



CASE REPORT

Acquired Megaesophagus Associated with Accidental Overdose of Vincristine in a Dog

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ARTICLE HISTORY (18-174)

Received: May 13, 2018
Revised: September 18, 2018
Accepted: September 20, 2018
Published online: October 21, 2018

Key words:

Dog
Megaesophagus
Overdose
Vincristine

ABSTRACT

A 15-year-old, castrated male, mixed dog presented for evaluation of bilateral submandibular lymphadenopathy. Fine needle aspiration of the lymph node revealed multicentric lymphoma, and chemotherapy was performed following CHOP protocol. After first administration of vincristine, anorexia, hemorrhagic diarrhea and regurgitation were noted. An accidental overdose of vincristine was found and symptomatic treatments was initiated to prevent the further adverse reaction of chemotherapy. However, an acquired megaesophagus was noted the next day and there was no clinical improvement. The dog died 17 days after the accidental high-dose vincristine administration. This is first case described an acquired megaesophagus in association with accidental overdose administration of vincristine during chemotherapy in a dog.

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To Cite This Article: Chae MJ, Kim TW, Park HM and Kang MH, 2018. Acquired megaesophagus associated with accidental overdose of vincristine in a dog. Pak Vet J, <http://dx.doi.org/10.29261/pakvetj/2018.097>

INTRODUCTION

Megaesophagus is a generalized esophageal dilation resulting from an aperistaltic esophagus, secondary to a neuromuscular disorder (Charles, 2015). It results in regurgitation, vomiting, anorexia, halitosis and aspiration pneumonia (Hopper *et al.*, 2001; Charles, 2015). Megaesophagus can occur as a congenital or acquired disorder, or as an adult onset idiopathic disease (Quintavalla *et al.*, 2017). Acquired megaesophagus can be caused by any diseases that inhibits esophageal peristalsis by disrupting central, efferent or afferent pathways, or function of the esophageal muscles (Hopper *et al.*, 2001; Masoud *et al.*, 2009; Mosallanejad *et al.*, 2010; Charles, 2015). These diseases include polymyositis, myasthenia gravis, peripheral neuropathies and central nervous system disease (Hopper *et al.*, 2001).

Vincristine is the vinca alkaloid class anticancer agent that is used for canine lymphoma or other hematopoietic tumors (Tsukamoto *et al.*, 2011). Vincristine administration is known to have several side effects in dogs, including hematologic, gastrointestinal, and neurologic toxicity (Hopper *et al.*, 2001; Masoud *et al.*, 2009; Tsukamoto *et al.*, 2011). These neurologic side effects include polyneuropathy and polymyopathy and can appear immediately during or shortly after administration of the drug but sometimes after cessation of chemotherapy treatment (Masoud *et al.*, 2009).

To the best of the authors' knowledge, megaesophagus has not previously been reported in association with vincristine. This report describes a case in which megaesophagus developed in association with overdose administration of vincristine during chemotherapy against lymphoma in a dog.

Case history and findings: A 15-years-old, castrated male, mixed dog was presented for evaluation of bilateral submandibular lymphadenopathy. On physical examination, the dog had solitary, well-circumscribed, hard, subcutaneous masses in bilateral submandibular region (2 cm in size, respectively). Fine needle aspiration of these masses showed uniform populations of large-sized lymphoblasts with malignant findings including prominent nucleoli and mitotic figures (Fig. 1). Routine hematology and biochemistry were unremarkable. Thoracic radiographs and abdominal ultrasound showed no remarkable findings (Fig. 2A). Based on the clinical examination and test results, the dog was diagnosed as multicentric lymphoma (stage II; involvement of many lymph nodes in a regional area). Treatment was initiated with CHOP protocol (cyclophosphamide, doxorubicin, vincristine, and prednisone). Oral prednisolone, 30mg/m² daily for week was started and the dog was prescribed to receive the first dose vincristine (Vincran, Reyon Pharm, Seoul, Korea) 0.5mg/m² IV.

