REVIEW ARTICLE

Feline Papillomas and Papillomaviruses

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Abstract. Papillomaviruses (PVs) are highly species- and site-specific pathogens of stratified squamous epithelium. Although PV infections in the various Felidae are rarely reported, we identified productive infections in six cat species. PV-induced proliferative skin or mucous membrane lesions were confirmed by immunohistochemical screening for papillomavirus-specific capsid antigens. Seven monoclonal antibodies, each of which reacts with an immunodominant antigenic determinant of the bovine papillomavirus L1 gene product, revealed that feline PV capsid epitopes were conserved to various degrees. This battery of monoclonal antibodies established differential expression patterns among cutaneous and oral PVs of snow leopards and domestic cats, suggesting that they represent distinct viruses. Clinically, the lesions in all species and anatomic sites were locally extensive and frequently multiple. Histologically, the areas of epidermal hyperplasia were flat with a similarity to benign tumors induced by cutaneotropic, carcinogenic PVs in immunosuppressed human patients. Limited restriction endonuclease analyses of viral genomic DNA confirmed the variability among three viral genomes recovered from available frozen tissue. Because most previous PV isolates have been species specific, these studies suggest that at least eight different cat papillomaviruses infect the oral cavity (tentative designations: Asian lion, *Panthera leo,* P1PV; snow leopard, *Panthera uncia,* PuPV-1; bobcat, *Felis rufus,* FrPV; Florida panther, *Felis concolor,* FcPV; clouded leopard, *Neofelis nebulosa,* NnPV; and domestic cat, *Felis domesticus,* FdPV-2) or skin (domestic cat, *F. domesticus,* FdPV-1; and snow leopard, *P. uncia,* PuPV-2).

Key words: Bobcats; cats; domestic cats; feline; leopards; lions; oral mucosa; panthers; papillomavirus; skin.

Many domestic and wild species of mammals and birds can be infected by one or more species-specific papillomaviruses (PVs).[20,26] However, until recently, reports of papillomavirus infections in cats have been infrequent. Three reports on a total of four domestic cats suggest that this species is susceptible to infection.[3,4,13] Three of the cats were Persians, two of which had coat color dilution suggestive of Chediak–Higashi

Table 1. Clinical features of feline papillomas positive for papillomavirus infection.

