Gut microbiota and relevant abundances of *Prevotella copri*, Lachnospiraceae, *Collinsella*, *Helicobacter cinaedi*, *Desulfovibrio,* and *Escherichia coli* among cats with *Pemphigus foliaceus*

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Abstract

The cat gut-inhabitant conjoint microbiota is a peculiar ecosystem in relationship with several bodily functions and immunity. Gut microbiota dysbiosis could participate within autoimmune disease pathogenesis, whereas its niche, whether causative or influencing role regarding systemic immunity in autoimmune diseases, remains fugitive. The purpose of the present study was to identify gut microbiota alterations and probable mechanisms that participated in *the development of Pemphigus foliaceus for a better understanding of future effective therapeutical armamentarium based on* gut microbiota. In the present article, the authors investigated gut microbiota alterations to those of eight cats diagnosed with Pemphigus foliaceus. Furthermore, the study thoroughly analyzed pathogenic bacteria species as triggers of autoimmunity. The diagnostic algorithm involved two distinct sides: i) on referral with the first criteria was proof of evidence for possible autoimmunity, and ii) Pemphigus foliaceus diagnosis with relevant analytes. A total of eight cats were enrolled, and gut microbiomes were detected by the use of the MIDOG All-in-One Microbial Test targeting Next-Generation DNA Sequencing. By this methodology, we analyzed the dysbiosis network for bacterial kingdoms and determined the relationship between disease activity related to *Pemphigus foliaceus* and gut microbiota. The data showed increasing abundances of *Collinsella*, Lachnospiroceae, and *Escherichia coli* and decreasing *Desulfovibrio piger*, *Prevotella copri,* and *Helicobacter cianedi* among cats with pemphigus foliaceus. For the first time in Turkey, the gut microbiota of cats with pemphigus foliaceus were detected, the results of which could be cautiously taken into consideration for novel and effective therapeutical approaches.

Keywords: Cat; Microbiota; Pemphigus.

Introduction

Autoimmune diseases are composed of an assorted cloud of disorders presented by abnormal B/T cell reactivity to normal host tissue (Arbuckle *et al*., 2003; Mu *et al*., 2020; Volkov *et al*., 2020). For the vast majority of this group of disorders, frequently recognized immunological reflection is autoantibody production, allowing clinicians to provide important biomarkers for diagnosis, classification, and activity of disease (Arbuckle *et al*., 2003; Mu *et al*., 2020; Volkov *et al*., 2020; Psetsky, 2023). Infection has been postulated as a frequent common trigger of autoimmunity, whereas gut microbiota might influence pathogenesis (Ercolini *et al*., 2009; Christovich and Luo, 2022; Qui *et al*., 2019; Xu *et al*., 2019).

The core microbiome pool of the intestine has been detected to alter disease conditions (Christovich and Luo, 2022) in association with the stage of systemic lupus erythematosus participation of regulatory B (Breg) cells altered. Given the onset of the disease, the latter cells exhibited protection, whereas later on, they seemed to aggravate the condition (Mu *et al*., 2020). This data is linked to the B cells' tendency to exhibit autoantigens to T cells and existing autoantibodies (Jacob and Stohl, 2010; Dörner *et al*., 2011). Moreover, bacteria appeared to participate in this protection, through which oral usage of bacterial DNA was capable of inducing Breg cells and diminished autoimmunity (Mu *et al*., 2020). It was suggested that the selected gut microbiota pool of lupus-prone mice contributed to pathogenesis (Johnson *et al*., 2020). Fecal microbiota transplantation showed that the female microbiota fostered, whereas male ones deliberated the disease (Johnson *et al*., 2020). There still exists a question of whether alterations in gut microbiota composition have a causality or effective interaction with systemic lupus erythematosus and even if it contributed to the onset of the disorder or aggravated disease activity (Mu *et al*., 2020). Moreover, there is lacking data regarding the relationship between gut microbiota and pemphigus foliaceus among cats, which prompted us to perform this study aiming at this route.

Material and methods

The diagnostic algorithm involved two distinct sides. On referral, the first (I.) criterion was proof of evidence for possible autoimmunity (Huve *et al*., 2020) (Table 1). Any cat that met this criterion was enrolled in this study.

Cats enrolled in the present study were retrospectively archived between February 2017 and May 2022. Other relevant diagnostic criteria (II.) were previously described (Bizikova and Burrow, 2019).

