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Successful pain control with add-on methadone for refractory neuropathic pain due to radiation necrosis in pontine metastatic lesion: a case report

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Abstract

Background Central pain, characterized by neuropathic pain, can manifest due to injury to the superior spinothalamic tract. The brainstem includes sensory and motor pathways as well as nuclei of the cranial nerves, and therefore cancer metastasis in the region requires early intervention. Although stereotactic radiosurgery (SRS) is commonly employed for the treatment of brain metastasis, it poses risks of late complications like radiation necrosis (RN). RN exacerbates the progression of brain lesions within the irradiated area, and in the brainstem, it can damage multiple nerves, including the superior spinothalamic tract. Central neuropathic pain is often intractable and empirically managed with a combination of conventional drugs, such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and anticonvulsants. However, their efficacy is often limited, leading to a decline in performance status (PS) and quality of life (QOL).

Case presentation We present the case of a 53-year-old man diagnosed with stage IV lung cancer, referred to our palliative care team for managing severe central pain resulting from SRS-related RN in the pons. Despite administration of opioids, including oxycodone and hydromorphone, and adjuvant analgesics, the patient continued to require frequent use of immediate-release opioids. The addition of methadone alone proved successful in achieving optimal pain control.

Conclusions Provided that RN in the brainstem can lead to intractable neuropathic pain, it is advisable to avoid SRS for brainstem metastasis when possible. Add-on methadone should be considered as a viable pain management medication for patients experiencing unresolved central pain.

Keywords Central pain, Brainstem metastasis, Stereotactic radiosurgery, Radiation necrosis, Methadone

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Background

Central pain, often referred to as thalamic pain or central post-stroke pain (CPSP), arises from disruptions in the ascending sensory pathway, particularly involving the thalamus [1]. However, injury to the superior spinothalamic tract in the brainstem can also develop central pain [2]. Central pain commonly manifests as neuropathic pain within six months following an injury [1], and its underlying causes range from strokes to traumatic brain injuries [3]. The pain can be characterized by sensations such as pricking, aching, lancinating, tearing, shooting, and squeezing, often accompanied by dysaesthesia, hyperalgesia, and allodynia [2]. The prognosis of central pain is typically poor, and once this type of pain develops, it can be persistent and life-long [1].

The brainstem regulates vital cardiac and respiratory functions, and metastasis in this area necessitates early intervention with radiation therapy [4]. Although stereotactic radiosurgery (SRS) is a preferred option for solitary lesions because of its minimized impact on non-cancerous brain tissues, it elevates the risk of radiation necrosis (RN) as a late complication [5]. Therefore, SRS for brainstem metastasis is generally avoided because it may damage crucial nerves [4]. Our report details the case of a lung cancer patient with RN induced by SRS for brainstem metastasis, experiencing severe central neuropathic pain, effectively managed with low-dose add-on methadone. There have been no reports of RN accompanied by intractable neuropathic pain that our patient describes as unbearable. Inadequate pain control not only lowers performance status (PS) and quality of life (QOL) but also hinders cancer treatment. This report aims to offer oncologists a potential pain management option for addressing intractable central neuropathic pain.

Case presentation

A 53-year-old man presented with double vision and was subsequently diagnosed with stage IV non-small cell lung cancer, accompanied by a solitary pontine metastasis (Fig. 1a, b). Due to the enlargement of the pontine lesion and the presence of other brain metastases, he underwent CyberKnife SRS for the pontine lesion (20 Gy) and the right parietal lobe counterpart (23 Gy) prior to systemic chemotherapy. Six months post-radiosurgery, the patient developed neuralgia in his right upper and lower limbs. Initially suspected of development of the pontine lesion (Fig. 1c, d), 11 C-methionine (MET)-positron emission tomography (PET) revealed no recurrence

