A case series of canine cutaneous inverted papilloma with one case showing evidence of recurrence

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Background – This article describes a case of multiple, recurrent, cutaneous inverted papillomas (CIPs) in a German shepherd dog, combined with a retrospective follow-up assessment of eight cases.

Methods – A 3-year-old, black, female German shepherd dog presented with four rapidly growing, alopecic, domed, hyperpigmented, shiny nodules, compatible with CIP. The dog was managed for pruritus, associated with atopic dermatitis, with long-term prednisolone therapy and this therapy was continued after the surgical excision. Twelve months after the initial presentation the dog was represented for two new CIP lesions, coinciding with an increased dosage of prednisolone during an allergic flare-up period.

Results – Histopathological evaluation was conducted on both the original and subsequent lesions from the case with recurrence. Eight cases of CIP, based on histopathological findings, were identified retrospectively from the authors’ diagnostic pathology service over the previous two years. All nine cases had lesions that exhibited varying degrees of inverted epithelial hyperplasia, multiple, endophytic, papillary epidermal projections, a cup-shaped base with central hyperkeratosis and active viral pathological findings (koilocytes). The submitting veterinarians were contacted and follow-up regarding recurrence and concurrent medications was obtained.

Conclusions and clinical importance – CIP is uncommonly reported, typically as a single lesion with no previous reports of recurrence, although one group of dogs with severe combined immunodeficiency developed invasive malignancies. In seven of eight retrospective cases no recurrence of CIP was recorded. The authors speculate that the recurrence in the German shepherd dog may have been associated with chronic (although low-dose) glucocorticoid administration.

Introduction

Canine papilloma virus (CPV) is an aetiological agent for a variety of skin lesions in dogs.1 Clinical presentations include pigmented viral plaques, oral papillomatosis (OPV), exophytic cutaneous papillomas, cutaneous inverted (endophytic) papillomas (CIPs), digital papillomatosis and genital papillomas.2,3 The common exophytic variants develop in young dogs on the face, ears and extremities; they typically resolve spontaneously over weeks to months.1 The CIP variant has been reported most commonly on the ventrum, digits and pawpads,1,4 and also on the ventral neck and concave pinna, or disseminated multifocally.4,5 The typical appearance is solitary grey to flesh-coloured, elevated, alopecic, dome-shaped masses of 1–2 cm in diameter containing a wide central pore.5,6 One boxer dog with distinctive histological features of CIP had multiple, black 2 mm papules.4 In a colony of laboratory beagle dogs with severe combined immunodeficiency (SCID), CIP lesions (mostly interdigitally and footpad located) were reported along with some exophytic papilloma lesions.7

To the best of the authors’ knowledge, there are 12 cases of CIPs reported in published studies and in all cases recurrence has not been reported.4–7

Case history

A female, intact, 2-year-old black German shepherd dog initially presented with four nonpruritic, indolent, smooth-walled, hyperpigmented, exophytic masses with a central, rough, indented crater, on the ventral abdomen. They ranged from 3 mm to 1 cm (Figure 1) and developed over a 12 day period. The dog had signs of atopic dermatitis (AD) from <12 months of age and an 18 month course of constant prednisolone administration at a dose of 0.19 mg/kg per os on alternating days, which the owner had elected to administer after informed veterinary advice. Historically, a 50% dose reduction led to marked pruritus within a week and disseminated pustules and
The ventral abdomen shows two crateriform nodules and two hyperpigmented papules.

Figure 1. Canine cutaneous inverted papilloma; clinical findings at first presentation.

The ventral abdomen shows two crateriform nodules and two hyperpigmented papules.
Stress and immunosuppression may increase virus expression. In dogs various treatments for exophytic papillomas have been reported, although the interpretation of therapeutic success is complicated by the fact that exophytic papillomas typically resolve spontaneously. Topical therapy with imiquimod, autologous vaccines, surgical excision, cryotherapy or laser therapy have all been recommended; interferon-alpha was reported to be helpful in canine cutaneous and oral papillomas. Azithromycin was reportedly effective in the treatment of exophytic papillomas in one case series. Cimetidine is an effective treatment for papillomavirus warts in human medicine and has been used anecdotally in dogs. The only reported specific treatment for CIP has been surgical excision.

