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Morphine-induced fever: a case report and review of the literature

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Abstract

Background Morphine is widely used to treat moderate-to-severe cancer pain. However, it causes various adverse effects, with morphine-induced fever being an extremely rare and poorly understood symptom.

Case presentation We report the case of a 58-year-old Chinese woman with advanced lung cancer. Due to the ineffectiveness of tramadol for pain relief, her treatment regimen was switched to morphine. Following the change, she developed nausea, vomiting, dizziness, and elevated body temperature. A similar episode occurred subsequently. After a drug review, the pharmacist speculated that morphine was the most likely causative agent. Upon discontinuation of morphine, her body temperature returned to baseline levels.

Conclusions This case highlights the need for healthcare providers to consider morphine as a potential cause of unexplained fever in patients. The fever may be caused by a hypersensitive response, as there was a significant increase in eosinophils during the fever episodes.

Keywords Case report, Morphine, Opioids, Drug fever, Hypersensitivity

Introduction

Drug fever is a common adverse reaction characterized by fever following the administration of certain medications, resolving upon discontinuation of the offending agent. Drug fever is mostly induced by antibiotics, anticonvulsants, antineoplastics, immunoregulators, and other cardiac agents [1]. However, fever induced by morphine is exceedingly rare and infrequently reported [2, 3].

Morphine is widely utilized for its potent analgesic effects, primarily through its action on the μ-opioid receptor. Common adverse effects associated with morphine include constipation, nausea, vomiting, somnolence, itching, dizziness, urinary retention, delirium, cognitive impairment, and respiratory depression, while fever is not typically among these adverse effects [2, 3].

In this manuscript, we share a case of fever induced by morphine injection used for analgesia, and we conduct a literature review and analysis of the potential mechanisms involved. This case represents a rare exception, as morphine is not commonly recognized as a cause of drug fever.

Case summary

A 58-year-old Chinese female, gravidity 4 parity 3 (G4P3), presented with a cough and chest pain in March 2021. Diagnostic workup revealed lung cancer (Fig. 1) with multiple metastases to the cervical lymph nodes, brain, and bone. On 15 March 2021, she was administered chemotherapy intravenously with pemetrexed and

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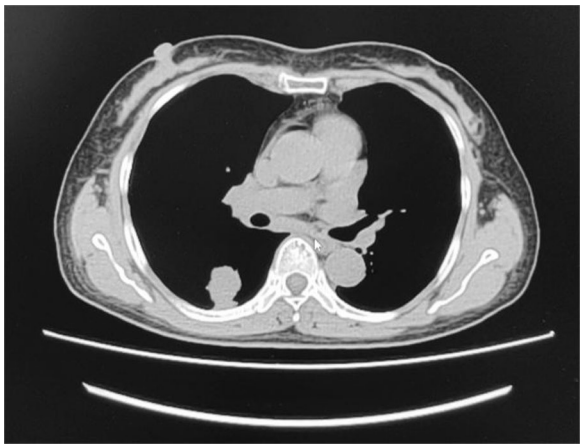

Fig. 1 Computed tomography showing right lung mass

carboplatin, along with bevacizummab. Subsequently, on 11 April 2021, based on genetic testing results, her treatment regimen was adjusted to dacomitinib (oral, once daily). The patient has been adherent to this targeted therapy regimen since then. On 29 April 2022, she was admitted to the hospital due to lumbosacral pain and discomfort, accompanied by slight numbness in the left lower limb. The patient had a history of hypertension but no other significant personal or family history. She, a farmer, has no history of smoking, drinking, or morphine use.

Upon admission, her vital signs were normal: weight 60 kg, height 165 cm, temperature 36.6 ℃, blood pressure 122/76 mmHg, respiratory rate 20 breaths/minute, and pulse rate 80 beats/minute. Physical examination showed lumbosacral tenderness, with no other remarkable findings in the systemic examination. A complete neurological examination including mental state was normal. She reported lumbosacral soreness with a Numeric Rating Scale (NRS) score of 2 (0 = no pain, 10 = worst possible pain). Lumbar radiation therapy was initialed on the day of admission. By day 9 (D9), radiotherapy had reduced her pain and stabilized her NRS score at 1. However, she reported increased stool frequency without abdominal pain, fever, or other discomforts. Infection marker detection revealed normal procalcitonin (PCT) and C-reactive protein (CRP) levels. Routine urine and stool analyses indicated no clinical abnormalities. Radiation enteritis was considered, and she was treated with montmorillonite powder, dexamethasone, and vitamin B_{12}.