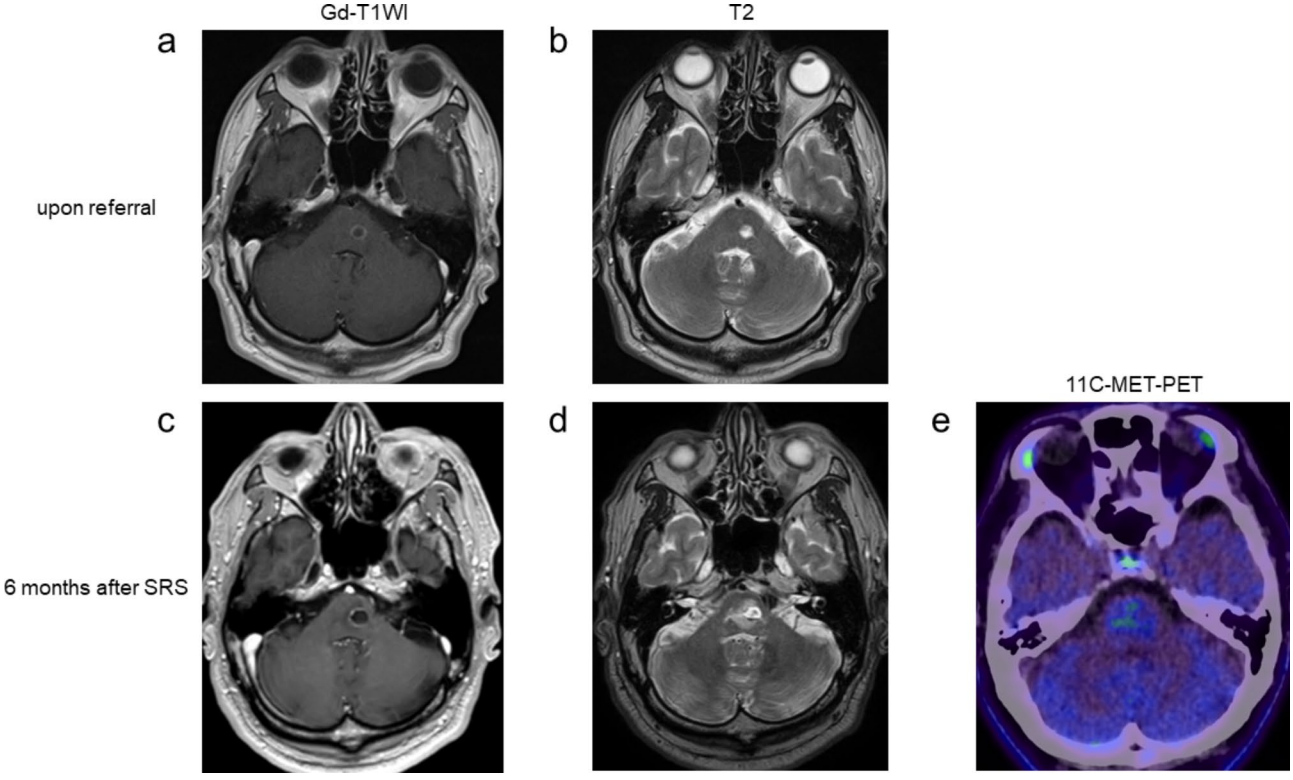

Fig. 1 Imaging findings upon referral (panels **a**, **b**) and at 6 months post-stereotactic radiosurgery (SRS) (panels c, d, e). (**a**, **c**) Brain MRI with gadolinium-enhanced T1-weighted imaging (Gd-T1WI) shows (**a**) a ring-shaped 6 mm nodule on the left side of the pons upon referral, and (**c**) an enlargement of the nodule at the same site, observed at 6 months post-SRS. (**b**, **d**) T2-weighted MRI displays (**b**) high signal intensity of the nodule without accompanying edema upon referral, and (**d**) a water-like signal intensity surrounding the enlarged lesion in the pons, indicative of edematous change due to radiation necrosis (RN), at 6 months post-SRS. (**e**) No significant 11 C-methionine (MET) uptake in the irradiated lesion of the pons at 6 months post-SRS.

