Case Reports
Intrathecal Catheter Granuloma Associated with Continuous Sufentanil Infusion

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Implications Statement: This case report involves the development of an intrathecal granuloma in a patient receiving intrathecal sufentanil therapy. Although sufentanil is uncommonly used for intrathecal infusions, the risk of catheter-associated granuloma must be considered in all patients receiving intrathecal sufentanil. Special attention should be focused on those patients presenting with altered neurological function and/or a significant increase in drug requirement in response to escalating pain. These patients will require careful evaluation and appropriate imaging to determine the etiology of their clinical presentation.

Abstract
Intrathecal sufentanil is a minimally utilized opioid for patients with intractable pain refractory to traditional intrathecal medications. We present an 86-year-old female with a history of multiple spine surgeries who eventually progressed to having chronic, intractable, and diffuse low back pain. After failing medical management, she underwent a successful intrathecal trial of opioid therapy and was subsequently treated with an implantable drug delivery system (IDDS) or intrathecal pump. We describe the first reported case of formation of a catheter tip granuloma associated with intrathecal infusion of sufentanil.

Due to increasing opioid requirements and gradually escalating pain, a computed tomography myelogram was performed to explore neuraxial etiologies of her symptoms. This investigation revealed the presence of a catheter tip-associated inflammatory mass (granuloma). All patients receiving intrathecal medications, including sufentanil, must be considered for the possibility of catheter-associated granuloma, particularly with symptoms of altered neurological function and/or increasing medication requirements associated with worsening pain.

Key Words. Interventional; Chronic Pain; FBSS (Failed Back Surgery Syndrome)

Introduction
Failed back surgery syndrome (FBSS) or post-laminectomy syndrome describes a clinical syndrome in which patients report persistent back and/or leg pain following one or more surgical procedures performed to correct their lumbosacral spine disease [1]. The syndrome may result in recurrent disk herniation, segmental spinal instability, facet joint disease, permanent nerve root damage, epidural fibrosis, or arachnoiditis [2-5]. Many of these processes can produce neuropathic pain. FBSS patients who have experienced neuropathic pain and/or radicular symptoms prior to surgery may continue to suffer from the same symptoms after the procedure and experience debilitating pain, as well as a reduced quality of life [6]. FBSS is a complex condition generally requiring multidisciplinary and advanced pain treatment modalities.

FBSS may reflect a failure of outcome agreement between patient and surgeon prior to the procedure, resulting from
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an incorrect initial diagnosis, poor patient selection, incomplete decompression, or decompression at the incorrect level. According to Guyer et al., several readily identifiable etiologies for FBSS have been defined. These include poor patient selection, incorrect diagnosis, unrealistic expectations on the part of the surgeon and/or patient, incorrect procedure selection based on patient pathology, inadequate operative technique, failure to achieve surgical goals despite otherwise proper operative technique, and natural progression of the particular disease [7,8].

Treatment for FBSS is dependent on many factors, which include severity of pain and physical dysfunction, type and location of the pain, ongoing medical conditions, and age [9–12]. For patients with residual foraminal and spinal stenosis, or recurrent herniated nucleus pulposus with spinal instability, re-operation may become necessary [13]. Painful disc disease may benefit from a minimally invasive procedure known as intradiscal electrothermal therapy (IDET), or even re-operation [13]. FBSS often requires a multidisciplinary approach that incorporates pharmacologic therapies with physical therapy, neural blockade, or advanced pain techniques with intrathecal medications or spinal cord stimulation [13]. This case report is the first to describe the development of a catheter tip inflammatory mass possibly associated with the use of intrathecal sufentanil for failed back surgery syndrome.

