Thesis for the degree of Master of Veterinary Medicine

Intestinal Stenosis after Chemotherapy in a Cat with High-Grade Alimentary Lymphoma

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by **Hyun Jeong Hong**
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Abstract

A 3-year-old, castrated male, domestic short-hair cat was presented to the Western Referral Animal Medical Center (Seoul, Korea) with lethargy, anorexia, and melena of two days of duration. Abdominal ultrasonography revealed that the small intestinal mass (6 × 3.5 cm) was hypoechoic and had disrupted normal wall layering. High-grade alimentary lymphoma was diagnosed based on fine-needle aspiration cytology. During cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)-based chemotherapy, the patient was admitted to emergency care because of vomiting and depression. Abdominal ultrasonography revealed an intestinal stenosis at the lymphoma site. The patient underwent surgery to resolve the mechanical ileus. The remains in complete remission at the time of this report. To the best of our knowledge, this is the first reported case of an intestinal stenosis that might be occurred after CHOP-based chemotherapy for high-grade alimentary lymphoma.

Keywords: Alimentary lymphoma, Chemotherapy, Intestinal Stenosis, Feline

I. Introduction

Alimentary lymphoma is the most common form of lymphoma and is frequently diagnosed in cats [2, 8, 12]. Feline alimentary lymphoma can be classified into three types based on histopathology and immunohistopathology, namely (1) low-grade alimentary lymphoma, (2) intermediated- or high-grade alimentary lymphoma (I/HGAL), and (3) large granular lymphoma. In case with I/HGAL, an aggressive combination chemotherapy is considered for treatment [3]. While administering multidrug chemotherapy, such as cyclophosphamide, vincristine, prednisolone (COP)- or cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP)-based protocols, low-grade hematologic and gastrointestinal toxicosis are common [6, 10].

While treating feline I/HGAL with a chemotherapy-first approach, surgical emergencies are restricted to intestinal obstruction due to poor response or intestinal perforation with peritonitis [3]. However, in humans, there are several cases of intestinal stricture, also requiring surgical intervention, after intestinal lymphoma with a complete response to chemotherapy [5, 7].

There is a study regarding ultrasonographic features with feline intestinal fibrotic stricture [4]. As abdominal ultrasonography can easily employed in veterinary practice, feline intestinal stricture following chemotherapy could be diagnosed without using computed tomography.

Herein, we present a first case report of intestinal stenosis following CHOP-based chemotherapy in a feline high-grade alimentary lymphoma. A feline patient in this case underwent ileocolic anastomosis due to mechanical obstruction.

II. Materials and Methods

1. Clinical history of the feline patient

A 3-year-old, 4.67 kg, castrated male, domestic short-hair cat was presented to the Western Referral Animal Medical Center (Seoul, Korea) with lethargy, anorexia, and melena of two days duration. Physical examination the patient was depressed with pale mucous membranes, tachycardia, tachypnea and a palpable abdominal mass.

2. Laboratory examination

Complete blood count (CBC) was evaluated using the ADVIA2120i analyzer (Siemens, USA). Serum chemistry was performed using the HITACHI7020 (HITACHI, Japan). Blood typing was performed using a Feline A/B typing Qtest kit (Celltrix, Korea).

3. Imagimg examination

Abdominal ultrasonography was performed using the Aplio 400 ultrasound machine (Canon medical systems corporation, Tokyo, Japan).

4. Cytologic examination

Fine-needle aspiration samples are stained using Diff quick stain.

5. Pathologic examination

Excisional biopsy samples stained with hematoxylin and eosin at the laboratory of Veterinary Pathology in IDEXX (USA).

6. Polymerase chain reaction for Antigen Receptor Rearrangements (PARR)

PARR assay performed at the laboratory of Pobanilab (Guri, Republic of

Korea).