but rather necrosis caused by the previous radiotherapy (Fig. 1e). Therefore, the patient's pain was treated with oxycodone (40 mg per day) and various adjunctive painkillers, including nonsteroidal anti-inflammatory agents, acetaminophen, eperisone, pregabalin, and dexamethasone, but the efficacy was insufficient. Consequently, he was referred to our palliative care team for further management of his severe pain control. At the time, the patient described constant pain (numerical rating scale [NRS] 6) as dull and aching, with intermittent shooting and squeezing pain (NRS 10). He also complained of hyperalgesia and allodynia in his right forearm, and both right limbs were becoming paralyzed. Based on these characteristic symptoms and imaging findings, the pain was diagnosed as central neuropathic pain caused by RN in the pons. Duloxetine was introduced, and an attempt was made to switch the opioid from oxycodone to hydromorphone (12 mg per day). However, the pain relief was temporary, leading him to resort to using immediate-release hydromorphone (IRH) an average of five times a day (Fig. 2a). Due to progressive pain (NRS 7 at rest) and insufficient pain relief, 5 mg of methadone was additionally incorporated (Fig. 2b), leading to a notable reduction in pain (NRS 5) within a week (Fig. 2c). As a result, the frequency of IRH usage significantly decreased to 0–1 times a day. Subsequently, the doses of methadone were gradually increased (total of 15 mg per day) whenever he experienced intense pain (Fig. 2d). The status of his lung cancer was that complete remission (CR) has been achieved after 2 years of chemotherapy with an anti-vascular endothelial growth factor (VEGF) drug, and his pontine lesion remains stable. Nevertheless, during the recent admission, the pain reached its peak (NRS 10 at rest), requiring the use of rescue medication with IRH over ten times daily (Fig. 2e). He reported that none of the following drugs, including frequent use of IR drugs and additional adjunctive painkillers such as duloxetine (40 mg), acetaminophen (3000 mg), and carbamazepine (200 mg), provided relief for his intolerable pain. In a critical turn, the patient developed severe distress, including crying, yelling, loss of appetite, insomnia, and even suicidal ideation. As a last resort, an additional 5 mg of methadone was administered to the original dose (total of 20 mg a day), resulting in rapid pain relief (NRS from 10 to 5) (Fig. 2f), restored appetite, and a decrease in IRH requirement to twice a day. His pain is currently effectively managed through the administration of daily doses of methadone (25 mg) and hydromorphone (8 mg), with a concurrent reduction or suspension of other adjunctive drugs, including duloxetine, acetaminophen, and carbamazepine (Fig. 2g).

