INDONESIAN JOURNAL OF ANESTHESIOLOGY AND REANIMATION
Volume 5 (1), January 2023: 37-44

Case Report

USING MULTIMODAL ANALGESIA FOR BREAKTHROUGH PAIN IN STAGE IV BREAST CANCER PATIENT

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ABSTRACT

Introduction: Breakthrough Pain (BTP) is experienced as mild to moderate-severe pain, from only a few seconds to hours. It causes a decrease in the quality of life and functional capacities. Furthermore, BPT must be recognizable, assessed, and controlled to prevent its relapse and severity. **Case report:** A woman, 45 years old, having breast cancer along with pulmonary, femur, and cervical metastases, came with the main complaint of pain. The patient had a pain score of NRS 9, which was felt intermittently for the last 3 months. Treatment has been carried out with MST 10 mg/8 hours and a Durogesic® patch (fentanyl 50 mcg/h) but the pain did not subside. Moreover, the patient was unable to identify any precipitating factors or pain relievers, while the diagnosis confirmed BTP. The rescue dose was administered in a range of 10 – 20% of the total daily dose in the last 24 hours equivalent to 11 – 22 mg intravenous Morphine or equianalgesic with 110 – 220 mcg of fentanyl. For immediate effect, transmucosal fentanyl was recommended, but this preparation is currently unavailable. Moreover, therapy was carried out with the continuous administration of Morphine, and the pain reduced to NRS 0 – 3 on the second day. **Conclusion:** Transmucosal fentanyl, either buccal, sublingual, oral, or nasal mucosa, was proven to be effective in treating BTP. However, when transmucosal fentanyl is not available, multimodal analgesia is an effective alternative.

Keywords: Breakthrough Pain; Breakthrough Pain Assessment; Cancer Pain; Multimodal Analgesia

ABSTRAK

Pendahuluan: Renjatan nyeri (*breakthrough pain*) dirasakan sebagai nyeri ringan hingga sedang-berat, dari hanya hitungan detik hingga jam. Renjatan nyeri (*breakthrough pain*) menyebabkan penurunan kualitas hidup dan kapasitas fungsional. Renjatan nyeri (*breakthrough pain*) diharapkan dapat dikenali, dinilai dari awal, dan dapat diprediksi untuk dikontrol dengan cepat serta mencegah kekambuhan dan keparahannya. **Laporan kasus:** Seorang wanita, 45 tahun, dengan kanker payudara kanan dan kiri stadium IV metastase pulmonal, os femur, cervical datang dengan keluhan utama nyeri, dengan skala nyeri NRS 9, yang dirasakan hilang kambuh sejak 3 bulan terakhir dan telah mendapat MST 10 mg/8 jam dan Durogesic patch (fentanil 50 mcg/jam) namun nyeri bertambah berat dan tidak membaik dengan analgetik yang sehari – hari dikonsumsi. Pasien tidak dapat mengidentifikasi faktor pencetus maupun pereda nyeri. Pasien didiagnosis renjatan nyeri (*breakthrough pain*). *Rescue dose* menggunakan 10 – 20% dari total dosis harian (atau total dosis dalam 24 jam terakhir) yaitu 11 – 22 mg Morphine intravena atau ekuinalgesik dengan 110 – 220 mcg fentanyl intravena. Untuk efek yang cepat, direkomendasikan fentanyl transmukosal, namun sediaan ini belum tersedia. Pain service mensubtitusi terapi menjadi pemberian Morphine kotinu dan terpantau renjatan nyeri Ny. L berkurang menjadi NRS 0 – 3 pada hari kedua terapi. **Kesimpulan:** Fentanyl transmucosal dikatakan efektif mengatasi renjatan nyeri. Namun, jika fentanyl transmucosal tidak tersedia, analgesia multimodal dapat menjadi subtitusi dalam mengurangi renjatan nyeri.