7. CHOP-based protocol for the patient in this case

Week 1	Vincristine 0.5 mg/m^2 IV, Prednisolone 2mg/kg PO q24hr
Week 2	Cyclophosphamide 200mg/m^2 PO, Prednisolone 2mg/kg PO q24hr
Week 3	Vincristine 0.6 mg/m^2 IV, Prednisolone 1mg/kg PO q24hr
Week 6	Doxorubicin 25mg/m^2 IV, Prednisolone 1mg/kg PO q48hr
Week 8	Vincristine 0.6 mg/m^2 IV, Prednisolone 1mg/kg PO q48hr
Week 9	Cyclophosphamide 200mg/m^2 PO, Prednisolone 1mg/kg PO q48hr
Week 10	Vincristine 0.6 mg/m^2 IV, Prednisolone 1mg/kg PO q48hr
Week 11	Doxorubicin 25mg/m^2 IV, Prednisolone 1mg/kg PO q48hr
Week 13	Vincristine 0.6 mg/m^2 IV, Prednisolone 1mg/kg PO q48hr
Week 15	Cyclophosphamide 200mg/m^2 PO, Prednisolone 1mg/kg PO q48hr
Week 17	Vincristine 0.6 mg/m^2 IV, Prednisolone 1mg/kg PO q48hr
Week 19	Doxorubicin 25mg/m^2 IV, Prednisolone 1mg/kg PO q48hr
Week 21	Vincristine 0.6 mg/m^2 IV, Prednisolone 1mg/kg PO q48hr
Week 23	Cyclophosphamide 200mg/m^2 PO, Prednisolone 1mg/kg PO q48hr
Week 25	Vincristine 0.6 mg/m^2 IV, Prednisolone 1mg/kg PO q48hr
Week 27	Doxorubicin 25mg/m^2 IV, Prednisolone 1mg/kg PO q48hr

IV, intravenous; PO, per oral (by mouth)

III. Results

The biochemical profile of this patient showed increased in ALP (139 U/L) and total bilirubin (0.23 mg/dl) (Table 1). As the patient is anorectic for two days and these abnormalities improved during hospitalization, hepatic lipidosis is considered rather than hemolytic anemia. The CBC results revealed regenerative anaemia (hematocrit [HCT]= 11.8%, reference interval(RI), 27.7-46.8% and reticulocyte count [RETIC#]= 131.5 K/μL, RI, 15.0-81.0 K/μL). Abdominal radiography revealed a large, round, soft tissue opaque mass in the center of the abdomen. Abdominal ultrasonography revealed a hypoechoic small intestinal mass (6 × 3.5 cm) with disrupted normal wall layering. Ultrasound-guided fine-needle aspiration of the abdominal mass revealed high cellularity with medium-to-large lymphocytes. High-grade alimentary lymphoma (HGAL) was diagnosed based on the cytology (Figure 1). A PARR assay performed using the cells aspirated from the intestinal mass revealed monoclonality of T-cell lineage. Feline immunodeficiency virus antibody and feline leukaemia virus antigen tests were negative. No other lymph node enlargements were detected on physical examination or thoracic radiography.

Table 1. Results of serum chemistry analysis of this patient

	Reference	Result		Unit
		Day 1	Day 2	
ALT/GPT	28 - 106	34		g/dl
ALP	9 - 53	139	82	U/L
Total protein	6.6 - 8.4	6.7		g/dl
Albumin	1.9 - 3.9	3.0		g/dl
Total bilirubin	0.0 - 0.2	0.23	0.18	mg/dl
Phosphorous	3.2 - 6.3	5.0		mg/dl

