Sensory-Motor Neuropathy Due to Vincristine Treatment in a Dog

Bernardo De Caro Martins, Guilherme De Caro Martins, Rodrigo dos Santos Horta, Bruno Benetti Junta Torres, Stephanie Elise Muniz Tavares Branco & Gleidice Eunice Lavalle

ABSTRACT

Background: Peripheral neuropathies secondary to chemotherapy drugs, especially when it comes to the use of vincristine, are common in humans, but rare in dogs. Neurologic manifestation depends on the kind of axonal fibers involved. When motor fibers are affected, weakness and ataxia are observed. Sensory fibers involvement, which can lead to hyperesthesia, hypoesthesia or paresthesia was reported experimentally in rats, and is common in humans but were never reported in dogs. Thus, this report aims at describing a mixed neuropathy, with sensory and motor involvement, in a dog after vincristine treatment.

Case: A one year old mixed breed dog, rescued from the street, was presented with multiple nodular and ulcerated lesions, disseminated on the head, gums, flank and limbs, with progressive worsening in the last two months. Cytology of two subcutaneous and one gum nodule revealed an intense concentration of neutrophils and round cells with abnormally clumped chromatin patterns, prominent nucleoli and multiple cytoplasmic vacuoles, compatible with TVT. Treatment was initiated with a weekly administration of vincristine (0,75 mg/m²) combined with anti-emetic (maropitant) and H1 receptor inhibitor (ranitidine). Fast remission of the cutaneous lesions occurred. However, after the second chemo session, generalized hyperesthesia, mild ataxia, intermittent collapse and vomiting were observed. Suspicion of a mixed (sensory-motor) neuropathy induced by vincristine emerged, and vincristine was ceased. No other chemotherapy treatment was instituted due to negative cytological results of the remaining lesions. Treatment with gabapentin (10 mg/kg, twice a day, orally) was initiated so that neuropathic pain was suppressed. After one week, the patient no longer demonstrated pain, walked normally and lesion remission was complete. The animal has been monitored for eight months and is currently stable, with no lesions, pain or any changes that compromises its quality of life.

Discussion: Although vincristine is considered to be the most effective and least toxic chemotherapy drug used for treating this neoplasia, some side effects may occur, such as vomiting, anorexia, depression and myelosuppression. In addition, some animals may suddenly develop peripheral neuropathy, with the involvement of motor fibers, which results in weakness and ataxia. Involvement of sensory fibers, in combination or not with motor fibers, as vincristine treatment side effect, is commonly notice in humans but never observed in dogs, wherein allodynia and paresthesia can be manifested. In this case, the diagnosis of peripheral mix neuropathy, with motor and sensory fibers involvement, was made by identifying clinical signs after vincristine treatment initiation and immediate remission after discontinuation. This is often enough for a definitive diagnosis, as there are no additional tests that identify, in an early matter, neuropathy caused by chemotherapy. Despite there is no specific treatment, gabapentin can be used to control neuropathic pain as it increases GABA and serotonin concentration, reducing nociceptive ascending impulses. After chemotherapy discontinuation and gabapentin treatment, there was remission of neurological signs. Vincristine-induced neuropathies constitute a persistent limitation of animal’s quality of life, especially when there is irreversible damage. It is important to identify early motor and sensory neurological signs so that chemotherapy can be immediately suspended. Therefore, the clinician must be able to identify the best moment to discontinue chemotherapy at the expense of patient’s clinical oncology state improvement, while prioritizing the animal’s quality of life.

Keywords: peripheral neuropathy, allodynia, chemotherapy.
INTRODUCTION

Peripheral neuropathies secondary to chemotherapy drugs, especially when it comes to the use of vincristine, are common in humans, but rare in dogs [1,4,8]. These result from functional or structural impairment of motor, sensory and/or autonomic fibers of the peripheral nerve [4,9]. When associated with more than one type of fiber, are classified as mixed neuropathy. Motor sensory involvement results in ataxia and paresis while sensory fibers involvement results in an increased response to painful stimuli (hyperesthesia), response to a stimulus that does not normally provoke pain (allodynia), tingling (paresthesia) and loss of sensation (hypoesthesia) [9].

Vincristine sulfate is considered to be a safe chemotherapeutic drug, extensively used in veterinary medicine for treatment of solid and hematopoietic tumors [4,10]. However some side effects, such as peripheral neuropathy can occur. Neurological-clinical manifestation of sensory fibers involvement, as allodynia and painful paresthesia, have been experimentally described in rats and observed in humans, but still have not been reported in dogs [1,2,4].

Herein, this paper aims at reporting the first case of mixed neuropathy with sensory-motor component in a dog after vincristine treatment.

CASE

A one-year-old male mixed breed dog, rescued from the street, was presented to the Veterinary Hospital of the Universidade Federal de Minas Gerais, Brazil, (UFMG) with a history of multiple nodular and ulcerated lesions, disseminated on the head, gums, flank (Figure 1A) and limbs, with progressive worsening in the last two months. The dog was submitted to complete blood count and serum biochemistry analysis, where no significant abnormality was observed. Cytology of two subcutaneous and one gum nodule was performed with fine needle aspiration, while imprint cytology was used on the ulcerated flank nodule. An intense concentration of neutrophils and round cells with abnormally clumped chromatin patterns, prominent nucleoli and multiple cytoplasmic vacuoles, compatible with TVT, was identified in all the cytology smears (Figure 2).