Kata kunci: Renjatan Nyeri; Asesmen Renjatan Nyeri, Nyeri Kanker; Analgesia Multimodal

Article info: Received: March, 23th 2022; Revised: May, 17th 2022; Accepted: December, 30th 2022; Published: January, 20th 2023

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V5I12023.37-44

INTRODUCTION

Breakthrough Pain (BTP) is an acute and transient exacerbation that occurs in pain previously controlled by routine opioids. In BTP, an additional dose of the routine opioids might be needed when the pain cannot be controlled (1,2). The prevalence of this condition in cancer patients (Breakthrough Cancer Pain/BTcP) is fairly higher at 33-95% compared to the non-cancer chronic disease patients with an average of 59.2%. According to the American Pain Foundation, BTP is experienced by 50%–90% of all hospitalized cancer patients, 89% of home care-terminal-patients, and 35% of all ambulatory care cancer patients, where 30% of these cases are moderate to severe pain (2–4).

BTP is experienced as mild to moderate-severe pain which occurs up to 4 times a day on average. The duration varies, from only a few seconds to hours with an average of 30 minutes. The reported pain types also vary, from somatic (33%), visceral (20%), and neuropathic pain (27%), to the combinations of them (1).

Furthermore, BTP causes a decrease in the quality of life and functional capacities. According to previous studies, patients reported either physical or psychological effects, which limits their daily routines, including mood swings, sleep disturbances, psycho-emotive deficits, increased anxiety, and depression levels. BTP also affects interpersonal relationships with one another, including a perception of being a burden to their caregivers (5). BTP should be recognizable and predictable to prevent its relapse as well as reduce the severity. Various guideline recommends the use of rapid-onset and short-duration opioids which are not always available in some hospitals. Therefore, this study presents a case of BTP that occurred in a cancer patient. The hospital did not have the recommended medication preparation and multimodal analgesia was used to control the pain.

CASE REPORT

Mrs. L, 45 years old, came into the hospital with chief complaints of pain, supported by the NRS of 9, and did not become better after using the routinely-consumed analgetic. Early diagnoses suggested stage IV right and left breasts as well as pulmonary and cervical metastases. The patient had also undergone a radical mastectomy on the right and left breasts, while the history of chemotherapy and radiotherapy numbers could not be remembered.

The patient complained of pain in the neck and back area 3 months before the hospital admission. When the first pain was felt, morphine sulfate (MST continuous) 10 mg/12 hours was initially administered and then the dose was increased to 10 mg/8 hours, with further addition of a Durogesic ® patch (fentanyl 50 mcg/hour). With this therapy, it was confirmed that the pain was relieved completely, while adequate sleeping and eating were restored. The patient continued to take the medication regularly but 1 month before the hospital admission, the pain sometimes become worsened and the severity increased from NRS 6 – 9. The pain was described as “tense, tight, heavy” and sometimes could only be described as “uncomfortable”. The patient also felt discomfort in the abdominal area, along with bloating, and constipation. Both the patient and families did not pay attention to the factors/activities which might trigger the pain. More specifically, pain usually occurs when the patient is asleep or not moving. Although the patient often tried to change the position of the body, the pain still did not reduce.

The blood pressure was 130/80 mmHg, heart rate 82 bpm, peripheral oxygen saturation 98% room air, and body temperature was 36,5

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^{o}C. Based on the chest x-ray results, pneumonia-type metastasis, massive pleural effusion, left breast and pleural-type pulmonary metastasis were found, while no visible skeletal metastasis was observed in the visualized bone system. Laboratory examination showed anemia with Hb 9,5 g/dL, and other components within the normal range.

Pain service used the algorithm in Diagram 1 to assess the pain and the patient answered "yes" to all questions. The intermittent pain might go in minutes, but also might last for hours. Therefore, the pain service diagnosed the patient with cancer or BTP with stage IV skeletal and pulmonary metastases.

