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Case Report

Intrathecal Granuloma in a Patient Receiving High Dose Hydromorphone

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Intrathecal granuloma formation has commonly been described with morphine therapy. It has been suggested that a high concentration of intrathecal morphine may be responsible for this complication. Much less commonly, intrathecal hydromorphone has been associated with intrathecal granuloma formation.

In the current case we report the evaluation and management of an intrathecal granuloma in a patient receiving a relatively high concentration of intrathecal hydromorphone.

A nonsurgical, conservative approach to management involves stopping the infusion and observing the patient for improvement as the granuloma mass often slowly resolves once the infusion is stopped. Cessation of the infusion or addition of clonidine to the IDDS admixture in conjunction with close clinical monitoring may be reasonable treatment options in patients with an asymptomatic or mildly symptomatic inflammatory mass. In the current study, rapidly declining neurologic function with a confirmed inflammatory mass adherent to the spinal canal necessitated urgent surgical intervention.

Though use of intrathecal hydromorphone still represents an off label application, this opiate is commonly employed as an alternative first line analgesic agent. This case report highlights the potential of high-dose and high infusate concentration intrathecal hydromorphone to form an inflammatory granuloma.

Key words: Intrathecal hydromorphone, intrathecal granuloma, inflamatory mass, intraspinal drug delivery

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Granuloma formation associated with intrathecal drug infusion is a rare but recognized complication (1). A growing awareness of this problem has lead to numerous case reports in the literature, and more recently, a large case review of reported incidents of granuloma formation (1). In this review, by far the most common drug associated with granuloma formation was morphine (1). In contrast, granuloma formation with hydromorphone was a significantly less common occurrence. We report the diagnosis, surgical treatment, and outcome of a patient receiving a relatively high concentration and daily dose of intrathecal hydromorphone with significant neurological impairment secondary to granuloma formation.

Case Description

We present the case of a 52-year-old male with a history of chronic lumbar spine pain. Previous therapies included surgical lumbar laminectomy, lumbar epidural steroid injections, and facet blocks by

physicians outside of our institution. Ultimately the patient received an intrathecal drug delivery system (IDDS) placed and managed for approximately 8 years by a physician also outside of our institution. By patient history, morphine was the initial drug chosen for therapy, however approximately 2 years ago he recalls being switched to hydromorphone. He was referred to our institution for urgent evaluation after experiencing increasing back pain and gait instability in the preceding 4 weeks. Additionally, recent onset urinary retention and weakness in the lower extremities was noted. He rated his pain as a 10/10 on a numeric pain rating scale. On physical examination, the patient had decreased range of motion and severe pain in the lumbar/thoracic spine exacerbated by flexion. He had a diminished sensory examination at the T9 dermatome, hyperreflexia, and sustained clonus in his lower extremities, and normal rectal tone. Interrogation of the IDDS revealed that the patient was receiving hydromorphone, 85 mg/mL concentration, at an infusion rate of 19.8 mg/day. His human immunodeficiency virus (HIV), c-reaction protein (CRP), erythrocyte sedimentation rate (ESR), and white blood count (WBC) studies were all within normal limits. A magnetic resonance imaging (MRI) and computed tomography (CT) scan revealed an intradural-extramedullary lesion at the level of T8-9 with cord compression and contrast enhancement (Fig. 1 and 2).

The patient was taken to the operating room for decompressive laminectomy and exploration which at that time showed an approximately 1 cm mass adherent to the spinal cord, adjacent to the tip of the intrathecal catheter. This mass was associated with multiple subarachnoidal adhesions and discoloration of the arachnoid. Due to the gross adherence of the mass to the spinal cord, the decision was made initially to biopsy the lesion. Once the lesion was determined to be an inflammatory mass, it was carefully dissected away from the spinal cord under microscopic visualization. The IDDS catheter was cut so as to end 2 levels below the lesion.

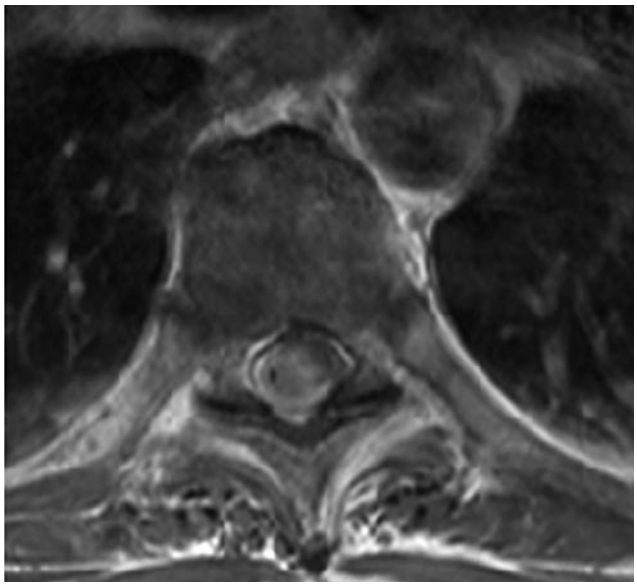

Fig.1. *T1 contrasted axial image which shows the granuloma. Note the dark area in the right of the spinal canal which is the catheter tip*