On D15, her symptoms of radiation enteritis worsened, and she experienced breakthrough pain with an NRS score of 5 at 8:58. A tramadol 100 mg injection was administered, but it did not provide adequate pain relief, and she suffered abdomen pain with an NRS score of 3. Later, she complained of renewed abdominal pain with an NRS score of 8 at 13:36, and was immediately treated with a morphine 10 mg injection. Morphine relieved her pain and stabilized her NRS score at 2 after about half an hour. However, she developed nausea, vomiting, and dizziness. By 18:00, her body temperature had increased to 38.0 ℃. Her body temperature was cooled down by physical cooling and her other conditions were stable.

At 00:29 on D16, she was treated with another morphine 10 mg injection for abdominal pain with an NRS score of 6, which relieved her pain and stabilized her NRS score at 2. She suffered a fever again by 5:00 with a body temperature of 39.2 ℃. After 18 hours of physical cooling her body temperature returned to normal range (Fig. 2). During the fever period, her pulse rate increased to 100 beats/minute, and eosinophilia (with levels of 0.08×10^9/L on D8 and 0.17×10^9/L on D16) was noted.

The doctor included clinical pharmacists in the patient's treatment team to analyze the causes of the patient's symptoms and to collaboratively discuss treatment options. After a systematic medication review, drug-induced fever was suspected, and morphine was speculated to be the most likely offending agent (Table 1). Consequently, anisodamine/tramadol replaced morphine. Then neither fever nor other discomforts reappeared. The patient requested discharge on D26, her general status was satisfactory, and the pain had subsided. The laboratory workup is summarized in Tables 2, 3, 4, 5, and 6.

Discussion

We present a patient with lung cancer that developed fever after being infused with a conventional dose of morphine. The fever subsided quickly after discontinuation of morphine and reappeared upon readministration of the drug. While literature sporadically mentions body temperature alterations in relation to morphine use, these predominantly focus on hypothermia [9, 10, 12]. Previous cases of morphine-induced fever, such as those documented by ManiSha Bhagat and Graczyk M, are rare and have not conclusively linked the fever to a hypersensitivity reaction [2, 3]. This case, however, indicated a possible hypersensitive reaction, due to the rarity of this association, making it a rare and noteworthy example of morphine-induced fever in a lung cancer patient.

Drug fever is a common but often misdiagnosed pharmaceutical adverse reaction. It is characterized by a febrile response that coincides temporally with drug administration and resolves upon discontinuation of the offending drug. The diagnosis of drug fever is typically one of exclusion, considered when other causes of fever have been ruled out. Readministration of the causative