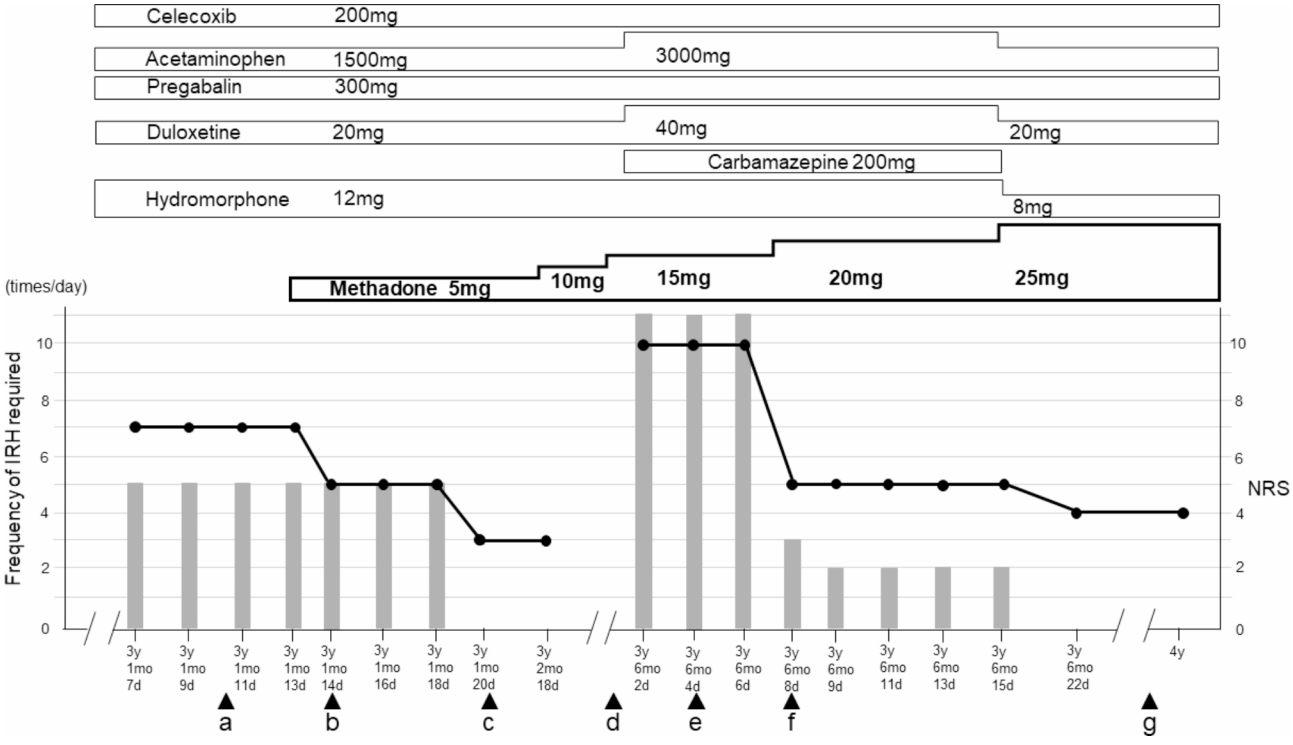

Fig. 2 Administered analgesics and the clinical course of the patient's pain management. The horizontal bar chart in the upper section displays the details of the medications. The gray bars indicate the daily frequency of immediate-release hydromorphone (IRH) required, while the black line chart plots the patient's daily pain intensity on a numerical rating scale (NRS) from 0 to 10. "y," "mo," and "d" correspond to years, months, and days post-referral, respectively.

Discussion and conclusions

This case suggests that spinothalamic tract injury resulting from SRS for brainstem metastasis in lung cancer is associated with progressive neuropathic pain in this patient. Additionally, methadone has proven to be the most effective treatment in managing the patient's intractable central neuropathic pain.

Brain metastases are prevalent in lung cancer, with over 10% of patients diagnosed at the initial stage [6] and up to 40–50% during disease progression [6, 7]. Radiation therapy is commonly employed for multiple brain metastases, with SRS recommended for patients with a limited number (up to four) and size (<3 cm) of metastases, rather than whole-brain radiation therapy (WBRT) [8]. SRS has become a preferred treatment option due to improved accessibility and availability, along with increased concerns about the neurocognitive adverse effects of WBRT. However, SRS for brainstem metastases may damage the density of nuclei and white matter tracts, causing serious complications [4]. Therefore, brainstem metastases are basically treated with WBRT alone, or if ever, with SRS at a lower dose [9]. SRS also carries a higher risk of RN developing in 8–25% of patients treated with SRS [5, 10]. RN is regarded as a late complication of radiotherapy for brain metastases and typically manifests between six months and two years after SRS. Symptoms including headache, seizures, and focal neurologic deficits are present in half of the cases of RN, yet the intractable central neuropathic pain as our patient experienced is infrequent.

In the present case, the pontine lesion is situated in a paramedian to lateral position, affecting the spinothalamic, corticospinal, and abducent tracts. The enlarged necrosis in the pons due to SRS caused damage to the involved cerebral nerves (e.g., trigeminal and abducent nerves) as well as sensory and motor nerve tracts, resulting in ipsilateral face disturbances and contralateral hemiparesis [11]. The injury of nerve fibers and microglial activation in pain transmissions pathways caused central sensitization and disinhibition, leading to thalamic hyperexcitability, which confused the peripheral afferent sensation as central neuropathic pain [2]. When the patient underwent SRS, two additional metastases were discovered in the temporal lobe of the cerebrum. Therefore, WBRT would have been more suitable, as it is less likely to induce radiation necrosis.