After the treatment, nausea, anorexia, hemorrhagic diarrhea and regurgitation were shown for 2 days. After reviewing the medical records, we found that inappropriate dosage of vincristine (10 times the prescribed dose) was injected in this dog. The dog was hospitalized and fluid therapy was started. A complete blood counts showed leukopenia ($3.8 \times 10^9/L$; reference interval, $6-17 \times 10^9/L$) and thrombocytopenia ($0 \times 10^9/L$; reference interval, $200-500 \times 10^9/L$). The serum biochemical examination revealed increased lipase (465 U/L; reference interval, 49-160 U/L). Broad spectrum antibiotics was started to prevent the secondary infection. Antiemetics including maropitant citrate (Cerenia, Zoetis, New jersey, United States) 1mg/kg SC q24h and ondansetron 0.2 mg/kg slowly IV q 12h (Zofran, GlaxoSmithKline, Brentford, UK) was administered to reduce the nausea and regurgitation, but the dog was not responded. To differentiate gastrointestinal diseases causing these clinical signs, thoracic radiographs and the abdominal ultrasounds was re-evaluated on day 7. Plain thoracic radiographs and contrast esophagram revealed megaesophagus with the partly retention of contrast agents in the esophagus (Fig. 2B&C). The abdominal ultrasounds showed edematous pancreas. The dog showed positive result on a SNAP cPL test. Based on these findings, the adverse reaction of overdose vincristine such as bone marrow suppression, damaged gut villi and pancreatitis was presumed. Differential diagnoses for megaesophagus in this dog included hypoadrenocorticism, acquired myasthenia gravis (MG), and esophagitis. Response to an adrenocorticotrophic hormone stimulation test was normal, ruling out hypoadrenocorticism. Endoscopy showed generalized dilation of esophagus rumen and closed esophageal sphincter without esophagitis. Neostigmine stimulation test (0.05mg/kg IM; Neostigmine methylsulfate, Dai han pharm, Seoul, Korea) was performed and revealed temporary improvement in esophageal movement. This response to anticholinesterase administration was most suggestive of a diagnosis of MG. Unfortunately, serum antibodies against acetylcholine receptor was not evaluated in this dog. However, regurgitation and megaesophagus was presented after the chemotherapy and other possible causes of megaesophagus was ruled out. Thus, acquired megaesophagus could be caused by vincristine-overdose injection in this dog. Pyridostigmine (0.5mg/kg q12h; Dosmin, Hana pharm, Seoul, Korea), the anticholinesterase inhibitor, was immediately prescribed, but regurgitation was intermittently continued. The dog

was slowly deteriorated and dead due to sudden cardiopulmonary arrest 17 days after the overdose vincristine injection.

DISCUSSION

Vincristine is well known for a potent action that causes autonomic neuropathy and myopathy (Hopper *et al.*, 2001; Masoud *et al.*, 2009). In humans, vincristine-induced neuropathy can be associated with gastrointestinal motility disorders such as constipation, abdominal pain, and paralytic ileus (Tsukamoto *et al.*, 2011). Because any condition inducing neuropathies and myopathies can result in disruption of the neural reflex controlling of swallowing or affects function of the esophageal muscles, vincristine toxicity can be responsible for causing acquired megaesophagus (Hopper *et al.*, 2001; Masoud *et al.*, 2009; Tsuboi *et al.*, 2013).

In the present case, the dog had acquired megaesophagus after inappropriately overdose administration of vincristine. According to the previous report (Hopper *et al.*, 2001), megaesophagus occurred during the periodical chemotherapy with vincristine, but the acquired megaesophagus occurred on the way of chemotherapy with normal therapeutic dose and was immediately treated by vincristine withdrawal after immediate diagnosis of polyneuropathy through further tests such as nerve biopsy.

