NOTE *Pathology*

Feline Epidermal Nevi Resembling Human Inflammatory Linear Verrucous Epidermal Nevus

Masafumi SATO[1)], Kazuhiro KARIYA[1)], Munetaka MATSUMOTO[1)], Miyuki ITOH[2)], Yoshiyasu KOBAYASHI[2)], Koji NISHIFUJI[3)], Junichi KAMIIE[4)] and Kinji SHIROTA[4)]*

[1)]*AC Plaza Kariya Animal Hospital, 5–20–2 Morishita, Koto-ku, Tokyo 135–0004, Japan*
[2)]*Laboratory of Veterinary Pathology, Division of Pathological Science, Department of Basic Veterinary Medicine, Obihiro University of Agriculture and Veterinary Medicine, Inada-cho, Obihiro, Hokkaido 080–8555, Japan*
[3)]*Laboratory of Veterinary Internal Medicine, Tokyo University of Agriculture and Technology, 3–5–8 Saiwai-cho, Fuchu, Tokyo 183–8509, Japan*
[4)]*Laboratory of Veterinary Pathology, School of Veterinary Medicine, Azabu University, 1–17–71 Fuchinobe, Chuo-Ku, Sagamihara, Kanagawa 252–5201, Japan*

(Received 14 March 2012/Accepted 11 May 2012/Published online in J-STAGE 25 May 2012)

ABSTRACT. Multiple, pigmented, verrucous, cutaneous lesions in a 2-year-old female cat were pathologically examined. The lesions were linearly arranged on the right side of the body, and had developed along with moderate pruritus since infancy. Histologically, prominent exophytic, papillomatous outgrowths of the epidermis and acanthosis with intense ortho and parakeratotic hyperkeratosis were characteristic of the lesions. Dermal inflammation with mononuclear cells, neutrophils, and eosinophils was also noted. Inclusion bodies, cellular degeneration, and intranuclear viral particles suggesting papillomavirus infection in the keratinocytes were not observed. Papillomavirus antigen and DNA were not detected in the lesions by immunohistochemistry and polymerase chain reaction, respectively. In accordance with these clinical and histopathological features, the cutaneous lesions of the present cat were diagnosed as epidermal nevi, which were consistent with human inflammatory linear verrucous epidermal nevi.

KEY WORDS: dermatopathology, feline, nevus, papilloma, skin disease.

doi: 10.1292/jvms.12-0117; *J. Vet. Med. Sci.* 74(10): 1337–1339, 2012

Cutaneous papilloma, or verrucous lesions, which are rarely seen in cats, may be caused by viral infections, developmental anomalies, or traumatic stimuli of the skin [5]. The time of onset, gross appearance, and pathological features of the skin lesions are important for differential diagnosis. Two cases of feline cutaneous papilloma associated with papillomavirus (PV) infection have been reported [3, 9], although cases of congenital origin have not been described. We report a young cat with multiple, characteristic, linearly arranged, cutaneous, verrucous lesions that had developed during infancy. Pathological features of the lesions did not accord with PV infection, and rather similar to those of inflammatory linear verrucous epidermal nevus (ILVEN), a variant of epidermal nevi in humans [1, 7].

A 2-year-old female domestic short-haired cat developed multiple, verrucous lesions with erythematous margins arranged in a linear pattern on the right side of the body (Fig. 1). The lesions ranged from 5 mm to 30 mm in diameter and were moderately pigmented, although their surfaces were often light brown. According to the owner, these cutaneous lesions along with moderate pruritus had been observed since infancy. The cat had been reported to present with right-sided ataxia and intention tremor.

