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Proliferative and necrotizing otitis externa in a kitten: Case report with literature review

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ABSTRACT: Proliferative and necrotizing otitis externa (PNOE) is a rare dermatitis with unknown etiology affecting kittens between 2 to 6-months-old and adult cats. Its clinical signs are unique and diagnosis is based on skin histopathology. Lesions develop rapidly and in kittens may regress spontaneously. A 6.5-month-old, male, Siamese kitten was presented with chronic proliferative, erythematous and necrotic lesions covered with thick dark-brown keratinous debris on the concave aspect of both pinnae and the vertical ear canal leading to secondary otitis infection due to obstruction. Lesions were not pruritic or painful even though erosions and ulceration were seen focally. Previous treatment with commercial otic preparations was of no avail. Ear otoscopy could not be performed due to stenosis and ear canal cytology showed numerous bacteria intermingled with keratinocytes and debris. Radiography further confirmed ear canal stenosis. Histopathological examination revealed orthokeratotic and parakeratotic hyperkeratosis, epidermal hyperplasia with several apoptotic cells at all levels of the epidermis and neutrophilic crusts mixed with cocci. Topical treatment with 0.1% tacrolimus was prescribed twice daily and otic solutions for secondary otitis externa. Complete clinical cure was achieved two months after first admittance. This is the first report of PNOE in Greece. Topical tacrolimus appears to be an effective treatment for lesions that do not spontaneously regress.

Keywords: feline necrotizing and proliferative otitis externa

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INTRODUCTION

A unique proliferative and necrotizing otitis has been rarely reported in cats. Its etiopathogenesis is unknown. There is no evidence to link this disease with virus presence (Mauldin et al., 2007) and it may be immune-mediated since there is a demonstration of T-cell induced keratinocyte apoptosis (Videmont and Pin, 2010). It typically affects the concave pinnae and the ear canals and in some cats the preauricular region of the face (Gross et al., 2005). The skin disease is usually seen in young cats and kittens, two to six months of age. However, this disease may have a wider age range since there are few reports in three, four (Mauldin et al., 2007) and fourteen-year-old (Momota et al., 2017) cats. Lesions are typically bilateral and characterized by proliferative, erythematous and necrotic tissue that is friable and bleeds easily. A thick dark brown exudate covers lesional area and its removal reveals underlying ulcers and erosions. Bacterial or yeast colonization is typically seen with cytological examination (Mauldin et al., 2007; Videmont and Pin, 2010; Borio et al., 2012; Stevens and Linder, 2012; Momota et al., 2016; Momota et al., 2017; McAuliffe et al., 2020; Panzuti et al., 2021). Animals are otherwise healthy. In some cases, lesions can be painful or pruritic due to ulcerations and secondary infection, respectively. Lesions occur rapidly and may spontaneously regress when the cat reaches the age of twelve to twenty-four months (Gross et al., 2005; Mauldin et al., 2007; Videmont and Pin, 2010; Stevens and Linder, 2012). Diagnosis is considered easy due to its unique clinical signs and can be confirmed further with histopathological examination. Parakeratotic

hyperkeratosis, neutrophilic crusts, marked epidermal hyperplasia and hypereosinophilic and apoptotic keratinocytes with occasionally lymphocytic satellitosis are usual histopathological findings. Apoptotic keratinocytes can also be seen in the outer root sheath of hair follicles. Topical antimicrobials, antibiotherapy, oral or topical corticosteroids and hydrolyzed protein diets have been proven unsuccessful (Mauldin et al., 2007). However, three cases have been controlled with topical or systemic corticosteroids (Mauldin et al., 2007; Momota et al., 2016; Momota et al., 2017). Momota et al. (2017) hypothesized that this is maybe attributed to differences in the potency of the glucocorticoids used, or individual differences of the patients. Considering the lymphocyte-mediated etiopathogenesis, topical tacrolimus and oral cyclosporine (calcineurin inhibitors) may be of benefit in the treatment of lesions that do not spontaneously regress.