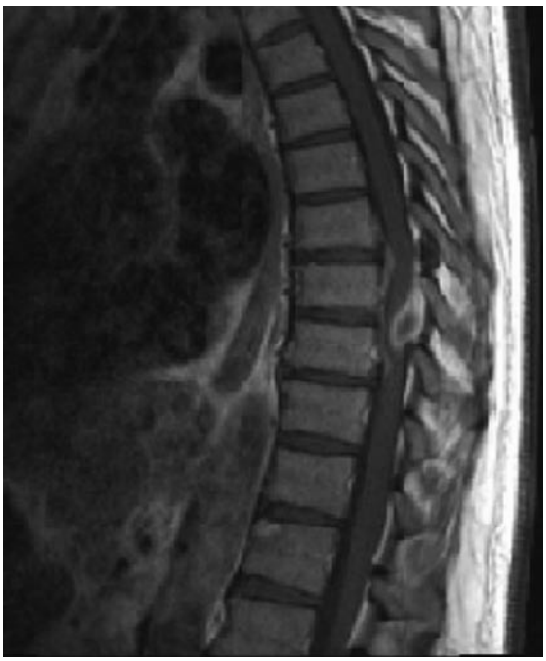

Fig. 2 *T1 sagital contrasted which clearly shows the lesion at hand.*

Pathological examination of the specimen showed extensive inflammatory changes and development of fibroconnective tissue, with focal necrosis. Also present was lymphocytic and histiocytic inflammation with an absence of neutrophils. The Gomori's Methenamine Silver (GMS) stain performed for micro-organisms was negative. There was no evidence of tumor in the tissue sampled. A significant portion of the mass was carefully dissected from the spinal canal and the operation concluded. All cultures of the specimens obtained showed no growth and the patient was discharged home after 2 days with a stable but improving neurologic exam.

A follow-up MRI at 4 months postoperatively showed no residual mass lesion except faint dural enhancement where the lesion had previously been located. The patient continued to show signs of neurologic improvement in terms of myelopathy, with decreased pain scores, however he had persistent numbness in his lower extremities. He subsequently elected to have the IDDS removed by his treating pain physician and was converted to oral analgesics.

Discussion

Intrathecal drug administration is becoming increasingly common in the treatment of benign chronic pain. One of the recognized complications of this therapy is catheter tip inflammatory mass/granuloma formation. Since first being reported in 1991, there have been numerous case studies reporting the management and treatment outcomes of this phenomenon. The incidence of granuloma formation had previously been estimated at 0.04% at one year of therapy increasing to 1.15% at 6 years (2). Recent communications from Medtronic Inc. (Updated information for physicians-inflammatory mass 2008, Minneapolis, MN) placed the incidence as high as 0.49%; 5 times the 0.1% incidence reported in 2001 by this company (Medtronic Inc. Minneapolis MN, Updated information 2001). Further, in a recent report of 208 asymptomatic patients screened for occult granuloma formation, approximately 3% of that population was identified as having developed some degree of an inflammatory mass (3).

The opioid most commonly associated with development of an inflammatory mass lesion is morphine (1). This is likely because morphine is the only opioid approved by the Food and Drug Administration for intrathecal infusion and therefore the most commonly used (1). As patients become tolerant to the analgesic effects of morphine they are often rotated to other opiates, with hydromorphone being a common alternative first-line drug choice (4). Since hydromorphone is less commonly utilized as an intrathecal drug, the literature is less clear as to the incidence of inflammatory mass formation with this opioid.

It has been shown in dogs that opiates at equianalgesic doses differ in the rate of granuloma formation (5). In this study, administration of maximally tolerated doses of morphine and hydromorphone resulted in granuloma formation 100% of the time. Interestingly, in this report, maximally tolerated doses of fentanyl resulted in no granulomas. Preliminary evidence from these studies suggests that dural mast cell degranulation and concomitant release of inflammatory mediators such as histamine may be responsible for granuloma formation (5,6). In the largest and most comprehensive report to date in humans, only 9 of 41 cases of granuloma formation were associated with hydromorphone infusion (1). Further, the dose range for these patients was 1 – 64.8 mg/day of intrathecal hydromorphone and the drug concentration ranged from 10 to 100 mg/mL (1). In the current case report, the 19.8 mg/day infusion that the patient was receiving would be in the upper third of patients in the Coffey study (1), while the 85 mg/mL concentration would represent the second highest hydromorphone concentration in that report. This is important because opiate concentration has been identified as an important covariate in inflammatory mass formation (1,5). In the Coffey study it was suggested that 20 mg/day of intrathecal morphine may be a reasonable upper limit for avoidance of mass formation; however no guidelines for infusion of intrathecal hydromorphone were given. Since that report a consensus panel has suggested that the maximum concentration and daily dose for intrathecal hydromorphone administration should be 10 mg/mL and 4 mg/day respectively (4).

