

Intestinal Lymphangiectasia in a Yorkshire terrier Dog: Clinical Outcome, Clinicopathological and Histopathological Findings

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(Accepted: April 3, 2006)

Abstract : A 7-year-old, 3.16 kg intact male Yorkshire terrier had the history of abdominal distension, diarrhea, and weight loss. On the basis of history takings, physical examination, laboratory tests, radiography, ultrasonography, exploratory laparotomy, and histopathological examination, the dog was diagnosed definitely as intestinal lymphangiectasia. In this case, signs and results are consistent with those of other reports, but some clinicopathological findings such as hypocalcemia and hypocholesterolemia are not. This means that the findings were not completely in accord with the typical ones of intestinal lymphangiectasia in this dog. Prednisolone was prescribed to treat. However, it was not effective sufficiently. Thus, azathioprine was added to the regimen used in the first trial, and it was quite efficient in inducing remission in intestinal lymphangiectasia. The clinical signs were improved to the combined therapy. This case report demonstrates that the combined therapy for intestinal lymphangiectasia can be used as an alternative to only glucocorticoid therapy.

Key words : intestinal lymphangiectasia, ascites, hypoproteinemia, glucocorticosteroid, azathioprine.

Introduction

Intestinal lymphangiectasia is one of protein-losing enteropathies (PLE) in dogs (7). The PLE is the disorder which loses larger molecules such as proteins into the lumen. It is related to the abnormal barrier function of the gut or to acquired or congenital abnormalities in intestinal lymphatic or vascular drainage (15). Especially, intestinal lymphangiectasia is caused by the obstruction of normal lymphatic and venous flow, which results in the dilation and dysfunction of intestinal lymphatics. Intestinal lymphangiectasia may be a primary disorder in which lymph flow is reduced because of insufficient numbers of lymphatic vessels (1). Secondary or acquired intestinal lymphangiectasia has many causes which include the obstruction of lymphatics by an inflammation, fibrosis, or neoplasm, obstruction of the thoracic duct, and right-sided heart failure from congestive heart failure or cardiac tamponade (6). Generally, hypoproteinemia, lymphocytopenia, and hypocholesterolemia are often present due to the enteric loss of lymph. As a result, diarrhea, steatorrhea, profound weight loss, ascites and/or edema can be seen (11). Gross findings at laparotomy are dilated lymphatics which are visible throughout the mesentery and serosal surface (15). Histopathologic findings include a ballooning distortion of villi caused by markedly dilated lacteals. Diffuse or multifocal accumulations

of lymphocytes and plasma cells can be identified in the lamina propria (6,11).

The purpose of this report is to describe the clinical, radiographic, ultrasonographic and histopathologic findings in a Yorkshire terrier dog with intestinal lymphangiectasia, and to clarify the clinical efficiency of the prednisolone and azathioprine medication in intestinal lymphangiectasia.

Case Report

A 7-year-old, intact male Yorkshire terrier weighing 3.16 kg was presented to the Veterinary Medical Teaching Hospital of Konkuk University. He had the history of repetitive abdominal distension for 3 months, malodorous mucous diarrhea, and weight loss. On physical examination, marked abdominal distension, tachycardia, watery mucous malodorous diarrhea, and mildly dehydrated state (capillary refill time, CRT=2 seconds) were found.

Results of complete blood counts (CBC) revealed that neutrophilia (neutrophil=83 of 100; normal range, 60-77) and lymphocytopenia (lymphocyte=11 of 100; normal range, 12-30) on differential counting. Results of serum biochemical profiles revealed that mildly elevated alanine aminotransferase (ALT) (ALT=74 U/L; normal range, 13-53), hypocholesterolemia (chloride =102 mmol/L; normal range, 102-117), and hypoproteinemia (total protein=3.1 g/dl; normal range, 5.0-7.1) with hypoalbuminemia (albumin=1.3 g/dl; normal range, 2.6-3.9)

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On abdominal radiography, there were diffuse fluid density of abdomen, including decreased abdominal details and abdominal contrast loss along with abdominal distension. Also, hepatomegaly and diffuse bowel loops were seen (Fig 1).

