NOTE *Internal Medicine*

Polypoid Adenomas Secondary to Inflammatory Colorectal Polyps in 2 Miniature Dachshunds

Hirotaka IGARASHI[1)], Koichi OHNO[1)]*, Aki OHMI[1)], Atsushi TSUKAMOTO[1)], Ko NAKASHIMA[1)], Yasuhito FUJINO[1)], Kazuyuki UCHIDA[2)] and Hajime TSUJIMOTO[1)]

[1)]*Department of Veterinary Internal Medicine, Graduate School of Agricultural and Life Science, The University of Tokyo, 1–1–1 Yayoi, Bunkyo-ku, Tokyo 113–8657, Japan*

[2)]*Department of Veterinary Pathology, Graduate School of Agricultural and Life Science, The University of Tokyo, 1–1–1 Yayoi, Bunkyo-ku, Tokyo 113–8657, Japan*

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ABSTRACT. Two miniature dachshunds, a 7-year-old neutered male and an 8-year-old male, presented with chronic hematochezia and tenesmus. A solitary pedunculated or multiple diffuse colorectal polyps were identified by colonoscopy and resected by polypectomy. Inflammatory colorectal polyps (ICRPs) were diagnosed according to histopathological findings. Both cases were treated with immunosuppressive therapy, and the clinical signs were resolved, although the colorectal polyps remained to some extent. Several months after the initial diagnosis, both cases presented with recurrence of hematochezia and enlargement of the polyps. A second colonoscopic polypectomy was performed, and adenoma was diagnosed histopathologically in both cases. ICRPs are a nonneoplastic disease, but their long-term prognosis is unknown. Careful follow-up seems to be important, and repetitive biopsy is recommended when growth of polyps is identified in miniature dachshunds with ICRPs.

KEY WORDS: inflammatory colorectal polyp, miniature dachshunds, polypoid adenoma.

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Polyps are derived from neoplasms or nonneoplastic lesions, such as inflammatory polyps. In dogs, colorectal polyps are relatively common in the gastrointestinal tract; they are derived from neoplasms, such as polypoid adenomas and adenocarcinomas [7, 15, 19, 20]. Polypoid adenomas and adenocarcinomas are commonly observed as solitary masses in the rectum. Most polyps form friable, pedunculated, sessile or lobulated lesions on the mucosa. Surgical resection is recommended for colorectal polyps in dogs [1, 3, 11]. In addition, endoscopic treatment and piroxicam are also reported as alternative therapies for colorectal neoplasms [5, 6, 8].

However, few reports describe the clinical features of inflammatory colorectal polyps (ICRPs) in dogs [20]. In humans, ICRPs and polypoid lesions occur in association with inflammatory bowel disease (IBD) and other inflammatory diseases, such as ischemic and infective colitis [2, 9, 13]. We recently reported that the miniature dachshund is the breed most commonly affected by colorectal polyps, especially ICRPs [12]. ICRPs in miniature dachshunds are characterized by multiple diffuse polyps localized in the colon or rectum. Immunosuppressive therapy with prednisolone and cyclosporine is suggested to be an effective treatment for ICRPs [12]. However, in some cases, immunosuppressive treatment results in a poor therapeutic response, ultimately requiring surgical removal. We previously reported that 1 of the 30 dogs included in a retrospective study developed adenoma during immunosuppressive therapy [12]. However, we later observed another dog developing adenoma secondary to ICRP that had been included as a dog with ICRPs that were well controlled with immunosuppressive therapy. Because the etiology and specific treatments for ICRPs have not been fully clarified, the long-term prognosis has not been investigated. In this report, we describe the detailed course of two cases of ICRPs in miniature dachshunds (case 1, newly diagnosed; case 2, previously included case developing adenoma) that developed polypoid adenomas at the same lesion during a long-term course of treatment using immunosuppressive agents.