Case Description

An 86-year-old woman with a history of FBSS (e.g., two lumbar laminectomies with fusion and rod placement from T12 to L5 followed by a discectomy) was referred to the interventional pain clinic for worsening low back and buttock pain. She had a history of osteoarthritis, rheumatoid arthritis, hypertension, and hypothyroidism. The patient complained of persistent low back pain for the last 10 years. The pain was localized to the lower lumbosacral spine, with radiation to the buttocks. She described the pain as constant, sharp, burning, and pressure like, and rated it 7–8/10 on the numerical analog scale. Sitting up, standing, walking, or remaining stationary for even a short time worsened the pain, while lying down improved the symptoms. In sum, the patient felt incapacitated from inadequate pain control. After several unsuccessful trials of medical management, epidural steroid injections, medial branch blocks, and a trial of spinal cord stimulation, an inpatient intrathecal trial was performed. Several intrathecal agents were attempted before a ziconotide trial was reported to relieve the patient’s intractable low back pain by 50% and increase the patient’s ability to ambulate. For example, intrathecal morphine, hydromorphone, and dual therapy with bupivacaine and clonidine were trialed separately without relief. A 20-mL SynchroMed® (Medtronic, Minneapolis, MN, USA) intrathecal drug delivery system (IDDS) containing ziconotide was subsequently implanted due to the benefit associated with this agent.

During the surgery, the tip of the Medtronic intrathecal catheter was positioned at T11. Intrathecal ziconotide was initiated at 2.4 mcg/d (25 mcg/ml) and escalated to a maximum of 4.8 mcg/d over 2 months. The patient derived some relief for a couple of months, but increasing cognitive dysfunction and progressively reduced pain relief despite changes in ziconotide dosing prompted the pain team to consider alternative intrathecal agents. The patient had been reporting lumbar spasm unrelieved with oral muscle relaxants; therefore, baclofen seemed a reasonable choice. Doses of intrathecal baclofen were only escalated to 30 mcg/d (1,000 mcg/ml) given the patient’s persistent confusion, hallucinations, somnolence, gait disturbance, and occasional bowel and bladder incontinence, and subsequently discontinued at 2 months. Since the patient had previously failed more traditional intrathecal therapies, intrathecal fentanyl seemed an appropriate alternative [14]. During the ensuing 7 months, intrathecal fentanyl doses were increased from 10 mcg/d (80 mcg/ml) to slightly over 100 mcg/d due to noticeable benefit with this therapy. The patient reported a maximum of 50% pain relief, enhanced mobility at home, and an improved quality of life with no adverse effects during the first 2 months of treatment. However, 2 months following the initiation of intrathecal fentanyl, the patient underwent lumbar spine hardware removal due to the belief the patient’s pain maybe related to spinal hardware malposition. During the surgery, the intrathecal catheter was inadvertently pierced, but immediately repaired. Complaints of increased pain, problems with weight bearing, and somnolence prompted an intrathecal dye study, which revealed a myelogram and no contrast extravasation outside the catheter or pump. Because the patient’s pain was no longer controlled with intrathecal fentanyl despite an intact catheter and pump system, fentanyl was replaced with sufentanil. Doses began at 12 mcg/d (80 mcg/ml) and escalated to 17.2 mcg/d, with some reduction in pain and a greater ability to ambulate in her home (Table 1).

Approximately 2 years after intrathecal therapy implantation and 6 weeks following the introduction of intrathecal sufentanil, the patient was admitted to her local hospital for lower extremity weakness, sensory changes, and intractable lumbar pain. To assess the integrity of the IDDS and to explore the etiology of her pain, a computerized tomography (CT) myelogram was performed. The images demonstrated the presence of a granuloma confirmed by a radiologist at the local hospital, as well as a radiologist at our institution, and were reviewed meticulously for identification of the granuloma, which are best depicted in Figures 1 and 2. MRI revealed the presence of a left-sided, 4-mm epidural mass indenting the left anterior aspect of

<table>
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<tr>
<th>Table 1</th>
<th>Sufentanil dosage initiation and titration</th>
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<tr>
<td>Dosage</td>
<td>Days</td>
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<tr>
<td>Sufentanil 12 mcg/day</td>
<td>Day 0–30</td>
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<tr>
<td>Sufentanil 17.2 mcg/day</td>
<td>Day 31–44</td>
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Figure 1 Computed tomography myelogram displaying an intrathecal fibrous mass consistent with a catheter-tip associated granuloma. Arrow depicts the mass in cross-section.