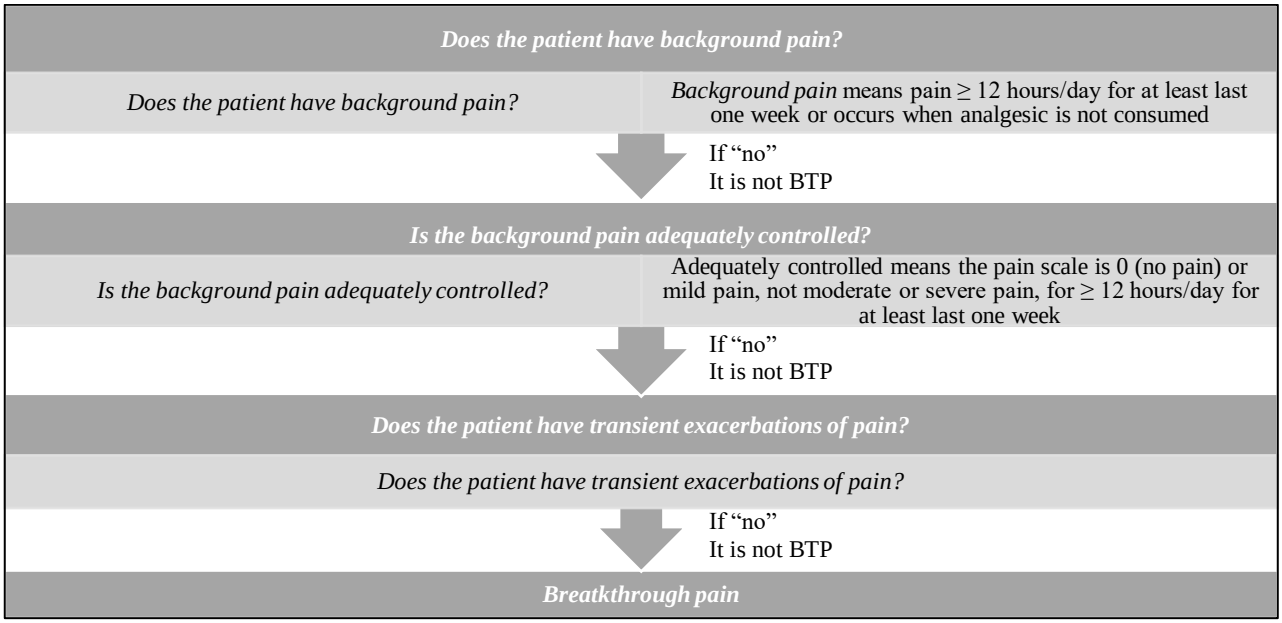

Diagram 1. Breakthrough Pain Diagnosis Algorithm(6)

The pain characteristics was analyzed by using the Breakthrough Pain Assessment Tool (BAT), wherein a pain diary was filled by the patient for 2 x24 hours with the assistance of the relatives, and the data are presented in Table 1. On the first day in inpatient care, the patient complained of pains at 08.30 a.m., 10.22 p.m., 10.35 p.m., and 11.24 p.m, while on the second day, pains were felt at 02.15 a.m. 3.15 p.m., and 8.15 p.m. The entire pains were at NRS level of 6-9 with the description of being "tense, heavy, uncomfortable, and restless". Most of the pain durations were around 10-30 minutes, while some were more than 30 minutes. Further consultation culminated in neurosurgery for pathological fracture of the 7th cervical spine and thoracic cardiovascular surgeon for massive pleura effusion thoracentesis procedure. The rescue dose needed was calculated as in the Diagram 2.

The initial treatment given was Morphine 2 mg iv bolus in a single dose and 10 mg in 50 cc of normal saline at a rate of 3 ml/hour (titration dose), Ketamine 6 mg iv bolus (single dose), Midazolam 2 mg iv bolus (single dose), Paracetamol 1 gr iv (extra), as well as Amitriptyline 25 mcg/24 hours orally. These administrations were still below the recommended doses of morphine at 14.4 mg/day compared to calculations of 43 mg/day. It was observed that the BPT decreased

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immediately to NRS 1 – 2 after the second day of therapy.