| Common Name	Scientific Name	No. Cases	Age Range	Anatomic Site	Symbol
Domestic cat	*Felis domesticus*	5	7 months–15 years	Haired skin	FdPV-1
Domestic cat	*Felis domesticus*	2	6 months–9 years	Tongue	FdPV-2
Florida panther	*Felis concolor*	2	Adult	Tongue	FcPV
Bobcat	*Felis rufus*	2	Adult	Tongue	FvPV
Asian lion	*Panthera leo*	4	Adult	Tongue	PlPV
Snow leopard	*Panthera uncia*	3	5–16 years	Oral cavity	PuPV-1
Snow leopard	*Panthera uncia*	1	6 years	Haired skin	PuPV-2
Clouded leopard	*Neofelis nebulosa*	1	Adult	Tongue	NnPV
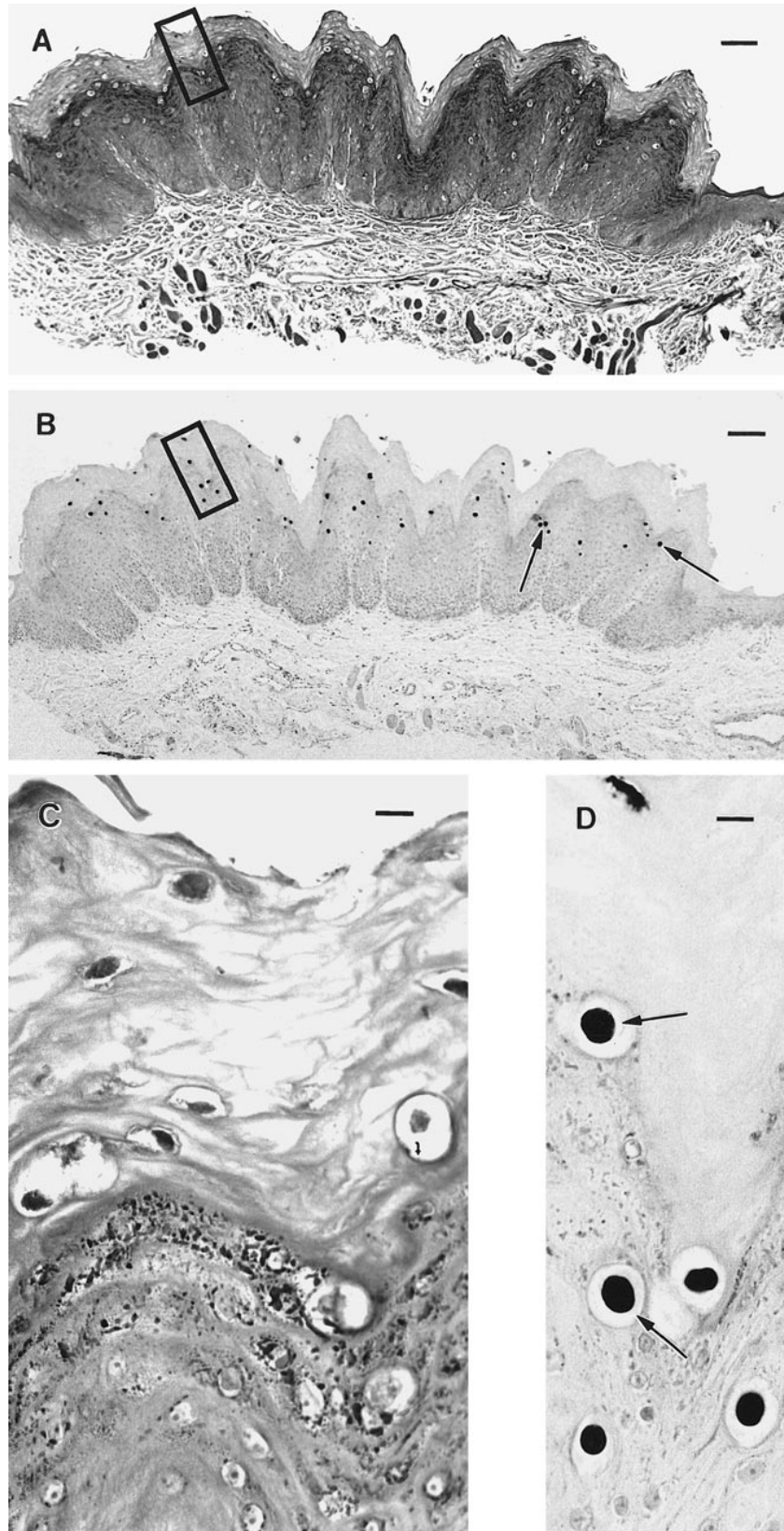
Fig. 1A. Small papilloma on tongue; 5-year-old male snow leopard. HE. Bar = 100 μm. **Fig. 1B.** Serial section of **A** demonstrates presence of papillomavirus antigens (arrows). Immunoperoxidase, PV group-specific rabbit antibody, hematoxylin counterstain. Bar = 100 μm. **Fig. 1C.** Higher magnification of boxed area in **A** illustrating koilocytotic atypia (arrow). HE. Bar = 10 μm. **Fig. 1D.** Higher magnification of boxed area in **B** illustrating presence of papillomavirus antigens in koilocytes (arrows). Immunoperoxidase, DAKO PV group-specific rabbit antibody, hematoxylin counterstain. Bar = 10 μm.
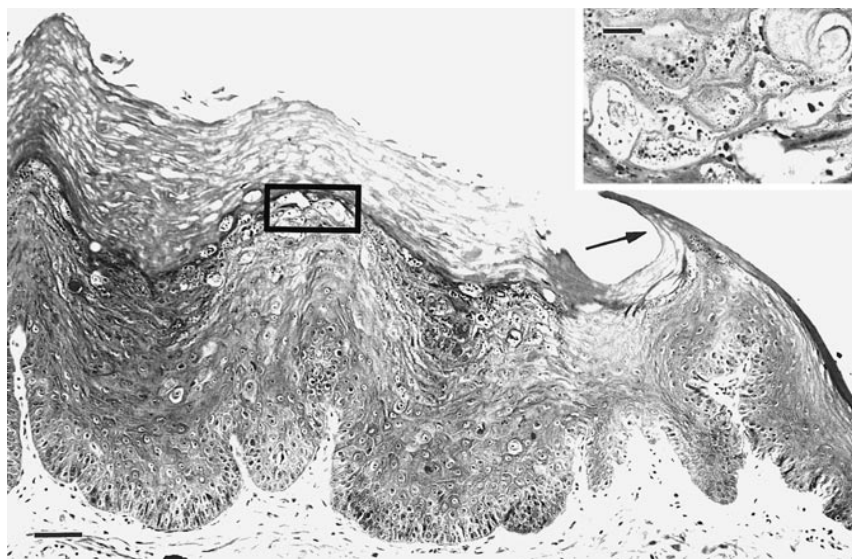
Fig. 2. Tongue papilloma adjacent a normal filiform papilla (arrow); 16-year-old female snow leopard. HE. Bar = 50 μm. *Inset:* Higher magnification of boxed area to illustrate cytopathic effect of the virus in the upper epithelium. HE. Bar = 10 μm.

syndrome, a form of immunodeficiency.[3] The fourth cat had feline immunodeficiency virus infection, which may have predisposed the animal to infection.[4] Immunodeficiency is known to predispose both humans and dogs to papillomavirus infection.[9,24] These observations suggest that these animals were susceptible to a papillomavirus that causes lesions in immunodeficient cats. In another case series consisting of 63 cutaneous squamous cell carcinomas in situ in domestic cats, 30 cases were PV positive by immunohistochemistry. The immune status was not reported for these cats.[10] Available evidence suggests that PVs are host species-specific or cause papillomatosis only in phylogenetically closely related hosts.

