these patients, pain can be treated using WHO stepladder approach for pain management.[1] Use of strong opioids like morphine as analgesics for painful conditions in haematological malignancies is a challenging task complicated by the dynamic nature of disease and the risk for multiple toxicities.[2 3] Patients with high-grade malignancies like Burkitt lymphoma or malignancies with high initial cell counts on cytotoxic chemotherapy may have metabolic derangements like tumour lysis syndrome due to massive cell lysis. Renal dysfunction being a part of spectrum of tumour lysis makes these patients susceptible to opioid-related adverse effects.[4]

We report a unique case of chronic myelomonocytic leukaemia (CMML) on chemotherapy, and oral morphine 5 mg every 4 hours for pain abdomen due to splenomegaly. Patient presented with suspected opioid overdose; detailed history and investigations pointed towards morphine toxicity superimposed on underlying tumour lysis syndrome. The dynamic nature of disease with rapid cell turnover, risk of chemotoxicity and associated metabolic anomalies may have a variable clinical presentation and may pose a diagnostic dilemma to the treating physician.

CASE PRESENTATION

A 67-year-old woman—a case of suspected haematological malignancy under evaluation—was referred to our pain clinic with pain in the abdomen. The pain was localised on the left side of the abdomen and remained throughout the day with no aggravating or relieving factors. The patient reported a Numeric Rating Score of 7/10 and pain severely limited her daily routine. On abdominal examination, the patient was found to have splenomegaly. Ultrasound abdomen showed hepatosplenomegaly, with splenic size of 16.8 cm. Attributing the left-sided abdominal pain to the enlarged splenic mass, we started the patient on tramadol 50 mg three times a day and paracetamol 500 mg four times a day; the patient was asked to follow up after a week.

On follow-up visit to the pain clinic after a week, it was noted that evaluation for the primary disorder investigations revealed leucocytosis and monocytosis; bone marrow examination and cytogenetic analysis had revealed a diagnosis of CMML, and the patient was on third day of hydroxyurea induction therapy.

She had no relief in pain on tramadol and paracetamol. In view of persistent pain, oral morphine was started at a dose of 5 mg every 4 hours with paracetamol (500 mg four times a day).

After 2 days of starting oral morphine, the patient was brought to the emergency department with excessive drowsiness and unresponsive state. There was no associated fever, headache or seizures. On clinical examination, Glasgow Coma Score (GCS) was E1V1M1 with bilateral pupils constricted and non-reactive to light. Respiratory rate was 14–15 breaths/min with room air oxygen saturation of 83%. Emergency investigations revealed blood sugar of 48 mg/dL, with metabolic acidosis in arterial blood gas. The patient was intubated and electively ventilated in view of poor GCS and compromised ventilation. CT brain was done to rule out intracranial causes of impaired GCS, and was found to be normal.

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Initial diagnosis of opioid overdose or hypoglycaemic coma was made. Detailed blood workup revealed major metabolic anomalies in the form of hyperuricaemia (21 mg%), hyperphosphataemia (5.4 mg/dL), hyperkalaemia (6.3 mg/dL), hypocalcaemia (7.7 mg/dL), raised urea (127 mg%) and creatinine (3.8 mg %). These pointed towards tumour lysis syndrome, and uraemic encephalopathy may have caused the depressed consciousness. The patient was started on febuxostat and intravenous hydration as supportive management for tumour lysis.

Keeping in mind the suspected diagnosis of opioid overdose as the patient had presented with depressed consciousness and pinpoint pupils, we decided to start with intravenous naloxone. However, as the patient had a respiratory rate of >8 (14–15 breaths/min), we decided against giving naloxone in bolus doses and an infusion at 1 μg/kg/hour was started.

Detailed history revealed that patient had recurrent vomiting, poor oral intake and decreased urine output since the start of hydroxyurea therapy and had taken a total of five doses of 5 mg morphine over 2 days before the onset of present symptoms. Thus, a final probable diagnosis of opioid overdose superimposed on underlying tumour lysis syndrome and uraemic encephalopathy due to acute renal dysfunction was made.

To confirm the diagnosis of opioid overdose, urine was sent for analysis of morphine levels. Supportive treatment in the form of naloxone infusion, ventilator support, febuxostat and intravenous hydration were continued.

Urine output and biochemical parameters improved with continued hydration. Serum creatinine, urea, potassium, phosphate gradually decreased over the next 72 hours. After 72 hours of ventilation, naloxone infusion and other supportive measures, GCS improved to E3VtM5. With improvement in GCS, we decided to taper and stop naloxone infusion; however, on bringing down naloxone dose to 0.5 μg/kg/hour,the patient again became drowsy and GCS deteriorated to E2VtM3.

As the patient's biochemical parameters had normalised (urea 63 mg%, creatinine 1.1 mg%), uraemic encephalopathy was ruled out as the cause of depressed consciousness. GCS had deteriorated after stopping naloxone infusion. We suspected that metabolites of morphine might still be persistent in the body causing the depressed consciousness. Thus, naloxone infusion at 1 μg/kg/hour was continued.

OUTCOME AND FOLLOW-UP

On the fifth day of ventilation and naloxone infusion, the patient was fully awake and responding to commands. She was gradually weaned off ventilator and extubated. Naloxone infusion was tapered to 0.5 μg/kg/hour and was stopped on the sixth day of intensive care unit (ICU) admission. No signs of naloxone overdose like agitation, delirium and hyperalgesia, were observed. The patient was encouraged to start taking feeds orally and was observed over the next 24 hours for signs of depressed consciousness or respiratory depression. Repeat urinalysis was sent for morphine levels.