Data regarding lesion location/distribution, the existence of systemic clinical findings, therapy outcome, and duration of the follow-up period were all recorded by a well-experienced assistant and simultaneously extracted to an Excel sheet.

Sampling procedure

Microbiome analysis was conducted using collected fecal material. Experienced veterinary surgeons participated in manual withdrawal of gaita through rectal swabbing at a veterinary healthcare setting (Aydin Adnan Menderes University, Faculty of Veterinary) (Ural *et al.*, 2023). Briefly, test material obtained from Midog Center was composed of sterile swabs, which were used to take rectal sampling. The MiDOG® All-in-One Microbial Test, executed at the MiDOG® Test Center located in Irvine, CA, is recognized for its precise NextGeneration DNA Sequencing capabilities. This analytical service is adept at pinpointing and profiling unique molecular patterns that are indicative of specific microbial entities. Ensured by rigorous methods of sample preservation and transport by our investigative team, the process includes comprehensive DNA extraction from the entirety of the microbial population in the specimen. This is succeeded by the selective amplification of microbial DNA and subsequent sequencing using cutting-edge technologies provided by Illumina (Illumina, Inc., San Diego, CA). The data processing is conducted through well-maintained microbial databases, which facilitate the accurate alignment of DNA sequences, thereby enabling the precise identification of fungi down to the species level within the sample. The absence of fungal detection in the sample could be attributed to an extremely low microbial load or a diminutive concentration of microbial DNA.

Mycobiome analysis-methodology

The MiDOG® All-in-One Microbial Test is denoted as a targeted, Next-generation DNA sequencing testing. This testing service is capable of identifying molecular signatures dedicated to the identity and character of a specific microorganism. The latter test is based on safeguarded preservation and transportation of obtained samples (by our research group), thoroughly extracted DNA (from entire microbes that existed within the specimen), selected am-

plification of microbial DNA followed by Next-generation DNA sequencing [by use of the latest/novelty technologies from Illumina (Illumina, Inc., San Diego, CA). Data maneuver is performed via curated microbial databases to align DNA sequences accurately to ensure precise and accurate (species-level) identification of all fungi present in the collected sample. Even if no fungal species were detected, relevant reasons should, therefore, involve a very low microbial load and/or low concentration of microbial DNA within the sample sent to the testing center. Briefly, Each specimen was immediately secured in DNA/RNA Shield™ (supplied by Zymo Research Corp.; Catalog No. R1108, Irvine, CA, USA) and remained there until it was time for processing at MiDOG LLC's laboratory located in Tustin, CA, USA. The ZymoBIOMICS™-96 DNA kit (Catalog No. D4304, Zymo Research Corp., Irvine, CA, USA) was utilized to purify the genomic DNA. Zymo Research Corp. handled the library construction and subsequent data interpretation for microbial assessments, employing the Quick-16S NGS Library Prep Kit (Catalog No. D6400, Zymo Research Corp., Irvine, CA, USA) and making necessary adaptations. The primer sequences, exclusive to MiDOG LLC, are designed to amplify the 16S rDNA V1–V3 regions for bacteria and the ITS-2 regions for fungi. Sequencing was undertaken with the Illumina HiSeq 1500 system, followed by data curation using the Dada2 (R package version 3.4). Microbial composition was quantified as a percentage relative to the aggregate sequence count per sample. The comparative abundance of bacteria and fungi was estimated by equating a single 16S rDNA instance to one fungal ITS copy. The precision at the species level afforded by the sequencing technique herein has been corroborated by prior shotgun sequencing studies (Callahan *et al.,* 2016; Tang *et al.,* 2020).

Antinuclear antibody (ANA) and other clinical assessments were done using a routine clinical and laboratory approach. Our research was conducted as part of routine clinical evaluations and involved obtaining informed consent forms from the animal owners after providing them with the necessary information. All cases were represented individually, and the relative abundance of microbial diversity was represented in graphs using Microsoft Excel (Office 365).

Results

In a total of eight cats from various breeds at the age of 2 to 7 years old of both sexes (5 female and two male) diagnostic tree with clinical findings and their distribution based on individual (Figure 1) along with *Pemphigus foliaceus* lesion distribution diagram (Figure 2), clinical photos (Figure 3-5) and

gut microbiota analytes (Figure 6-11) at phylum, genus, family and species level with special reference to abundant bacterial agents. For the diagnosis of *Pemphigus foliaceous,* the method recommended by Bizikova *et al.* (2019) was adopted (Table 1).