The use of intrathecal morphine probably offers the best evidence base for safety and effectiveness in relieving pain. In fact, morphine is the only opioid approved for use intrathecally by the Food and Drug Association (FDA). In 1976, Yaksh et al. found that there was a selective analgesic effect of morphine when given intrathecally [16]. In 1980, Yaksh et al. further discovered that substance P release was inhibited at the spinal cord level [17] by delivering morphine intrathecally. Other researchers such as Wang et al. demonstrated that malignant pain was diminished with direct intrathecal administration of morphine [18]. Finally, a case review by Maesyaerdt of 38 patients with non-malignant pain showed an impressive 94% of patients reporting good, very good, or excellent pain relief from the use of intrathecal morphine [19].

Intrathecal opioid dosage titration is often limited by concurrent adverse effects that include memory impairment, constipation, bladder disturbances, excessive sweating, and libido impairment [19]. It has been noted that high levels of intrathecal morphine-3-glucuronide, a metabolite of morphine, have been associated with drowsiness, allodynia, hyperalgesia, and myoclonus [20]. In contrast, intrathecal sufentanil produces analgesic effects comparatively more potent than morphine and requires fewer functional receptors than morphine to provide comparable analgesia.

Discussion

Intrathecal therapy for chronic, intractable pain can be a vital treatment option for the FBSS patient population. The intrathecal route of delivering a drug often reduces the impact of certain toxicities linked to high-dose opioid therapy, such as excessive sedation, cognitive disturbance, and severe constipation. Further, clinical evidence suggests that intrathecal drug delivery can provide more effective analgesia than systemically administered drug [15].

There are a number of intrathecal medications that can be infused into the cerebrospinal fluid in order to relieve severe pain, reduce disabling adverse effects of oral and transdermal analgesics, and promote a higher quality of life. This modality may be considered for those patients with failed back surgery syndrome in whom long-acting oral or transdermal opioid medications have not provided adequate pain relief. There are several classes of agents that may be used for intrathecal delivery in chronic pain states. These include opioids, alpha-agonists, ziconotide, local anesthetics, and GABA agonists, such as baclofen.

Figure 2 Computed tomography myelogram displaying an intrathecal fibrous mass consistent with a catheter-tip associated granuloma. Arrow depicts the mass in sagittal view.
analgesia [21]. Compared with morphine, sufentanil elicits less drug tolerance. Sufentanil’s greater potency allows it to maintain efficacy after sustained exposure [21].

Intrathecal opioids have been associated with the development of granuloma formation [20-24]. In fact, approximately 41 cases of intrathecal granuloma formation were reported between 1990 and 2000 [25,26]. In these reports, opioids or admixtures of opioids were infused. Granulomas were described with all intrathecal agents except sufentanil, rarely fentanyl, and even clonidine was reported to induce an inflammatory response alone or in combination with other agents [25,26]. Granuloma formation has been associated with the specific medication administered, catheter position, low CSF volume, and the dose, as well as the concentration. Concentration, however remains the presumed major causal factor [25,26]. The length of time prior to identification of granuloma development based on patient symptomatology is reported to vary from 0.5 to 72 months, with an average time of 24 months [27]. The diagnosis of this problem is often made after neurological symptoms or signs develop [27]. Most commonly, patients will present with intractable pain and loss of effective pain relief, requiring dose escalation, dermatomal symptoms in the distribution of the catheter tip location, change in proprioception and sensation, and motor, bowel, and bladder changes in later stages of development. Initially, physical examination may not detect specific findings; however, granuloma-induced spinal cord impingement may involve subtle changes in reflexes, sensation, and/or motor function [27]. Given the increasing frequency of pain treatment with intrathecal opioids, the risk of development of intrathecal granulomas must be considered in patients receiving intrathecal opioid therapy.

Proposed etiologies of intrathecal granulomas include the development of an inflammatory response related to the intrathecal medications alone, formulation and compounding impurities, or an allergic reaction to the silicone catheter, which often resolves once the intrathecal catheter is removed [28-30]. Current consensus opinion ranks the MRI with and without intravenous gadolinium as the gold standard for surveillance when suspecting a catheter-related inflammatory mass, although CT myelo-

**Table 2** 2007 recommendations: diagnosis, treatment, and prevention of catheter-tip granuloma formation [26]

**Prevention**

1. Minimize concentrations and doses of intrathecal (IT) agents, especially of morphine sulfate and hydromorphone.
2. Avoid ultra-slow flow rates.
3. Refill pumps more often (e.g., every 1–2 months) to keep concentration low.
4. Add clonidine to single opioid or nonopioid analgesic combination.
5. Switch to fentanyl or sufentanil alone or combined with nonopioid medications if concerned about granuloma formation.