CASE DESCRIPTION

A 6.5-month-old, male, Siamese kitten was presented with 40 days history of progressive pinnal lesions. Humans and cat in contact were clinically healthy. Previous treatment with commercial otic preparations was of no avail. Additionally systemic antibiotherapy and short-term use of systemic prednisolone were ineffective. Dermatological examination revealed proliferative, erythematous and necrotic lesions covered with thick dark-brown keratinous debris on the concave aspect of both pinnae and the vertical ear canals (Figure 1a-b). No otoscopy was performed due to severe stenosis. Lesions were not pruritic or painful, but mild discomfort was seen due



Figure 1. (a) Clinical presentation showing exophytic brown, yellow and friable proliferative tissue covering erythematous and necrotic lesions on the concave pinna and the entrance of vertical ear canal. (b) Manipulation of the plaque that covers left ear led to erosions or ulcers. Thick purulent exudate is also visible

to erosions and ulceration found following debridement of the hyperplastic tissue. Ear canal cytology showed numerous bacteria intermingled with keratinocytes and debris. Radiography further confirmed ear canal stenosis (Figure 2). Two biopsy samples (6mm) were obtained from lesional areas for histopathological examination. Biopsy samples were fixed in 10% buffered formalin, embedded in paraffin and stained with haematoxylin and eosin. Histopathological examination revealed orthokeratotic and parakeratotic hyperkeratosis, epidermal hyperplasia with several scattered hyper eosinophilic cells with condensed chromatin (dyskeratotic and apoptotic cells) at all levels of the epidermis, lymphocytic exocytosis and neutrophilic serocellular crusts mixed with bacterial colonies (Figures 3-5). Superficial dermis was severely infiltrated by neutrophils, eosinophils and fewer lymphocytes, plasma cells and mast cells. Topical treatment with 0.1% tacrolimus (Protopic®, Leo Pharma) was prescribed twice daily for 14 days and otic solutions (ear cleaner and topical antibacterial) for secondary otitis externa. The owner was advised to continue with tacrolimus therapy once daily until re-exam in 3 weeks. The patient never returned for that re-examination and according to the owner topical treatment stopped after 2 weeks without tapering. Complete clinical cure was achieved two months after first admittance (Figure 6a-b). No relapse was noticed the following 4.5 months.

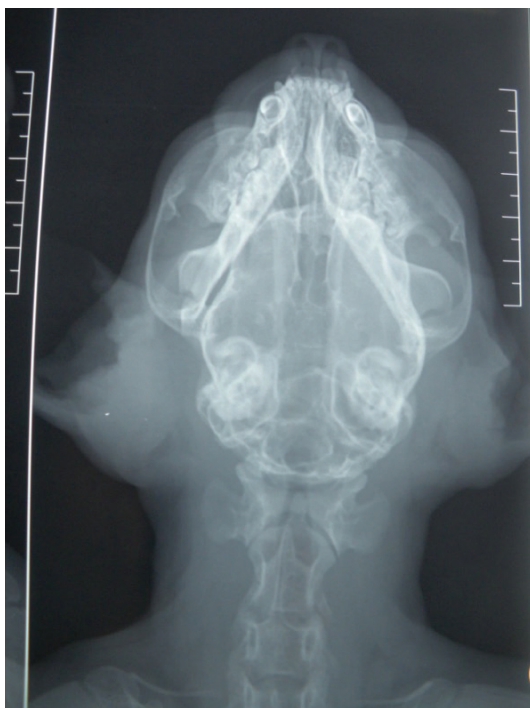


Figure 2. Vento-dorsal radiograph of the skull showing occlusion of both external acoustic canals

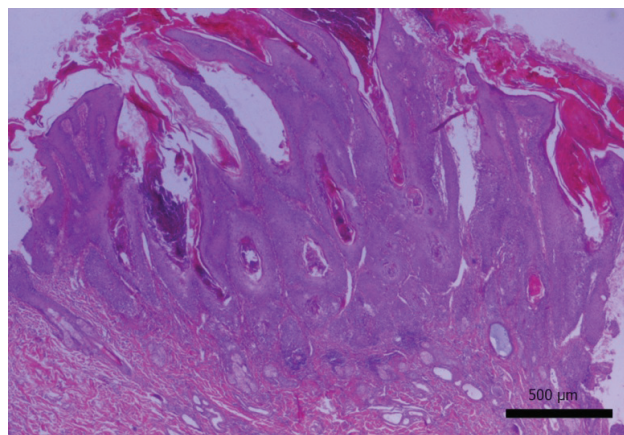


Figure 3. Severe epidermal hyperkeratosis and hyperplasia resulting in exophytic projections covered by serocellular crust. Haematoxylin-eosin staining, scale bar 500 µm