In routine diagnostic cases, with the use of histology and genus-specific markers by immunohistochemistry, a high degree of similarity is found among the PV capsid antigens such that human papillomavirus (HPV) cannot be distinguished from the PVs of other animals without knowing the host animal. Different PVs that infect a single species can be genotyped by various polymerase chain reaction methods, restriction fragment length polymorphisms (RFLPs), hybridization studies, and serotyping by patterns of antibody reactivities with linear and/or conformational capsid epitopes.[8,12] A case series of oral papillomatosis affecting the ventral tongues of Asian lions (*Panthera leo persica*) identified another feline papillomavirus that had a different epitope conservation pattern and genomic DNA restriction pattern from the domestic cat cutaneous papillomavirus.[23] This study compares the first two reported feline papillomaviruses[3,23] in relation to the pathology and conservation of capsid epitopes with six potentially new feline papillomaviruses.

Materials and Methods

Clinical data

Previously published cases of cutaneous papillomas in two Persian cats[3] and four Asian lions[23] were included in this report as positive controls for morphologic, immunohistochemical, and molecular comparison and for completeness because these are the only two feline papillomaviruses characterized in any detail. Clinical data were limited and signalments are summarized in Table 1 for all the cases received that were positive for papillomavirus antigens by immunohistochemistry. Asian lions, Florida bobcats, and Florida panthers were free living. Only the bobcats and panthers possibly overlapped in territory. The other exotic cats came from different zoos. Domestic cats were individual cases from all over North America.

Tissues

Serial sections of paraffin-embedded tissues were stained with hematoxylin and eosin or tested for papillomavirus genus-specific antigens with a rabbit polyclonal antibody (catalog number B580, DAKO Corp., Carpenteria, CA) that broadly cross-reacts with mammalian and avian papillomaviruses.[8,12,22] A panel of mouse monoclonal antibodies directed against linear epitopes of the bovine papillomavirus type-1 (BPV-1) L1 and L2 gene products that are phylogenetically conserved to various degrees was also used.[8,12,26] The reaction was developed by a modification of the avidin-biotin complex technique.[12] Positive controls included bovine cutaneous fibropapillomas containing either BPV-1 or BPV-2 and a canine oral papilloma containing the canine
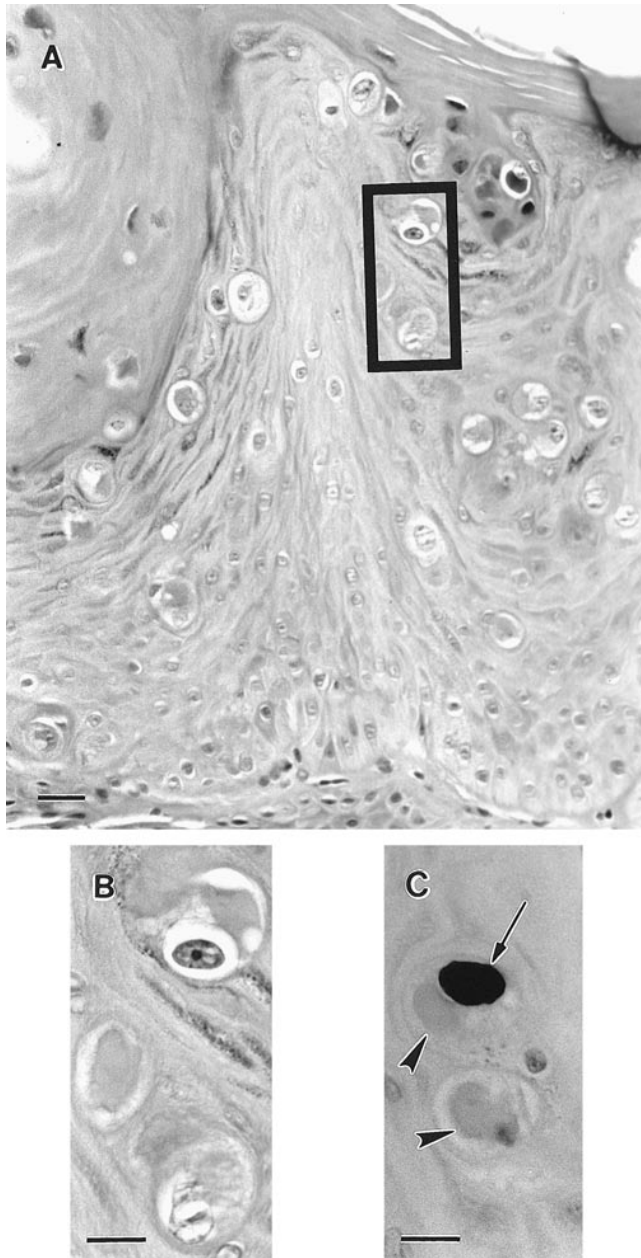
Fig. 3A. Papilloma from the tongue; adult Asian lion. Koilocytotic atypia of individual cells of the stratum spinosum and granulosum with cytoplasmic inclusions is illustrated. HE. Bar = 20 μm. **Fig. 3B.** Higher magnification of boxed area in **A** detailing the cytoplasmic inclusions. HE. Bar = 10 μm. **Fig. 3C.** Nuclei within these cells were positive for viral antigens (arrow) but not the cytoplasmic inclusions (arrowheads). Immunoperoxidase, DAKO PV genus-specific rabbit antibody, hematoxylin counterstain. Bar = 10 μm.

oral papillomavirus, all of which were typed by RFLP analysis from DNA in frozen biopsies.