Table 1. Clinical details of eight dogs each diagnosed histologically with a single cutaneous inverted papilloma lesion

| Case number | Breed                | Age (years) | Sex | Lesion location | Recurrence                                      |
|-------------|----------------------|-------------|-----|-----------------|-------------------------------------------------|
| 1           | Swiss mountain dog   | 2           | Female | Extremity       | Otherwise healthy dog – excised, no further treatment, no recurrence |
| 2           | Galgo                | 12          | Female | Dorsal neck     | Otherwise healthy dog – excised, no further treatment, no recurrence |
| 3           | Epagneul Breton      | 5           | FS    | Dorsal paw      | Leishmaniasis case, excised and a papilloma auto-vaccine injected; no recurrence |
| 4           | Mixed breed          | 2           | Female | Dorsal paw      | Otherwise healthy dog – excised, no further treatment, no recurrence |
| 5           | English bulldog      | 0.9         | Male | Inguinal area   | Otherwise healthy dog – excised, no further treatment, no recurrence |
| 6           | Mixed breed          | 3           | Female | Extremity       | Otherwise healthy dog – excised, no further treatment, no recurrence |
| 7           | Malinois             | 2           | Male | Dorsal paw      | Otherwise healthy dog – excised, no further treatment, no recurrence |
| 8           | Mixed breed          | 1           | Male | Inguinal area   | Lost to follow-up |

Figure 2. Canine cutaneous inverted papilloma in haired skin; histopathological and immunohistochemical findings
(a) Papillomatous lesion with inverted endophytic growth. The multiple papillary epidermal projections open superficially into a central keratin core and extend downward to form the cup-shaped architecture. Haematoxylin & eosin, x40.
(b) Close up of the epithelial papillary projections with keratinocyte hyperplasia and dysplasia; H&E, x200.
(c) Multiple keratinocytes in the stratum granulosum have basophilic cytoplasm that is compatible with viral cytopathic effect (black arrows); as well as an eosinophilic intranuclear inclusion body (white arrow head) and two apoptotic/necrotic cells (see black arrow heads). Other cells have clear cytoplasm and numerous enlarged keratohyalin granules (koilocytes), H&E, x400.
(d) Immunohistochemical staining for papillomavirus (with a commercial anti-bovine papilloma virus E2 antibody (ab1072, Abcam; Cambridge, UK)) reveals positively staining nuclei in the stratum granulosum and upper stratum spinosum (see black arrow heads).
Because viral infections can be a consequence of immunosuppression in dogs, it is possible that in the case with recurrence the CIPs developed both initially and a year later as a result of ongoing prednisolone therapy. Most CIP lesions reported to date have been in dogs that were not considered to be immunocompromised. Three reports of CIP natural progression have been associated with a degree of immunosuppression, including the SCID beagle dogs which progressed to invasive squamous cell carcinoma, one bitch where the lesions developed post-neutering and spontaneously resolved, and a boxer dog with multiple papules with iatrogenic Cushing’s disease in which all lesions resolved spontaneously upon withdrawal of prednisolone. Previous reports and textbooks in which all lesions resolved spontaneously upon withdrawal of prednisolone as the immunosuppressive dose for dogs and <$1 mg/kg as “anti-inflammatory”. However, the anti-inflammatory to immunosuppressive dosage of glucocorticoids in dogs may be individual and published studies indicating clear cut-off values are lacking.

With respect to the case with recurrence; this was temporally associated with an atopy flare and associated increased dosage of prednisolone to 0.2 mg/kg prednisolone once or twice daily. The authors speculate that a plausible local immunomodulatory effect could have led to the development of the CIPs. In humans, proinflammatory cytokines are reported to upregulate glucocorticoid receptor gene expression, which leads to focal accumulation and increased glucocorticoid action in inflamed tissue. Such focal attenuation of a dosage otherwise regarded as “nonimmunosuppressive” in this dog, due to the inflammation associated with the AD flare, could have made the virus replication possible and triggered the formation of the CIP. Papilloma viruses are ubiquitous on canine skin, allowing opportunistic infection.

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Resumen

Introducción – este artículo describe un caso de papilomas invertidos cutáneos (CIPs) múltiples y recurrentes en un perro pastor alemán, combinado con una evaluación de seguimiento retrospectiva de ocho casos.