Step 1. Current therapy
- MST 10 mg/8 hours (per oral)
- Durogesic® patch (fentanyl 50 mcg/hour)

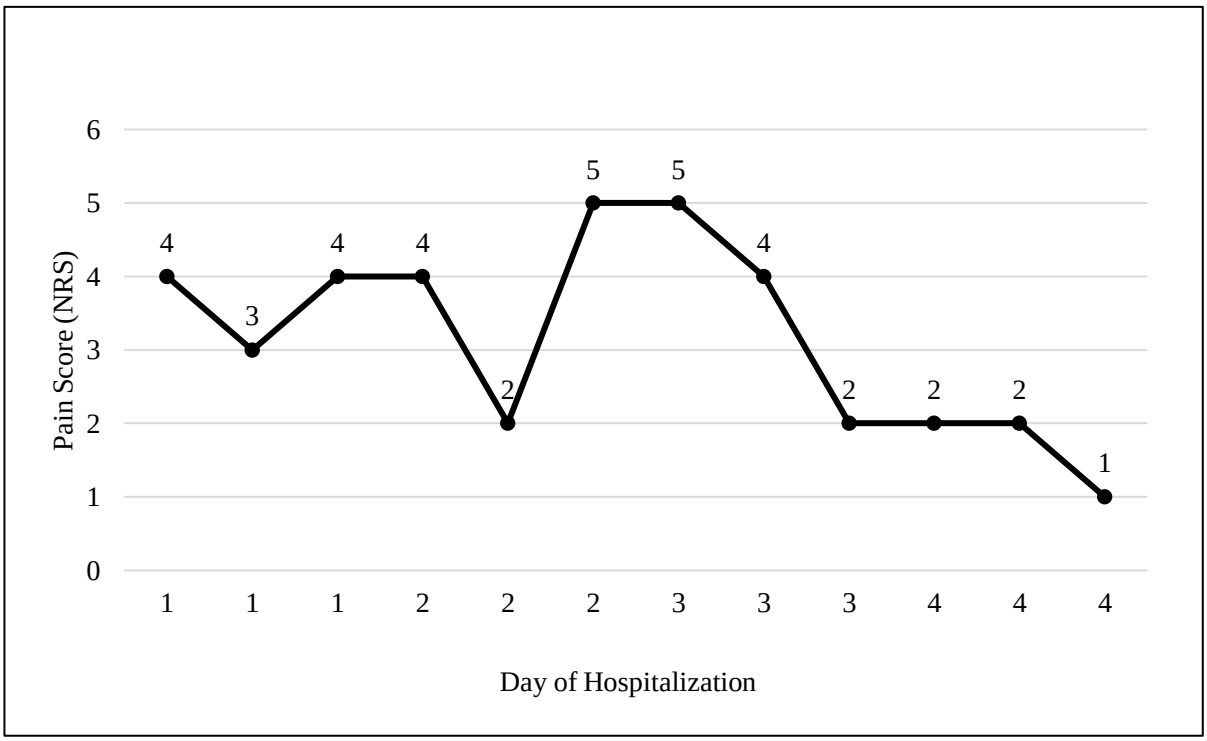
Step 2. Equianalgesic with
- MST 10 mg/8 hours (peroral) = Total Morphine 30 mg/day peroral
- Durogesic® patch (fentanyl 50 mcg/hour) → equivalent to Morphine 100 mg/day per oral

Step 3. Total daily dose Morphine = 130 mg/day peroral → equivalent to intravenous Morphine 43 mg/day

Step 4. Rescue dose uses is 10 – 20% of the total daily dose (or total dose in the last 24 hours)
- which is 4,3 – 8,6 mg of intravenous Morphine
- This dose is equianalgesic with 43 – 86 mcg intravenous fentanyl

Diagram 2. Rescue Dose Calculation for Mrs. L's BTP

Due to the condition, the pain diary filling was assisted by relatives and several assessment items were asked verbally. Some questions were also not filled by the relatives, for example, "what was the analgesic consumed to relieve the pain?". They did not fill it because the patient's medicines were given directly by the nurse, either peroral or through injection. Despite the weaknesses, the pain occurrence documentation in the pain diary provided enough overview of the pain which was experienced 3-4 times a day from moderate with NRS 4-6 to mild intensity of NRS 1-2. The following chart is Mrs. L pain monitoring by the room nurse (Graphic 1).



