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The Use of Intrathecal Drug Delivery System to Manage Refractory Abdominal Pain From Systemic Amyloidosis

Muhammad Shahzad, FRCS[1], Somnath Bagchi, MD[2], David Hutchins, FRCA[2], and Samiul Muquit, FRCS[1]

Background: Systemic amyloidosis can cause severe refractory pain, often inadequately managed with conventional analgesics. Intrathecal drug delivery systems (IDDS) have been used for chronic pain control but are rarely reported in amyloidosis cases.

Case Report: We present a female patient in her late 50s with systemic light-chain amyloidosis and type III intestinal failure, experiencing significant weight loss and debilitating abdominal pain during enteral and parenteral feeding. After unsuccessful trials of oral analgesics, antineuropathic medications, and interventional procedures, an IDDS was implanted to deliver a combination of bupivacaine and morphine. The therapy allowed her to resume enteral and parenteral nutrition, reduce opioid consumption, gain weight, improve functionality, and decrease hospital admissions despite disease progression.

Conclusions: This case highlights the efficacy of intrathecal analgesia in managing severe refractory pain from amyloidosis. Early consideration of IDDS may improve quality of life in similar patients by providing effective long-term pain control.

Key words: Systemic amyloidosis, intrathecal drug delivery device, personal therapy manager

BACKGROUND

Systemic amyloidosis is a rare and progressive disease characterized by the extracellular deposition of misfolded amyloid fibrils in various organs, leading to organ dysfunction and diverse clinical manifestations (1,2). In immunoglobulin light-chain (AL) amyloidosis, approximately one-third of patients develop peripheral neuropathy, typically managed with oral or topical analgesics alongside treatments targeting the underlying plasma cell dyscrasia (3,4). Visceral neuropathy due to amyloid deposition is less common but can result in severe, refractory pain that significantly impairs quality of life (5,6). Intrathecal drug delivery systems (IDDS) have been utilized for chronic pain management but are rarely reported in the context of amyloidosis-related visceral pain (7). We present a case of a woman in her late 50s with AL-type systemic amyloidosis and type III intestinal failure, experiencing severe refractory abdominal pain during enteral and parenteral feeding, who was successfully managed with an IDDS.

CASE PRESENTATION

Patient Description

A female patient in her late 50s with a history of systemic AL-type amyloidosis and type III intestinal failure presented with severe refractory abdominal pain and significant weight loss.

Case History

Two years prior to the diagnosis of systemic amyloidosis, the patient experienced a gradual onset of decreased

From: [1]Southwest Neurosurgery Centre, University Hospitals Plymouth NHS Trust, Plymouth, United Kingdom; [2]Department of Anesthesia and Pain Medicine, University Hospitals Plymouth NHS Trust, Plymouth, United Kingdom

Corresponding Author: Muhammad Shahzad, FRCS, E-mail: m.shahzad3@nhs.net
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appetite, early satiety, and postprandial abdominal pain, characterized as severe, pulsating, and contracting episodes, radiating from the right upper quadrant of the abdomen to the back. Her first hospital admission occurred in November 2019 due to the abdominal pain, leading to a diagnosis of recurrent pancreatitis. Subsequently, she was diagnosed with sphincter of Oddi dysfunction and underwent a sphincterotomy, which did not alleviate her symptoms; instead, her abdominal pain intensified.

In March 2020, investigations revealed markedly elevated lambda ALs (> 1,000 mg/L), and a bone marrow biopsy showed plasma cell dyscrasia consistent with smoldering multiple myeloma. Despite aggressive treatments, including chemotherapy and an autologous stem cell transplant, her abdominal symptoms worsened, leading to an inability to eat without severe pain and significant weight loss from 70 kg to 54 kg.

To address malnutrition, a percutaneous endoscopic gastrojejunostomy tube was inserted in April 2020 for jejunal feeding, but enteral feeding continued to provoke severe pain (Numeric Rating Scale [NRS-11] 8-10/10). In March 2022, she was established on total parenteral nutrition (TPN) with gut rest. Initially, this improved her pain; however, she soon began to experience pain during TPN infusions, typically occurring 2-3 hours after commencement and lasting 3-4 hours postinfusion.

Past Medical History

Cholecystectomy 2007, gastroesophageal reflux disease, appendicectomy 2017, and CREST syndrome 2006.

Physical Examination Results

Physical examination revealed a cachectic woman with significant weight loss. Abdominal examination was unremarkable, with no palpable masses or organomegaly. Neurological examination showed no signs of peripheral neuropathy.

Results of Pathological Tests and Other Investigations

Laboratory tests showed elevated lambda ALs (> 1,000 mg/L). Bone marrow biopsy confirmed plasma cell dyscrasia consistent with smoldering multiple myeloma. Despite extensive investigations, including imaging studies and consultations at the National Amyloidosis Centre, amyloid deposition was not histologically confirmed but was presumed based on clinical presentation and central review.