All masses were surgically removed and tissue samples were fixed in 10% neutral-buffered formalin and embedded in paraffin wax. The sections (4 μm) were cut and stained with hematoxylin and eosin (HE). A standard immunoperoxidase technique was used for the immunohistochemical detection of the PV antigen. The paraffin sections were treated with rabbit polyclonal anti-bovine papillomavirus (BPV-1) antibody (DakoCytomation, Carpinteria, CA, U.S.A.). Before incubation with the primary antibody, the deparaffinized sections were treated with 0.1% trypsin for 1 hr at 37°C. Peroxidase-conjugated anti-rabbit IgG [Histofine Simple Stain MAX-PO (R); Nichirei, Tokyo, Japan] was used as the secondary antibody. The reaction products were visualized by 3,3'-diaminobenzidine tetrahydrochloride (Wako Pure Chemical Industries, Ltd., Tokyo, Japan), and the sections were counterstained with Mayer's hematoxylin. As a positive control for immunostaining of PV antigen, we used paraffin sections of canine cutaneous viral papilloma and canine pigmented viral plaque. For electron microscopy, small pieces of formalin-fixed tissue were refixed in 2.5% glutaraldehyde, post-fixed in 1% osmium tetraoxide, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate and examined using a JOEL 1210 transmission electron microscope (JOEL, Tokyo, Japan) at 80 kV.

DNA was extracted from the paraffin sections as follows. Deparaffinized sections were suspended in a buffer containing 20 mg/m*l* proteinase K (Wako), 3.75 mol/*l* NaCl,

*CORRESPONDENCE TO: SHIROTA, K., Laboratory of Veterinary Pathology, School of Veterinary Medicine, Azabu University, 1–17–71 Fuchinobe, Chuo-Ku, Sagamihara, Kanagawa 252–5201, Japan. e-mail: shirota@azabu-u.ac.jp