**Screening/detection clinical assessment/patient history/surveillance**

1. Take patient history and perform physical examinations on patients with IT therapy often. Patients of low risk should receive surveillance, at least annually, but preferably every 3–4 months. Patients at high risk (patients with high doses/high concentrations of IT analgesics/antispasmodics) should have examinations and even screening imaging more often.
2. If patient complains of insufficient analgesia, sudden loss of analgesia, onset of new pain, or if neurologic signs and symptoms, including decrease in deep tendon reflexes or clonus have appeared, perform a magnetic resonance imaging (MRI) (T1-weighted MRI with gadolinium) or computed tomography myelogram.
3. If imaging is negative and symptoms persist, change clinical direction by increasing the dose, changing the agent infused, adding another synergistic analgesic, or moving the catheter.
4. If a mass is confirmed move the catheter out of the granuloma (continue IT therapy at lower doses/concentrations or change the drug) or replace the catheter, and resume systemic analgesics.

**Treatment**

1. If no neurologic impairment, try moving the catheter down 2–3 cm. Change drug concentration/dose down and or change to safer medication such as fentanyl/ziconotide.
2. If symptoms persist, in spite of moving catheter, quickly wean patient off of IT opiates, remove drug from pump, and fill pump with saline. Be careful of withdrawal signs and symptoms and treat, especially in patients with back pain and/or clonidine.
3. If symptoms decrease after pulling catheter out of mass, perform scan again within 6 months.
4. If a small granuloma is detected by MRI at follow-up after pulling catheter back, weigh advantages of catheter adjustment vs a catheter explant.
5. If granuloma causes spinal cord compression and/or neurologic signs or symptoms persist, removal is recommended.
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Table 2 summarizes the consensus guidelines for intrathecal granuloma prevention, diagnosis, and treatment. Treatment generally involves conservative management, including discontinuing the offending agent, surgical repositioning of the catheter, and occasional explantation of the intrathecal pump [27]. Expert opinion recommends using the lowest effective intrathecal dose and concentration for the longest duration possible in order to reduce the odds of occurrence.

In our patient, the onset of changes in the neurological examination coupled with intractable pain prompted immediate evaluation with a CT myelogram. We hypothesize that sufentanil was implicated in the development of the intrathecal granuloma due to increasing dosage requirement with concomitant intractable pain, the concurrent use of no other intrathecal agent, and no development of signs of neurologic compromise with previous intrathecal therapies. Further, the patient had significant benefit from the initiation of intrathecal sufentanil, with subsequent development of intractable pain approximately 6 weeks following initiation of the medication. The temporal relationship between sufentanil use and the onset of symptoms falls within the range of granuloma development and lends support to our theory of a sufentanil-induced granuloma. We concede that prior use of intrathecal fentanyl, baclofen, or ziconotide could have initiated the inflammatory process because no previous imaging was obtained to rule out such an event. Furthermore, there was no washout period after removing any of the previous agents and prior to beginning sufentanil; hence, the onset of granuloma formation may have begun with pump implantation approximately 2 years earlier. The use of multiple agents may be a precursor to the development of an intrathecal granuloma and remains a controversial point in this particular case. However, use of intrathecal sufentanil has been used infrequently, and any related complications to its use should be discussed further. Furthermore, the literature is not consistent in reporting whether cases of intrathecal granulomas may actually result from multiple agents infused consecutively over time, which may contribute to a cumulative inflammatory effect [25–29].

Although intrathecal granuloma development is rare and to date represents an unreported phenomena possibly associated with sufentanil administration, clinicians must nevertheless be mindful of the potential of this adverse event. A relationship probably exists between mass formation and intrathecal opioids doses and/or concentration. Other factors remain to be investigated [25–29]. Intrathecal pain management practices continue to evolve as the options for treatment increase. As the scientific literature grows, the cost-effectiveness, clinical efficacy, patient access and patient safety must also be considered [30]. This is a provocative case demonstrating the importance of evaluating patients for intrathecal granuloma and also the overall use of this therapy for patients with FBSS.

References