Molecular studies

Frozen hyperplastic or sessile lesions from Asian lions, Florida panthers, and bobcats were finely minced, and ge-

nomic DNA was prepared as previously described.[25] Briefly, the tissue was digested with proteinase K (Boehringer Mannheim, Indianapolis, IN), treated with DNase free RNase A (Boerhinger Mannheim), extracted with phenol and chloroform, and precipitated with 70% ethanol. Total cellular DNA (5 μg) was digested with *Bam*HI restriction endonuclease and electrophoretically separated on a 1% agarose gel. The DNA on the gel was depurinated, denatured, and transferred under alkaline conditions to a charge modified nylon membrane (Genescreen Plus, NEN Products, Boston, MA).[19] The membrane was hybridized under low stringency conditions with a radiolabelled cocktail-probe consisting of equal amounts (50 ng each) of HPV-1, HPV-11, HPV-16, and HPV-18 DNA. After posthybridization washing of the membranes under low stringency conditions, the membrane was exposed to Kodak XAR-5 film for 72 hours at −70 °C with intensifying screens (Cronex Lightning-Plus, Du Pont de Nemours, Wilmington, DE).

Electron microscopy

Thin sections of the glutaraldehyde-fixed specimens (domestic cat cutaneous plaques, Asian lion oral papillomas) were prepared by standard embedding techniques. One-micrometer sections, stained with Richardson's stain, were examined by light microscopy to select sites for electron microscopic evaluation. Ultrathin sections were stained with uranyl acetate and lead citrate and examined. Negative stain preparations from cells scraped from the surface of the plaques were prepared as previously described.[5,23]

Results

Clinical features

Signalments, diagnosis, and sites of lesions are summarized in Table 1 for 20 cases affecting six species of felines that had PV antigen-positive lesions. Gross presentation of oral lesions in all species had similar features. Oral papillomas were multifocal, small, soft, light-pink, oval, slightly raised flat, sessile lesions on the ventral lingual surfaces. In the snow leopards, lesions were also present on the tip and dorsal surface of the tongue as well as the buccal mucosa. Lesions ranged in size from 4 to 8 mm in diameter at the largest axis. Cutaneous papillomas in domestic cats and a snow leopard presented with numerous rough, raised, unpigmented to heavily pigmented (depending upon the skin color of the cat), scaly, greasy plaques, 3–5 mm in greatest diameter on the skin of the torso.

Histopathology

Oral papillomas in all six species had many similar features. Small sessile or papillomatous lesions (Fig. 1A) composed of hyperplastic keratinocytes were raised above the surface of the tongue. Thin fibrovascular stalks occasionally supported the hyperplastic epithelium. An abrupt change in thickness occurred at the junction between the lesion and adjacent normal tissue (Figs. 1A, 2). The stratified squamous epitheli-
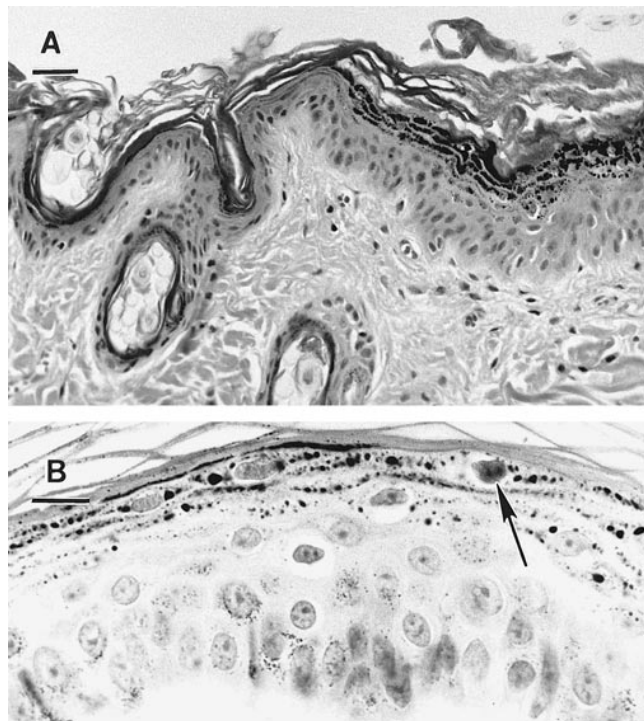
Fig. 4A. Cutaneous hyperplastic plaques; 15-year-old male castrate domestic short-haired cat. The change from normal to hyperplastic epidermis is illustrated. HE. Bar = 20 μm. **Fig. 4B.** Koilocytes in the upper epidermis express papillomavirus antigens (arrow). Immunoperoxidase, DAKO PV genus-specific rabbit antibody, hematoxylin counterstain. Bar = 10 μm.