©2012 The Japanese Society of Veterinary Science

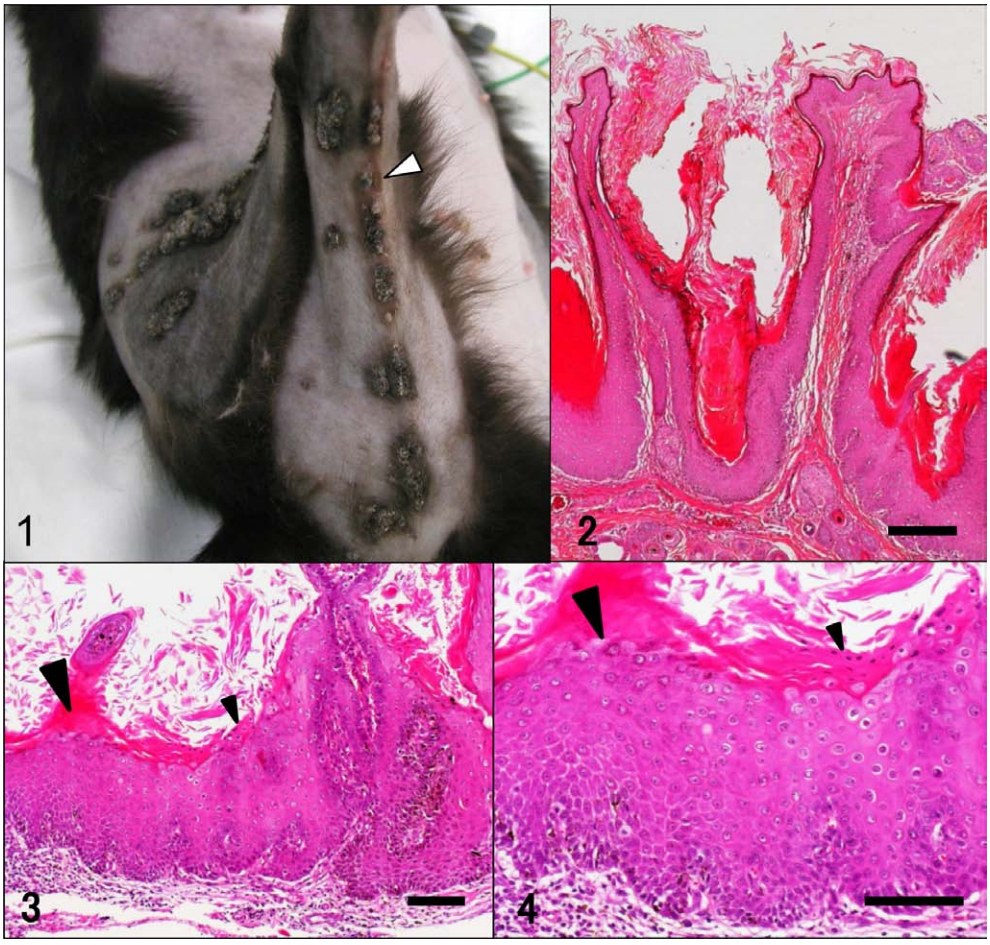


Fig. 1. Linearly arranged, pigmented, verrucous lesions with erythematous margins (arrowhead) on the right caudal thigh.
Fig. 2. Exophytic, papillomatous growth of the epidermis with intense ortho and parakeratotic hyperkeratosis. HE. Bar: 200 μm.
Fig. 3. Irregular acanthosis with orthokeratotic (large arrowhead) and parakeratotic (small arrowhead) hyperkeratosis, hyperpigmentation, and dermal inflammation. HE. Bar: 100 μm.
Fig. 4. Higher magnification of Fig. 3 showing altering areas of hypergranulosis and overlaying orthokeratotic hyperkeratosis (large arrowhead), and agranulosis and overlaying parakeratotic hyperkeratosis (small arrowhead). HE. Bar: 100 μm.

100 mmol/*l* Tris-HCl (pH 8.0), 500 mmol/*l* EDTA (pH 8.0), and sodium dodecyl sulfate, and were incubated at 37°C for 24 hr. DNA was then extracted in phenol and chloroform-isoamyl alcohol (CIA, 24:1). The extracted DNA sample was subjected to touchdown polymerase chain reaction (PCR) using consensus IFNR2 and IDNT2 primer pairs that amplify a portion of the *L1* gene of PV [11].

Histological findings included prominent, irregular, exophytic, papillomatous growths of the epidermis and irregular acanthosis with striking ortho and parakeratotic hyperkeratosis (Figs. 2 and 3). Sharply demarcated alternating portions of hypergranulosis with orthkeratotic hyperkeratosis and agranulosis with parakeratosis were often observed (Fig. 4). Hyperpigmentation was also associated with epidermal proliferation. Cellular infiltration composed of mononuclear cells, neutrophils, and eosinophils, vascular dilation and pigmentary incontinence developed in the upper dermis (Fig. 3). Intense proliferation of mast cells was also detected in the superficial dermis. Proliferation and hyperkeratosis of the infundibular follicular epithelium resulting in luminal distention developed characteristically (Fig. 2). Acantholysis and epidermolysis with granular degeneration of the keratinocytes were not observed. Vacuolated keratinocytes were scattered in the superficial layer of the epidermis and follicular epithelium, whereas characteristic koilocytosis or intranuclear inclusions suggesting PV infection was not observed. A few *Demodex* mites were found in some distended follicles. Electron microscopy revealed no viral particles in the lesion.

With immunohistochemistry, the PV antigen was clearly

detected in the nuclei of affected keratinocytes in the tissues of canine cutaneous viral papilloma and canine pigmented viral plaque. However, there were no PV antigen-positive cells in the present case. With PCR, the specific amplicon, which was a 102-bp fragment of the *L1* gene of PV was not found in tissue samples.

No recurrence was observed during 75 months after complete surgical resection of the cutaneous lesions.

The gross appearance of the multiple verrucous lesions seen in this case was suggestive of PV infection. Two cases of feline cutaneous papilloma [3, 9] and four cases of feline hyperkeratotic plaque associated with PV infection were previously reported [2, 4, 8, 10]. In these reports, the histological features of feline PV infections were characterized by koilocytosis and intranuclear inclusions in the cutaneous lesions. In contrast, the present case did not show any of the characteristic changes of PV infection. Moreover, there was no evidence of PV infection in the present case. Therefore, it is unlikely that PV infection was the cause of the cutaneous lesions in the present case.