Table 1. The second diagnostic tree (Huve *et al.*, 2020) on behalf of referral to our clinic with a presumptive diagnosis of autoimmune dermatitis among cats herein involved. These criteria were adopted in an attempt to exclude cases with *Pemphigus foliaceus.*

Pemphigus foliaceous diagnosis (Bizikova* *et al.*, 2019) was adopted in this study.	clinical proof of superficial pustule/erosion or crust
	b) unresponsive antibacterial trial (21 days and above)
	microscopical evidence of acantholytic cells [histopathology or cytology]
	monitorization for 90 days or more

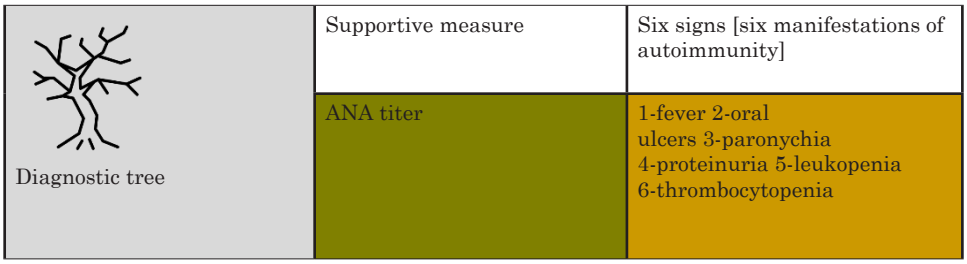

Figure 1. First diagnostic tree (Huve *et al.*, 2020) on behalf of referral to our clinic with a presumptive diagnosis of autoimmune dermatitis among cats herein involved.

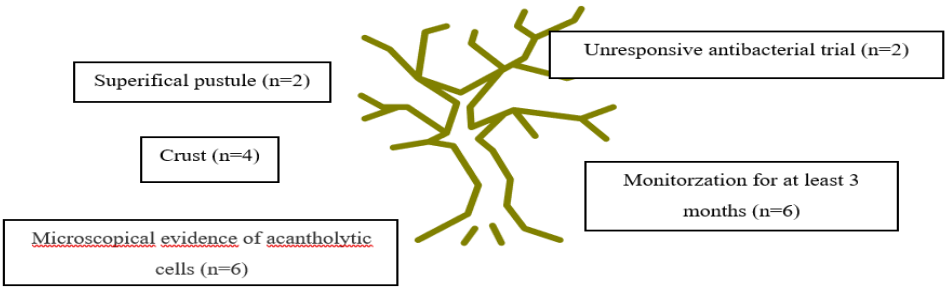

Figure 2. Diagnostic tree with lesional invasion mapping of individual distribution.

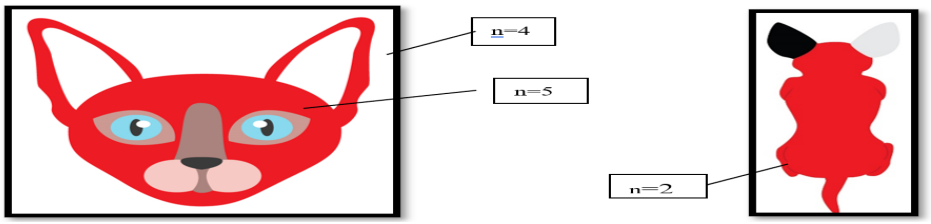

Figure 3. Feline *Pemphigus foliaceus* lesion distribution diagram and individual data regarding lesional distribution in a total of 8 cats involved herein.

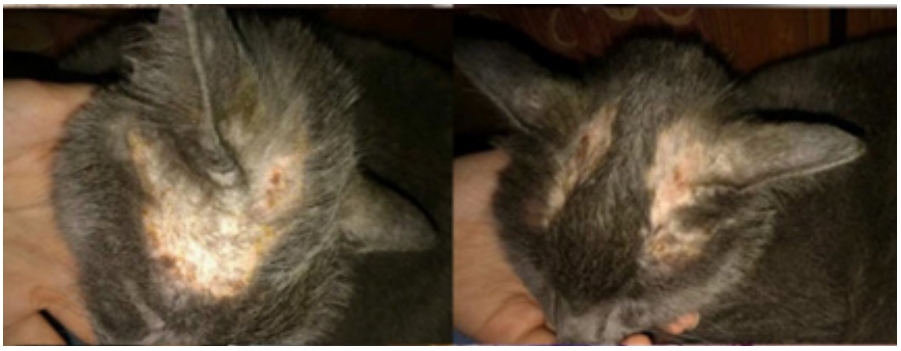

Figure 4. One of the eight cats involved presenting clinical photos depicting characteristic dermatological invasion with multifocal coalescing erosions and crusts on the face.

