Case Study: Management of multiple painful comorbidities in a geriatric cat

Introduction: Geriatric patients with multiple comorbidities are increasingly common in practice as veterinary medicine advances. This case report examines a medically complex cat who was presented for palliative management of his multiple illnesses, including degenerative joint disease and inflammatory bowel disease. The patient's pain was assessed using the FMPI-sf, which has been validated for musculoskeletal pain and shown responsiveness to changes throughout treatment.[1] This requires creating a highly individualized plan taking into account the specific client and patient's priorities. Pain management is a vital aspect of this treatment goal.[2]

Clinical Report: Ralph, a 3kg, 17-year old neutered male domestic short hair, initially presented for palliative care of multiple comorbidities. The patient had a history of inflammatory bowel disease with chronic diarrhea, degenerative joint disease, and an elevated proBNP. The patient's current medications were frunevetmab 2mg/kg SQ once monthly and a probiotic once daily. The client's primary concerns related to weight loss, pain, and perceived frailty. The client expressed that a priority was reducing the stress of treatment for the patient, including limiting administration of oral medications and frequent clinic visits. On labwork the patient was revealed to be hyperthyroid. On physical exam the patient had a body condition score of 2/5. The patient was intolerant of a comprehensive exam, but pain was suspected over the L-S spine and the elbows. No arrhythmia was ausculted, although the client reported a historical gallop. The client declined diagnostic imaging. Upon discussion, the client described the patient having increasing difficulty posturing to urinate and defecate in the litterbox resulting in defecation outside the litterbox, jumping on and off furniture, and going up and down stairs over the previous year. The patient scored 1.55 on the FMPI-sf. Item 5 ("Play with toys and/or chase objects")[1] was omitted

from this and all subsequent pain scores as the client reported the patient was historically uninterested in toys.

As a medically complex patient, the treatment plan involved pharmacological and non-pharmacological therapies, as well as environmental and lifestyle changes. The client elected to treat the newly diagnosed hyperthyroidism with methimazole 2.5mg TD BID and begin a hydrolyzed protein diet trial to address the IBD. In addition to the frunevetmab, ketamine 0.5mg/kg SQ was administered in the office and the patient was prescribed Welactin® (omega-3 fatty acids) with a goal dosage of approximately 120mg/kg PO SID. The client was counseled on home and lifestyle accommodations, such as use of steps to allow the patient access to perches, raised food and water dishes, and changing locations of resources. The potential for use of a house call service for additional care was discussed but declined.

At the 30 day follow-up the client reported that the patient's appetite had normalized, his mobility had improved slightly, and he was more engaged with the other cat in the household. The patient's weight was 3kg. The patient's pain score on the FMPI-sf was 1.46. The client did report that on Welactin® 120mg/kg the patient had two episodes of hematemesis as well as liquid diarrhea that were treated symptomatically at a different facility, and the dosage was reduced to 88mg/kg. The client was instructed in basic stretching and weight shifting exercises, as well as provided with contact information for a house call service to provide photobiomodulation 1000J/cm^2 to the L-S spine, hips, stifles, elbows, and caudal abdomen 2-3 times weekly for two weeks followed by once monthly treatments. Frunevetmab 2mg/kg SQ and ketamine 0.5mg/kg SQ were administered.

The patient was temporarily lost to follow-up and presented four months later for a recheck T4 and to address worsening diarrhea. The client reported having used the house call

service for photobiomodulation, as well as monthly frunevetmab and ketamine injections, although one dose was missed. No pain scores were available from this time. On physical exam the patient had gained 1kg and his body condition score was 3/5. The patient's pain score was 1.25 on the FMPI-sf. On discussion, the client was found not to have been compliant with the hydrolyzed protein diet and was educated on the importance of the diet trial. Via email two weeks later the client reported that the diarrhea was improving on solely the hydrolyzed protein diet.

Clinical Outcome: The client reported overall satisfaction with improvements in the patient's mobility and comfort. The patient stopped defecating outside the litterbox and had resumed performing activities that had been impossible, such as jumping onto the kitchen counter and walking down the basement stairs. The client was instructed to continue the treatment plan of frunevetmab, ketamine, photobiomodulation, therapeutic diet, and exercise, with recheck scheduled for three months, and encouraged to communicate any concerns.