Case 1: A 7-year-old neutered male miniature dachshund with chronic hematochezia and tenesmus continuing for 3 months was referred to the Veterinary Medical Center of the University of Tokyo (VMC-UT). A colorectal polyp was identified by rectal palpation. No other abnormalities were observed upon physical examination. The serum C-reactive protein level was elevated (9.0 mg/d*l*), whereas the complete blood cell count (CBC) and other biochemical parameters were within the normal ranges. Colonoscopy revealed a large solitary pedunculated polyp localized in the colorectal mucosa approximately 7–8 cm from the anus and a roughly thickened colonic mucosa (Fig. 1A). The polyp was resected by polypectomy and histopathologically diagnosed as an ICRP (Fig. 2A). The dog was treated with prednisolone (1 mg/kg SID) for 4 weeks, and the dose was tapered (0.5 mg/kg SID). Cyclosporine (5 mg/kg SID) was subsequently added on day 124, because recurrence of the polyp was observed. However, hematochezia did not improve, and the polyp was

*CORRESPONDENCE TO: OHNO, K., Department of Veterinary Internal Medicine, Graduate School of Agricultural and Life Science, The University of Tokyo, 1–1–1 Yayoi, Bunkyo-ku, Tokyo 113–8657, Japan.
e-mail: aohno@mail.ecc.u-tokyo.ac.jp

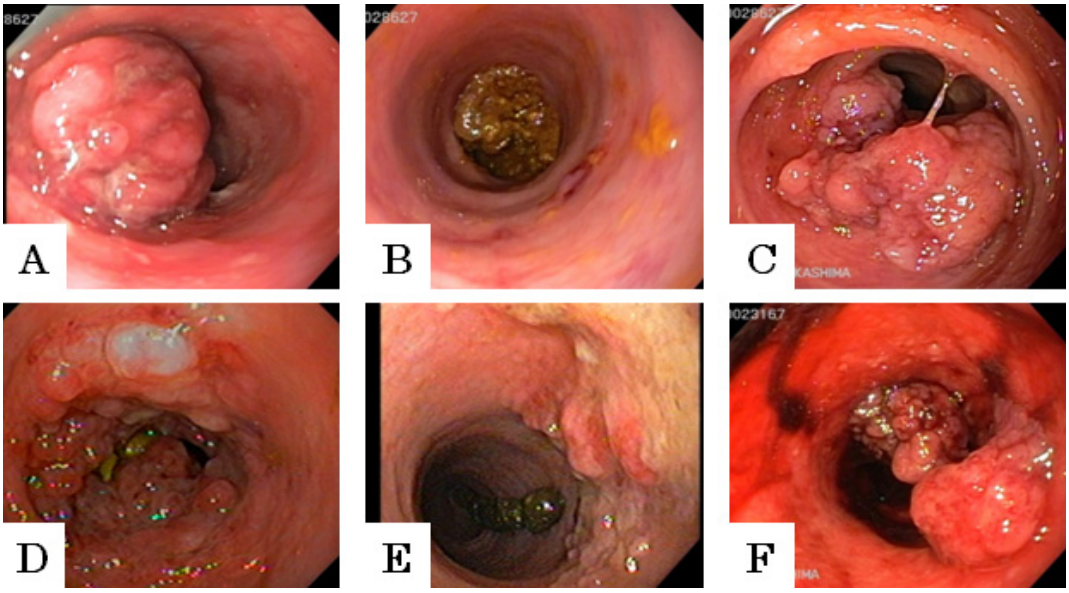

Fig. 1. Endoscopic findings in the colorectal region. Case 1 (A, B, C) and case 2 (D, E, F). (A) Before treatment of the polyp (day 1). A large solitary pedunculated polyp was observed. (B) The colorectal lesion after the treatment with prednisolone and leflunomide (day 524). (C) Enlargement of the polyp (day 848). (D) Before treatment of the polyps (day 1). (E) Colorectal lesions after treatment with prednisolone and cyclosporine (day 75). Multiple diffuse small polyps remained despite resolution of the clinical signs. (F) Enlargement of the polyps (day 1,268).