Graphic 1. Mrs. L Pain Monitoring

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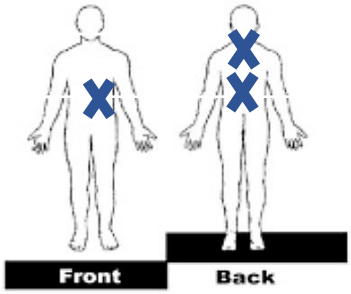
Table 1. Breakthrough Pain Assessment Tool (BAT) of Mrs. L/45 years old (5)

Breakthrough Pain Assessment Tool (BAT) **Mrs. L/45 years old**	
Guideline: These questions are related to BTP you experienced for a recent week. BTP refers to the cancer pain you experience for a short time.	
Questions	**The patient's Answer**
Which body parts feel BTP? Give an "X" mark on the picture!	
How often do you feel BTP? a. < 1 time a day b. 1 – 2 times a day c. 3 – 4 times a day d. > 4 times a day	3 – 4 times a day
Is there any trigger for the occurrence of BTP? If there are any, please write them down!	"No idea, because there is no specific trigger that causes the pain. The pain may occur when sleeping."
Is there anything to relieve BTP you experience (analgesic or another)? If there are any, please write them down!	"No. All of the body positions feel the same. Sometimes, I feel comfortable leaning to either left or right, but sometimes it is better when the bed is lightly elevated, sometimes the pain still feels tense despite the change in the position."
How long does it take for you to feel BTP whenever it relapses? a. < 5 minutes b. 5 – 15 minutes c. 15 – 30 minutes d. 30 – 60 minutes e. > 60 minutes	"I do not precisely count how long, sometimes it is only in a matter of minutes, sometimes it occurs all night that I cannot sleep."
How heavy/how painful is BTP at its heaviest? Starting from 0 means no pain at all and 10 which means the pain is the heaviest you could imagine.	0 1 2 3 4 5 6 7 8 **9** 10
How heavy/how painful is BTP you usually experience? Starting from 0 means no pain at all and 10 which means the pain is the heaviest you could imagine.	0 1 2 3 4 5 **6** 7 8 9 10
How troublesome is your BTP? Starting from 0 means not troublesome at all and 10 means the pain is highly troublesome.	0 1 2 3 4 5 6 7 8 9 **10**
How much is BTP preventing you from living a normal life? Starting from 0 means no problem at all and 10 means the pain is entirely preventing you from living a normal life.	0 1 2 3 4 5 6 7 8 **9** 10
What analgesic do you take to relieve BTP? If there is any, please write the type and dose.	"Usually I do not take medication, except the ones given by the doctor. Once, I took the MST earlier because the pain was unbearable."
How effective is the analgesic you consume to relieve the pain? Starting from 0 means not effective at all and 10 meaning highly effective.	0 1 2 **3** 4 5 6 7 8 9 10
How long it takes for the analgesic to be in effect? a. No effect b. 0 – 10 minutes c. 10 – 20 minutes d. 20 – 30 minutes e. > 30 minutes	"Often no effect."
Questions	**The patient's Answer**

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Is there any side effect from the analgesic you take to relieve BTP? If there is any, please write what is the side effect!	"No."
If there is any side effect, how disturbing was the side effect you experienced earlier? Starting from 0 means not disturbing and 10 means highly disturbing.	"No Side Effects." 0 1 2 3 4 5 6 7 8 9 10

DISCUSSION

Case discussion focuses on pain management and the underlying diseases treated by the neurosurgeon as well as the thoracic cardiovascular surgeon. Furthermore, pain management starts with a proper assessment which involves diagnosing BTP. To decide the appropriate therapy, BTP has to be evaluated and categorized into the following (1):

a. Incident pain: pain related to specific activities or certain accidents, could be treated by short-acting opioids to anticipate any occurrence of pain caused by its trigger factors
b. End-of-dose failure pain: the pain relapses at the end of the scheduled daily opioids duration, and can be treated by increasing the dose or frequency of daily opioids administration. This condition occurs when the interval for the schedule of analgesia administration exceeds the duration of the opioids given, or when the duration of opioids action is insufficient from an average of 4 hours to 2 – 3 hours. This is due to the differences of opioids' metabolism rates per dose for every individual(2).
c. Uncontrolled persistent pain: pain that is uncontrolled by scheduled daily opioids which have been consumed for the whole time, and could be treated by adjusting the dose.