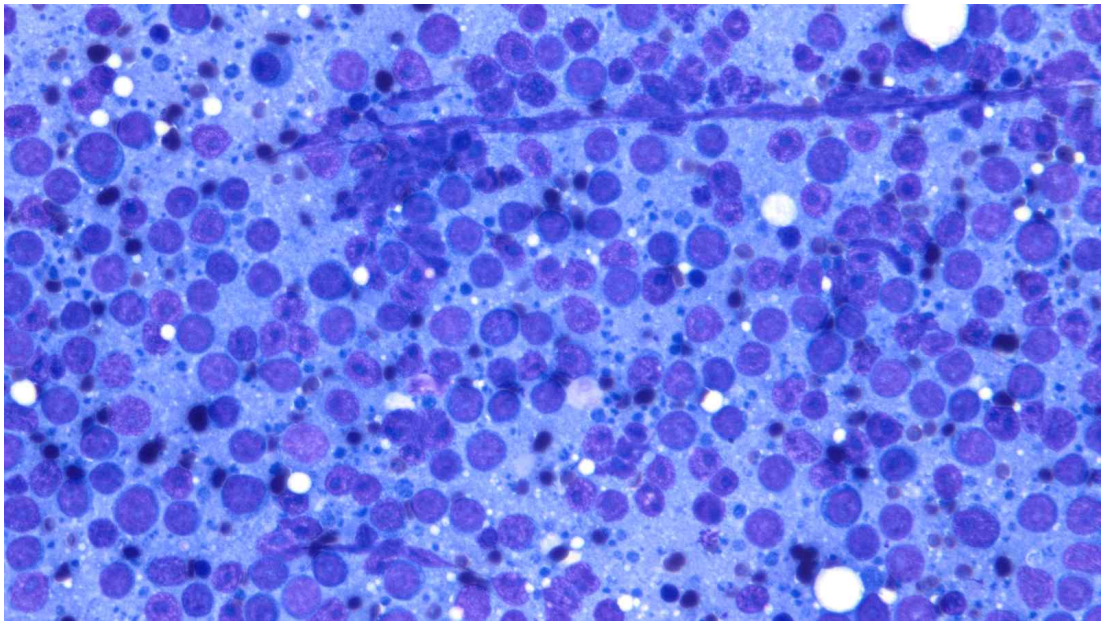


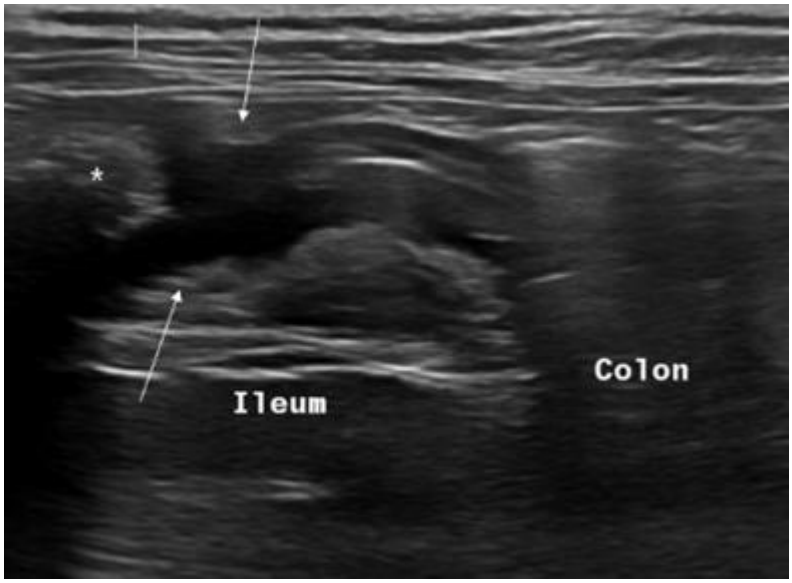
Figure 1. Fine-needle aspiration sample from the intestinal mass of this patient. Immature and large lymphocytes are predominant. These cells have more abundant cytoplasm, pale chromatin, and one or more nucleoli.

As the patient experienced melena during hospitalization, intestinal haemorrhage was considered the cause of regenerative anaemia. In-house blood typing was performed and the patient was classified as Type A and 40ml of packed red blood cells, which was the only blood available at that time, was transfused. Other treatments included nasogastric tube feeding, oxygen supplementation, and intravenous administration of 0.9% normal saline. In addition, antibiotics including cefotaxime (Pharmgen Cefotaxime Sodium Inj.; 30 mg/kg, twice a day, intravenous; Pharmgenscience Pharmaceutical, Korea) and metronidazole (Metrinal Inj.; 15 mg/kg, twice a day, intravenous; Daihan Pharmaceutical, Korea) to prevent bacterial translocation. Mucosal protectants including famotidine (Gaster Inj.; 0.5 mg/kg, twice a day, intravenous; Donga-st Pharmaceutical, Korea) and sodium alginate (Algid solution; 100 mg/cat, twice a day, per os; SCD Pharmaceutical, Korea) to manage gastrointestinal haemorrhage, Maropitant (Cerenia; 1 mg/kg, once a day, per os; Zoetis, US) for nausea, and Ferric Hydroxide Polymaltose complex (Ferromax solution; 200 mg/cat, once a day, per os; Hanmi Pharmaceutical, Korea) for anemia were also provided.