Abdominal ultrasonographic findings exhibited peritoneal effusion, thickened intestinal wall, and mineralization of kidney. In particular, the thickening of the intestinal wall was remarkable (4.2-4.5 mm, average thickness=2-3 mm (12)) (Fig 2). The intestinal wall layers were indistinct and disruptive, and the echogenicity was irregular.

Based on these results, the differential diagnosis was made as hepatic disease, nephropathy, PLE (inflammatory bowel disease, lymphangiectasia, and intestinal lymphoma), and exocrine pancreatic insufficiency (EPI). The hepatic disease was ruled out by the result of serum bile acids test (fasting: 3.5 $\mu\text{mol/L}$, postprandial: 31.1 $\mu\text{mol/L}$; normal range, fasting: below 2 $\mu\text{mol/L}$, postprandial: below 10 $\mu\text{mol/L}$; generally, we regard it as abnormal when the value of postprandial is

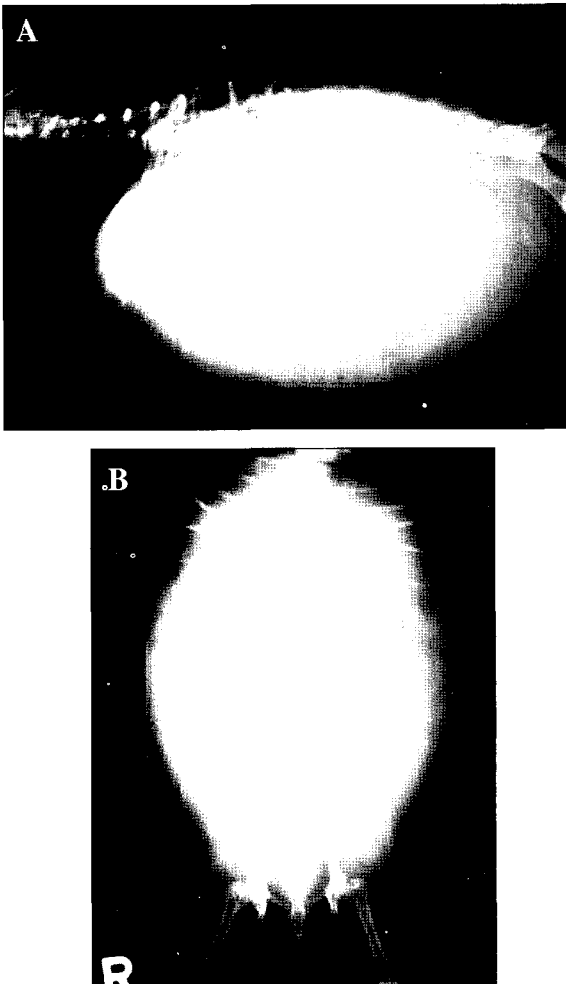


Fig 1. Right lateral (A) and ventrodorsal (B) abdominal radiographs of the dog. As a whole, the abdomen is radiopaque and remarkably distended. Loss of the intra-abdominal contrast existed, and no visualization of serosal surface due to diffuse fluid density of abdomen.



Fig 2. Ultrasonographic examination of the small intestine of the dog. Thickened intestinal wall is seen definitely. The thickness of the wall is 4.5 mm. The intestinal wall layers were indistinct, and the echogenicity was irregular.

above 100 $\mu\text{mol/L}$ (6)). As for nephropathy, mild proteinuria and calcium oxalate crystals were present in the urinalysis. However, it might be transient signs due to the mineralization of the kidney. The EPI could be ruled out without the measurement of serum canine trypsin-like immunoreactivity (14). It was because ascites was not typical sign of EPI, and abdominal effusion was transudate (clear and colorless, 700 cells/ μl , Total protein=0.1 g/dl, negative in culture). Fecal examination was negative to endoparasitism. The results of laboratory analyses and diagnostic images were not enough to rule out PLE. For the more definitive diagnosis, exploratory laparotomy and histological examination were needed.