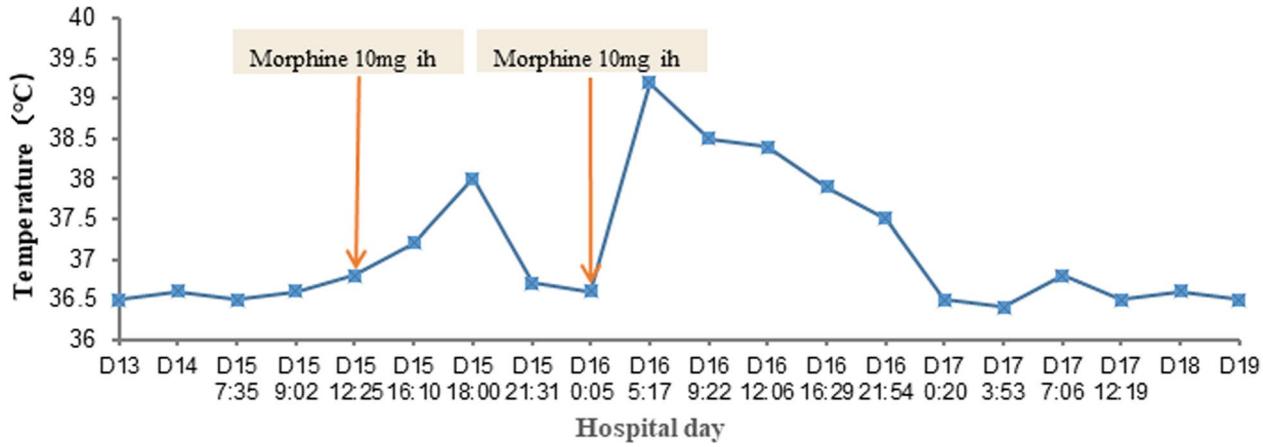

Fig. 2 The change in the patient's body temperature during hospitalization. After the first injection of morphine at 12:25 on day 15, the patient's body temperature gradually increased and peaked at 38 ℃ at 18:00. The fever subsided after physical cooling. However, the patient's temperature rose to 39 ℃ at 05:17 on day 16 when morphine was given again at 0:05 on day 19 due to abdominal pain with an NRS of 6, then the fever subsided after physical cooling within 18 hours

Table 1 Medications administered from admission to discharge

Hospital day	Medication
D1–D26	Dacomitinib (p.o., 30 mg qd)
D7–D26	Glutamine (p.o., 0.5 g tid)
D7–D25	Alanyl glutamine injection (intravenous, 10 g qd)
D7–D12	5 mg dexamethasone + 1 mg vitamin B_{12} + 50 ml sodium chloride injection (p.r. qd)
D10–D26	Bacillus licheniformis capsules (p.o., 0.5 g tid)
D12–D18	Granulocyte–macrophage colony-stimulating factor (i.h., 75 μg qd)
D12–D18	5 mg dexamethasone + 1 mg vitamin B_{12} + 3 g montmorillonite powder + 50 ml sodium chloride injection(p.r., qd)
D15–D25	Ilaprazolecas (intravenous, 10 mg qd)
D17–D26	Potassium citrate (p.o., 2 g tid)
D18–D25	10 mg dexamethasone + 2 mg vitamin B_{12} + 3 g montmorillonite powder + 0.1 g Lidocaine + 50 ml sodium chloride injection (p.r., qd)
D22–D25	225 μg Granulocyte–macrophage colony-stimulating factor + 50 ml sodium chloride injection 50 ml (p.r., qd)
D15 09:11, D17 06:47	Tramadol (i.m., 100 mg st)
D15 16:42, D16 09:54, D16 19:00, D16 23:07, D17 06:26, D17 13:52, D17 17:00, D17 23:38, D18 06:42, D18 11:36, D18 12:00, D18 22:02, D19 08:23, D19 10:40, D19 10:50, D19 17:17, D20 03:03, D20 08:37, D20 12:17, D20 14:08, D20 16:30, D21 03:02, D22 08:54, D23 04:40, D23 18:50	Anisodamine (i.m., 10 mg st)
D15 13:36, D16 02:29	Morphine (i.h., 10 mg st)
D15 16:42	Metoclopramide (i.m., 10 mg st)
D19, D20, D21	Octreotide acetate (intravenous–v.p. 0.3 mg st)
Discharge medications	Dacomitinib (p.o., 30 mg qd)
Discharge medications	Glutamine (p.o., 0.5 g tid)
Discharge medications	Bacillus licheniformis capsules (p.o., 0.5 g tid)
Discharge medications	Potassium citrate (p.o., 2 g tid)

This table presents all the patient's medications taken during hospital stay and follow-up

Table 2 Complete blood cell and leukocyte differential count during hospitalization

