Successful treatment of florid papillomatosis in a dog using subcutaneous feline recombinant interferon-ω

O. FANTINI, E. VIDEMONT, D. PIN*

Dermatology–Dermatopathology Unit, VetAgro Sup Veterinary Campus Lyon, 1 Avenue Claude Bourgelat, Marcy l’Etoile, 69280 - France

* Corresponding author: didier.pin@vetagro-sup.fr

ABSTRACT

An eight-month-old Pug dog was presented for treatment-resistant disseminated exophytic papillomatosis affecting the oral mucosa, and the haired skin. Two courses of recombinant feline interferon-ω given by subcutaneous injection once daily for 5 consecutive days at two-week intervals, allowed a complete regression of papillomatosis with no adverse effects.

Keywords: Dog, papillomavirus, oral and cutaneous papillomatosis, feline recombinant interferon-ω.

Introduction

The papillomaviruses (PV) are a large group of species-specific, small nonenveloped double-stranded DNA viruses that have a tropism for the skin and for mucosal membranes, and are associated with various hyperplastic, dysplastic and neoplastic conditions in humans and animals [13].

Fifteen papillomaviruses have been cloned from and appear to be associated with certain clinical lesions in the dog. In this species, papillomatosis is, in general, a self-limiting disease, requiring no treatment. However, persistent lesions may be associated with defective cell-mediated immunity and treatment may be necessary [33].

Various treatment of papillomatosis in dogs have been described: oral azithromycin [33], cimetidine [6], etretinate [22] and human recombinant interferon-α 2a [27], intramuscular Propionibacterium acnes [21], intravenous taurolidine [3], subcutaneous live papillomavirus vaccine [4], topical applications of 5-fluorouracil or imiquimod and surgical excision, crushing laser surgery or cryosurgical intervention [22]. However, no single treatment has been shown to be superior. Topical application and/or subcutaneous injection of Thuja occidentalis has been used, in human, dog and cattle, to treat verruca vulgaris [14], canine oral papillomatosis [19] and cutaneous papilloma [31]. Intravenous magnesium chloride has been reported to be effective in bovine cutaneous papillomatosis [11].

This report describes the clinical and histopathological features of a severe refractory case of oral and cutaneous papillomatosis in a dog successfully treated by subcutaneous injections of rFeIFN-ω.

Case report

An 8-month-old male Pug dog was referred with alopecia, erythematous suppurative dermatitis, and disseminated cauliflower-like exophytic warts affecting the oral mucosa, face and appendicular haired skin, appeared 3 months before. Two other dogs in the household were reported to show the same lesions with spontaneous resolution. Treatment prior to referral included a six-week course of twice weekly 0.5ml/kg intravenous magnesium chloride, a 10-day-course of daily oral spiramycin and metronidazole (Stomorgyl; Merial), and a 30-day-course of 10mg/kg once daily oral azithromycin (Zitromax; Pfizer).

Physical examination revealed white, smooth, flat shiny plaques and firm, hyperkeratotic, pedunculated cauliflower-like masses on lips, oral cavity, face and front legs (Fig 1).

Figure 1: Numerous white, smooth, flat shiny plaques and firm, hyperkeratotic, pedunculated cauliflower-like masses were observed on face and lips.
Cytological examination of impression smears revealed cocci and some degenerate neutrophils. Biopsies were performed under local anesthesia. Tissue samples were fixed in 10% buffered formalin and processed routinely. Histological examination of haematoxylin and eosin stained sections revealed hyperkeratosis, papillary epidermal hyperplasia with marked expansion of the stratum corneum. Keratinocytes of the stratum granulosum contained giant keratohyalin granules and increased amount of wispy grey-blue cytoplasm, consistent with viral cytopathic change (Fig2). Some koilocytes (keratinocytes with swollen, clear cytoplasm and a pyknotic nucleus) were observed (Fig2). A refractory florid papillomatosis was diagnosed.

Treatment was initiated with 1 MU/kg rFeIFN-ω given by subcutaneous injection once daily for 5 consecutive days. One further 5-day treatment was realized 14 days later.

A shampoo containing 3% of chlorhexidine digluconate and 0.5% of climbazole (DouxoPyo; Sogeval) was realized twice a week and followed by application of a moisturizer (Humiderm; Virbac).

The dog was examined after 2, 4, 8, 12 weeks. After 2 weeks, a significant reduction in extension and number of papillomas was observed (Fig 3). Only ten small warts were still present by day 30 on the face. Complete regression of papillomas in the oral cavity and on the body was observed by day 50 (Fig 4). There was no recurrence of papillomatosis in the treated dog during a follow-up period of 12 months. No adverse effects were seen.

**Discussion**

Canine PVs have been associated with exophytic warts as in canine oral papillomatosis, endophytic warts, and pigmented plaques and, in some cases, squamous cell carcinomas [17].