Treatment Plan

Initial management included trials of various oral and topical analgesics, including antineuropathic medications (pregabalin 150 mg bid, amitriptyline 30 mg x HS), opioids (fentanyl patches 12-25 mcg/h, oxycodone 40 mg/d), sublingual buprenorphine 200-400 mcg tid, and subcutaneous ketamine infusions (1-2.5 mg/kg/24 h titrated up to 400 mg/24 h), with limited efficacy and undesirable side effects. Nonpharmacological therapies, such as psychological counseling, aromatherapy, and Reiki were also initiated.

Interventional procedures were attempted, including bilateral thoracic (T6-T8) splanchnic nerve pulsed radiofrequency (RF) ablation in June 2022 (Fig. 1), which provided significant pain relief (NRS-11 reduced from 9/10 to 0-3/10) for 8 weeks before symptoms recurred. During this period, her compliance with TPN, sleep quality, and physical activity improved. A thoracic epidural block was performed in October 2022 without lasting benefit. A trial of spinal cord stimulation (SCS) with leads placed at T4-T6 in January 2023 was unsuccessful and induced new bilateral radicular pain in the lower limbs (Fig. 2).

Given the refractory nature of her pain, an IDDS with personal therapy manager (PTM) functionality was proposed and discussed in a multidisciplinary team (MDT) meeting. After comprehensive psychological assessment and informed consent, an IDDS was implanted in June 2023.

Treatment Plan Details

The IDDS consisted of a 40 mL SynchroMed II pump (Medtronic Ltd, Minneapolis, MN) implanted in the right abdominal wall. A silicone catheter was inserted into the intrathecal space at the L2-L3 level, with the tip positioned at the mid-T6 vertebra to target the thoracic sympathetic innervation of the pancreas. The catheter was anchored to the paravertebral muscles and fascia and tunneled subcutaneously to the pump.

The pump delivered a combination of bupivacaine (600 mg in 40 mL, concentration 15 mg/mL) and morphine (200 mg in 40 mL, concentration 5 mg/mL) as a simple continuous infusion at a rate providing 0.72 mg of bupivacaine and 0.26 mg of morphine per day. A PTM was later added to allow patient-initiated boluses containing 0.1 mg of bupivacaine and 0.033 mg of morphine, with a lockout interval of 2 hours and a maximum of 4 activations per 24 hours.

Prior to the pump, the patient was on a fentanyl

25 mcg/h patch, amitriptyline 30 mg x HS, sublingual buprenorphine 200-400 mcg tid, paracetamol 1 g qid, and pregabalin 150 mg bid. Concomitant with the pump, she was maintained on a fentanyl 12 mcg/h patch, amitriptyline 10 mg x HS, paracetamol 1 g qid, and pregabalin 75 mg bid.

Expected Outcome of the Treatment Plan

The expected outcome was to achieve satisfactory analgesia, reduce oral opioid consumption, improve nutritional status by allowing tolerance of TPN, enhance quality of life, and decrease hospital admissions related to pain management.

Actual Outcome

Postimplantation, the patient experienced significant pain relief, with NRS-11 scores ranging from 0-2/10. She was able to tolerate TPN infusions without severe pain, leading to improved sleep, increased physical activity, and weight gain from 54 kg to 72 kg over 18 months. Oral opioid use was significantly reduced and eventually discontinued. The patient reported a subjective improvement in well-being and had fewer hospitalizations for pain management.

DISCUSSION

Systemic amyloidosis is characterized by the deposition of misfolded proteins in various organs, leading to progressive dysfunction and diverse clinical manifestations (1-3). Gastrointestinal involvement, particularly in AL amyloidosis, can result in symptoms ranging from malabsorption and diarrhea to severe visceral pain due to amyloid infiltration of the muscularis propria or autonomic neuropathy (4-6). Our patient's case is noteworthy due to the severe refractory abdominal pain associated with presumed visceral neuropathy from amyloid deposition, complicated by type III intestinal failure, and the successful management of her pain with an IDDS.

Pain in systemic amyloidosis is often neuropathic, arising from peripheral or autonomic nerve involvement (7). Management typically involves addressing the underlying plasma cell dyscrasia with chemotherapy or autologous stem cell transplantation and symptom control with oral or topical analgesics (8). However, refractory pain remains a significant challenge, impacting patients' quality of life and functionality.

In our case, conventional analgesics and multiple interventional procedures provided limited or temporary relief. Antineuropathic medications, opioids, and ketamine infusions were insufficient or had intolerable side effects. Clinically, the refractory pain had a predominant neuropathic element, so we undertook bilateral thoracic (T6-T8) splanchnic pulsed RF ablation. The sympathetic nervous system modulates various pain signals, including neuronal, visceral, vascular, and musculoskeletal, with inputs from hormonal and immune systems. Given the diffuse nature of innervation of the splanchnic nerves and celiac plexus, interrupting the signal in the splanchnic nerves can help to reduce various types of abdominal pain. The neurolytic blocks of the celiac plexus with alcohol provide a short benefit of around 4-8 weeks and often leave the patient with refractory residual pain. The advantage of the pulsed RF is that the lesion can be controlled compared to the neurolytic with less tissue damage than continuous RF (9), and the lesioning is repeatable. The other reason we opted for the pulsed RF is that there are case reports of long-term