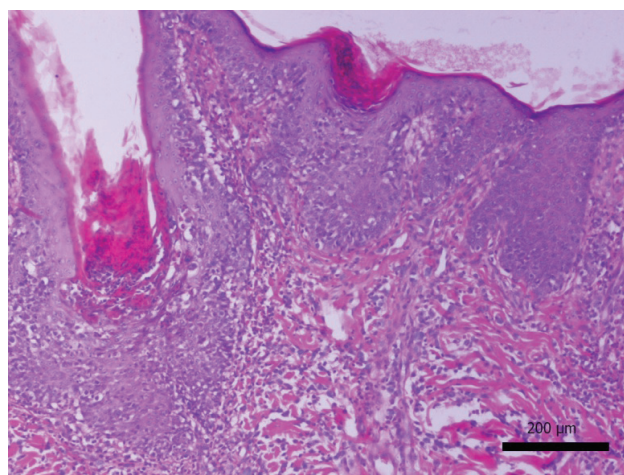


Figure 4. Epidermal hyperkeratosis and hyperplasia accompanied by inflammatory infiltration of the superficial dermis. Haematoxylin-eosin staining, scale bar 200 µm

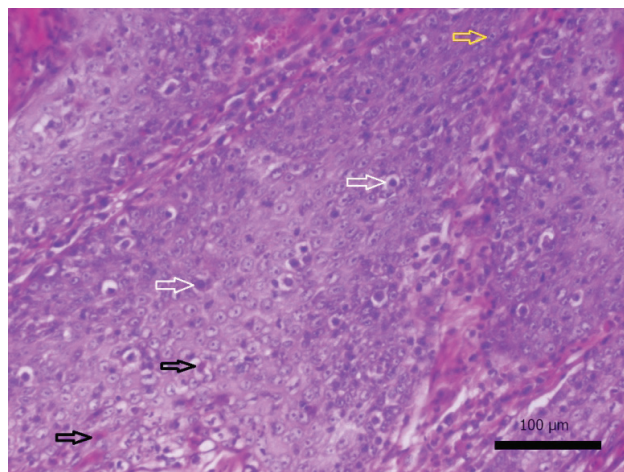


Figure 5. Epidermal hyperplasia with lymphocytic exocytosis (white arrows) and presence of apoptotic (yellow arrow) and dyskeratotic cells (black arrows). Haematoxylin-eosin staining, scale bar 100 µm