Blood routine test	Hospital day					Blood routine test	Hospital day				
	D8	D16	D17	D20	D25		D8	D16	D17	D20	D25
Red blood cell count, $\times 10^{12}$/L	3.61	3.32	3.62	3.41	3.44	Eosinophil percent, %	2.3	5.1	6.9	24.2	0
Hemoglobin assay, g/L	100	95	100	98	96	Basophil percent, %	0.1	0	0	0.1	0
Hematocrit, %	31.4	29.3	31.7	29.8	30.8	Neutrophil count, $\times 10^9$ g/L	3.03	2.87	2.43	1.52	3.16
Mean corpuscular volume, fL	87	88.2	87.6	87.4	89.4	Lymphocyte count, $\times 10^9$ g/L	0.38	0.05	0.11	0.18	0.2
Mean corpuscular hemoglobin, pg	27.8	28.7	27.6	28.7	27.9	Monocyte count, $\times 10^9$ g/L	0.17	0.22	0.08	0.28	0.23
Mean corpuscular hemoglobin concentration, g/L	320	325	315	329	312	Eosinophil count, $\times 10^9$ g/L	0.08	0.17	0.2	0.63	0
Coefficient variation of red blood cell volume distribution width, %	14.8	16.2	16.4	16.2	16.7	Basinophil count, $\times 10^9$ g/L	0	0	0	0	0
Standard deviation in red blood cell volume distribution width, fL	47	50.6	49.3	51.5	51.1	Platelet count, $\times 10^9$ g/L	193	116	125	103	127
White blood cell count, $\times 10^9$ g/L	3.66	3.31	2.82	2.61	3.59	Platelet distribution width	15.9	15.5	16.2	15.9	16
Neutrophil percent, %	82	86.7	86.6	58.1	87.8	Mean platelet volume, fL	12	11	10.9	12.1	12.1
Lymphocyte percent, %	10	1.4	3.8	7	5.7	Plateletcrit, %	0.232	0.127	0.14	0.125	0.153
Monocyte percent, %	4.6	6.8	2.7	10.6	6.5	Platelet larger cell ratio, %	38.9	30.7	31.6	39.3	39.4

Table 3 Laboratory tests during hospitalization

Laboratory tests	Hospital day						Laboratory tests	Hospital day					
	D7	D8	D16	D17	D20	D25		D7	D8	D16	D17	D20	D25
Kalium, mmol/L	3.12		2.92	3.1	3.22	2.94	Creatinine, μmol/L	51.1			63.9	62.9	41.6
Natrium, mmol/L	140		133	133	139.4	135.9	Anion gap, mmol/L	8.6		5.6	6.2	5.8	10.3
Chloride, mmol/L	109		105.3	106	116	102.1	Phosphorus, mmol/L	0.85		0.44	0.62	0.42	0.6
Bicarbonate, mmol/L	22.7		22.1	20.8	17.6	23.5	Magnesium, mmol/L	0.83		0.77	0.92	0.91	0.75
Calcium, mmol/L	2.13		1.76	1.64	1.76	1.76	Uric acid, μmol/L	254			156	239	
Urea, mmol/L	5.65			6.1	0.56	3.86	Endogenous creatinine clearance rate, ml/minute	113			87.6	89.2	143.7
Lactic acid	1.87		1.47	1.18	2.07	2.64	Glomerular filtration rate, ml/minute	103			92.3	94.1	112
Total protein, g/L						46.4	Alkaline phosphatase, U/L						52
Albumin, g/L						26.8	γ-glutamyltransferase, U/L						86
Globulin, g/L						19.6	Prealbumin, mg/L						271
Alanine aminotransferase, U/L						90	5-nucleotidase, U/L						5.8
Aspartate aminotransferase, U/L						18	Cholinesterase,U/L						3.87
Procalcitonin, ng/ml		0.04	0.03		0.07	0.14	C-reactive protein, mg/L		< 5	< 5	< 5	11.9	< 5
Heparin-binding protein, ng/ml			14.55				Hypersensitive C-reactive protein, mg/L		1.62	1.34	1.22	> 5	1.73

This table presents the pertinent laboratory tests throughout the patient's hospital stay, including liver function test, kidney function test, electrolytes, and inflammatory markers

Table 4 Stool sample test throughout patient's hospital stay

Stool test	Hospital day			Stool test	Hospital day		
	D9	D16	D17		D9	D16	D17
Color	Yellow	Yellow	Yellow	Ova of roundworm	Negative	Negative	Negative
Characteristic	Soft	Soft	Loose	Ova of hookworm	Negative	Negative	Negative
Leukocyte, /HP	0	0	1–2	Ova of whipworm	Negative	Negative	Negative
Phagocyte, /HP	Negative	Negative	Negative	Ova of pinworm	Negative	Negative	Negative
Erythrocyte, /HP	0	0	0	Entamoeba histolytica	Negative	Negative	Negative
Fat globule, /HP	0	0	A few	Fecal occult blood test	Negative	Negative	Positive

drug usually results in the recurrence of fever, further confirming the diagnosis [4, 5].