The patient was treated using a CHOP-based chemotherapy protocol. Following the first vincristine dose(Vincran; 0.6 mg/m^2; REYON Pharmaceutical, Korea; 1st week), the melena was improved and HCT increased from 14.9% to 23.9%. Five days after the first cyclophosphamide dose (Alkyloxan; 200mg/m^2, per os; JW Pharmaceutical, Korea; 2nd week), the patient presented with vomiting. Maropitant prescribed until next visit to prevent further vomiting. The second Vincristine dose (3rd week) was infused intravenously as scheduled. Two days later, the patient was admitted to emergency care department because of vomiting and depression. The intestinal mass had decreased in size (2.4 × 0.7cm), as observed using abdominal ultrasonography, suggesting that the patient had partial remission of HGAL. Segmental intestinal dilation with a kink at the original site of lymphoma (Figure 2) was observed and was considered nondilatable, namely, intestinal stenosis [3, 4]. Surgical intervention was performed.

Approximately 2 cm of either side of the lesion was resected during ileocecalectomy and an end-to-end anastomosis was performed. Although the patient developed a fever during the first three postoperative days, the patient was discharged from our hospital on the 6th day of hospitalization without any gastrointestinal complications. Histopathological examination of the resected ileocecal junction revealed mural ulceration with transmural inflammatory infiltrates (Figure 3). Though PARR had not performed, atypical lymphocytes were not observed in the resected tissue section.

A



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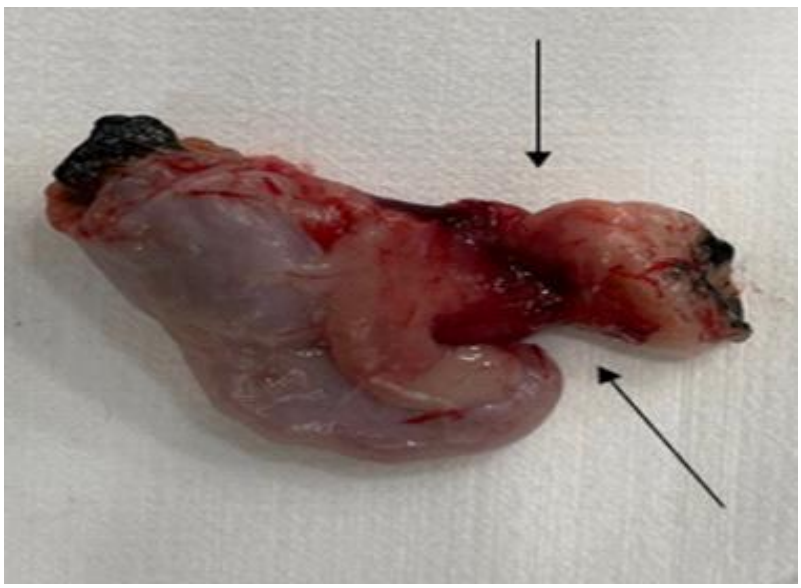

Figure 2. Ileocecal stricture in the patient on ultrasonography (A) and resected specimen (B). The original site of lymphoma (arrows) is narrow with marker dilation of the proximal intestine (asterisk).

