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CINGULOTOMY FOR REFRACTORY PAIN IN METASTATIC CLEAR CELL SARCOMA

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Background: Malignant pain is prevalent and often difficult to control. General management begins with the World Health Organization's analgesic guidelines and may further incorporate interventional techniques. For pain refractory to these measures, neuroablative procedures such as cingulotomy can be considered. We present the first known case of cingulotomy used in clear cell sarcoma.

Case Report: A 22-year-old man with metastatic clear cell sarcoma of the thigh presented with debilitating bilateral lower extremity pain. Initial management consisted of aggressive systemic pharmacotherapy, radiotherapy, and ultimately the implantation of an intrathecal drug delivery system. Despite these interventions, his pain remained unremitting. He was therefore deemed a candidate for bilateral anterior cingulotomy, which was performed without complication. Postoperatively, the patient reported immediate pain relief, which allowed for significant functional improvement in the following weeks.

Conclusion: Cingulotomy can be an effective intervention in oncologic patients with diffuse pain that is refractory to conventional management.

Key words: Cancer pain, case report, cingulotomy, clear cell sarcoma

BACKGROUND

Pain is a prevalent burden of malignancy and often challenging to manage. Over 50% of all cancer patients and 66.4% with advanced disease experience cancer-related pain (1). Among general providers, cancer pain management usually follows the World Health Organization (WHO) analgesic ladder, which outlines a stepwise approach to the combination of non-opioid analgesics, opioids, and adjuvants according to pain severity (2). While this approach can adequately control pain in the majority of cancer patients, approximately 30% remain resistant to even optimal medical therapy (1). Interventional procedures in the hands of trained specialists have hence been proposed as an additional step in the WHO ladder (3). Neurolytic blocks, neuromodulation, radiofrequency ablation, vertebral augmentation, and neurosurgical techniques have all been supported by varying degrees of evidence in specific settings (4).

Cingulotomy, a neuroablative procedure, has emerged as a treatment option for diffuse and intractable oncological pain (5). Anterior cingulotomy targets the anterior cingulate cortex, which is part of the limbic circuit. It is believed to play a major role in cognitive and emotional processing, including the affective component of nociception (6). Thus, the expected postoperative outcome is reduced perception of and reaction to pain (7). There are 2 principal techniques for performing cingulotomy: radiofrequency ablation, which can be performed under intravenous sedation, and laser interstitial thermal therapy (LITT) under magnetic resonance imaging (MRI) guidance, which requires general anesthesia (8). During LITT, MR thermometry is used to monitor in real time the ablation of the

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cingulate gyri. This approach is minimally invasive and generally well tolerated (6-8).

Current literature on the efficacy of cingulotomy for the management of cancer pain is limited. Existing case series have described pain relief with this procedure in various primary malignancies and pain distributions (9-22). While these have included sarcomas, a systematic search of major databases did not reveal any published report of cingulotomy utilized in the setting of clear cell sarcoma, also known as malignant melanoma of soft parts. This rare tumor comprises less than 1% of sarcomas and can present anywhere in the body (23). In this case, cingulotomy was selected for a young man suffering from refractory lower extremity pain secondary to metastatic clear cell sarcoma of the thigh.

CASE

A 22-year-old man with history of clear cell sarcoma of the left thigh status post excision presented with intractable pain secondary to tumor recurrence and metastases to the pelvis, bilateral femurs, and iliac lymph nodes (Fig. 1). He had undergone radiation therapy and initial immunotherapy with nivolumab and ipilimumab. Due to uncontrolled pain despite escalating opioid doses and consequent side effects, an intrathecal pump was implanted with hydromorphone and bupivacaine combination therapy. However, the patient further required patient-controlled analgesia with hydromorphone, ketamine infusion, and eventual palliative sedation with dexmedetomidine.

Despite these interventions, he continued to suffer from severe pain, now with additional metastases to the thorax, abdomen, spine, and skull. He lost the ability to ambulate or even sit up without assistance. He also required supplemental oxygen due to respiratory difficulty in the setting of his thoracic lesions and escalating medications. Given the diffuse and debilitating nature of his pain, the patient and his family decided to pursue neurosurgical intervention. He underwent LITT of the bilateral cingulate gyri under MRI guidance without any complications (Fig. 2).