Differentiating RN from tumor recurrence on magnetic resonance imaging (MRI) can be challenging, as both may exhibit similar radiologic findings when the treated lesion progresses [5, 10]. Numerous reports have revealed that 11 C-MET-PET exhibits superior detection capability in distinguishing between the two entities [12], although the availability of facilities for this imaging modality is limited due to the short half-life of 11 C-MET [13]. In our case, an accurate diagnosis of RN was made, and sustained CR of lung cancer was confirmed with 11 C-MET-PET, avoiding unnecessary additional treatment. Hence, 11 C-MET-PET should be performed in cases of progression of SRS-treated brain lesions.

The majority of symptomatic cases of RN have been treated with corticosteroids and VEGF inhibitors in an attempt to reduce cerebral edema, while these interventions have presented benefits on a trial basis [5]. However, our patient did not experience any relief with these drugs, and only add-on methadone achieved a beneficial effect on his severe pain. The pharmacological approach for central pain follows the general treatment protocol for neuropathic pain [14]. Antidepressants, such as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (SNRIs), are frequently prescribed as first-line therapy. Anticonvulsants, including pregabalin and carbamazepine, are chosen as second-line drugs, although their efficacy has been limited. Opioid analgesics are not recommended primarily due to safety concerns associated with long-term use, including the risk of overdose and addiction. Methadone, the key drug in our case, is a synthetic strong opioid that stimulates mu-opioid and delta-opioid receptors [15]. It inhibits serotonin-norepinephrine reuptake and exerts an inhibitory effect on the upregulated N-methyl-D-aspartate (NMDA) receptor associated with injuries to the spinothalamic tract [16]. It also exhibits a low tendency to develop opioid tolerance [15], contributing to the favorable outcome in the patient suffering from uncontrolled pain. Although methadone is promising for managing intractable neuropathic pain, there are challenges such as the risk of QT prolongation and bioaccumulation due to its long half-life [16, 17]. Furthermore, when considering the transition to methadone, the stop-and-go rotation or the 3-day switch approach is generally employed, but it raises potential risks of increasing pain and overdose, due to the absence of an established conversion ratio from other opioids to methadone [15, 18]. Recently, however, the add-on approach for methadone enables easy introduction and shows superior efficacy for cancer-related intractable pain [19] because the addition of low-dose methadone to ongoing opioids carries fewer risks of worsening pain and reduces the aforementioned adverse effects.

In summary, we present the first case of central neuropathic pain resulting from RN caused by SRS for pontine metastasis in lung cancer. The irreversible RN involving the spinothalamic tract leads to progressive pain, emphasizing the importance of avoiding SRS for this specific tract. Add-on methadone at a low dose is a safe and beneficial treatment for patients suffering from unresolved central pain.

Abbreviations

SRS	Stereotactic radiosurgery
RN	Radiation necrosis
SNRIs	Serotonin-norepinephrine reuptake inhibitors
PS	Performance status
QOL	Quality of life
CPSP	Central post-stroke pain
MET	Methionine
PET	Positron emission tomography
NRS	Numerical rating scale
IRH	Immediate-release hydromorphone
CR	Complete remission
VEGF	Vascular endothelial growth factor
WBRT	Whole brain radiation therapy
NMDA	N-methyl-D-aspartate

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Author contributions
FK managed the patient and drafted the manuscript. AT, MT, AS and KT were the attending physicians throughout the patient's disease course. MB and MM provided supervision for this manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and was approved by Jichi Medical University Hospital Bioethics Committee for Clinical Research (Approval No. Rinfu 23 – 012). Informed consent was obtained from the patient.

Consent for publication
Written informed consent for the publication of this case report, including personal and clinical details along with any accompanying images, was obtained from the patient.

Competing interests
The authors declare no competing interests.

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