Discussion: Degenerative joint disease (DJD) is common in cats, with radiographic evidence found in 60-90% of cats, making it a significant cause of inflammatory, maladaptive pain.[3, 4] The somatic pain of DJD is transmitted via A-delta and C fibers to the dorsal horn of the spinal cord where it undergoes modulation.[5] DJD is an umbrella term referring to degenerative damage to all types of joints, unlike osteoarthritis, which is a specific disease process affecting synovial joints.[2] DJD is a "whole joint" disease, affecting all structures within and surrounding the joint in a cycle that can become self-perpetuating as increasing joint instability leads to synovial effusion, osteophyte formation, muscle atrophy, and worsening pain.[7] Age is the greatest risk factor,

although other factors such as obesity and history of injury may contribute. It is a degenerative, incurable disease process, although treatment can improve pain, slow disease progress, and improve function. The first-line treatments are NSAIDs and anti-NFG monoclonal antibodies, combined with non-pharmaceutical recommendations such as weight optimization, physical rehabilitation, and environmental changes.[2]

Along with the somatic pain of DJD, this patient also likely experienced maladaptive visceral pain from inflammatory bowel disease (IBD). IBD is an immune-mediated inflammatory condition affecting various parts of the gastrointestinal tract, causing clinical signs such as decreased appetite, diarrhea, vomiting, and weight loss. Treatment can include therapeutic diets, immunosuppressive medications, and antibiotics. Dietary change to a novel or hydrolyzed protein has shown to be successful in reducing symptoms of IBD in 50% of cats.[8] While this patient was not responsive to abdominal palpation on exam, 50-70% of human patients with IBD report pain and it is therefore reasonable to assume that this is a painful condition.[9] Visceral pain differs from somatic pain in several key ways. Due to the complex nature of visceral innervation, in which afferent A-delta and C fibers branch over multiple spinal segments, and visceral and somatic afferent nerves converge causing referred pain, visceral pain is difficult to localize and has a diffuse quality.[5,10] Visceral pain is generally the result of ischemia, distension, or inflammation, and the degree of pain sensation may be disproportionate to the severity of illness.[11]

The pain scale used in this case, the FMPI-sf, is a validated pain scale for musculoskeletal pain and does not assess visceral pain.[1] This is a shortcoming of this assessment method, however there are no validated pain scales that specifically address both chronic musculoskeletal and visceral pain in cats. The FMPI-sf contains nine questions to be filled out by

the client, each related to mobility or social interactions.[1] A validated Health-Related Quality of Life Scale such as the Vetmetrica tool would have been another potential option to monitor this patient's progress, however it was unavailable.[12]

Frunevetmab is an anti-nerve growth factor monoclonal antibody labeled for treatment of osteoarthritis. Nerve growth factor (NGF) is pro-nociceptive and contributes to both peripheral and central sensitization. NGF increases the release of inflammatory mediators and peptides such as bradykinin, substance P, and histamine. It increases nerve conduction velocity and decreases the activation threshold of specific peripheral neurons, and activates silent neurons. Frunevetmab binds to nerve growth factor, preventing it from binding to the TrkA and p^{75} receptors.[13] While more research is necessary as current studies show conflicting results, it is known that NGF is expressed and upregulates nociceptive signals in visceral diseases, making it a potential target for analgesic therapy.[14] Anti-NGF monoclonal antibodies are considered a first line analgesic for feline osteoarthritis by the American Animal Hospital Association and was used in this case both due to the client's difficulty in administering oral medication and the concern for gastrointestinal side effects of an NSAID in a patient with concurrent poorly controlled IBD.[15]