Postoperatively, the patient had immediate improvement of pain that allowed discontinuation of ketamine and weaning of dexmedetomidine and hydromorphone. By the end of the first postoperative week, he transitioned to methadone plus hydromorphone as needed for breakthrough pain. He was also weaned to room air and appeared happier and more animated. By the third week, his pain was well controlled on methadone, gabapentin, and intrathecal hydromorphone and bupivacaine.

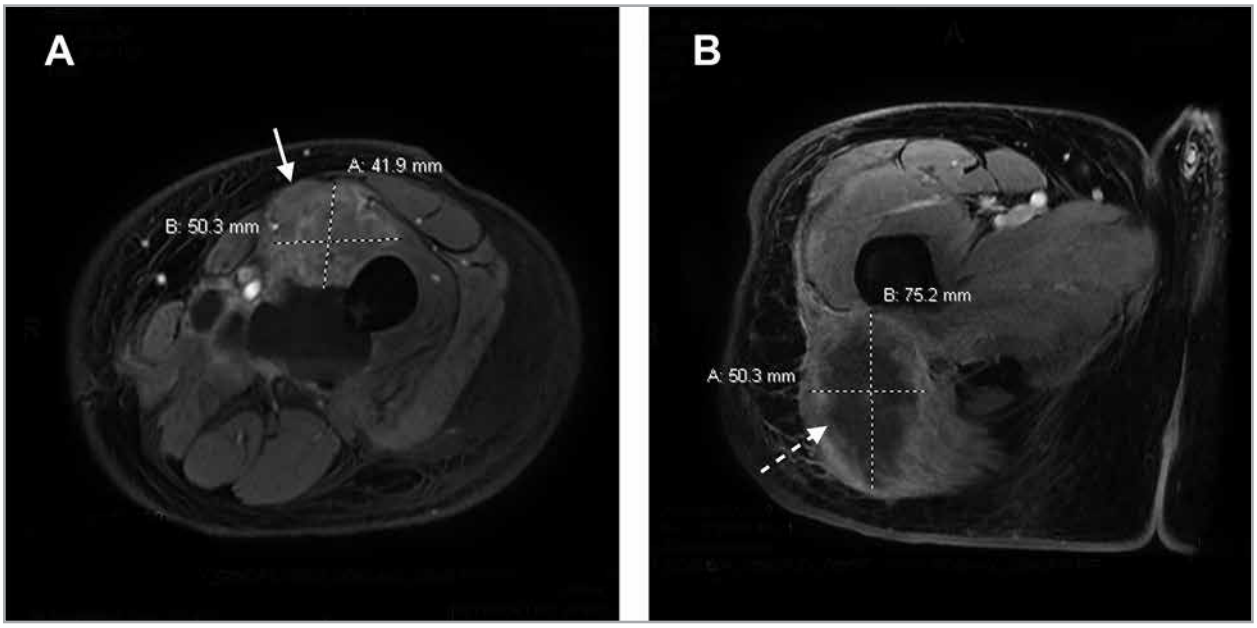

Fig. 1. Magnetic resonance images of the (A) left thigh and (B) right hemi-pelvis demonstrate centrally necrotic masses consistent with advanced malignancy. The recurrent tumor in the left anterior vastus medialis muscle (arrow) measures 4.2 cm x 5.0 cm in cross section, while the metastasis in the right gluteus maximus muscle (dashed arrow) measures approximately 5.0 cm x 7.5 cm in cross section and extends at least 10.5 cm in length.