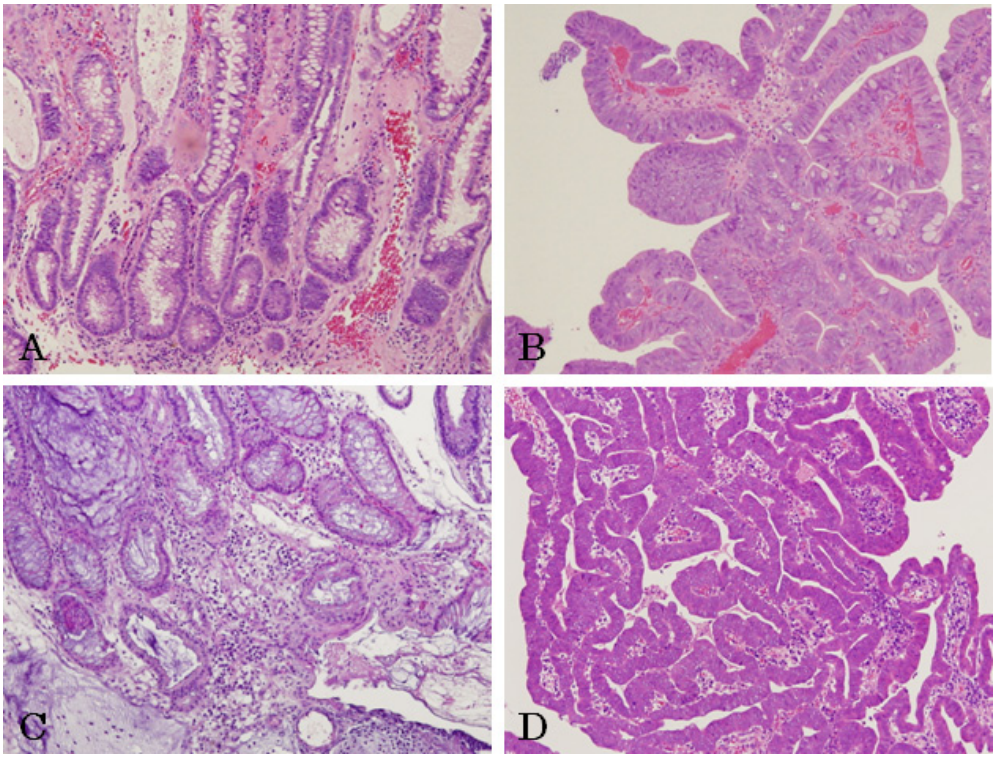

Fig. 2. Histopathological findings of the colorectal polyps. Case 1 (A, B) and case 2 (C, D). (A, C) The polyps at the initial diagnosis (day 1 of each case). Epithelial proliferation, mucus overproduction, severe fibrosis, mild edema and hemorrhage in the lamina propria and moderate to severe neutrophil and macrophage infiltration were observed; no dysplasia or neoplastic changes were observed. (B, D) The polyps resected by the second polypectomy (day 848 of case 1 and day 1,268 of case 2). Neoplastic papillary proliferation of epithelial cells with moderate dysplasia was observed. Hematoxylin-eosin stain, ×100.

enlarged. Therefore, we started treatment with prednisolone (0.5 mg/kg SID) and leflunomide (4 mg/kg SID) on day 222, which resulted in gradual improvement of the clinical signs and polyp. We repetitively performed colonoscopy and observed the gross reduction of the polyp on day 295, 330, 428 and 524 (Fig. 1B). Prednisolone was then tapered (0.5 mg/kg every other day) on day 524.

On day 615, the dog re-presented with recurrence of a large solitary polyp at the same position. On day 762, polyp enlargement and hematochezia recurrence were observed. The treatment was then changed to firocoxib (5 mg/kg SID); however, the signs and size of the polyp worsened. A second endoscopic polypectomy was performed on day 848 (Fig. 1C). Histopathologically, the polyp was diagnosed as an adenoma (Fig. 2B). We treated the case with piroxicam (0.3 mg/kg SID) for another 4 months; however, the polyp relapsed at the same location, and the clinical signs remained. Subsequently, on day 967, we returned the treatment to prednisolone and leflunomide and followed the case until day 995 (final day of this report). Although the clinical signs had resolved, the growth of the polyp was not controlled sufficiently; therefore, we planned to perform repetitive polypectomy, argon plasma coagulation or surgical methods.

Case 2: An 8-year-old intact male miniature dachshund with chronic hematochezia and tenesmus continuing for 2 months was referred to the VMC-UT. Multiple colorectal polyps were identified by rectal palpation, whereas a physical examination, CBC, biochemical test and thoracoabdominal radiography did not reveal any other abnormalities. Colonoscopy was performed and revealed multiple diffuse small polyps localized at the colorectal mucosa (Fig. 1D). Parts of the polyps were resected by polypectomy and diagnosed as ICRPs (Fig. 2C). The dog was treated with prednisolone (0.7 mg/kg SID, tapered to 0.35 mg/kg SID on day 42). Cyclosporine (7 mg/kg SID) was subsequently added, because little response was observed. The clinical signs then resolved within 4 weeks, but the polyps did not resolve completely (Fig. 1E). We followed the case, performing colonoscopy every 3 months over 3 years to evaluate the polyps; however, the gross findings did not change during this time. Based on the histopathological examination results, the polyps were diagnosed as ICRPs on day 547 (data not shown).