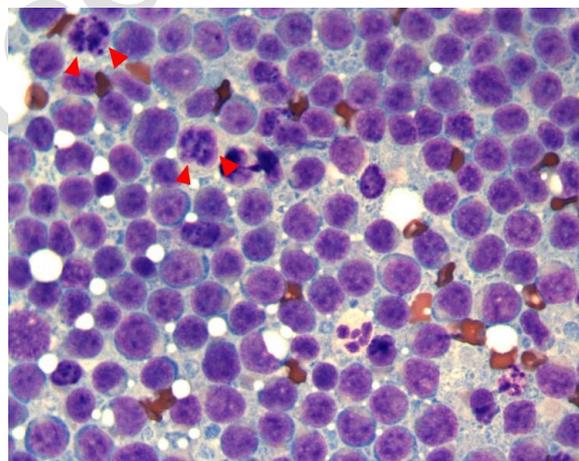


Fig. 1: A cytologic appearance of submandibular mass by fine needle aspiration. Note the uniform population of large lymphoid cells with prominent nucleoli, some of which have mitotic figures (red arrowheads). The granular background is karyorrhectic debris. (H&E stain, X630).

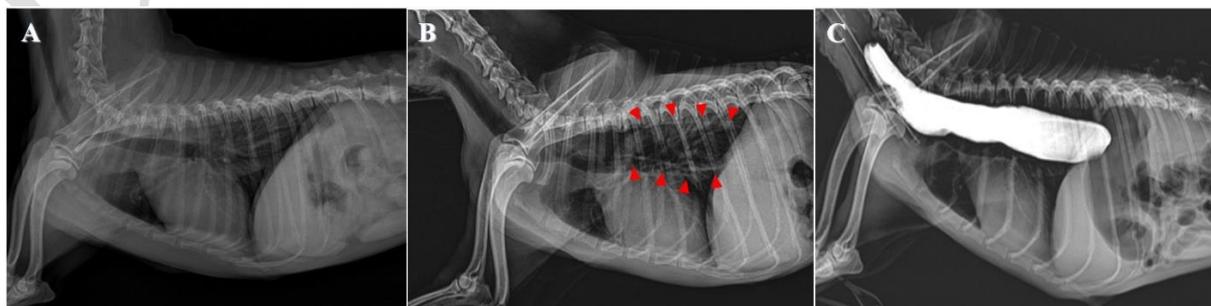


Fig. 2: Radiographic appearance of the dog with Right lateral view by plain and contrast radiography. (A) Thoracic radiograph showed no specific findings on admission. A week after the chemotherapy (B), the esophagus was dilated and visible on plain radiographs (arrow heads). (C) The contrast radiography revealed megaesophagus with the partly retention of contrast agents in the esophagus.

In this case, the dose of vincristine was incorrectly calculated and administered 10 times more than the normal dose. In the literatures, maximally tolerated dose of vincristine in dogs was reported to 0.06 mg/kg once a week, and the total administered dose in this case was approximately 5 times more than these maximally tolerated dose (Plumb, 2011). Thus, we suspected that chemotherapy induced polyneuropathy (Hopper *et al.*, 2001; Masoud *et al.*, 2009; Tsukamoto *et al.*, 2011) caused acquired megaesophagus in this dog.

Conclusions: This case demonstrates clinical characteristics and treatment outcome in a dog with acquired megaesophagus. Megaesophagus was developed in association with overdose administration of vincristine during chemotherapy against lymphoma in this dog. Thus, it is needed for specialized attention for dose and concentration of prescribing chemotherapeutic agents to minimized the possibility of accidental inadvertent administration.

Acknowledgements: This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (2016M3A9B6903437).

Authors contribution: CMJ and KTW took part in the care of the patient. KMH, CMS and KTW contributed in

preparation of the manuscript. The manuscript was prepared by CMJ and KTW under the supervision of PHM and KMH. All authors critically revised the manuscript and approved the final manuscript.

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