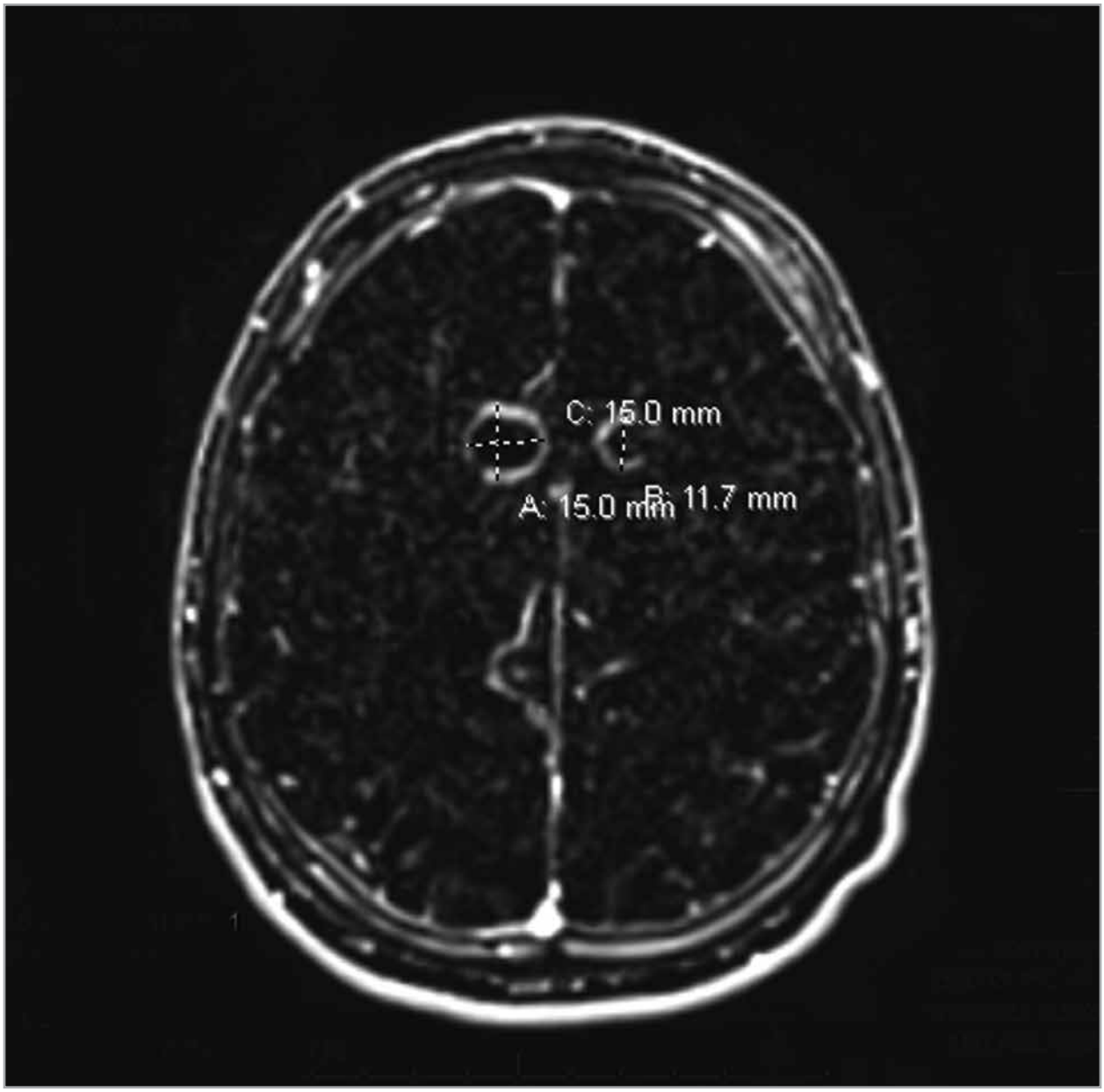

Fig. 2. Posttreatment subtraction magnetic resonance image of the brain shows coverage ablation cavities within the bilateral anterior cingulate gyri with thin peripheral reactive enhancement and restricted diffusion. The right cavity approximates 1.5 cm (A) x 1.2 cm (B), and the left cavity measures 1.5 cm (C).

Whereas his pain scores had consistently been 7 to 10 out of 10 prior to the procedure, he was now rating his pain 0 to 2 out of 10 and progressing with physical therapy to regain the function he had lost during this period. Unfortunately, the patient suffered cardiac arrest with unsuccessful resuscitation in the setting of disease progression, including massive pleural effusion and sepsis.