Treatment began with a weekly administration of vincristine1 (0,75 mg/m²) combined with an antiemetic, maropitant2 (1mg/Kg) and a H1 receptor inhibitor, ranitidine3 (1mg/kg), which were administrated 20 min before the chemotherapy application to reduce the occurrence of possible side effects. Before each chemotherapy session, blood samples were collected for hematologic analysis, so that the drug-induced myelosuppression peak (nadir) could be assessed conditioning treatment persistence.

Fast remission of the cutaneous lesions occurred. However, after the second chemotherapy session, the patient began to present generalized hyperesthesia, mild ataxia, intermittent collapse and vomiting. Suspicion of a mixed (sensory-motor) neuropathy induced by vincristine emerged, and vincristine applications were ceased. No other chemotherapy treatment was instituted due to negative cytological results of the remaining lesions. Treatment with gabapentin4 (10 mg/kg, twice a day, orally) was initiated so that neuropathic pain could be suppressed. After one week, the patient no longer demonstrated pain, walked normally and lesion remission was complete (Figure 1B).

This patient has been monitored for eight months and is currently stable, with no lesions, pain or any changes that compromises its quality of life.

Figure 1. A one-year-old mixed breed dog with nodular and ulcerated lesions on the flank, before (A) and after (B) vincristine treatment.
DISCUSSION

Vincristine is considered to be a safe chemotherapy drug used in veterinary medicine as a monotherapy in treatment for lymphoma, leukemia and solid tumors [3,12,15]. However, clinical use of vincristine, even at therapeutic doses, has been associated with some side effects, such as vomiting, anorexia, depression and myelosuppression [4,16]. Additionally, some patients may suddenly develop peripheral neuropathy, with the involvement of motor fibers, which results in weakness and ataxia [4,8]. Unlike dogs, which are more resistant to the neurotoxic effects, vincristine neuropathy is frequent in humans and is associated with higher and cumulative doses [13,16]. Mixed neuropathies involving motor and sensory fibers are reported in these patients, and they develop not only weakness and ataxia, but also allodynia and painful paresthesia [16]. To the present time, mixed neuropathy secondary to vincristine with a sensory component had not been reported in dogs.

Vincristine antineoplastic effects are related to the inhibition of microtubule dynamics in the mitotic spindle, preventing neoplastic cell division. However, it also acts in neural microtubules impairing axonal transport, myelin sheath, Schwann cells and, consequently, peripheral nerves function [5,14]. Histological studies reveal impaired structure and function of myelinated and unmyelinated sensory axons, which result in demyelination and axonal degeneration [2,11].

Vincristine-induced sensory neuropathy, described in humans and observed experimentally in rats [1], is directly related to microtubule disorganization and endoneurial swelling in myelinated and in unmyelinated sensory axons along with hyperresponsive activity in C fiber nociceptive neurons. These changes sensitize dorsal horn neurons leading to central sensitization [9,14]. Another study demonstrated that blockade of type-T calcium channels with ethosuximide, was able to alleviate allodynia, which suggests that activation of these channels is important in the development of sensory neuropathy in patients treated with vincristine [7].

Identification of clinical signs after vincristine treatment outset and immediate remission after discontinuation, as was observed in this case, is often enough for a definitive diagnosis, as there are no additional tests that identify, in an early matter, neuropathy caused by chemotherapy [13]. Results of electromyographic could be consistent with muscle denervation and decrease motor nerve conduction velocity [8]. Additional tests, such as neuronal biopsy, may reveal axonal degeneration, endoneurial fibrosis and demyelination [4]. Due to rapid clinical improvement, our patient did not undergo to electromyographic examination and biopsy procedure.

Neuropathy, in some cases, is reversible, as the peripheral nervous system has high capacity for regeneration. However, if the primary injury is not quickly removed, the damage becomes irreversible, decreasing animal’s quality of life [4,13,16]. Factors such as dose, duration of treatment and adjacent peripheral neuropathic disease, contribute to the severity of the injury [13]. The pharmacotherapy for neuropathic pain has
had a limited success with little or no response to commonly used pain reducing drugs, such as opiates, but gabapentin can be used to control neuropathic pain as it increases GABA and serotonin concentration, and inhibits the action of aspartate and glutamate, reducing nociceptive ascending impulses [14]. In this case, after the second session of chemotherapy using vincristine, the patient presented neurological deficits compatible with a sensory-motor neuropathy. Thus, chemotherapy had to be interrupted, and gabapentin was administrated at a dosage of 10 mg/kg, twice a day, followed by rapid improvement of neurological clinical signs.

Vincristine-induced neuropathies constitute a persistent limitation of animal’s quality of life, especially when there is irreversible damage. It is important to identify early motor and sensory neurological signs so that chemotherapy can be immediately suspended. Therefore, the clinician must be able to identify the best moment to discontinue chemotherapy at the expense of patient’s clinical oncology state improvement, while prioritizing the animal’s quality of life.

SOURCES AND MANUFACTURERS

1 Vincizina®, Pfizer, Guarulhos, SP, Brazil.
2 Cerenia®, Zoetis, São Paulo, SP, Brazil.
3 Cloridrato de ranitidina, Farmace, Barbalha, CE, Brazil.
4 Gabapentina, Germed, Hortolândia, SP, Brazil.

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REFERENCES