A

B

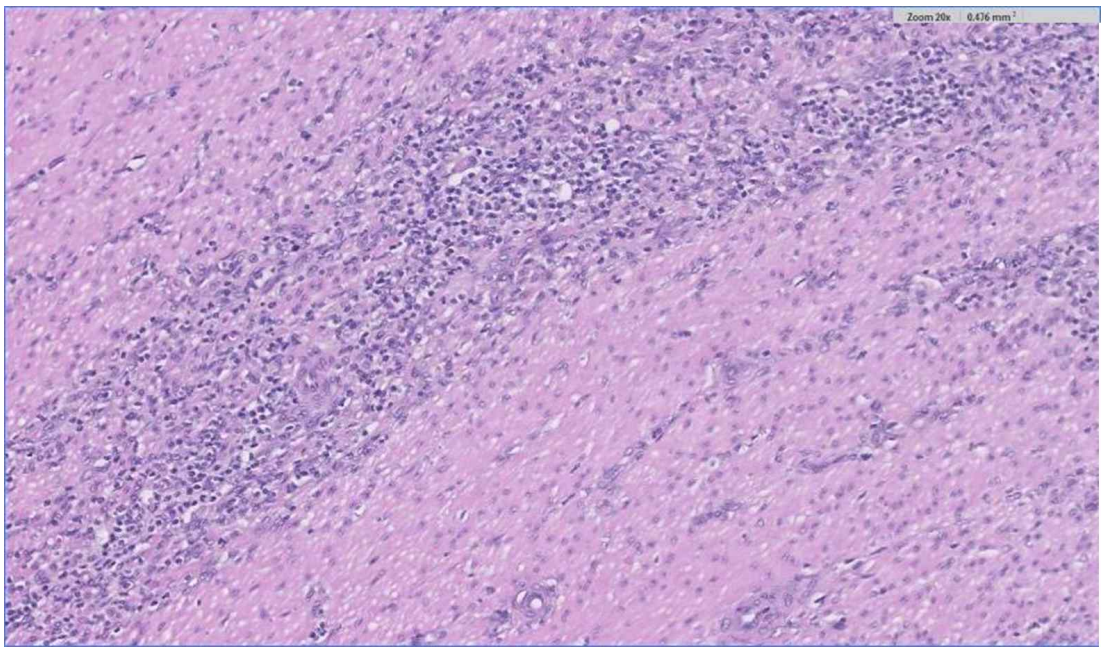

Figure 3. Histological section of the stricture. In (A), there is an area of ulceration within mucosa (arrow). (B) shows a high-resolution image of asterisk on (A). There are transmural mixed inflammatory infiltrates.

After the HGAL lesion was resected, the patient was assumed to be in complete remission. Seven hundred and sixty days after completing CHOP-based chemotherapy, the patient remained in complete remission.

IV. Discussion

Intestinal stricture is an unreported complication of chemotherapy in veterinary medicine. However, in humans, it is regarded as a major complication that may occur during or after gastrointestinal lymphoma chemotherapy [5]. The pathophysiology of postchemotherapy intestinal strictures remains unknown; however, mucosal injury and inflammation have been suggested as probable causes [7, 9]. This patient in the presents case presented to the hospital with melena, indicating severe enteritis. Mucosal injury following chemotherapy could have resulted in excessive and atypical reactions in the already damaged intestine of the patient. Thus, we suggest ulcerative enteritis in patients HGAL is a predisposing factor for intestinal strictures in patients treated wit CHOP-based chemotherapy. Moreover, the innately narrow feature of the ileocecal junction could be considered a predisposing factor for strictures.

Because histopathology in this patient was performed after chemotherapy and surgery, it is difficult to determine whether the intestinal stenosis, resulting in mechanical obstruction, existed before or after chemotherapy. However, lymphoma is unlikely to cause desmoplastic reaction [9]. Additionally, since our patients gastrointestinal symptoms worsened after administration of the second dose of vincristine (3^{rd} week), it is deducible that intestinal stenosis might have progress with the chemotherapy.

In a study by Crouse et al, post-chemotherapy GI perforation occurred in 17% of the feline patients with I/HGAL. In half of these patients with GI perforation, the events occurred within three days after vincristine administration. Our patient was diagnosed with an intestinal stenosis two days after receiving the second dose of vincristine (3^{rd} week). Although this was

observed in only one patient, which hinders generalizability, it is beneficial to closely monitor GI toxicosis in veterinary patients, especially after administration of vincristine.

