Intrathecal granuloma complicating chronic spinal infusion of morphine

Report of three cases

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Intrathecal morphine delivered by implanted pumps has been used in the treatment of pain caused by terminal cancer. Some authors support its use in benign pain as well. The authors present three cases in which chronic infiltration of intraspinal narcotic medication was complicated by the formation of a granulomatous mass that became large enough to exert mass effect and induce neurological dysfunction.

KEY WORDS • chronic pain • pump • granuloma

Case Reports

Case 1

History. This 46-year-old man suffered from spinal arachnoiditis after undergoing multiple back surgeries for failed-back syndrome. Oral therapy, behavioral modification, and physical therapy provided little relief to the patient and an epidural catheter was initially placed in 1988. Good pain relief was obtained and the catheter was moved to a subdural location. Moderate-to-high (10–12 mg/day) doses of morphine sulfate kept his pain well controlled.

Examination. Twenty-six months after subdural implantation of the catheter, the patient presented with progressive pain followed by incontinence and paraparesis, which prompted neurosurgical referral. Preoperative examination revealed a complete paraplegia with a sensory level 2 to 3 cm above the umbilicus. A thoracic computerized tomography (CT) scan with intrathecal contrast enhancement revealed an intradural mass centered around the intrathecal catheter and compressing the spinal cord at T-10 (Fig. 1 left). A magnetic resonance (MR) study of the thoracic spine showed an extramedullary, ring-enhancing mass with cord compression and edema (Fig. 1 right).

Operation. At operation, a 1.5-cm mass was encountered that enwrapped the distal tip of the infusion catheter and displaced the spinal cord anterolaterally. Total removal of the mass was performed without complication.

Postoperative Course and Findings. Postoperatively, the patient’s neurological status improved and he now ambulates with a walker. Routine aerobic cultures were negative. Histological evaluation of the mass revealed homogeneous dense granulomatous inflammation with rare areas of necrosis.

Case 2

History. This 64-year-old woman suffered chronic dysesthetic pain in her lower extremities. After the failure of conservative management, use of a subdural catheter and infusion pump was instituted. Pain control was obtained with administration of 12 to 14 mg of morphine sulfate per day.
Examination. A new type of burning bilateral leg pain was observed by the patient 24 months after placement of the catheter and was associated with diminished bladder control. No new neurological abnormalities were detected on clinical examination. An MR image (Fig. 2) revealed a midline intradural extramedullary lesion at L-1 with ring enhancement, and the patient was referred for neurosurgical opinion.

Operation. At operation a 1-cm granulomatous mass was encountered that ensheathed the distal end of the infusion catheter as well as the tip of the conus medullaris and several exiting nerve roots. A subtotal removal of the mass was performed because of dense involvement of surrounding nerve roots.

Postoperative Course and Findings. Considerable improvement in bladder function was observed postoperatively. Routine aerobic cultures were negative.

Case 3

History. This 38-year-old man suffered from chronic back pain following a work-related accident that resulted in five lumbar surgeries. Behavior modification, physical therapy, and oral analgesic medications were all tried but provided no lasting relief.

An intrathecal catheter and indwelling pump were placed in the patient but required removal due to a staphylococcal infection of the silastic infusion catheter. The system was reinstalled after a course of antibiotic medications with no evidence of further infection. The patient had excellent symptomatic pain relief for 8 months, although the dosage required for adequate analgesia was gradually elevated to 19 mg of morphine sulphate per day.

Examination. The patient was readmitted after noting progressive numbness in the soles of his feet that extended to involve the legs below the knees. Neurological examination revealed an asymmetric mild loss of pinprick sensation below the knees bilaterally. An MR image of the thoracolumbar spine (Fig. 3) revealed a ring-enhancing, intradural, extramedullary mass at the T10-11 level, which displaced the cord anteriorly.

Operation. At operation a 1-cm granulomatous mass against the posterior columns of the cord was identified and completely removed.

Postoperative Course and Findings. Aerobic cultures proved to be negative but anaerobic cultures yielded a heavy growth of Propionibacterium acnes. This was treated successfully with penicillin after removal of the pump and catheter.

Discussion

The intrathecal route of morphine administration has proved effective for patients with chronic, unremitting pain caused by end-stage malignancy. We have previously reported favorable results using chronic intrathe-
cal morphine therapy in the treatment of patients with spasticity. Intrathecal morphine also has been advocated in the treatment of chronic pain of benign origin, although this remains controversial. The most common non-oncological application of intraspinal morphine is for chronic lumbosacral pain arising from failed-back syndrome or spinal arachnoiditis.