DISCUSSION

For cancer pain unresponsive to maximal pharmacotherapy, neuroablative procedures are promising yet understudied treatment tools. Our case exemplifies the life-altering potential of cingulotomy in a previously undescribed setting. Clear cell sarcoma is a rare soft tissue tumor that typically affects peripheral tendons

Table 1. Outcomes after cingulotomy for cancer pain: Summary of selected studies.

Authors	Year	Setting	n	Outcomes	Complications
Hochberg et al. (9)	2020	Advanced metastatic cancer	19	Immediate substantial pain relief (NRS 9 ≥ 2, *P* = .001), sustained at 3 months	Mild transient limb paresis (n = 2), permanent hemiparesis (n = 1), transient gait ataxia (n = 4), transient positional headaches (n = 10)
Berger et al. (10)	2019	Advanced metastatic cancer	20	19/20 patients with immediate pain relief, 7/11 with good relief at one month	No major morbidity or mortality
Strauss et al. (11)	2017	Sarcoma, CRC, parotid cancer, cervical cancer, chordoma, lymphoma, small cell lung cancer	13	At one month, mean VAS decreased from 9 ± 0.9 to 4 ± 2.7 (*P* = .003), BPI pain severity from 29 ± 4 to 16 ± 12 (*P* = .028), interference scores from 55 ± 12 to 37 ± 15 (*P* = .043). 5/7 patients at 3 months with good relief. 3/6 bedridden patients ambulated shortly after surgery.	Transient confusion or mild apathy (n = 5) lasting 1-4 weeks
Patel et al. (12)	2015	Liposarcoma, CRC, breast cancer	3	Median preoperative pain severity and interference scores decreased from 7.7 and 9.9 to 1.6 and 2.0, respectively	No adverse effects
Yen et al. (13)	2009	Terminal cancer	10	6/10 patients with fair to good relief at one week, 5/10 at one month, 6/10 at 3 months	Decline in focused attention performance; other neurocognitive functions unaffected
Yen et al. (14)	2005	Cancer: lung, breast, thyroid, hepatocellular, mesothelioma, esophageal, uteral, lymphoma	15	12/15 patients with significant pain relief at one week, 9/15 at one month, 7/12 at 3 months, 5/10 at 6 months	Transient confusion (n = 2), mild gastrointestinal bleeding (n = 2). Subtle cognitive impairment and attention deficits were detected through neuropsychological evaluation.
Wong et al. (15)	1997	Metastatic melanoma, cholangiocarcinoma, SCC	3	2/3 patients with significant pain relief and reduced opioid use	Deficits in executive function (n = 1)
Pillay (16)	1992	Cancer: lung, breast, myeloma, chordoma, rectal. Metastases in spine, ribs, pelvis	10	Pain relief was judged excellent (n = 4), good (n = 2), fair (n = 1), poor (n = 2) at 6 months' follow-up	None noted
Hassenbusch et al. (17)	1990	Various cancers	4	All with good pain relief and lower use of opioids	Perilesional edema for 10 days (n = 1)
Voris et al. (18)	1975	Various cancers	5	All had pain relief before death, up to 12 months	Hemiparesis (n = 1)
Hurt et al. (19)	1974	Cancer: oropharynx, lung, CRC, pancreas, uterus, bladder, melanoma, osteosarcoma, liposarcoma	32	18/32 patients with moderate to complete relief at 3 months or less, 2/9 at > 3 months	Transient headache and fever, incontinence, confusion (< one week)
Wilson et al. (20)	1974	Metastatic cancer	19	10/19 patients had pain relief	None noted
Faillace et al. (21)	1971	Terminal cancer	7	3/7 patients with improvement lasting from 3 days to 3 months	Significant decrease in performance on a nonverbal ordering test. Overall cognition did not show significant changes from baseline
Foltz et al. (22)	1968	Head and neck cancer	11	9/11 patients with good to excellent outcome	Transient mild hemiparesis (n = 1), hemiplegia (n = 1), seizure (n = 1)
Foltz et al. (7)	1962	Various primaries, metastases in back, hip, arm	6	5/6 patients with good or excellent outcome up to 9 months	Transient (1-2 days) mild confusion, change in affect

Abbreviations: BPI, Brief Pain Inventory; CRC, colorectal cancer; n, number of oncologic patients who underwent cingulotomy; NRS, Numeric Rating Scale; SCC, squamous cell carcinoma; VAS, Visual Analog Scale.

and aponeuroses in young adults (23). Treatment includes surgical resection and radiation therapy, but 5-year survival is only 50% and much lower in stage 3 or 4 disease (24). As with many malignancies, there are neither guidelines nor available literature about pain management specific to clear cell sarcoma. It is hence pertinent to share the success of cingulotomy in this instance of debilitating malignant pain refractory to conventional treatments. Furthermore, although our case involves a rare condition limited to one patient, it underlines important commonalities with existing reports on this procedure.

