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First Report of Inverted Papilloma Progressing to Squamous Cell Carcinoma in the Equine Conjunctiva

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ABSTRACT

A five-year-old Arabian mare was examined after a six-month history of a painless swelling on the conjunctiva of her right eye. Clinical assessment revealed a dense, fleshy, and uniformly smooth lesion, initially suspected to be a conjunctival tumor. Microscopic study demonstrated an inward-growing mass made up of elongated papillary folds of thickened squamous epithelium supported by slender fibrovascular cores. Within the lesion, cellular irregularities and infiltration of neighboring tissue—hallmarks of squamous cell carcinoma—were evident. The findings supported a diagnosis of an inverted papilloma that had undergone malignant change. During a 12-month follow-up period, no regrowth was observed. According to available data, this appears to be the first documented occurrence of inverted papilloma in a horse; its evolution toward carcinoma underscores the need to recognize this lesion among potential conjunctival tumors when determining diagnosis and treatment.

Keywords: Equine, Ophthalmology, conjunctival lesion, Tumor pathology; inverted papilloma, Squamous carcinoma

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Introduction

Papillomas, or warts, are frequently encountered skin proliferations in horses under two years of age, usually between 12 and 24 months, and may arise either from equine papillomavirus infection or from non-infectious irritants [1, 2]. Only virus-related lesions are classed as papillomatosis. These nodules generally enlarge slowly and are most often seen around the muzzle, eyelids, or ears. Roughly 7% of all equine eye tumors belong to this group [3]. Externally, papillomas are keratinized, raised, lobulated growths often appearing in clusters measuring 2–10 cm [2]. They are benign, outward-growing (exophytic) lesions that usually regress on their own within one to six months, seldom needing therapy [4]. Histologically, they consist of thin connective cores with proliferative epithelial layers. Their orientation can be either exophytic, extending outward from the surface, or endophytic (inverted), growing downward into the underlying tissue [5].

The inverted type, an uncommon benign proliferation directed into the dermis, has been reported only in humans and dogs [6]. In dogs, these isolated nodules tend to appear on the abdomen or limbs but have not been found in the conjunctiva, though the more common outward-growing form can occur there. In human medicine, inverted papillomas are predominantly seen in the nasal passages and paranasal sinuses; their appearance on the conjunctiva is extremely rare, particularly when combined with squamous cell carcinoma (SCC) [7].

Materials and Methods

An intact five-year-old Arabian mare weighing approximately 400 kg presented with a 2-cm conjunctival growth on the lower eyelid of the right eye (RE). The owner described gradual enlargement of the lesion and mild tearing over a six-month period. The animal remained otherwise healthy and active, having received topical tobramycin for four weeks without noticeable improvement.

Both eyes were examined using a transilluminator (Heine, Gilching, Germany), a portable slit-lamp (SL-14, Kowa, Osaka, Japan), and a direct ophthalmoscope (Heine BETA 200®, Heine, Gilching, Germany). Tear output was evaluated with the Schirmer tear test (Biovision Ltd., Dunstable, UK), and intraocular pressure was measured using a TonoPen® XL (Reichert Technologies, Depew, NY, USA). The main differential considerations included neoplastic lesions and inflammatory masses such as granulomas.

Surgical excision was approved by the owner through written consent. A comprehensive health check was performed, including complete blood count and serum chemistry (total protein, albumin, urea, creatinine, bilirubin, AST, and ALT), all within physiological limits.

Premedication consisted of acepromazine (Prequillan®, Fatro, Bologna, Italy) at 0.03 mg/kg IV. Sedation was achieved using detomidine (Demosedan®, Vétoquinol Italia, Bertinoro, Italy) 0.03 mg/kg and butorphanol (Dolorex®, MSD Animal Health, Milan, Italy) 0.01 mg/kg IV. Local anesthesia was induced by topical instillation of 0.4% oxybuprocaine hydrochloride (Benoxinato Cl®, Alfa Intes, Casoria, Italy) followed by a retrobulbar block with 5 mL of 2% lidocaine (Ecuphar Italia, Milan, Italy).