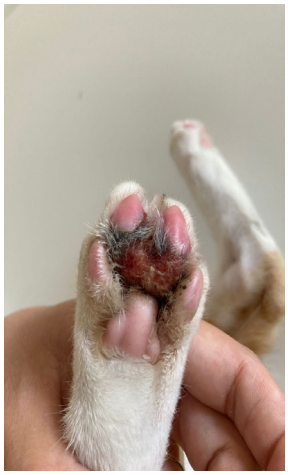

Figure 5. Thick crusting and eroded pustules on a pawpad of a cat involved herein.

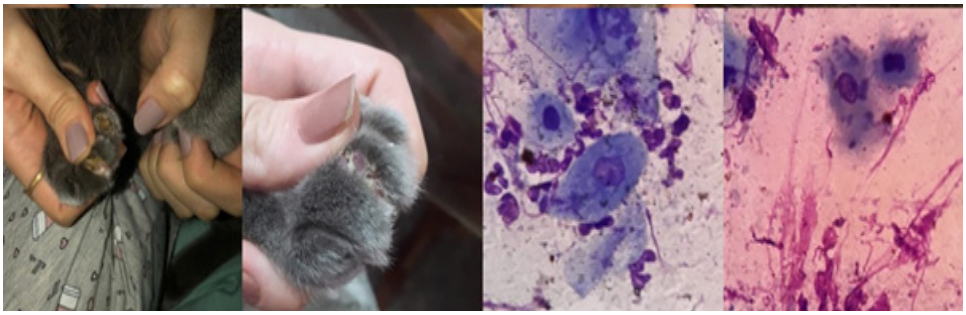

Figure 6. As a part of the diagnostic tree and algorithm adopted in this study, a) and b) paronychia (on the first occasion detective sign) and c) and d) acantholytic cells on microscopy were evident in a cat involved in this study.

k_Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Prevotellaceae;g__Prevotella;s__copri							
0.2%	0.0%	0.2%	1.3%	0.0%	0.3%	0.0%	0.0%

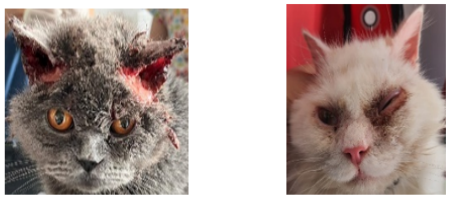

Figure 7. Relative abundance of *Prevotella copri* among cats involved herein.

k__Bacteria;p__Proteobacteria;c__Deltaproteobacteria;o__Desulfovibrionales;f__Desulfovibrionaceae;g__Desulfovibrio;s__piger							
0.3%	0.0%	0.0%	0.0%	2.3%	0.0%	0.0%	0.0%

Figure 8. Relative abundance of *Desulfovibrio piger* among cats involved herein.

k__Bacteria;p__Proteobacteria;c__Epsilonproteobacteria;o__Campylobacterales;f__Helicobacteraceae;g__Helicobacter;s__cinaedi								
0.2%	0.0%	0.5%	0.2%	0.0%	0.0%	0.0%	0.7%	0.0%

Figure 9. Relative abundance of *Helicobacter cinaedi* among cats involved herein.

k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae							
47.4%	2.4%	22.3%	4.7%	25.1%	28.7%	2.3%	5.3%

Figure 10. Relative abundance of *Lachnospiraceae* among cats involved herein.

k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Enterobacterales;f__Enterobacteriaceae;g__Escherichia;s__coli							
7.3%	1.3%	0.2%	3.5%	2.1%	6.2%	0.8%	5.3%

Figure 11. Relative abundance of *E. coli* among cats involved herein.

k__Bacteria;p__Actinobacteria;c__Coriobacteriia;o__Coriobacteriales;f__Coriobacteriaceae;g__Collinsella							
0.0%	0.1%	18.9%	4.4%	16.9%	0.0%	3.1%	1.2%

Figure 12. Relative abundance of *Colinsella* among cats involved herein.