As mentioned previously, it has been suggested that the concentration rather than the daily dose of the selected opiate is the primary contributing factor to granuloma formation (4,5). The local concentration of opiate at the catheter tip presumably leads to activation of the inflammatory cascade, mast degranulation and histamine release resulting in mass formation (3,7). Since it is believed that the incidence of granuloma formation is directly related to opioid concentration and/or flow rate, the 2007 Consensus Panel has therefore recommended that hydromorphone concentration intrathecally not exceed 10 mg/mL and 4

mg/day respectively. In the present case, the concentration was approximately 8 times this recommendation and the daily dosage approximately 4 times this recommendation (4).

With regard to nonopioid agents approved for intrathecal use, to our knowledge there are no reports of granulomas with ziconotide. Additionally, one recent long-term trial with ziconotide showed no inflammatory mass formation in 640 patients (8). In contrast, however there are 2 reports of granuloma formation with baclofen as the sole agent (9,10). Interestingly, baclofen has not been associated with histamine release in animal studies and despite extensive experience with this agent, prior to 2007 there had been no prior reports of granuloma with this drug (7,11). The 3 patients in the case reports of baclofen-induced granuloma were maintained on 150, 400, and 2,000 mcg per day of intrathecal baclofen (9,10). The third infusion rate required special compounding of the drug to a final concentration of 4,000 mcg/mL (10). The authors did not speculate as to the mechanism of granuloma formation in these cases. However, Coffey and Allen (7) in response to the Murphy (9) case report suggested that this inflammatory mass may have been secondary to impurities in compounding of the drug. It is clear from these reports that the potential for baclofen to form a granuloma may exist. As the literature on this topic is evolving, the clinician caring for intrathecal baclofen patients must continue to have a high index of suspicion for mass formation if there is a sudden lack of drug efficacy or return of spasticity occurs.

Likewise, the most common presentation associated with granuloma mass formation in opioid infusion is a relatively sudden or rapidly progressive loss of analgesic effect (3). This often triggers the pain practitioner to evaluate the IDDS and concomitantly, discovery of the inflammatory mass. One recent study prospectively evaluated asymptomatic patients receiving intrathecal opioids with CT or MRI scanning. Of the 208 patients evaluated, 6 were found to have inflammatory mass lesions (3). Of these 6 patients, 5 were asymptomatic at the time of granuloma discovery, while one was found to be experiencing increased radicular pain but had not yet sought medical consultation (3). All 6 patients underwent catheter revision and choose to continue receiving intrathecal therapy. Two of the asymptomatic granuloma patients were receiving hydromorphone; however the concentration of the infusate was significantly less than that in the current report (2 and 10 mg/mL (6) verses 85 mg/mL current report).

Common presenting symptoms are, as previously mentioned, loss of drug effect, new-onset radicular pain, cauda equina syndrome, and para or monoparesis (1,12). Inflammatory changes with and without a central necrotic core are common findings on pathologic examination of the granuloma mass (1,12). Less common findings are mass fibrosis and calcification (1). In the current study the patient presented with loss of analgesic effect and rapidly declining motor function. Intraoperatively, the mass was carefully dissected from the attachment point at the anterior portion of the spinal cord at T9 which is consistent with operative management described previously. Histology of the mass lesion revealed fibrosis with a central necrotic core.

A nonsurgical, conservative approach to management involves stopping the infusion and observing the patient for improvement as the granuloma mass often slowly resolves once the infusion is stopped (3,10,13). Catheter revision or relocation in the awake, responsive patient may also be appropriate (3). Any pain or paresthesia with catheter manipulation however would warrant neurosurgical intervention (3). One animal study suggested that clonidine could prevent granuloma formation in dogs receiving an infusion of intrathecal morphine (11), however one clinical case report of continuous infusion of clonidine, did not prevent inflammatory mass formation in a patient also receiving morphine (13). Cessation of the infusion or addition of clonidine to the IDDS admixture in conjunction with close clinical monitoring may be reasonable treatment options in patients with an asymptomatic or mildly symptomatic inflammatory mass. In the current study, rapidly declining neurologic function with a confirmed inflammatory mass adherent to the spinal canal necessitated urgent surgical intervention.

Conclusion

We present a case of surgical management of an intrathecal granuloma in a patient receiving high concentration/daily dose hydromorphone therapy. Though use of intrathecal hydromorphone still represents an off label application, this opiate is commonly employed as an alternative first line analgesic agent (4). This case report highlights the potential of high-dose and high infusate concentration intrathecal hydromorphone to form an inflammatory granuloma.

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