The lesion was cleanly excised while the horse remained quiet and pain-free. The specimen was submitted to the Veterinary Teaching Hospital, University of Messina, for histopathological analysis. The sample was fixed in formalin, embedded in paraffin (FFPE), sectioned, and stained with hematoxylin and eosin.

Microscopic evaluation was conducted using a Leica DMI6000 light microscope (Leica Microsystems, Wetzlar, Germany) connected to imaging software (Leica Application Suite X, Leica Microsystems, Wetzlar, Germany). Mitotic figures were counted within a 2.37-mm² field at 400× magnification.

Results and Discussion

Ophthalmological findings

Microscopic slit-lamp inspection of the right eye (RE) revealed moderate vascular congestion of both the third eyelid and the conjunctiva, along with a pale gray-white elevation that was smooth, uniform, and rose distinctly above the adjacent tissue. The lesion measured around 2 cm in diameter and was situated near the nasal (medial) canthus of the lower eyelid conjunctiva **(Figure 1).**

Figure 1. A grayish-white conjunctival elevation, roughly 2 cm in diameter, at the medial corner of the right lower eyelid.

The mass was firm to touch yet slightly fragile. Examination of the anterior chamber, iris, vitreous, and fundus revealed no abnormalities. Schirmer tear test values measured 18 mm/min in the right eye and 27 mm/min in the left. Intraocular pressure (IOP) readings were 25 mmHg (RE) and 23 mmHg (LE).

The lesion was excised under general anesthesia. Upon clamping, the mass detached completely, revealing its inner surface, which displayed numerous fine, pointed, keratinized filaments **(Figure 2)**.

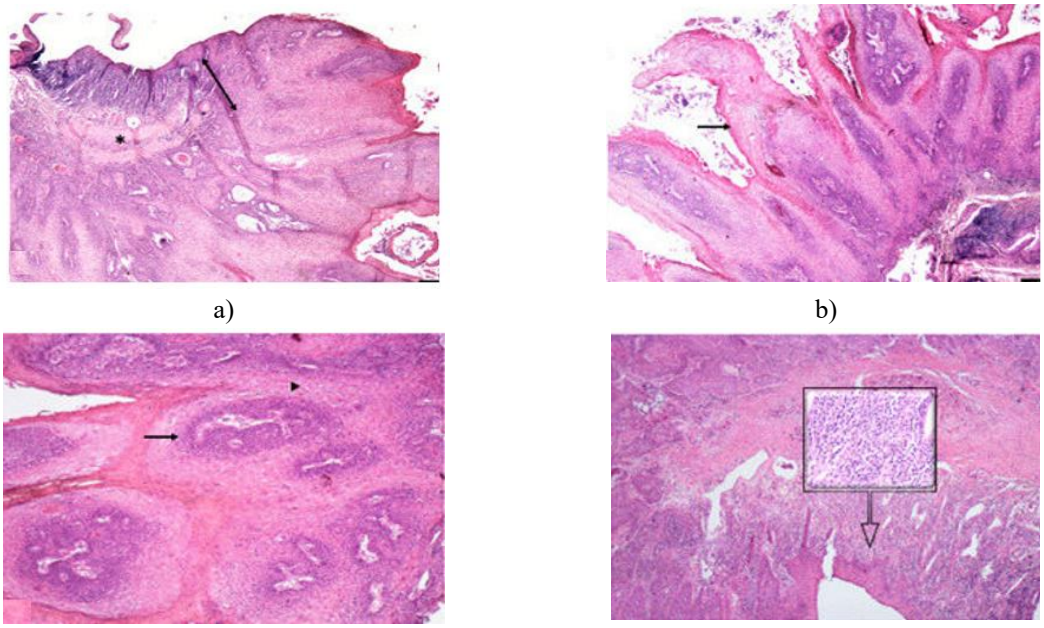
Figure 2. Inner aspect of the excised lesion, showing elongated keratinized projections.

The tumor did not invade the cornea and maintained a diameter close to 2 cm. Postoperative treatment consisted of a topical ointment containing chlortetracycline hydrochloride 10 mg/g (Ophtocycline, Dechra Veterinary Products S.r.l., Torino, Italy) applied four times daily for 15 days. The horse was re-evaluated every two months for one year following surgery; no recurrence or ocular complications were observed.