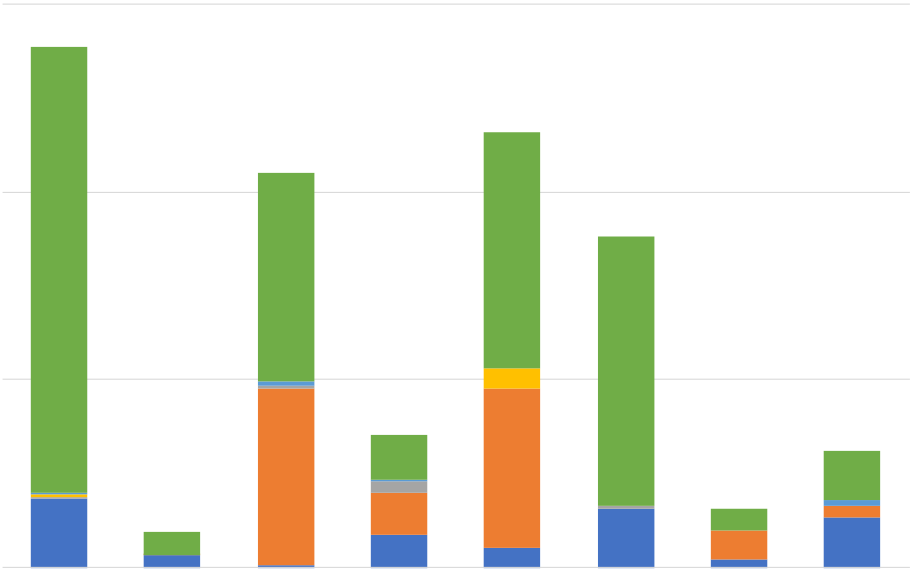

Figure 13. Relative abundances at selected family, genus, and species levels.

Documented clinical findings across the feline subjects were as follows: two exhibited superficial pustules, two others were non-responsive to antibacterial treatment protocols, crust formations were evident in four subjects, and acantholytic cells were detected microscopically in six cases. Figure 4 illustrates a characteristic dermatological manifestation in one feline, presenting with multifocal coalescing erosions and crusts on the facial integument. In Figure 5, we observe substantial crusting and eroded pustules on a paw pad, whereas Figure 6 displays the microscopic visualization of acantholytic cells. Figures 7 through 13 delineate the relative bacterial abundances identified within each case, providing a comprehensive overview of the bacterial profiles encountered in this cohort.

Discussion

As two distinct sides of the diagnostic tree were deemed available in this study (Figure 1 and Table 1), those cats with a presumptive diagnosis of autoimmunity were subjected to ANA titer, which gave positive results. On the other side, classical and mostly adorable clinical signs (Faircloth and Montgomery, 1981; Gabbert, 1983; Scott, 1984; Bennett and Nash, 1988; Pedersen and Barlough, 1991; Day, 1996; Vitale et al., 1997) of systemic lupus erythematosus [i.e., proteinuria and anemia were not evident in any of the cats involved] were not entirely evident. In contrast, cutaneous lesions were evident, mimicking Pemphigus foliaceous on the first occasion, which was then supported by diagnostic tree modality (Table 1 and Figure 12). This diagnostic tree (Figure 1 and Table 1) approach and its consequences (Figures 2 and 3) would have helped veterinary surgeons in field conditions with limited access to diagnostic approaches and laboratory facilities.

Given autoimmune disorders, i) digressive building of autoantibodies, ii) genetic and/or environmental factors [resulted within anomalous existence of autoantibody-producing B cells, autoreactive T cells, and proinflammatory cytokines], iii) hefty shifts among gut microbiome (Xu *et al*., 2019) are all involved within the pathogenesis as usual suspects. Dietary alterations and frequent usage of antibiotics all contribute to the disease state by altering the gut microbiome (Xu *et al*., 2019), of which two factors were evident in all diseased cats herein involved in the present study. Intriguingly, none of the cats were presented to our clinic without previous antibiotic usage. Briefly, all diseased cats were undernourished with high carbohydrate commercial diets (at least % 42; with different brands composed of 42 to 58% carbohydrate) in the pres-

ent study. Taking into account that a rapid and efficacious immune response is demanding, as the body could demolish viral pathogens and combat infection, clinicians must at least understand the relationship between insulin and the immune system. It was suggested that an association had been evidenced among insulin resistance, chronic inflammation, and poor immune response. A group of researchers from Toronto postulated that immune cells, denoted as T cells presented in abdominal fat, exhibited proinflammatory responses, negatively influencing the body's responsiveness to insulin (Tsai *et al*., 2018). As all cats herein involved were fed with high carbohydrates, insulin response might be abolished (although not analyzed), which could have participated in chronic inflammation.