Fig. 5A. Cutaneous hyperplastic plaques; 6-year-old male snow leopard. The transition from normal (right side of arrow) to marked papillomatous hyperplasia with marked orthokeratotic hyperkeratosis is illustrated. HE. Bar = 100 μm. **Fig. 5B.** Higher magnification of hyperplastic skin reveals pleomorphic keratohyalin granules in the stratum granulosum. HE. Bar = 10 μm.

um differentiated in a normal manner with all suprabasilar layers being expanded. The stratum granulosum was prominent in all cases compared with adjacent normal tissue that lacked a granular layer or had a very thin layer (Fig. 2). Within the granular layer, individual cells were swollen, having an abundance of clear cytoplasm around nuclei (koilocytes; Fig. 1C). Large and irregular keratohyalin-like cytoplasmic granules (putative E4 papillomavirus gene product; Fig. 2) or condensed cytoplasmic inclusions (Fig. 3) were features of degenerating keratinocytes, the phenotype of which is considered to be the cytopathic effect of productive PV infections. Immunohistochemistry revealed papillomavirus antigens only within nuclei of these koilocytes (Figs. 1B, D, 4B).

Cutaneous plaques from the domestic cat and snow leopards infected with PVs consisted of focal areas of epidermal and follicular hyperplasia that abruptly changed from the normal adjacent tissues (Figs. 4A, 5A, 6). Proliferation of all layers was evident, including plugging of hair follicles with cornified debris. Papilloma formation, typical of productive infections by papillomaviruses, was not a prominent feature (Figs. 4, 5A). Thickening of the stratum granulosum
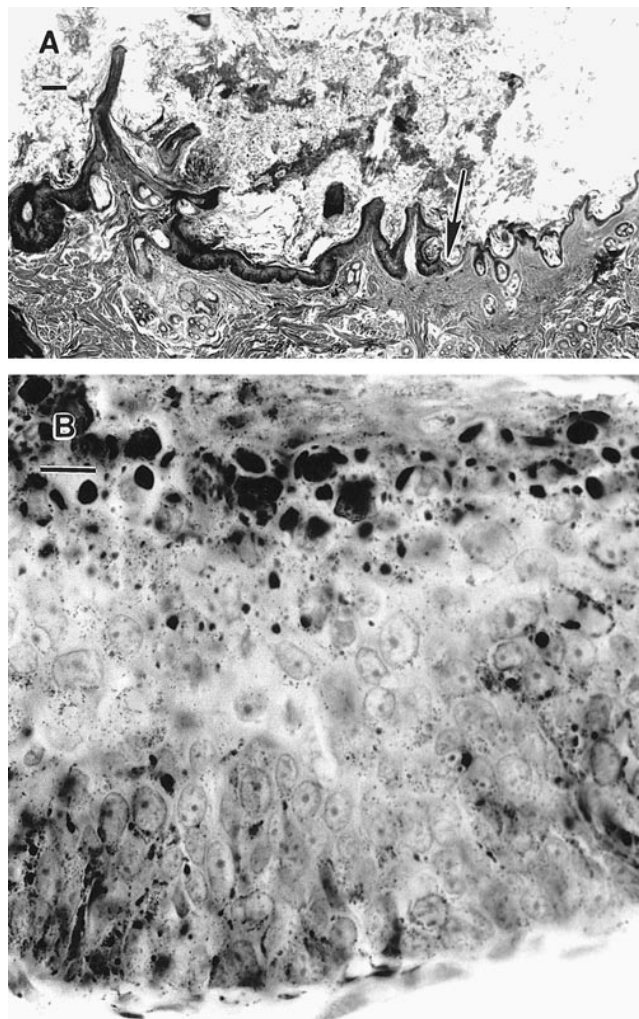
with formation of prominent pleomorphic amphophilic granules was evident in many cases. Solitary or small clusters of cells in the upper stratum spinosum and throughout the stratum granulosum were swollen with clear cytoplasm and a large round to oval vesicular nucleus (koilocytes). Within the cytoplasm was a large, solitary, irregularly shaped amphophilic inclusionlike structure. These cytoplasmic inclusions first appeared as a fine coalescing pink fibrillar mass in cells of the stratum spinosum. The fibrillar structure became compact and uniform in color in the stratum granulosum. Many of the cases superficially resembled seborrheic keratosis (Fig. 5A). Closer examination revealed thickening of all suprabasilar layers with heavy pigmentation in some cases, but hypergranulosis was
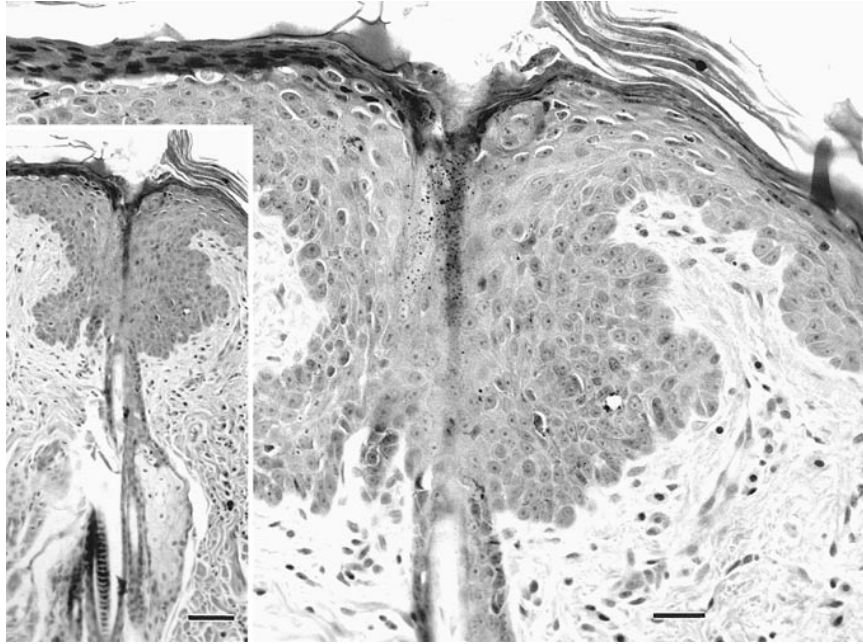
Fig. 6. Cutaneous hyperplastic plaques; 7-month-old, male castrate, domestic short-haired cat. Marked hyperplasia of the outer root sheath (infundibulum) of the hair follicle is revealed. HE. Bar = 20 μm. *Inset:* The hyperplasia develops above the sebaceous glands and, therefore, above the purported stem cells of the hair follicle. HE. Bar = 50 μm.