There are several benefits from chronic intrathecal narcotic therapy. First, the drug is highly localized and as such its analgesic efficacy is maximized at low doses. This decreases systemic toxicity and reduces narcotic dependency. Penn and Paice have observed that patients suffering from cancer pain became more alert and less depressed after their oral narcotic medications were substituted with intrathecal narcotic therapy. Because the duration of treatment is limited the incidence of complications in cancer patients is low. By contrast, patients suffering from pain of benign origin may be treated for prolonged periods, which places them at higher risk for complications. Respiratory depression, urinary retention, nausea/vomiting, pruritus, and local wound and catheter migration problems have been reported in both short term and chronic administration of intraspinal narcotic medications. Drug tolerance may occur within weeks or months, but is more commonly encountered in extended intraspinal narcotic regimens.

The relatively uncommon complication of intrathecal granuloma that produces neurological signs and symptoms has been reported only twice before in single case reports. Rodan and coworkers presented a single case of an epidural fibrous mass that was positioned at the tip of a catheter that had infused preservative-free morphine sulfate. Their patient presented with paraparesis 10 months after placement of the catheter and was found to have a thoracic myelopathy from an epidural granuloma. Experimental studies in animals and postmortem studies in humans have provided data that indicate that there is a higher reactivity to catheters in the epidural space than to catheters placed in the subdural space. Studies of animals and postmortem studies in humans have provided data that indicate that there is a higher reactivity to catheters in the epidural space than to catheters placed in the subdural space. Investigators have reported that intrathecal insertion of nylon catheters appeared minimally evocative of inflammation and was well tolerated over long periods. However, North, et al., reported the case of a patient with a slowly progressive paraparesis 14 months after placement of an intrathecal catheter for chronic administration of intraspinal narcotic medications. An intrathecal granuloma that compressed the spinal cord was found at the tip of the infusion catheter. These patients share several features in common with our patients. First, the onset of symptoms was delayed many months after initiation of intraspinal narcotic therapy. Second, the clinical presentation was marked by an increase in pain or subtle sensory change followed by slowly progressive signs and symptoms of neurological deterioration. Finally, positive cultures for the anaerobic diptheroid *P. acnes* were encountered.

Our patients presented 26, 24, and 9 months after the initiation of intrathecal therapy. This suggests that the development of the inflammatory mass is a slow and gradual process, an observation that is underscored by noting the size of the lesions and the degree of spinal cord compression with relatively retained neurological function. The underlying cause of this chronic inflammatory fibrosis is unknown, although several possibilities exist. In a small subset of patients the chronic infusion of the narcotic drug itself may induce an inflammatory response with subsequent fibrosis. Several authors have observed histological evidence of axonal degeneration and focal subarachnoid fibrosis, although there has been no clinical correlation with these findings. Focal areas of subdural and epidural fibrosis have been observed in locations adjacent to the catheter, but no solid granulomatous mass with sufficient size to exert mass effect has been observed in these studies. Our patients followed regimens of relatively large doses of intrathecal morphine. We have had many patients on smaller doses for up to 9 years without problems. This may suggest that long-term exposure to high doses of intrathecal morphine may induce the observed granulomatous reaction. Preservative-free morphine was used in all patients to avoid the neural risks of preservatives.

Over the interval in which these three patients were seen, a total of 60 patients received implantation of intrathecal pumps (Medtronic Synco-Med, Minneapolis, MN) by one of the authors (S.K.Y.) for treatment of chronic pain caused by a variety of etiologies. The operative technique used for the implantation includes the following steps: a paramedian stab wound is made in the lumbar spine after local anesthesia is induced in the patient. A 14-gauge spinal needle is then advanced under fluoroscopic guidance to penetrate the thecal sac, after which the intrathecal catheter is advanced over a wire under fluoroscopic guidance until the tip lies at the T9–10 interspace. Contrast material is administered to ensure that the catheter remains in the intrathecal space. The catheter is then secured and tunneled to the abdomen where a pocket is made in the subcutaneous tissue for the pump. At the time the second patient in this series was examined all patients underwent a screening MR study. No other patient was found to have an intrathecal granuloma. In addition, each patient who receives chronic intrathecal morphine obtains an annual MR screening. In one of our patients an area of increased signal was demonstrated at the catheter tip but no neurological signs were present in the patient. No clear mass was identified; however, the patient improved when the catheter was discontinued.