Current literature includes small-scale case series but no prospective studies on cingulotomy in the context of malignant pain (Table 1). Based on its central mechanism, this intervention is expected to target pain that is diffuse, involving both sides of the body, and usually musculoskeletal in origin (25,26). Patients are selected for the procedure after failing less invasive management, such as radiotherapy, pharmacotherapy, and neuromodulation. They also tend to be terminally ill with a life expectancy of less than 6 to 12 months (27). In this setting, an intervention with immediate benefits is desirable. Much like our case, recent retrospective studies have demonstrated rapid postoperative pain relief in the majority of patients undergoing cingulotomy (9-11). Several previously bedridden patients were also noted to be able to ambulate in the acute postoperative period (11). Furthermore, improvements in dyspnea and autonomic control of respiration have been reported, which may be particularly beneficial in the setting of thoracic disease and respiratory depression associated with opioid use (28). Moreover, despite its current label as a "last resort," cingulotomy is minimally invasive with few side effects. Reported postoperative symptoms include transient and self-resolving confusion and apathy lasting from a few days up to a month, mild attention and executive deficits for up to 3 months, and rare personality changes, seizures, and hemiparesis primarily seen when MRI guidance was not used (6,10,11).

The risks and benefits of cingulotomy should be weighed against those of other interventions when selecting the most appropriate analgesic approach in each oncologic patient. Its main advantage over other neurosurgical techniques such as cordotomy and myelotomy is that, by disrupting pain processing rather than specific tracts, it most effectively targets diffuse pain (5). Neuromodulation techniques have also become increasingly popular treatment options for chronic pain, with intrathecal drug delivery as the mainstay in the presence of advanced malignancy (4,26). Other modalities, e.g., spinal cord stimulation, have limited evidence in this setting (4). Benefits of intrathecal pumps include flexibility in the choice of agent, dosing, and reversibility. In contrast, neuroablative procedures are standardized and permanent, though their effects are thought to diminish over time (26). Nonetheless, both options are minimally invasive with relatively minor surgical risk when performed by well-trained providers, especially under appropriate imaging guidance. In fact, the transient cognitive changes seen with cingulotomy may be preferable to the dose-limiting and at times life-threatening sedation, confusion, and respiratory depression associated with systemic opioids. Secondary outcomes such as respiratory improvement and early ambulation after cingulotomy may also lead to improved function and quality of life. Moreover, cingulotomy is a one-time procedure resulting in immediate relief and requiring minimal follow-up, whereas pumps can be costly and labor-intensive (10). Certainly, these options are not mutually exclusive and may be used in tandem, as was done in our patient.

Unfortunately, case reports are of limited utility in guiding practice due to their size, specificity, and lack of controls. The setting of advanced cancer also presents the challenge of long-term follow-up due to short life expectancy, limiting the ability to determine the duration of both positive and negative effects of any interventions. Existing studies have suggested that postoperative pain relief after neuroablative procedures may diminish over time, but this may not hold clinical significance in the context of short prognoses (26). Prospective studies and randomized controlled trials are needed to establish clear guidelines regarding these interventions that may serve as a last hope for patients suffering from advanced malignant disease.

CONCLUSION

Cingulotomy can be an effective intervention for oncologic patients with diffuse pain that is refractory to conventional treatment. Higher quality evidence should be pursued to better establish the role of such neuroablative procedures in cancer pain management.

Author Contributions

EE wrote the manuscript. CV aided with the literature review and table. TC provided images and captions. All authors contributed edits and final review.

Informed Consent

As the patient is deceased and the case report is devoid of identifiable information, a HIPAA waiver for exemption was applied per institutional policy.

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