prominent, to the degree that positive nuclei in immunohistochemical studies were difficult to identify without high magnification.

Ultrastructure

By electron microscopy, the inclusions in the koilocytes of the Asian lion oral and domestic cat cutaneous papillomas appeared as finely granular (Fig. 7A) to fibrillar electron-dense cytoplasmic aggregates that often molded around nuclei. Within the nucleus of some of these cells were 50–52-nm virus particles, ultrastructurally identical with those of papillomaviruses (Fig. 7B). Negatively stained preparations from the domestic cat skin lesions revealed 50–55-nm papillomavirus-like particles.

Epitope mapping

Papillomavirus cross-reactive antigens, several of which are recognized by carefully characterized monoclonal antibodies,[8,12] were identified within the nuclei of koilocytotic cells (Figs. 1B, D, 3C, 4B). The cytoplasmic inclusion-like structures did not stain for structural viral proteins (Fig. 3C). Immunohistochemistry with a battery of monoclonal antibodies that reacted with some PVs but not others revealed that PV-induced tumors from the same site of one species all contained similar reactive epitopes. However, this was not the case for tumors in the same host that had different locations (skin versus oral mucosa). These results indicated that these were distinct host species-

specific papillomaviruses (Table 2). The novel papillomaviruses identified in this study were abbreviated following the nomenclature guidelines for nonhuman papillomaviruses as indicated in Table 1.[26]

Molecular studies

A low stringency Southern blot of *Bam*HI restriction endonuclease digests of the total DNA extracted from three different tumors hybridized with a cocktail probe of HPV-1, 11, 16, and 18 DNA revealed three distinct bands for the bobcat oral papillomavirus, one for the Asian lion oral papillomavirus, and two for the Florida panther oral papillomavirus, confirming that these are three different papillomavirus types (Fig. 8).