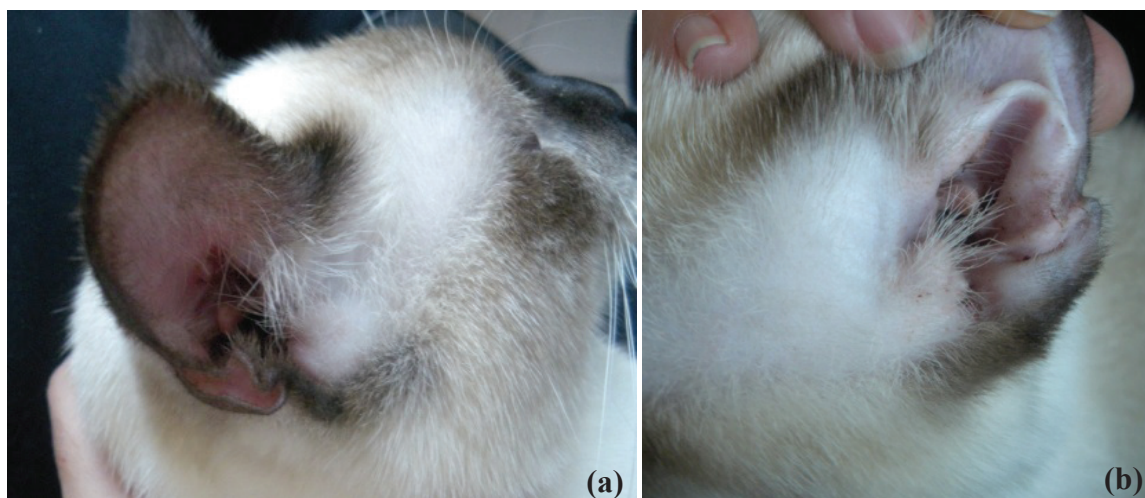


Figure 6. (a-b). Post treatment. Lesions have completely resolved

COMPREHENSIVE LITERATURE REVIEW

The literature search is summarized in Table 1. There are eight papers reporting cases of PNOE in cats. First publication was in 2007. Six publications reported a single case and two publications reported four and three cases, respectively. A total of thirteen cats with PNOE were included for review. The exact age of onset of disease was unknown for two of the cats. The others had symptoms that presented from 10 days up to 4.5 years of duration. At time of admittance cats' age ranged from 2 months to 14 years. Pruritus was reported in seven cases (7/13) and was described moderate or severe in four of them. All cats with PNOE presented proliferative ear canal lesions, except of one case (McAuliffe et al., 2020) that had only facial lesions. The aforementioned cat (McAuliffe et al., 2020) and other three cats (Panzuti et al., 2021) did not present pinnal lesions (4/13). In these three cats, extra-auricular lesions co-existed with pinnal and ear canal lesions (Panzuti et al., 2021). Cytological examination of dark thick debris confirmed bacterial colonization in 11/13 cases and yeast overgrowth only in 4/13. Key histopathological features are marked epidermal hyperplasia, hyperkeratosis and multifocal single cell necrosis of keratinocytes. In some cases lymphocytic exocytosis and satellitosis of the necrotic keratinocytes may be seen. Some authors have reported involvement of the follicular external root sheath (Mauldin et al., 2007; Videmont and Pin, 2010), while other authors have not (Gross et al., 2005). Spontaneous resolution was observed in 2 cases (15.4%, 2/13). Seven cats (53.8%, 7/13) received tacrolimus as a monotherapy or in combination with other drugs. Time to achieve complete cure ranged from 3 weeks to 12 months.

DISCUSSION

Even though more cases have been described over the years, etiology of PNOE remains unknown. At first a suggestion of virus involvement was speculated. However, no histological finding consistent with viral presence (intranuclear inclusion bodies) were ever described in any case of PNOE. In addition, in the following studies polymerase chain reaction testing for feline herpes virus was negative and immunohistochemical staining did not reveal evidence of herpesvirus, calicivirus or papillomavirus infection (Gross et al., 2005; Mauldin et al., 2007). Although evidence of viral etiology has not been found, it is possible that a virus may have triggered the reaction without persistence of the antigen or detection of the antigen with immunoperoxidase staining (Videmont and Pin, 2010). Immunologic basis of the disease is highly suspected. This hypothesis is demonstrated with immunohistochemical studies that have confirmed T-cell induced keratinocyte apoptosis (Videmont and Pin, 2010). Additionally, the lymphocytic infiltration that is described in histopathological findings and the beneficial use of immunomodulatory treatment support that suspicion. There has been some suggestion that the lesion may represent a unique drug eruption or hypersensitivity reaction, but this association remains highly speculative. In case of an adverse reaction to topicals, continuance of their use would have led to worsening of skin lesions that was never reported to any of the cases described in literature. Spontaneous remission seen in some cases supports both etiologic speculations, viral and immunologic origin.

Affected cats are otherwise healthy. Complete blood count and serum biochemistry tests done in

Table 1. Individual data of all published cases of feline PNOE, including this case.