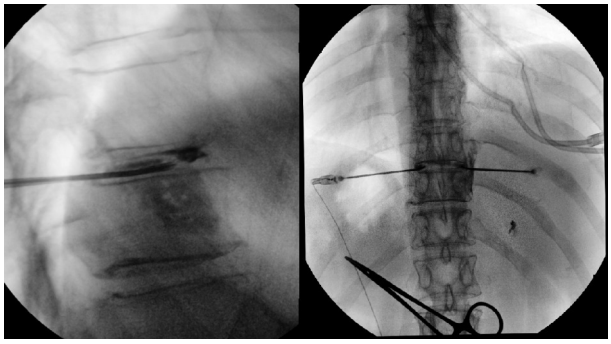

Fig. 1. Bilateral thoracic (T6-T8) splanchnic pulsed RF ablation. RF, radiofrequency.

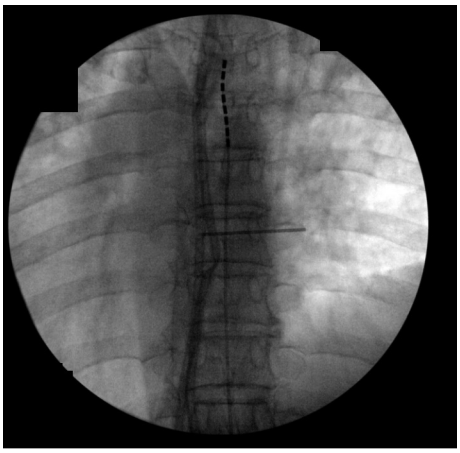

Fig. 2. SCS trial - marker at T7. SCS, spinal cord stimulator.

benefits in chronic abdominal pain syndromes like loin pain hematuria (10) and polycystic kidney disease (11). Similar results of long-term efficacy in terms of reduction in the Visual Analog Scale, decreased use of opioids, decreased anxiety, and less frequent recurrent hospital admissions with splanchnic nerve RF have been reported in case studies in chronic pancreatitis by Garcea et al (11) and Verhaegh et al (12). In our patient, it provided a very limited benefit of 8 weeks, so was not repeated.

SCS addresses the same sympathetic nerves and has been used in chronic abdominal visceral pain and chronic pancreatitis so we opted for it to provide a potential long-term benefit (13). A single-octad trial lead was placed percutaneously around T5 (T4-T6) and trailed for 8 days. The procedure provided no pain relief and started a new bilateral radicular pain in the lower limbs. Possible explanations for this leg pain are peripheral and central sensitization, postsurgical inflammatory neuropathy, or psychological factors as described by Baranidharan et al (14). As these procedures were not successful, she was again discussed in an MDT. In January 2023, a thoracic epidural targeting T5 was performed, but this did not have a lasting effect.

Patients with moderate-to-severe pain, not controlled with oral analgesics or having medication-related side effects, with a life expectancy of < 6 months, are ideal candidates for neurolysis, but in our case, patient was expected to survive > 6 months. A better alternative seemed to be intrathecal analgesia for its duration efficacy and cost advantages. A decision to implant an IDDS was taken. In our patient, the target dermatome was T6. Drug dispersal is known to affect one to two levels above and one to two levels below. This would cover most of the sympathetic innervation of the pancreas. We avoided a trial of IDDS as there is no valid way to do it in a single-shot spinal injection and also to prevent a delay in implantation. A port trial with an intrathecal catheter is an option but was not attempted due to the increased chance of infection in an immunocompromised patient. We did, however, have indirect confirmation of probable benefit from the thoracic splanchnic pulsed RF.

The use of IDDS for chronic pain management is well-documented in cancer-related pain and chronic nonmalignant pain conditions (15). Intrathecal administration allows for direct delivery of medications to the central nervous system at lower doses, reducing systemic side effects, and providing effective analgesia (16). The combination of bupivacaine and morphine has been shown to be effective in managing both nociceptive and neuropathic pain (17).

There is limited literature on the use of IDDS in amyloidosis-related pain. Warner et al (7) reported the use of intrathecal analgesia in refractory peripheral neuropathy due to amyloidosis. Our case contributes to the literature by demonstrating the efficacy of IDDS in managing severe refractory visceral pain associated with amyloidosis and intestinal failure.

The successful outcome in our patient emphasizes the importance of a multimodal approach to pain management in amyloidosis. Early consideration of intrathecal analgesia may be beneficial in patients with refractory pain nonresponsive to conventional therapies. The addition of a PTM provided the patient with autonomy to manage breakthrough pain, further improving her quality of life (18).

Limitations in our case include the lack of histological confirmation of amyloid deposition in the visceral nerves or pancreas, which is a recognized challenge in amyloidosis diagnosis (2). However, the clinical presentation and central review at the National Amyloidosis Centre supported the presumptive diagnosis.

CONCLUSIONS

This case highlights the potential role of IDDS in managing severe refractory visceral pain in systemic amyloidosis. A multidisciplinary approach, including early referral to pain specialists and consideration of advanced analgesic techniques, can significantly improve patient outcomes.

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