Each of our patients presented with subtle sensory changes followed by gradually progressive neurological signs and symptoms. An increase and change in the character of the patient’s chronic pain was the first manifestation of intraspinal granuloma. Although subjective changes are admittedly difficult to assess in patients with chronic pain, a progressive change in the character, quality, or intensity of pain should raise the possibility of an intrathecal granuloma in the clinician’s mind and should correspondingly change the requirements established for obtaining an imaging study of the spine. An additional clinical clue to the existence of an intrathecal granuloma is a considerable increase in the level and degree of the patient’s pain as the delivery rate of the drug is increased.

Imaging plays a key role in the evaluation of these complicated cases. The multiplanar capabilities of MR imaging make this modality the technique of choice for initial imaging evaluation. The intrathecal granulomata in all
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three patients had similar features. The lesions were relatively isointense with respect to the spinal cord on T₁-weighted images and hyperintense with a hypointense rim on T₂-weighted images. Ring enhancement was identified in all cases after administration of paramagnetic contrast agents. Hyperintensity of the spinal cord was also observed in Cases 1 and 3. This may be related to spinal cord compression or to a combination of compression and local inflammation from the granuloma. Low-grade infectious reactions directed toward the silicone plastic used in cerebrospinal fluid (CSF) shunts. They have suggested that the inflammatory infiltrate that results can cause focal clumps of cells to aggregate and induce sterile shunt malfunction. Infusion catheters are made of the same silicone plastic as CSF shunts (Silastic) and, as such, could be the target of a similar response. Chronic inflammatory reactions have also been observed with polyethylene and polyurethane catheters. However, this would not explain why the granuloma is located only at the catheter tip.

The finding of *P. acnes* infection in Case 3 is provocative. *Propionibacterium acnes* (formerly recognized as *Corynebacterium parvum*) is an anaerobic diphtheroid that has recently gained increased recognition as an important pathogen in infections associated with indwelling foreign devices. It is a well-described pathogen in CSF shunt infection and aortofemoral bypass graft infection and has been increasingly recognized as a cause of chronic osteomyelitis that is associated with prosthetic hip devices. In addition, the ophthalmological literature includes several cases of *Propionibacterium* infection complicating intraocular lens transplantation surgery. The common pattern shared by these infections is that of a low-grade, chronic, progressive inflammation that may be associated with considerable morbidity and mortality when not properly treated. The detection of *Propionibacterium* organisms can be difficult because the organism is a fastidious anaerobe that will only occasionally grow in aerobic culture. Regrettably, only routine aerobic cultures were obtained in our first two cases. Furthermore, *P. acnes* is ubiquitous and commensal skin bacterium that may be a frequent contaminant. Its rate of growth in culture is typically slow and as a result cultures need to be observed for a prolonged period of time (usually 7–10 days) before they can be judged negative. Indwelling catheters associated with infusion pumps are similar to cerebrospinal fluid shunt catheters. The propensity of *P. acnes* to infect CSF shunts raises the possibility that long-term chronic inflammation in response to chronic *P. acnes* infection may play some role in the pathogenesis of these intrathecal granulomas. Why this would result in a focal mass at the catheter tip is unknown. Interestingly, the patient reported by North, et al., also had cultures that appeared positive for *Corynebacterium* species, which are considered contaminants.

Conclusions

The chronic infiltration of intraspinal narcotic medications can be complicated by the formation of a granulomatous mass that may reach sufficient size to exert mass effect and induce neurological dysfunction. Early signs of intraspinal granuloma may include progressive pain or sensory loss. Contrast-enhanced MR imaging is the imaging modality of choice and appears to be safe provided that the infusion device is electronically disengaged prior to contact with the imaging apparatus. The lesions appear isointense with respect to the spinal cord on T₁-weighted images and hyperintense with a hypointense rim on T₂-weighted images. Ring enhancement is observed after administration of contrast medium. The pathophysiology of the mass is unknown but probably involves a chronic granulomatous reaction to either 1) anaerobic diphtheroids, 2) sustained high doses of preservative-free morphine sulfate, or 3) the silicone plastic infusion catheter. Prompt operative removal of the lesion along with the associated catheter resulted in clinical improvement in these cases.

References

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