Another interesting study was focused on the hypothesis that the gut microbiota bestow the ordinance of glucose metabolism (in pregnancy). Given the abundance of the genus *Collinsella*, which has been correlated with circulating insulin levels, the factors determining Collinsella's abundance have to be clarified. The latter study aimed to validate the correlation between *Collinsella* and insulin; therefore, the interpretation of whether macronutrient intake alters *Collinsella* abundance. In that study, *Collinsella* abundance positively exhibited a correlation with circulating insulin, whereas it negatively correlated with dietary fiber intake. According to the results obtained, low dietary fiber may hasten Collinsella's abundance (Gomez-Arango *et al*., 2018). As-fed, caloric basis (g/100 kcal) high fiber (3.1) or low-fiber (0.1) were defined in a prior study (Bennett *et al*., 2006). Comparatively, all eight cats involved in this study were fed high carbohydrate-low fiber diets (data not shown due to several different brands), which could all contribute to the overgrowth of *Collinsella* with autoimmune dermatitis in the present study. Relative abundances of *Collinsella (0.0 to 18.9%)* were strikingly high in 5 out of 8 cats involved herein.

Novel research exhibited a probable association between selected Gram-negative anaerobic bacilli and rheumatoid arthritis occurrence in people. The primary periodontal disorder caused by *Porphyromonas gingivalis* (Liao *et al*., 2009; Mikuls *et al*., 2009), followed by and the second is the prevalence of *P. copri* among gut microbiome (Scher *et al*., 2013). In the present study, out of 8 cats involved, 4 of those exhibited increased relative abundances of *P. copri* (Figures 7 and 13).

In the present study, solely *P. copri* (Figures 7 and 13) was evident among diseased cats herein involved. In humans with rheumatoid arthritis, low di-

versity, and gut microbiota exhibited significant participation within disease status (Chen *et al*., 2016; Scher *et al*., 2013), to those of which *P. copri* existed within the pathogenesis. The microbiota analytes presented elevated *P. copri* in new-onset untreated rheumatoid arthritis in comparison to healthy people. *P. copri* is capable of invigorating T-helper 1 cells in the new-onset untreated rheumatoid arthritis group through synthesizing 27 kD protein, consequently influencing the prognosis of the disease. The latter compound is a bracing abundance of specific immunoglobulin A (IgA) and immunoglobulin G (IgG) antibodies (Pianta *et al*., 2017). On the other hand, the latter negative outcome occurred strain-dependently. Moreover, mice with experimentally induced arthritis exhibited *Prevotella histicola*, which impedes the insurrection of arthritis, positively influencing rheumatoid arthritis (Marietta *et al*., 2016).

In the present study, among cats with pemphigus foliaceus *P. copri,* abundance was between 0.2 to 3.2% (Figures 7 and 13). A novel survey published in November 2022 detected the fecal microbial communities, denoting the core microbiome of North American domestic cats. According to the latter study, 30 different bacteria were found in the fecal microbiomes of most cats. The composition of the fecal microbiome depended on the diet of the cat, their age, and whether the cat lived in a private home or a shelter. In that study, 30 core bacterial genera were detected, including *Prevotella*, *Bacteroides*, *Collinsella*, *Blautia*, and *Megasphaera*, with vast majority abundances (Ganz *et al*., 2022). In the present study, 5 out of 8 diseased cats were female; a similar study in mice showed that, among mice, male androgens exhibited impaction on the gut microbiome, leading to diminished immunoreactivity and declined susceptibility against autoimmune diabetes (Gomez-Arango *et al*., 2018). Rheumatoid arthritis is more frequent among females, probably in association with the microbiota (Yurkovetskiy *et al*., 2013).