Confirmation of drug fever

Fever is a common clinical sign and is often attributed to infections, malignant tumors, acute gout, surgery, and trauma. Any persistent fever warrants a thorough infection workup and an investigation into various potential etiologies. However, when no obvious abnormalities are found and febrile episodes persist, despite negative laboratory findings, the possibility of drug-induced fever should be considered.

Our patient was diagnosed with malignant tumor and radiation enteritis, both potential causes of fever. However, her fever subsided quickly after discontinuation of morphine and did not recur. In contrast, malignant tumors typically do not improve with time and radiation enteritis subsided over a week, ruling out these conditions as the cause of fever. Furthermore, routine blood tests, CRP, PCT, and other examinations showed no significant abnormalities, and there were no clinical signs of infection such as cough, sputum production, frequent urination, or pain, making an infectious cause of fever unlikely.

The true incidence of drug fever during medical treatment may be higher than reported. Identifying the responsible drug is challenging, especially since patients often receive multiple medications concurrently. Opioids are not typically suspected of causing fever. However, in this case, the recurrence of fever upon morphine rechallenges supports the diagnosis. The temporal relationship between morphine administration, onset of fever, prompt recovery after discontinuation, and recurrence upon readministration strongly suggests a cause-and-effect relationship.

Although the exact mechanism of morphine-induced fever remains unknown, the manufacturer's instructions indicate that combining morphine with monoamine oxidase inhibitors (such as selegiline, linezolid, moclobemide, furazolidone) can cause serotonin syndrome, which includes symptoms such as hyperthermia, confusion, hypomania, and restlessness. Fortunately, our patient was not using any of these drugs (Table 1), making drug interactions an unlikely cause of the fever.

The Naranjo method [6] yielded a probability score of +8 for morphine, suggesting it was the probable cause of fever. Additionally, we assessed the causality using the World Health Organization–Uppsala Monitoring Centre (WHO–UMC) causality assessment system [7], which determined the causality to be "certain(ly)." According to the Hartwig's Severity Assessment Scale, this case was classified as a level 2–mild adverse drug reaction (ADR) [8].

Literature review and discussion

Drug fever may occur at any time during the treatment period and can be impacted by different drugs. The delay between drug initiation and fever onset can range from a few hours to over 30 days, with temperature typically returning to normal within 48–72 hours after drug discontinuation [1]. Drug fever is often diagnosed after an exhaustive search for other causes, with readministration of the offending drug typically causing the fever to recur, thus confirming the diagnosis [1, 4, 5]. The mechanisms of drug fever are numerous and not thoroughly understood. Drug fevers are generally classified into five categories: hypersensitivity reactions, altered thermoregulatory mechanisms, derelict reactions to drug administration, reactions extending from the pharmacologic action of the drug, and idiosyncratic reactions. Hypersensitivity and immune-mediated reactions are among the most likely theories [1].

Previous research suggests that drug fever caused by opioids may be related to their pharmacological effects rather than allergic reactions. Studies have found that opioids, such as morphine, can impact body temperature across various species, including humans [9–15]. Depending on the stimulated opioid receptor subtypes, body temperature changes can vary: low doses of morphine increase body temperature by stimulating

Table 5 Urine analysis throughout patient's hospital stay

Urine analysis	Hospital day (D9)	Urine analysis	Hospital day (D9)
Glucose	Negative	Nitrite	Negative
Protein	Negative	Leukocyte esterase	Negative
Bilirubin	Negative	Vitamin C	Negative
Urobilinogen	Negative	Color	Lightly yellow
Urine acidity	6	Transparency	Transparent
Specific gravity	1.025	Erythrocyte, /HP	0
Urinary occult blood	Negative	Leukocyte, /HP	0
Ketone	Negative	Cast, /HP	0