Alternatively, the clinical course that the cutaneous lesions had been presented since infancy indicated that the lesions were probably caused by nevoid etiology. In addition, the lesions occurred as linear bands along Blaschko's lines, which is similar to what is seen in human epidermal nevi [1, 7]. Human epidermal nevi are histologically divided into keratinocytic (non-organoid) nevi and organoid nevi [7]. The keratinocytic nevi are those with differentiation predominantly towards the keratinocytes as seen in this feline case, and they are classified into several subtypes [7]. Epidermal nevi have been reported in dogs that showed linearly arranged hyperkeratotic and hyperpigmented cutaneous lesions with moderate to severe pruritus from a young age, diagnosed with ILVEN [5, 6, 12]. The present cat shared a number of clinical and histological features with these dogs. The most characteristic histopathological changes in the present cat included nonepidermolytic epidermal proliferation with intense ortho and parakeratotic hyperkeratosis, and superficial dermal inflammation. In addition, alternating portions of hypergranulosis with orthokeratotic hyperkeratosis and agranulosis with parakeratosis sharply demarcated were frequently noted. Although psoriasform epidermal hyperplasia was not prominent, the histopathological changes in the present case were consistent with those of human ILVEN [7]. Epidermal nevi in humans may associate with several syndromes including neurologic, ocular, skeletal, cardiac, and renal anomalies [1]. The present cat had been reported to present with right-sided ataxia and intention tremor, however, the relationship between these neurologic abnormalities and the epidermal nevi was not clarified.

To the best of the author's knowledge, this is the first case report of feline epidermal nevi.

REFERENCES

1. Brandling-Bennett, H. A. and Morel, K. D. 2010. Epidermal nevi. *Pediatr. Clin. North Am.* **57**: 1177–1198. [Medline] [CrossRef]
2. Carney, H. C., England, J. J., Hodgin, E. C., Whiteley, H. E., Adkison, D. L. and Sundberg, J. P. 1990. Papillomavirus infection of aged Persian cats. *J. Vet. Diagn. Invest.* **2**: 294–299. [Medline] [CrossRef]
3. Carpenter, J. L., Kreider, J. W., Alroy, J. and Schmidt, G. M. 1992. Cutaneous xanthogranuloma and viral papilloma on an eyelid of a cat. *Vet. Dermatol.* **3**: 187–190. [CrossRef]
4. Egberink, H. F., Berrocal, A., Bax, H. A., van den Ingh, T. S., Walter, J. H. and Horzinek, M. C. 1992. Papillomavirus associated skin lesions in a cat seropositive for feline immunodeficiency virus. *Vet. Microbiol.* **31**: 117–125. [CrossRef]
5. Gross, T. L., Ihrke, P. J., Walder, E. J. and Affolter, V. K. 2005. Inflammed linear epidermal nevus. pp. 155–157. *In*: Skin Diseases of the Dog and Cat. Clinical and Histopathologic Diagnosis, 2nd ed., Blackwell Science Ltd., Oxford.
6. Gross, T. L., Ihrke, P. J., Walder, E. J. and Affolter, V. K. 2005. Epidermal tumors. pp. 564–571. *In*: Skin Diseases of the Dog and Cat. Clinical and Histopathologic Diagnosis, 2nd ed., Blackwell Science Ltd., Oxford.
7. Happle, R. and Rogers, M. 2002. Epidermal nevi. *Adv. Dermatol.* **18**: 175–201. [Medline]
8. Lozano-Alarcón, F., Lewis, T. P. 2nd., Clark, E. G., Bradley, G. A., Shupe, M. R. and Harqis, A. M. 1996. Persistent papillomavirus infection in a cat. *J. Am. Anim. Hosp. Assoc.* **32**: 392–396. [Medline]
9. Munday. J. S., Hanlon, E. M., Howe, L., Squires, R. A. and French, A. F. 2007. Feline cutaneous viral papilloma associated with huma papillomavirus type 9. *Vet. Pathol.* **44**: 924–927. [Medline] [CrossRef]
10. Sundberg, J. P., Van Ranst, M., Montali, R., Homer, B. L., Miller, W. H., Rowland, P. H., Scott, D. W., England, J. J., Dunstan, R. W., Mikaelian, I. and Jenson, A. B. 2000. Feline papillomas and papillomaviruses. *Vet. Pathol.* **37**: 1–10. [Medline] [CrossRef]
11. Teifke, J. P., Kidney, B. A., Lohr, C. H. and Yager, J. A. 2003. Detection of papillomavirus-DNA in mesenchymal tumor cells and not in the hyperplastic epithelium of feline sarcoids. *Vet. Dermatol.* **14**: 47–56. [Medline] [CrossRef]
12. White, S. D. W., Rosychuk, R. A. W., Scott, K. V., Hargis, A. M., Trettien, A. and Amy, T. 1992. Inflammatory linear verrucous epidermal nevus in four dogs. *Vet. Dermatol.* **3**: 107–113. [CrossRef]