Métodos – Una perra pastor alemán negra de 3 años presentó cuatro nódulos alopecícicos, abovedados, hiperpigmentados y brillantes de rápido crecimiento, compatibles con CIPs. El perro estaba siendo tratado por prurito, asociado con dermatitis atópica, con prednisolona de larga duración y esta terapia se continuó después de la escisión quirúrgica. Doce meses después de la presentación inicial, el perro estuvo se presentó por dos nuevas lesiones de CIP, coincidiendo con un aumento de la dosis de prednisolona durante un período de exacerbación alérgica.

Resultados – se realizó una evaluación histopatológica tanto de las lesiones originales como de las posteriores recidivas. Se identificaron retrospectivamente ocho casos de CIPs, basados en hallazgos histopatológicos, del servicio de patología diagnóstica de los autores durante los dos años anteriores. Los nueve casos tenían lesiones que presentaban diversos grados de hiperplasia epitelial invertida, múltiples proyecciones epidermicas papilares endofílicas, una base en forma de copa con hiperqueratosis central y hallazgos patológicos virales activos (coilocitos). Se contactó con los veterinarios remitentes y se realizó un seguimiento con respecto a la recurrencia y la medicación administrada.

Conclusiones e importancia clínica – los CIPs se observan con poca frecuencia, por lo general como una sola lesión sin recidivas, aunque un grupo de perros con inmunodeficiencia combinada grave desarrolló neoplasias malignas invasivas. En siete de ocho casos retrospectivos no se observó recidiva de CIPs. Los autores especulan que la recidiva en el perro pastor alemán puede haber estado asociada con la administración crónica (aunque en dosis bajas) de glucocorticoides.

Zusammenfassung

Hintergrund – In diesem Artikel wird der Fall eines multiplen, wiederkehrenden, kutan invertierten Papilloms (CIPs) bei einem Deutschen Schäferhund zusammen mit einer retrospektiven Follow-Up Analyse von acht Fällen beschrieben.

Methoden – Eine drei Jahre alte schwarze Deutsche Schäferhündin wurde mit vier rausch wachsenden, haarloosen, kuppelartigen, hyperpigmentierten, glänzenden Knoten, die mit CIP vergleichbar waren, vorge stellt. Der Hund wurde wegen Juckreiz im Zusammenhang mit atopischer Dermatitis mit einer Langzeit Prednisolon Therapie gemanagt und nach der chirurgischen Exzision wurde diese Therapie fortgesetzt. Zwölf Monate nach der Erstvorstellung wurde der Hund mit zwei neuen CIP Veränderungen vorgestellt, was mit einer Erhöhung der Prednisolon Dosis während einem allergischen Schub zusammenfiel.

Ergebnisse – Eine histopathologische Evaluierung wurde sowohl von der Erstveränderung wie auch von der nachfolgenden Veränderung während des Wiederauftretens durchgeführt. Acht Fälle von CIP wurden – basierend auf den Ergebnissen der histopathologischen Untersuchung – retrospektiv aus dem diagnostischen Pathologie Service des Autors über den Zeitraum der vorherigen zwei Jahre identifiziert. Alle neun Fälle wiesen Veränderungen auf, die ein unterschiedliches Ausmaß an invertierter epithelialer Hyperplasie, multiple, endophytische, papilläre epidermale Projektionen, eine Tassen-förmige Basis mit einer zentralen Hyperkeratose und aktive virale pathologische Befunde (Koilocyten) zeigten. Die überweisenden TierärztIn nen wurden kontaktiert und ein Follow-Up bezüglich eines Wiederauftretens und der Verabreichung begleitender Medikation wurde festgehalten.

Schlussfolgerungen und klinische Bedeutung – CIP wird selten beschrieben, typischerweise als einzelne Veränderung ohne einen Vorbericht eines Wiederauftretens, obwohl eine Gruppe von Hunden mit schwerer Immunodefizienz invasive Malignitäten entwickelt hatte. In sieben von acht retrospektiven Fällen wurde nicht von einem Wiederauftreten der CIP berichtet. Die Autoren spekulieren, dass das Wiederauftreten bei diesem Deutschen Schäferhund im Zusammenhang mit der chronischen (wenn auch niedrig dosierten) Glukokortikoidbehandlung gestanden haben dürfte.