Table 6 The patient's stool culture during hospitalization

Hospital day	Stool culture
D15	No salmonella, shigella, *Vibrio cholerae*, *Vibrio parahaemolyticus* were detected, and no *Escherichia coli* O157:H7 was grown
D17	No salmonella, shigella, *Vibrio cholerae*, *Vibrio parahaemolyticus* were detected, and no *Escherichia coli* O157:H7 was grown

μ-opioid receptors, while high-dose lower body temperature by activating κ-opioid receptors [11, 16–18]. There are very few studies specifically linking morphine to drug fever, and none have conclusively associated it with a hypersensitive reaction. For instance, ManiSha Bhagat reported only five cases of drug fever in more than 20,000 morphine users, none of which were linked to a hypersensitive reaction [3]. Similarly, Graczyk M described a case of morphine use, which was not attributed to a hypersensitive reaction [2].

The proposed mechanism of opioid-induced fever involves the stimulation of μ-opioid receptor on immune cells in genetically susceptible individuals, leading to the expression of proinflammatory cytokines and the generation of endogenous pyrogens. This triggers the hypothalamus and causes fever. Additionally, some researchers suggest that opioids may alter brain functions responsible for body temperature regulation.

Hypersensitivity reactions are the most common mechanism of drug fever [1], often accompanied by bradycardia, leukocytosis, eosinophilia, and rash. While hypersensitivity is not considered to be the root cause of morphine-induced fever, there are still some reports of hypernasality reaction caused by other opioids. For example, C. Vidal reported fever and rash in patients due to codeine [19], and Masaru Enomoto described a case of drug-induced hypersensitivity syndrome related to codeine phosphate, presenting with an erythematous, maculopapular rash that progressed to erythroderma and fever [20].

In our patient's case, her heart rate ranged from 72 to 93 beats per minute before the onset of fever (D1 to D15), increased to 100 beats per minute after the fever onset, and gradually returns to 72–93 beats per minute from D17 to D26. During the patient's fever period, eosinophil levels increased significantly (D8, D16, D17, and D20 were 0.08×10^9/L, 0.17×10^9/L, 0.2×10^9/L, and 0.63×10^9/L, respectively), while leukocyte counts were reduced due to radiotherapy (D8, D16, D17, and D20 counts of 3.66×10^9/L, 3.31×10^9/L, 2.82×10^9/L, and 2.61×10^9/L, respectively). Despite the lack of significant cutaneous symptoms, the correlation between fever and a hypersensitive reaction cannot be ruled out, especially given the concurrent rise in eosinophil levels and increased heart rate during radiotherapy.

Conclusions

Determining drug-induced fever remains challenging, particularly because most patients receive multiple medications for their primary conditions at the onset of fever. Additionally, intentionally rechallenging a patient with a suspected causative agent is controversial [21]. Morphine, commonly used as a pain reliever, is not typically suspected as a pyrogen. However, readministration of morphine in our case resulted in a febrile response, ultimately identifying it as the offending drug.

Current studies suggest that the drug fever caused by opioids may be related to their pharmacological effects rather than hypersensitive reactions. This case, however, indicated a possible hypersensitive reaction, as evidenced by a significant increase in eosinophilic granulocytes.

Clinicians should be aware of the potential for morphine to induce fever. Morphine-induced fever may present as moderate to high fever, necessitating thorough evaluation and supportive therapies. This is particularly important in cases where the withdrawal of morphine is controversial due to the need for severe pain.

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Author contributions
Chenkun Wang and Weiwei Jiang contributed to conception and design of the study. Lirong Zhu and Hua Ju prepared the study documents. Lirong Zhu and Zimin Zhang analyzed the data. The manuscript was drafted by Lirong Zhu and Zimin Zhang, and revised by Chenkun Wang and Weiwei Jiang. All authors reviewed manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Availability of data and materials
The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding authors.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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