Initial urinalysis revealed raised levels of morphine, and the second sample sent when the patient was fully awake and extubated was negative for morphine or its metabolites. The patient was discharged on the seventh day of ICU stay.

DISCUSSION

This case presents several learning points for pain physicians. In our practice, we rarely encounter patients with haematological malignancies on strong opiates like oral morphine given on outpatient basis. Haematological malignancies may present with pain due to various underlying causes which are listed in box 1.

As our patient had severe pain not responding to weak opioids, morphine was started at a low dose of 5 mg four hourly. CMML is not frequently associated with the development of tumour lysis syndrome.[4] High total cell count (65 000) at the time of diagnosis and old age may have predisposed the patient to development of tumour lysis with start of hydroxyurea therapy.[4–6]

Box 1 Probable aetiology of pain in haematological malignancies[3]

Disease related
- Nociceptive pain due to bone marrow or extramedullary involvement.
- Pain due to organomegaly.

Therapy related
- Diagnostic procedures like bone marrow aspiration.
- Bone marrow expansion due to growth factors.
- Steroid-induced osteoporosis/myopathy.
- Chemotherapy-associated peripheral neuropathy.

At the time of starting morphine, the patient had completed 3 days of hydroxyurea therapy and had severe pain in the abdomen, vomiting and poor oral intake. These could be attributed to adverse effects of hydroxyurea therapy.[5 6]

Owing to continued vomiting and dehydrated state, only 25 mg of total morphine intake over 2 days caused opioid toxicity. The toxic effects of morphine seen even with low-dose intake can be understood on the basis of morphine metabolism in the body.

The main metabolic pathway of morphine metabolism is glucuronidation in the liver by uridine 5'-diphospho-glucuronosyltransferase–enzymes into two major metabolites, namely, morphine-3-glucuronide (M3G) (45%–55%) and morphine-6-glucuronide (M6G) (9%–10%). M6G is the more potent morphine metabolite and exhibits analgesic activity through direct interaction with opioid receptors. M3G metabolite is associated with partial antagonism of morphine-induced analgesia. Both M3G and M6G are excreted by the kidney.[7] The accumulation of M6G (in renal failure or renal impairment) is associated with an increased incidence of morphine-like side effects, that is, prolonged respiratory depression, nausea, vomiting and profound unconsciousness.[8 9]

The patient had presented with unconsciousness, low GCS with pinpoint pupils but respiratory rate was maintained at 14–15 breaths/min. Thus, a direct diagnosis of opioid toxicity was not made and other causes depressed consciousness like intracranial haemorrhage or infarct were ruled out with CT brain. This differential effect, that is, profound unconsciousness with little effect on respiratory rate may be attributed to M6G and its effect at genetic level on splice variants of MOR 1 gene.[8 9]

As respiratory rate was maintained, naloxone was not given as boluses and a continuous low-dose infusion was started keeping in mind the delayed washout of M6G from the body. We could not find any concrete guideline on the duration of naloxone infusion in such patients.[10 11]

Treatment for tumour lysis syndrome was continued, and the patient gradually improved with these supportive measures.

This case highlights a lot of learning points for prescribing morphine to a patient with haematological malignancy. Baseline blood investigations including total counts should be reviewed and both general and cancer-specific risk factors should be assessed at every visit for the development of adverse effects like tumour lysis syndrome.

Varied clinical presentation of a patient with tumour lysis due to the wide spectrum of underlying biochemical anomalies may make its diagnosis difficult. The treating physician should be highly suspicious of underlying kidney damage or poor hydration state as these

may render the patient susceptible to opioid toxicity at low opioid doses.

Thus, a close collaboration and teamwork are needed between the treating oncologist and the pain physician to prevent such unsuspected and rare overlap of two clinical conditions.

Patient's perspective

(Written by the patient's son)

My mother, a patient of blood cancer, is on treatment at IRCH, AIIMS. She was unconscious for 1 week and was treated in the intensive care unit. I understand that she had side effects of morphine and chemotherapy which led to her problem. Now I understand the effect of these medicines. My mother is doing well now and is on chemotherapy and pain medications. I am satisfied by the treatment being given to my mother.

Learning points

- Prescription of strong opioids like morphine on outpatient basis for pain in haematological malignancies is a challenging task.
- Even small doses of morphine may have prolonged effect in patients with underlying renal dysfunction.
- Opioid overdose in rare cases may be manifested by depressed consciousness with normal respiratory rate which may be due to the differential effect of M6G at genetic level.
- Details of chemotherapy drugs, their related adverse effects and baseline blood investigations like serum creatinine should be kept in mind while prescribing opioids.
- Haematological malignancies with high initial cell counts on cytotoxic chemotherapy have risk of complications like tumour lysis syndrome with renal dysfunction. This makes prescribing morphine as analgesic in such patients a daunting task.

Contributors SV was involved in managing the patient in intensive care unit (ICU), collecting relevant literature pertinent to the case, writing the initial draft and subsequent final draft of the case and keeping in touch with patients relatives for consent and patient perspective. SM was involved in admitting and managing the case in ICU and editing the final manuscript. KR was involved in managing the case in ICU and reviewing relevant literature for the case. SB was involved in literature search and drafting the manuscript for the case.

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