要約

背景 – 本論文は、ジャーマン・シェパード・ドッグに発生した多発性、再発性反転性乳頭腫 (CIP) の1例を、8例の回顧的追跡調査合わせて報告する。

方法 – 3歳、黒い、ジャーマン・シェパード・ドッグの雌犬が、CIPと思われる急速に成長する脱毛したドーム状の色素沈着した光沢のある4つの小結節を呈した。本症例はアトピー性皮膚炎に伴う搔痒のためプレドニゾロンの長期投与を受けており、外科的切除後もプレドニゾロン治療を継続した。初診時から12ヶ月後、本症例は2つの新しいCIP変化のために来院したが、これはアレルギーの再燃期間中にプレドニゾロンの投与量を増やしたことと一致していた。

結果 – 症例の初期変化およびその後の再発変化の両方について、病理組織学的評価を実施した。病理組織学的見解に基づいて、過去2年間に著者の診断病理サービスから週に8例のCIPを同定した。9例すべての変化は、程度の差こそあれ、反転した上皮過形成、覆数の、内生した、乳頭状の表皮突起、中央に
背景 — 本文描述了一例德国牧羊犬多发性、复发性皮肤内翻性乳头状瘤(CIP)，并结合8个病例的回顾性随访评估。

方法 — 一只3岁黑色雄性德国牧羊犬出现了4个快速生长、脱毛、圆顶、色素沉着、有光泽的结节，与CIP一致，该犬长期进行波尼松龙治疗以管理特应性皮炎的症状，并在手术切除后继续该治疗，初次就诊后12个月，犬出现2处新的CIP病变，与过敏发作期间波尼松龙剂量增加同步发生。

结果 — 对复发病例的原发和后续病灶进行组织病理学评价。回顾两年来的组织病理学结果，据此确定了8例CIP。这些结果来自作者所在的病理学诊断服务机构。9例均存在不同程度的内翻性上皮增生、多发性、内生性，乳头状表皮突起、杯状底伴中央乳头状过度和活动性病毒病理表现(koilocytes)的病变，联系了诊检兽医，并获得了关于复发和同时用药的随访。

结论和临床重要性 — CIP常不被报告，通常为单一病变，之前未报告复发。尽管一组并发联合免疫缺陷的患犬发生了侵袭性恶性肿瘤，在8个回顾性病例的7例中，无CIP复发记录。作者推测，德国牧羊犬的复发可能与长期(尽管剂量低)给予糖皮质激素相关。

Resumo

Contexto – Este artigo descreve um caso de papilomas cutâneos invertidos (PCIs) múltiplos e recorrentes em um cão pastor alemão, combinado com uma avaliação de acompanhamento retrospectivo de oito casos.

Métodos – Uma cadela pastor alemão de 3 anos de idade, preta, apresentou quatro nódulos alopecícos, abaulados, hiperpigmentados e brilhantes de crescimento rápido, compatíveis com PCI. O cão foi tratado para prurido associado a dermatite atópica com prednisolona a longo prazo e esta terapia foi continuada após a excisão cirúrgica. Doze meses após a apresentação inicial, o cão foi apresentado por duas novas lesões PCI, coincidindo com um aumento da dosagem de prednisolona durante um período de crise alérgica.

Resultados – A avaliação histopatológica foi realizada nas lesões originais e subsequentes do caso com recidiva. Oito casos de PCI foram identificados retrospectivamente com base em achados histopatológicos do serviço de patologia diagnóstica dos autores nos últimos dois anos. Todos os oito casos tinham lesões que exibiam vários graus de hiperplasia epitelial invertida, múltiplas projeções epidérmicas papilares endófiticas, uma base em forma de copo com hiperqueratose central e achados patológicos virais ativos (koilocytes). Os veterinários foram contatados e o acompanhamento com relação à recorrência e medicamentos simulantes foi obtido.

Conclusões e importância clínica – A PCI é raramente relatada, geralmente como uma lesão única sem relatos anteriores de recorrência, embora um grupo de cães com imunodeficiência combinada grave tenha desenvolvido malignidades invasivas. Em sete dos oito casos retrospectivos, nenhuma recorrência de PCI foi registrada. Os autores especulam que a recorrência no cão pastor alemão pode ter sido associada à administração crónica (embora em baixa dosagem) de glicocorticoides.