On day 1,268, the dog presented with a recurrence of hematochezia and enlargement of the polyps; therefore, a second endoscopic polypectomy was performed (Fig. 1F). Histopathologically, the polyps were diagnosed as an adenoma (Fig. 2D). After the procedure, recurrence of hematochezia and enlargement of the polyps were identified, and the polyps were resected by a third polypectomy on day 1,422; the histopathological diagnosis was adenoma, and the treatment was changed to firocoxib. We administered consecutive firocoxib treatments to the dog for an additional 6 months until day 1,611 (final day of this report). The gastrointestinal clinical signs were controlled successfully in this period, and the colonoscopic findings revealed no progression of the polyps.

We experienced 2 cases of polypoid adenomas developing secondary to ICRPs in miniature dachshunds. Both cases were initially diagnosed as ICRPs and responded to immunosuppressive therapy. However, adenomas subsequently occurred at the same lesions, suggesting that the polypoid adenomas were derived from ICRPs in both cases. The possibility of the existence of an adenoma at the initial diagnosis cannot be excluded. However, it is unlikely based on the following facts: histopathological examination was performed using large samples collected by polypectomy, clinical improvement and reduction of polyps with immunosuppressive therapy were clearly observed, and there was a sufficient amount of time after initial diagnosis for an adenoma to develop.

In humans, the association between inflammation and oncogenesis is well established and supported by many lines of evidence from genetic, pharmacological and epidemiological data. Young-age onset, long disease duration, extensive colonic involvement, concomitant inflammatory manifestations and a family history of colorectal carcinoma are established risk factors for IBD-related colorectal carcinoma [10]. It is reported that 18% of IBD (ulcerative colitis) patients develop colorectal carcinoma within 30 years of onset and that >50% of these patients will die from cancer [4, 16]. Chronic inflammation induces the production of various proinflammatory and inflammatory cytokines and chemokines; this results in the activation of transcriptional factors, such as nuclear factor-κB (NF-κB), signal transducer and activator of transcription 3 (STAT3) and activator protein-1 (AP-1), which regulate genes that control numerous processes, such as cell proliferation, tumor growth, resistance to cell death, angiogenesis and tumor progression and invasion [16]. In veterinary medicine, evidence of the association between gastrointestinal inflammation and oncogenesis is limited and controversial. In the present cases, both dogs initially responded to immunosuppressive therapy, but did not achieve complete resolution of ICRPs for long periods. Therefore, this might have played a role in the development of adenoma. Further studies are needed to investigate the association between persistent inflammation and malignant changes in ICRPs in miniature dachshunds. In addition, given that it has already been reported in humans [16, 18], the possibility of further progression to carcinoma, which has been suggested in dogs (but not proven), should be examined.

Administration of immunosuppressive or immunomodulatory agents is also thought to be another cause of oncogenesis, as they may suppress antitumor immune responses, especially at the early stages of tumor formation when tumors are small enough to be eliminated by the host immune response [16]. In the present cases, we used prednisolone, cyclosporine, firocoxib and/or leflunomide to control the clinical signs of ICRPs. There is 1 report suggesting that cyclosporine has oncogenicity in rat kidneys [14], whereas no evidence of oncogenicity in the gastrointestinal tract has been reported for other agents. However, the possibility that immunosuppressive therapy contributed to oncogenesis cannot be excluded.

In summary, we described how adenomatous colorectal polyps developed secondary to ICRPs in 2 miniature dachshunds over a long period of time. In a previous retrospective study, we briefly reported that 1 of 30 miniature dachshunds

with ICRP developed adenoma [12]. However, since a sufficient amount of time for adenoma development had elapsed after initial diagnosis in both cases, the possibility that other miniature dachshunds with well-controlled ICRPs would develop tumors in the future cannot be excluded. Therefore, we consider that the long-term prognosis of ICRP could not be confirmed simply as good. Because it is too difficult to distinguish adenomas from ICRPs macroscopically, careful follow-up seems to be important and repetitive biopsy is recommended when enlargement of polyps or recurrence is identified in miniature dachshunds with ICRPs. In addition, it might be better to consider removing the polyps by surgical methods, endoscopic polypectomy or argon plasma coagulation, another therapeutic option that we previously reported for refractory cases of ICRPs in miniature dachshunds [17], if the response to immunosuppressive therapy is insufficient. Further investigations of the long-term prognosis of miniature dachshunds with ICRPs in large-scale cohort studies are required.

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