In feline I/HGAL, the therapeutic impact of surgical excision on survival time compared with chemotherapy alone is unknown. Despite these controversies, this patient was alive at the time of completion of data collection 760 days after the first medical examination. It was longer than the mean survival time (MST) of cats with I/HGAL treated with multiagent combination chemotherapy. Two studies (Gouldin et al. and Tidd et al.) examined the effects of I/HGAL surgery followed by multi-agent chemotherapy. Gouldin et al. found that resectable single primary gastrointestinal tumors, regardless of mesenteric lymph node metastasis, showed better MST and disease-free intervals. Tidd et al. showed that complete surgical resection of a large intestinal mass also resulted in a longer MST. In this patient, there was a resectable single ileal lymphoma at the time of diagnosis with no residual malignant lymphoma on hisopathologic examination. Although the present case differed from the previous two studies wherein surgery was conducted before chemotherapy, this patient also had a good prognosis.

V. Conclusion

To the best of our knowledge, this is the first case of intestinal stenosis which is developed after complete response to CHOP-based chemotherapy in a cat with HGAL. The clinical manifestations of intestinal stenosis such as anorexia, vomiting and lethargy are similar to the common signs of gastrointestinal toxicity following chemotherapy or intestinal lymphoma. Although this is a rare case, intestinal stenosis could be included as a differential diagnosis when patients with HGAL present with gastrointestinal dysfunction after chemotherapy.

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고양이 고도 소화기 림프종에서 항암치료 후 발생한 소화관 협착 증례

홍 현 정

제주대학교 대학원 수의학과

요약

고양이에서 소화기 림프종은 림프종 중에서 가장 많이, 그리고 소화기 종양 중에서 가장 빈번하게 진단되는 종양이다. 미국 국립 암 연구소 (National Cancer Institute Working Formation) 의 기준을 바탕으로 고양이 소화기 림프종은 조직학적으로 저도, 중등도, 고도로 구분한다. 중등도, 고도 소화기 림프종의 경우, 사이클로포스파미드, 독소루비신, 빈크리스틴과 프레드니솔론 병용요법 (CHOP) 으로 대표되는 항암치료로 주로 치료를 시도한다. 중등도, 고도 소화기 림프종을 CHOP 복합 항암요법으로 치료하면서 가벼운 수준의 위장관 증상은 흔히 발생하는 것으로 알려져 있다. 그런데 웨스턴 동물의료센터 (서울, 대한민국) 에 내원한 한 고양이 고도 림프종 환자에서 처음 보는 유형의 위장관 부작용이 CHOP 복합 항암요법 이후 발생하였다.

3살 거세된 수컷 한국 토종 단모종 고양이가 2일간 지속된 기력저하, 식욕부진 그리고 흑변으로 웨스턴 동물의료센터에 내원하였다. 전혈구 검사 상에서 심한 재생성 빈혈이 확인 되었으며, 복부 초음파 상에서 정상적인 소장벽의 구조가 변형된, 저에코의 소장 종괴 (6 × 3.5 cm)가 확인되었다. 세침검사를 통해 고도 소화기 림프종이 진단되었다. CHOP로 항암치료를 하는 도중에 환자는 구토와 기력저하로 응급센터로 내원하였다. 복부 초음파 상에서 소화기 림프종이 위치했던 부분에 소장 협착이 발생한 것이 확인되었다. 기계적 폐색을 해소해주기 위한 수술을 진행했으며 환자는 760일에 이르는 현재까지

완전관해상태를 유지하고 있다. 저자가 아는 한, 이 논문은 고양이의 고도 소화기 림프종에서 CHOP 복합 항암요법 이후에 발생한 소장협착의 첫 번째 증례 보고이다.

주요어: 소화기 림프종, 항암요법, 위장관 협착, 고양이

감사의 글

곁에서 늘 응원해주시고 도와주시는 소중한 분들 덕분에 이 논문을 쓸 수 있었습니다. 한 글자 한 글자에 제 감사한 마음을 눌러 담습니다.

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