Finally, exploratory laparotomy was performed. On gross findings, clear abdominal fluid existed and the intestine was enlarged and the mesentery vessels were congested. Dilated, milky lymphatics were visible throughout the mesentery and serosal surface in the jejunum. Specifically, yellow-white nodular masses were observed multifocally on the serosal surface. For the definitive diagnosis, full-thickness biopsy specimens were obtained from the jejunum (Fig 3). Histopathological findings were numerous markedly dilated lacteals, and mild lymphocyte infiltrates (Fig 4). The final diagnosis was made as an intestinal lymphangiectasia.

The purpose of treatment of lymphangiectasia is to decrease the enteric loss of plasma protein, resolve associated intestinal or lymphatic inflammation, and control any edema or effusions (2,6). As the initial therapy, the patient was treated with the furosemide (Lasix[®], Handok Phama Co, Chungbuk, Korea, 2 mg/kg, PO, BID), prednisolone (Prednisolone Korus[®], Hankook Korus, Chungbuk, Korea, 2 mg/kg, PO, BID), Biphenyl-dimethyl-dicarboxylate (Lefotil[®], Cellat Pharm Korea, Kyunggi, Korea, 25 mg/kg, PO, BID), Ursodeoxycholic acid (Usosan[®], Korea United Pharm, Chungnam, Korea, 10 mg/kg, PO, SID), and metronidazole (Metronidazole Cellatpharm[®], Cellat Pharm

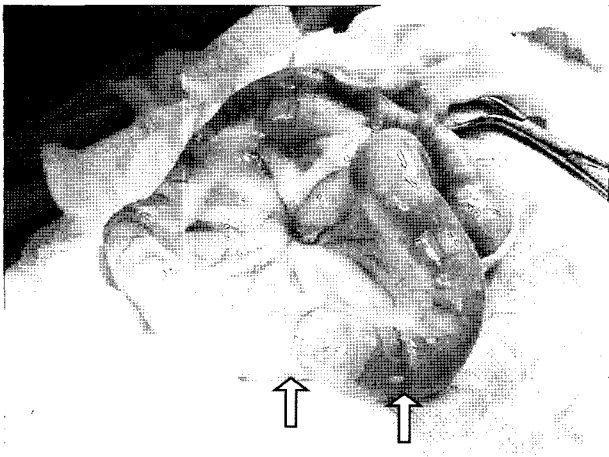


Fig 3. The gross finding of the small intestine at the exploratory laparotomy. Swollen intestinal wall and milky, distended lymphatic vessels are remarkable throughout the mesentery and serosal surface. Specifically, yellow-white nodular masses were observed on the surface of serosa (arrows).

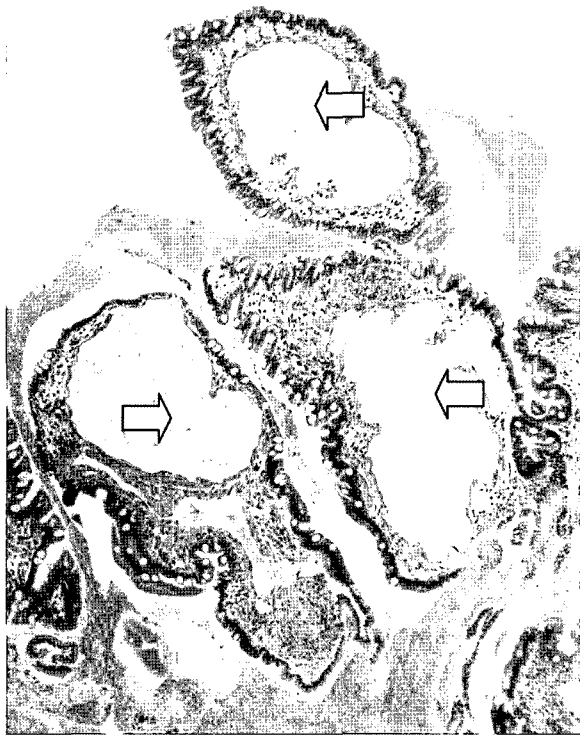


Fig 4. Histopathological findings in the jejunum of the dog (H&E. $\times 400$). There are numerous markedly dilated lacteals (arrows) and mild lymphocyte infiltrates.