Canine oral papillomas induced by CPV-1 [2] are common in puppies and are characterized by multiple, invasive, cauliflower-like hyperkeratotic masses typically in the oral mucosa including the lips and mucocutaneous...
In our case, the identification of the papillomavirus has not been performed.

Papillomatosis in dogs may be a self-limiting disease, and spontaneous regression of PV-induced exophytic warts is classically observed 4 to 8 weeks after the onset of symptoms [17]. Oral papillomas usually regress after 4 to 8 weeks, although they may persist for up to 24 months [32, 22]. Cutaneous papillomas may persist for 6 to 12 months before undergoing spontaneous regression [32, 22]. The exact mechanisms resulting in spontaneous regression or spread of papillomas are unknown. Papilloma regression is thought to be associated with the presence of CD4+ and CD8+ lymphocytes. These cells, especially the CD4+ cells, activate macrophages, inhibit viruses via cytokines, kill keratinocytes, or all of these [32, 22]. In one study, Nichols et al. [25], in order to investigate events during regression of mucosal papillomas, obtained chronologically biopsies from beagles experimentally infected with canine oral papillomavirus. Small raised, focal, smooth, domed single or multiple masses (8-12 mm) appeared 5 weeks post-infection; an increasing in size (14mm) of warts with multiple projecting papillae was observed by week 8 and a complete disappearance by week 11. Biopsies taken at week 8 showed multiple apoptotic keratinocytes and a prominent lymphocytic infiltrate that obscured the dermo-epidermal interface explaining the regression of warts. In our case, histopathological examination showed neither apoptotic keratinocytes nor prominent lymphocytic infiltrate, features compatible with a non-regressing form of papilloma.

Unusually severe or persistent and non self-limiting forms of papilloma are either associated with immunosuppression, old age and recent chemotherapy or corticosteroid and cyclosporine A therapy or without any identifiable underlying cause [28, 1, 20, 23, 10, 5, 8].

Occasionally, incomplete regression occurs, and a few papillomas persist indefinitely [32]. Nichols et al. described a case of naturally occurring extensive COPV infection in which the papillomas failed to regress and were refractory to all treatments, including vaccination [24].

Breed predispositions putatively associated with an inherited immune defect may exist, although the available data are very limited [17, 9]. Sundberg et al. reported two Shar Pei dogs from the same littermate with oral papillomatosis [28]. In our case informations about others dogs from the same littermate were not available. In Pug dogs genetic factors rather than viruses are thought to be primarily responsible for pigmented papillomas [33].

In our case, spontaneous wart regression was not observed. Furthermore, classic therapies as magnesium chloride, spiramycin and metronidazole, and azithromycin did not result in any improvement. On the contrary, a deterioration of the condition has been observed.

In human, IFN-α2a has, for several decades, been the drug of choice to treat recurrent and recalcitrant to therapy respiratory papillomatosis [16, 29, 15]. In veterinary medicine, orally human recombinant IFN-α2a has been anecdotally reported as an adjunct therapy for canine pigmented plaques in three adult dogs with hyperadrenocorticism and hypoglobulinemia, hypoglobulinemia, and hypothyroidism respectively [27]. rFeIFN-ω has been used in dogs as a well tolerated treatment with no adverse reaction. In laboratory and field trials the use of rFeIFN-ω has shown to reduce the mortality rate, clinical signs and lesions associated with canine parvovirus [7] but it has not been tested in canine papillomatosis.

The interferons are a group of cytokines produced by leukocytes in response to viral, bacterial and tumoral stimulation [26] but the exact mechanisms of action have not been fully elucidated.

One possibility is enhancement of an immunological response against the PV-infected cells, for example by increasing major histocompatibility complex (MHC) expression [26]. An increase in MHC expression would consequently increase the ability of the immune system to respond to and combat PV infection [12].

Another possibility could be that IFN increases the rate of apoptosis in virus-infected cells [29]. IFN-α is also known to exert anti-proliferative effects in many cell types and this has been suggested to be of importance in its anti-neoplastic activities [26].

In our case, surgical removal or topical application of drugs was not possible and other classical therapies as magnesium chloride, spiramycin and metronidazole and azithromycin have not been effective.

On the contrary, the lesions significantly improved 1 week after the first course of 5-day treatment and disappeared following the second 5-day treatment with 1 MU/kg rFeIFN-ω given subcutaneously.

Even though further studies in double-blind, placebo-control, are necessary to confirm the therapeutic efficacy of rFeIFN-ω in canine papillomatosis, we think that a delayed spontaneous regression is unlikely due to the histopathological findings, the rapid response to treatment and the significant reduction in extension and number of papillomas at 2 weeks.
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References