Discussion

Not all lesions diagnosed as papillomas in animals are caused by or contain papillomaviruses,[26] and feline species are no exception.[20] Of over 50 papillomas and fibropapillomas in domestic, wild, and exotic Felidae initially suspected of containing PVs (data not shown), only 20 had any evidence of virus, which are reported here. These observations are consistent with previous reports of using immunohistochemical means to screen for papillomavirus infections.[4,18,22] In a large case series of cutaneous squamous cell carcinoma in situ in domestic cats, 30 of 63 biopsies were positive for PV antigens.[10] It is possible that negative tumors in this and other studies were not associated with papillomavirus infections or that they were intermittently pro-
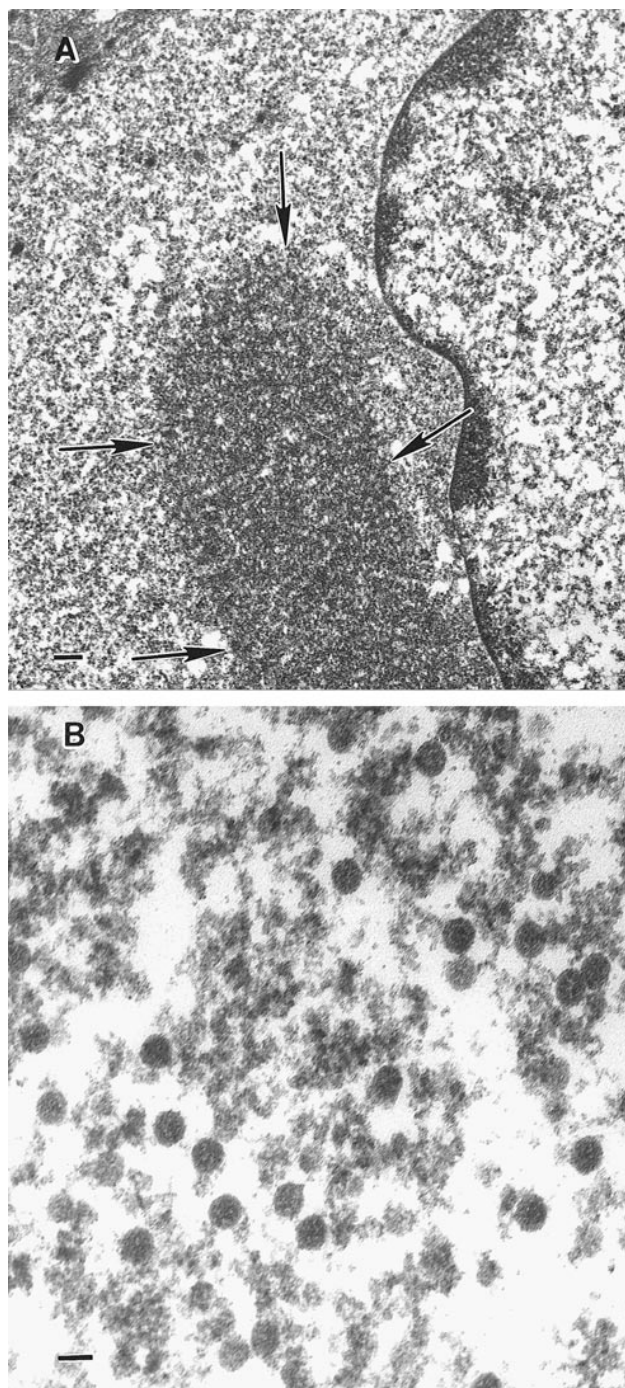
Fig. 7A. Cytoplasmic inclusions in oral papilloma; Asian lion. These consisted of electron-dense granular material. Bar = 200 nm. **Fig. 7B.** The nucleus of these cells contained numerous viruslike particles of uniform size. Bar = 50 nm.

cytopathic effect of PV infections. The main difference between the histologic features of cutaneous and mucosal papillomas was the prominence of a large inclusion-like body in the cytoplasm of mucosal koilocytes. In other species, these inclusions are associated with an early gene product (E4) of the PVs.[2] They have become prominent enough to be confused with Guanieri bodies by pathologists reviewing human tissues or poxviruses in some animal tissue. The latter is a concern because poxvirus infections have been reported in domestic cats.[15] These large cytoplasmic inclusions are also found in human papillomavirus type 1- (HPV-1, plantar warts) and canine papillomavirus type 2 (CfPV-2, cutaneous inverted warts)-induced lesions.[11] Cytoplasmic inclusions in the CfPV-2-induced tumors resembled those described in several of these cat lesions. Furthermore, at the ultrastructural level, the inclusions in the dog, domestic cats, and Asian lion papillomavirus-induced lesions all consisted of aberrant intermediate filament assembly.[3,11,23]

The papillomavirus-induced lesions in immunosuppressed domestic cats are similar to those of human patients with various degrees of immunosuppression, particularly individuals with the autosomal recessive trait epidermodysplasia verruciformis (EV) and iatrogenic immunosuppression, i.e., for renal transplantation.[14] Epidermodysplasia verruciformis is a rare syndrome, with most infected family members located in clusters. Because renal transplant recipients infected by EV-associated PVs are much more numerous and randomly localized (genetic background polymorphism), the reservoir for these viruses has been the source of much speculation, and recently the hair follicles have been proposed.[1,7] The immunohistochemical finding of PV infection in the hair follicle of one of the immunosuppressed cats[3] as well as proliferative changes in follicular root sheaths (infundibula) presented here in association with cutaneous infection suggests that EV-like feline viruses could cause latent infection of hair follicles in both species. In general, the cat lesions, like their human counterparts, are planar or flat warts with the clinical appearance of plaques. In the human lesions, those associated with HPV-5 and HPV-8 undergo conversion to malignancy in the presence of ultraviolet light in approximately 30% of individuals. This may be significant because cats frequently develop basal and squamous cell carcinomas.