Given detailed literature corresponding to gut microbiota linked to autoimmunity, MRL/*lpr* mice subjected to mixed antibacterial intervention post-disease onset presented extended lupus-like clinical signs along with elevated *Lactobacillus spp.* and diminished Lachnospiraceae (Mu *et al*., 2017). Moreover, it was suggested that *Lactobacillus* spp. is good while Lachnospiraceae is bad (Mu *et al*., 2017; Christovich and Luo, 2022). In the present study, Lachnospiraceae abundance was significantly high (ranging from 2.3 to 47.4%), indicating the role of this bacteria. The genera of the Lachnospiraceae family, as members of the Firmicutes phylum, are owned by core gut microbiome participate as the vast majority of SCFAs producers (Vacca *et al*., 2020). The human gut has been

detected to exhibit various dominant genera [i.e., the Lachnospiraceae family composed of *Blautia, Roseburia, Lachnospira*, and *L.Ruminococcus]* (Vacca *et al*., 2020) with anti-inflammatory and immunomodulatory efficacy (Abdugheni *et al*., 2022). Arousing interest in the investigation of Lachnospiraceae's participation in the maintenance of intestinal homeostasis is evident. In a prior study composed of 20 humans, systemic lupus erythematosus, diminished Lachnospiraceae, and Ruminococcaceae were detected at the remission stage (Hevia *et al*., 2014). In contrast, in our study, all diseased cats were exhibiting active clinical signs, suggesting not the remission stage but probably the active stage of disease, which could briefly explain the increased relative abundance of Lachnospiraceae for combatting anti-inflammatory efficacy or immune defense in an attempt to overwhelm disease.

In the present study, those cats enrolled with *Pemphigus foliaceus, P. copri*, Lachnospiraceae, *Collinsella*, *Helicobacter cinaedi,* and *Escherichia coli* were exhibited with varying degree of abundances (Figure 7-13). A similar study on systemic Lupus Erythematosus corresponds to elevated intestinal permeability, consequently causing upgraded systemic microbial exposure. Thus, diminishing microbial exposure or modulating barrier function could guide treatment interventions for Systemic Lupus Erythematosus patients (Petri, 2007). Moreover, gut microbiota-focused medical interventions might be beneficial (Li *et al*., 2019). Pronounced dysbiosis of the gut microbiota has been linked to active and remissive Systemic Lupus Erythematosus cases, which may have helped diagnose and predict the activity of the disease. It has been well recognized that systemic lupus erythematosus is associated with dynamic alterations of the gut microbiota in parallel line with disease activity. Dysbiosis in relationship with the latter disease involved the genera *Streptococcus, Campylobacter*, and *Veillonella* in positive correlation with lupus activity (Li *et al*., 2019).

In the present study, the relative abundance of several bacteria was altered, with significant abundances of *E. coli* and Lachnospiraceae (Figure 7-13). In a well-designed research study that attempted to highlight the concept of gut dysbiosis could participate in disease onset in rheumatoid arthritis, DQ8 mice were orally administered with rheumatoid arthritis-associated (*Eggerthella lenta*/*Collinsella aerofaciens*) and non-associated (*Prevotella histicola*/*Bifidobacterium* spp.) bacteria on alternate days for a week in naïve mice. The rheumatoid arthritis-associated bacteria elevated intestinal permeability, whereas rheumatoid arthritis non-associated bacteria surmount other relevant rheu-

matoid arthritis-associated bacteria even if gavaged/cultured together. To those mice administered with rheumatoid arthritis, non-associated bacteria exhibited lower levels of proinflammatory cytokines, suggesting that intestinal commensal bacteria impact immune responses by altering gut permeability and immunity. Dysbiosis might have helped the growth of rheumatoid arthritis-associated bacteria along with diminished beneficial bacteria (Balakrishnan *et al*., 2019).

In the present study, the relative abundance of *E. coli* was significantly increased (ranging from 0.2 to 7.3%), probably causing increased permeability among autoimmune diseased cats herein enrolled. Given obesity modality among rodents, *E. coli* elevated intestinal permeability and circulating levels of bacterial lipopolysaccharide, which could all contribute to systemic low-grade inflammation (Cani *et al*., 2008). Increased abundance of *E. coli* was also determined among humans with type 2 diabetes mellitus (Qin *et al*., 2012).

Conclusions

This study presents the first reported findings on gut microbiota alterations in cats with pemphigus foliaceus within Türkiye. These preliminary observations offer a foundational understanding that may guide future research endeavors. The implications of these alterations in the gut microbiota could potentially inform the development of novel treatment modalities. Further studies are warranted to explore the therapeutic potential and to elucidate the underlying mechanisms that could contribute to the advancement of clinical management strategies for this condition.

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