Korea, Kyunggi, Korea, 15 mg/kg, PO, BID). However, there was no response to the therapy sufficiently. Thus, azathioprine (Azaprine[®], Korea United Pharm, Chungnam, Korea, 1 mg/kg, PO, SID) was added to the initial therapy instead of pred-

nisolone, metronidazole, and sulfasalazine (Seromeien[®], Sinil Pharm Co, Chungnam, Korea, 20 mg/kg, PO, BID). In addition, as the dietary therapy, fat soluble vitamins, medium chain triglyceride oils, egg white, and k/d (Hill's Pet Products, Topeka, KS, U.S.A) was prescribed to furnish the appropriate nutrition for the patient. The therapy was quite effective. The ascites was improved, and the shape of feces became normal.

Discussion

The intestinal lymphangiectasia is a disorder of the lymphatic system of the gastrointestinal tract, resulting in dilation and rupture of intestinal lacteals. Because the plasma proteins, lymphocytes, and chylomicrons of the lymphatic contents are lost into the intestinal lumen, various clinicopathologic abnormalities are present (7).

In a recent study of 17 dogs with intestinal lymphangiectasia, the most common clinical signs were diarrhea (17/17, 100%), anorexia (14/17, 82.4%), lethargy (13/17, 76.5%), vomiting (11/17, 64.7%) and weight loss (8/17, 47%) (7). However, vomiting in this case was not noted. Abnormal physical examination findings included dehydration (13/17, 76.5%), ascites (7/17, 41.2%), and signs of pain on abdominal palpation (6/17, 35.3%). Eight of 17 were in normal body condition (8/17, 47.1%). In CBC and serum biochemical analyses, there were lymphocytopenia (8/14, 57.1%), hypoglobulinemia (6/14, 42.9%), hypocholesterolemia (5/14, 35.7%), and hypocalcemia (12/12, 100%) (7). In this case, the clinicopathologic findings showed lymphocytopenia, hypoproteinemia and hypocholesterolemia. Similarly like the recent report (7), there were lymphocytopenia and hypoproteinemia with hypoalbuminemia were present, but hypocholesterolemia and hypocalcemia were not detected in the case. This result is not in accord with that of the recent report (7) describing the intestinal lymphangiectasia. Thus, hypocalcemia is not always present in the intestinal lymphangiectasia.

Abdominal radiographic characteristics in the previous report (7) were gas or fluid-distended small intestine (5/6, 83.3%) and decreased abdominal detail compatible with peritoneal effusion (4/6, 66.7%). The abnormalities in the abdominal ultrasonography were peritoneal effusion (7/12, 58.3%), thickening of the small intestine wall (6/12, 50%), and hyperechoic mesentery (5/12, 41.7%) (7,8). Alike the results of the report, fluid density of abdomen, abdominal distension, and diffuse bowel loops were detected in the abdominal radiography, and a 5 cm thickened, and irregular layered intestinal wall was found in the abdominal ultrasonography.

In exploratory laparotomy, thickened small intestine (4/17, 23.5%), dilated lacteals (4/17, 23.5%) were found and, in histological examination, there were inflammatory cells infiltrates (15/17, 88.2%) such as lymphocytes, plasma cells, and eosinophils (7). In the exploratory laparotomy of the present case, the intestine was enlarged, and the lymphatics of the mesentery and serosal surface in the jejunum were dilated and whitish. These findings seemed to be typical in this case,

although they occupied only 25% of the signs in laparotomy in the previous report. On histopathological findings, dilated lacteals and lymphocytes infiltrates were noted.