Ketamine is an N-methyl-D-aspertate antagonist frequently used as part of a surgical pre-medication protocol which has recently become popular as part of a multi-modal protocol for chronic pain.[5] The NMDA receptor becomes active in chronic pain states when peripheral sensitization, which is caused by constant noxious stimuli carried by C fibers to the dorsal horn of the spinal cord, such as happens in both poorly controlled somatic and visceral pain, progresses to central sensitization.[5,16] This occurs when the excitatory neurotransmitter glutamate displaces the magnesium ion plug in the NMDA receptor, allowing a large influx of calcium and leading to increasing excitability and neuroplasticity, eventually culminating in central

sensitization. [5,16] By binding to the NMDA receptor and preventing this cascade of events, ketamine plays an important role in preventing and treating central sensitization and maladaptive pain. This patient had both somatic and visceral sources of maladaptive pain. While research on subcutaneous ketamine for analgesia is on-going, mechanistically it would appear to be most advantageous in patients demonstrating hyperalgesia and allodynia.[17] In this case, the patient was showing clinical signs such as heightened reactivity to subcutaneous injections and intolerance of gentle brushing in non-painful areas. Intravenous ketamine infusion, which has more evidence available than subcutaneous ketamine administration, could have been considered.[17] Another NMDA antagonist such as amantadine would also be appropriate, although in this case the client found oral medications challenging.[2]

This patient would have benefited from the analgesia of an NSAID or the anti-inflammatory properties of a corticosteroid, however it was felt that there was an unacceptable risk of acute adverse gastrointestinal effects considering the history of chronic diarrhea and recent hematemesis.[2] For this reason omega-3 fatty acids, which have been shown in cats and dogs to have therapeutic effects in patients with DJD or OA, were recommended as an adjunct.[18,19] Omega-3 fatty acids are anti-inflammatory, with eicosapentaenoic acid (EPA) replacing arachidonic acid in the inflammatory cascade. EPA degrades into PGE_3, which is less inflammatory than arachidonic acid's product PGE_2. EPA suppresses production of aggrenase, an enzyme that destroys cartilage, as well as inflammatory mediators interleukin-1, interleukin-2, and tumor necrosis factor.[19] Potential adverse effects do include vomiting and diarrhea, so the dosage was started at the label dosage of 88mg/kg and titrated to 120mg/kg over three weeks. The client reported adverse effects at this dosage so it was decreased to 88mg/kg.

Therapeutic exercise was used in this patient with the specific goal of improving strength and balance so the patient could resume normal litterbox usage. Exercise is also well documented in human osteoarthritis patients to provide pain relief on par with administration of NSAIDs.[20] The client was taught to perform active stretching for 15-30 seconds as tolerated by having the patient place their front limbs on a step and reach for a treat. This exercise stretches the hip and stifle flexors, as well as shifts body weight to the hindquarters.[21(p80)] The client was also instructed to perform weight shifting exercises with the patient standing square and gently pushing the patient from side to side, which improves balance and proprioception as the patient stabilizes themselves.[21(p103-105)] Exercise was begun after initiating pharmacologic pain management to increase patient comfort and acceptance of exercises.

Photobiomodulation is a rehabilitation modality used to decrease inflammation and provide analgesia. It uses infrared and near-infrared light to deliver energy to the target tissues. This has effects on all steps of the nociceptive pathway, including decreasing production of pro-inflammatory mediators, raising neuron action potential threshold, and increasing production of endogenous opioids and serotonin.[6] Dosage for chronic orthopedic conditions ranges from 10-20J/cm^2 beginning with three times weekly treatments until improvement is seen and then titrating down to maintenance treatments once or twice a month.[22(p350)] Due to the patient's inability to take systemic anti-inflammatories or immunosuppressives, the caudal abdomen was also treated for both anti-inflammatory and analgesic purposes. Photobiomodulation has been shown to improve colitis in mice, as well as improve the gut microbiome.[23] While the use of a home care practitioner for photobiomodulation allowed the client to access this treatment modality, it did reduce the follow-up visits that would have allowed for earlier discovery of the

dietary non-compliance and treatment of worsening diarrhea. More regular reassessment, potentially through telemedicine or email, would have benefited this patient.

Summary: This case emphasizes the need to create an individualized plan for each patient and client rather than relying on overarching protocols. Degenerative joint disease is a common cause of maladaptive pain and disability in senior cats. Care of geriatric cats can be complex as they are likely to have multiple comorbidities. In this case medication options were limited by both the patient's comorbid inflammatory bowel disease and the client's priorities for the patient. Nevertheless, through a combination of anti-nerve growth factor monoclonal antibodies, ketamine, and physical modalities, the patient's comfort and overall quality of life was improved as measured by the FMPI-sf.

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