In Mrs. L case, BTP was not related to certain activities or positions, and the interval of morphine administrated was already in accordance with the usage instruction along with Durogesic® (fentanyl) patch which provided a continuous analgesic effect. Therefore, the BTP experienced could be categorized as uncontrolled and persistent (1).

A pain diary was used to observe the BTP fluctuation and relapse time. The pain service used the diary developed by America Pain Foundation with several weaknesses. Due to language issues, the pain diary which is written in a foreign language was independently translated into Bahasa Indonesia.

National Comprehensive Cancer Network (NCCN) released a recommendation for BPT management, namely the administration of rescue doses to relieve the pain rapidly and adequately. The rescue dose should be an analgesic bolus, and increasing the titrated dose may take hours to take effect (7). Rescue dose is equivalent to 10 – 20% of the total daily dose in the last 24 hours. Furthermore, re-administration of rescue doses every hour was allowed while also monitoring the side effects of pain reduction. Repetitive rescue dose administration indicates the necessity of the re-adjustment of the therapy which has been given. Rapid onset and short-duration opioids are the options for rescue doses, for example, fentanyl. Transmucosal fentanyl, either buccal, sublingual, oral, or nasal mucosa, has been proven to be effective in treating BPT. Fentanyl administration starts with the lowest dose followed by slow titration (7–9). The occurrence of BPT has to be monitored within 1 day to determine whether a change in analgesic dose is required on the next day (10).

Oral Transmucosal Fentanyl Citrate (OTFC) is the recommended therapy to rapidly and adequately relieve BPT. Aside from being

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user-friendly for patients compared to intravenous preparations, it is available in stick-shaped packages of lozenges. The recommended dose is 5 – 20 to achieve peak plasma concentration in 15-30 minutes after its administration (11). However, the preparations are currently not yet available in the hospital. Pain service substituted the therapy by using multimodal analgesia.

Multimodal analgesia involves using 2 or more combinations of an analgesic, each with a different mechanism of action. Aside from opioids, drugs with distinct mechanisms of action target the pain pathways culminating in additive and synergistic effects. The multimodal analgesic approach is commonly recommended to treat acute or postoperative pain, as it can potentially reduce side effects and provide the benefit of treating pain through different cellular pathways. This raises the possibility of the approach being significantly relevant in BTP management (12). One of the main concerns is the need for rapid onset of analgesia, and multimodal analgesia has been shown to meet these needs.

In this case, pain service also used ketamine, an NMDA-receptor antagonist (N-methyl-D-aspartate receptor), that blocks glutamate. At low doses (subanesthetic), ketamine provides analgesia and limits/modulates central sensitization, hyperalgesia, and tolerance of opioids or other analgesics, although evidence is still limited (8).

Predicting the occurrence of BTP is expected to accelerate the administration of analgesics to help relieve pain severity, either in terms of its peak time or the pain duration itself. Patients with predictable BTP have a shorter time to experience peak pain at less than 10 minutes, and a shorter duration of pain namely 30 minutes vs 40 minutes with $p = 0.02$ (13). Predicting BTP requires the recognition of the precipitating factors. Movement in patients' bed is the most common trigger while coughing, sitting, standing, walking, defecation and urination also function similarly although not very often. However, patients are not always able to recognize these precipitating factors, to be precise, 23% responded that there is no specific precipitating factor and the pain might appear suddenly (13). In this case, the patient and relatives also reported the same occurrence, wherein there were no precipitating or mitigating factors for the BTP. The patient's condition might be caused by the short time monitoring carried out only on the 2nd day.

CONCLUSION

BTP might occur as a transient, acute, mild to moderate-severe intensity pain that can decrease the quality of life and functional capacity of the patient. It can be predicted by recognizing precipitating factors and administrating a rescue dose for rapid and adequate pain relief. Furthermore, Transmucosal fentanyl, either buccal, sublingual, oral, or nasal mucosa, has been proven to be effective in treating BPT. However, when transmucosal fentanyl is not available, multimodal analgesia can be used as an alternative to overcome BTP.

Acknowledgment
Not Applicable.

Conflict of Interest
All authors declared there are no conflicts of interest regarding this case report.

Funding Disclosure
Not Applicable.

Author Contribution
All authors read and approved the final manuscript.

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V5I12023.37-44

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