When glucocorticoid was administered to the patient, the mucoïd diarrhea was changed into the soft feces and the appetite was increased, but ascites was not improved. There are many reasons for the failure to adequately respond to glucocorticosteroid treatment (5,10,13). The reason why glucocorticoid was not effective in this dog is unclear, however, the degree of the disease might be too severe for the steroids to be efficacious enough, or there might exist an individual difference to the glucocorticoid. Because the dog was steroid-resistant, we used azathioprine as an alternative to the immunosuppressive therapy. After the therapy of azathioprine, abdominal distension disappeared and the state of feces became normal. The initial dosage of 0.5mg/kg azathioprine orally every 24 hours was given. After 26 days, however, the patient came to the hospital with the abdominal distension. The symptom might relapse due to the low dosage of azathioprine, and thus the dosage of azathioprine was increased to 1 mg/kg. The progress was good. The 24 days later, the ascites recurred even though the shape of feces and the appetite were normal. The abdominocentesis was done for the relief of abdominal distension, and the dosage of azathioprine was changed into 2 mg/kg. On 60 days, the dog came with the severe abdominal distension, and azathioprine was increased into 3 mg/kg. Shortly, as the maintenance therapy, the dosage of azathioprine was adjusted into 1.5 mg/kg given orally twice a day, and prednisolone was added as the dosage of 1 mg/kg given orally twice a day.

Differing from glucocorticoids, azathioprine improved the clinical signs such as the ascites and the character of feces remarkably. Also, it made the period of the recurrent period of ascites longer. Unfortunately, the treatment with azathioprine for the immune-suppression in the intestinal disease of the companion animals is not popular yet. In human, the effectiveness of azathioprine in the intestinal disease is described in many studies (3,4,9). Azathioprine has been used to suppress the immuno-response in the inflammatory bowel disease like ulcerative colitis, Crohn's disease, and indeterminate colitis (3). The successful roles of azathioprine in controlling immune-response are shown in more than 70% patients in the inflammatory disease (1). Azathioprine was shown to be effective in both steroid-dependent and steroid-refractory patients, resulting in the improvement and remission of the diseases (9). However, the side-effects of azathioprine are being reported, which are classified as either allergic (dose independent), such as fever, pancreatitis, rash, malaise, arthralgias, nausea and diarrhea, or non-allergic (dose and metabolism dependent), namely leucopenia, thrombocytopenia, infections, hepatitis, and malignancy simultaneously (3).

From this paper, we cannot assure the effectiveness of azathioprine in dogs like in human cases, because there is the result of just one dog treated with azathioprine, and are not any biochemical tests for the detailed informations such as

effects and side-effects. Nevertheless, it is possible to conclude that azathioprine was effectual in remitting intestinal lymphangiectasia in this dog. To confirm the efficacy of azathioprine in the intestinal lymphangiectasia in dogs, further studies are necessary. If more data are produced, treatment of dogs with azathioprine will be a valid therapeutic option.

In conclusion, this case demonstrates that azathioprine seemed to be effective in achieving remission in intestinal lymphangiectasia which did not respond to the previous therapy with the steroid.

Acknowledgements

We would like to thank Bora Lee, May Hyosun Namkung, and Ha-Young Jang in the department of veterinary surgery, for helping with the exploratory laparotomy.

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요크셔테리어견에서 발생한 Intestinal Lymphangiectasia: 임상적 결과와 임상병리학적, 조직병리학적 소견

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요 약: 3.16 kg의 몸무게를 가진, 7년령의 거세하지 않은 수컷 요크셔테리어견이 복부팽만, 설사, 체중감소로 내원하였다. 병력청취, 신체검사, 실험실검사, 방사선학적 검사, 초음파검사, 탐색적 개복술과 조직병리학적 검사 등을 통해 최종적으로 intestinal lymphangiectasia로 진단되었다. 본 증례에서 나타난 증상과 여러 검사 결과들은 이전에 보고된 증상 및 결과와 대체로 일치하였으나, 저칼슘혈증과 저콜레스테롤혈증을 나타내지 않았다는 점에서 기존의 증례와 차이가 있었다. 치료법으로 프레드니솔론 (Prednisolone Korus[®], 한국 코러스, 충북, 한국, 2 mg/kg, 경구투여, 1일 2회)을 사용하였지만 효과가 없었다. 따라서, 아자싸이아프린 (Azathioprine[®], 한국 유나이티드 제약, 충남, 한국, 1 mg/kg, 경구투여, 1일 1회)을 추가하여 복용시킨 결과 임상증상이 개선되었다.

주요어: intestinal lymphangiectasia, ascites, hypoproteinemia, glucocorticosteroid, azathioprine.