A number of mucosotropic HPVs are also closely linked with benign, premalignant, and malignant lesions. However, the HPVs that cause lingual carcinomas in immunocompetent patients do not cause lesions of the skin in immunocompromised individuals. Multiple HPV types induce tumors in the oral cavity of humans. Most lesions have an appearance of verrucae.

ductively infected, a phenomenon described for other PV-induced lesions.[21,27] Most cutaneous and mucosal lesions were relatively flat and characterized by productively infected keratinocytes degenerating into koilocytes. These features are characteristic of the general

Table 2. Detection of papillomavirus antigens that are group specific (polyclonal) and epitope specific (monoclonal) by immunohistochemistry in cat tumors.*

Host Species	Anatomic Site	Viral Symbol	Polyclonal DAKO B580	Monoclonal Antbody Clone Designation						
				1H8	AU1	AU2	AU3	AU4	AU5	AU6
Domestic cat	Skin	FdPV-1	+	+	+	−	−	−	−	+
Domestic cat	Tongue	FdPV-2	+	−	−	−	−	−	−	−
Florida panther	Tongue	FcPV	+	+	−	−	−	−	−	−
Bobcat	Tongue	FrPV	+	−	−	−	−	−	−	−
Asian lion	Tongue	PlPV	+	+	+	−	−	−	−	−
Snow leopard	Tongue	PuPV-1 (?)	+	+	−	−	−	−	−	−
Snow leopard	Skin	PuPV-2 (?)	+	+	+	−	−	−	−	−
Clouded leopard	Tongue	NnPV	+	+	+	−	−	−	−	−
Domestic dog	Mouth	COPV	+	+	+	−	−	−	−	−
Cattle	Skin	BPV-1	+	+	+	+	+	+	+	+
Cattle	Skin	BPV-2	+	+	+	−	+	+	+	+

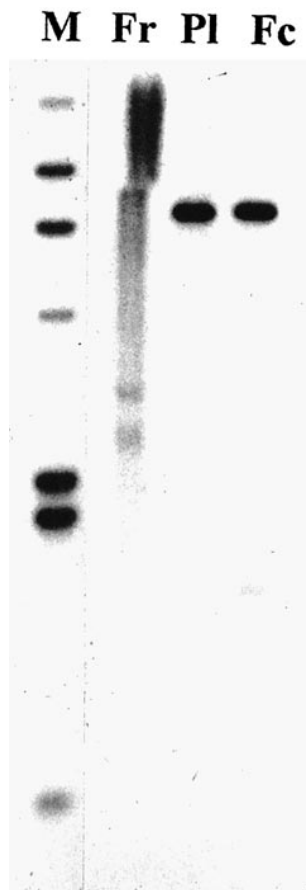*+ = positive staining of nuclei of koilocytes; − = negative staining of nuclei of koilocytes.

Fig. 8. Southern blot. Lanes, left to right: M, *Hind* III-generated lambda phage DNA fragments as a molecular marker; Fr, *Felis rufus* (bobcat); Pl, *Panthera leo* (lion); Fc, *Felis concolor* (panther) papillovirus genomes digested with *Bam*H1 reveals distinct fragment length patterns indicating each is a different feline papillomavirus.

However, one type, focal epithelial hyperplasia, is flat or grapelike in appearance. These lesions develop in individuals with a similar genetic background. For example, Native American Indians and Eskimos are more at risk to develop these lesions.[28,29] Molecularly and pathogenetically similar papillomaviruses infect pygmy chimpanzees (*Pan paniscus*) as well.[30] Both infected humans and infected chimpanzees have lesions that may persist for many years. Several HPVs, including HPV-3, cause benign flat lesions on both the skin and mucosa of these individuals. Further molecular studies are needed to determine if a relationship exists between papillomavirus infection and carcinomas in the cat.

Cutaneous plaques on the skin of domestic cats are commonly diagnosed as ''Bowen's disease'' or ''Bowen's-like disease.''[6,10] This term has been used loosely for a group of HPV-associated diseases in humans. Eponyms for human diseases are not commonly used for nonhuman diseases in the veterinary literature and should be avoided. Furthermore, multicentric squamous cell carcinoma in situ occurring predominantly in the anogenital area of humans has been diagnosed as Bowen's disease or Bowenoid papulosis until relatively recently. Because of the different histologic features, together with the age of the patient and predisposition of developing into an invasive cancer, this nomenclature has been dropped. Human lesions are now designated as intraepithelial neoplasia III with warty or basaloid, etc. phenotypes. Because this eponym-based nomenclature is not considered useful for human disease, it should not be misused to label these cat lesions.

The scattered case reports or series of various cat species with papillomavirus infections, in addition to this report, provide evidence that this family of car-

nivores is not exempt from infection and may yield an interesting model to investigate host–parasite coevolution, as has been shown for the cheetah with other virus infections.[16] Comparative genomics of cats has been studied extensively[17] and provides a resource to utilize sequence data, as it is generated, for the papillomaviruses reported here to investigate the coevolution and migration of cat species and their pathogens.

Acknowledgement

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