	Age	Sex	Breed	Pruritus	Pinnal lesions	Ear canal lesions	Extraauricular lesions	Treatment	Time to reach clinical cure
Mauldin et al. 2007 Case 1	5y	MC	DSH	Yes	Yes	Yes	No	0.01% fluocinolone acetone, 0.1% tacrolimus	8-12w
Mauldin et al. 2007 Case 2	6m	FS	DSH	Yes	No	Yes	No	Interferon- α , dexamethasone PO	12m
Mauldin et al. 2007 Case 3	3y	FS	DSH	NR	No	Yes	No	0.1% tacrolimus	80% improvement in 2w then LTFU
Mauldin et al. 2007 Case 4	4y	FS	DSH	Yes	Yes	Yes	No	0.1% tacrolimus, prednisolone PO	4-5m
Videmont and Pin 2010	3m	F	Persian	No	Yes	Yes	No	0.03% tacrolimus	3w
Borio et al. 2012	2y	MC	DSH	Yes	No	Yes	No	0.1% tacrolimus	6w
Stevens and Linder 2012	7m	M	DLH	No	Yes	Yes	No	0.1% tacrolimus	Improvement in 1m then LTFU
Momota et al. 2016	5m	MC	Persian	Yes	Yes	Yes	No	Intralesional methylprednisolone acetate, 0.05% clobetasol propionate	2m
Momota et al. 2017	14y	FS	Persian	Yes	Yes	Yes	No	Mometasone furoate, triamcinolone PO, prednisolone PO, triamcinolone acetone	15w
McAuliffe et al. 2020	2m	M	DSH	Yes	No	No	face	Prednisolone PO, cyclosporine PO	Euthanasia due to other disease
Panzuti et al. 2021 Case 1	6m	F	DSH	No	Yes	Yes	abdomen, ventral neck, axillary and inguinal area, thighs, face	0.1% tacrolimus, cyclosporine PO, tacrolimus and prednisolone PO	1m -10w
Panzuti et al., 2021 Case 2	8m	F	DSH	NR	Yes	Yes	eyelids	-	\leq 6m
Panzuti et al., 2021 Case 3	5m	F	DSH	No	Yes	Yes	eyelids, face, perineum	-	2m
Present case	6.5m	M	DSH	No	Yes	Yes	No	0.1% tacrolimus	2m

y=years, m=months, w=weeks, d=days, MC= male castrated, FS= female sterilized, F=female, M=male, DSH= Domestic shorthair, DLH= Domestic longhair, NR= not reported, LTFU=Lost to follow-up

most of the cases are within normal limits. Both feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are also investigated and found negative in these cats. So far, an underlying disease has not been reported. Additionally, there are no reports of relapses in these cases that would further support hypothesis of other diseases. Moreover, none of the cases reported had history of upper respiratory tract disease, rhinitis or conjunctivitis associated with herpesvirus or calicivirus infection.

Even though PNOE has been well described there are more to understand with this skin disease. It is not an exclusive juvenile skin disease, as it was first reported, since there are newer reports with adult affected cats (Mauldin et al., 2007; Borio et al., 2012; Momota et al., 2017). Some adult cats had symptoms

presented very early in life, before or very close to 1 year of age (Mauldin et al., 2007-case 1; Borio et al., 2012), however others do not. Moreover, skin lesions are not only present on the medial aspect of pinnae and the entrance of auditory canal. Video-otoscopy of the ear canal of an affected cat without pinnal involvement revealed digitally protruding lesions extending for the entire length of the canal and growing at 360° round the ear canal (Borio et al., 2012). Furthermore, in some cats lesions can be seen in the preauricular region of the face (Gross et al., 2005) and there are new reports on extra-auricular lesions in kittens. Three kittens were described with auricular and simultaneously extra-auricular lesions on the ventral abdomen, the eyelids and the face (Panzuti et al., 2021) and one kitten with only facial lesions (McAuliffe et al., 2020). In two of these cases lesions

healed spontaneously and in one case extra-auricular lesions resolved under oral cyclosporine and relapsed pinnal lesions were controlled with topical tacrolimus. The kitten with only facial lesions was euthanized due to other disease.

Erosive and hyperkeratotic lesions are linked with analogous histological findings. Key features are marked epidermal and hair follicular hyperplasia and T-cell cytotoxic attack on keratinocytes. Numerous hypereosinophilic keratinocytes with pycnotic nuclei (dyskeratotic or apoptotic cells) are seen in the epidermis and sometimes in the outer root sheath of follicular infundibulum.

Prognosis is good. Lesions are usually non painful, non-pruritic with a mild discomfort, but excep-

tions have been described. Typically, in kittens lesions spontaneously regress. There is no specific time frame for resolution. It can be seen in few weeks after diagnosis, up to 1-2 years of age. Not all cases resolve spontaneously. Complete disappearance of lesions, with no relapses, has been reported after 2 to 3 months with topical tacrolimus. In cases where relapse was reported after initial treatment with cyclosporine, topical tacrolimus was successful. Not one affected cat died or was euthanized due to this skin disease.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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