Histological findings

Microscopically, the conjunctival epithelium extended downward into the underlying tissue, forming numerous elongated, finger-like projections composed of thickened stratified squamous epithelium supported by delicate fibrovascular cores. Pockets of chronic inflammatory cells, mostly lymphocytes and plasma cells, were visible beneath the surface and around the margins. The basal epithelial layer overlying these cores exhibited hyperplasia and a mitotic index of 2–5 per high-power field. The tissue showed pronounced hyperkeratosis and abundant keratohyalin granules.

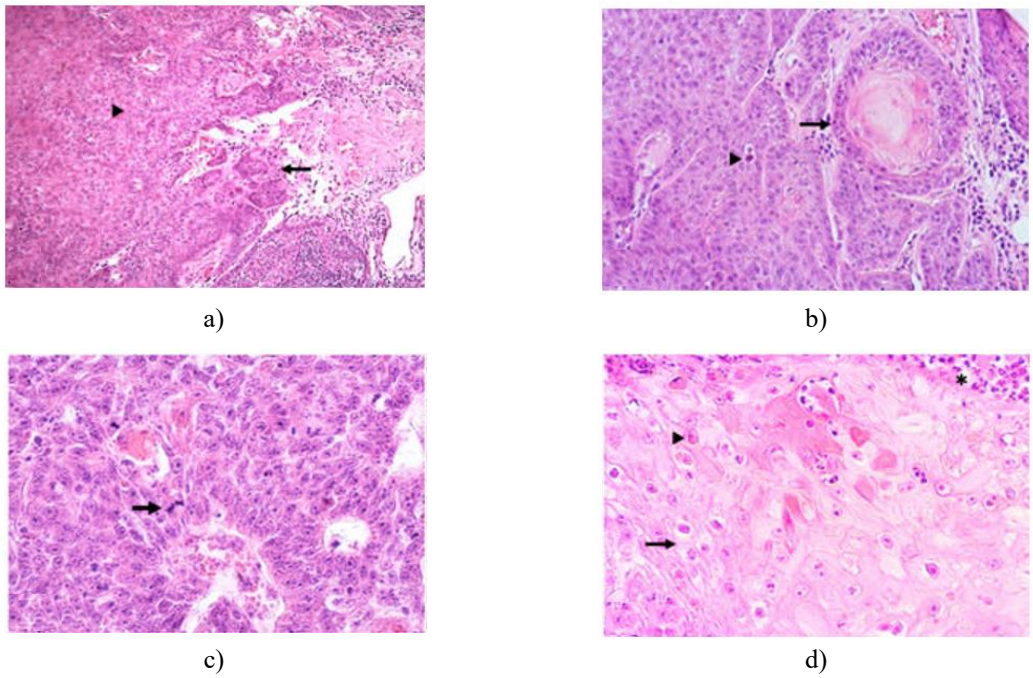
Although epithelial stratification was generally maintained, several granular-layer cells appeared swollen, with centrally located nuclei containing circular basophilic inclusions surrounded by a clear halo—findings typical of koilocytosis. Scattered acanthocytes were interspersed among normal epithelial cells. These changes aligned with papillomavirus-related cytopathic effects similar to those documented in other equine papillomatous growths **(Figures 3 and 4)**.



a) b) c) d)

Figure 3. (a) Downward extension of conjunctival epithelium (double arrow) into submucosa (asterisk, HE 5×); (b) elongated papillary outgrowths of stratified squamous epithelium (arrow, HE 5×); (c) transverse

section revealing fibrovascular cores surrounded by squamous epithelium with preserved layering (arrow, HE 10×); koilocytes visible (arrowhead). (d) Infiltrate of lymphocytes and plasma cells beneath surface epithelium (HE 2.5×; inset 40×).



a) b) c) d)

Figure 4. (a) Disorganized regions of tumor showing trabecular and papillary nests (arrowhead); invasive SCC in submucosa (arrow) (HE 2.5×). (b–d) SCC cells exhibiting moderate pleomorphism, dyskeratinization, and keratin pearl formation ((b) arrow, 20×); acantholytic cells ((b) arrowhead); elevated mitotic figures ((c) arrow, HE 40×); koilocytes ((d) arrow), intranuclear inclusions ((d) arrowhead), and neutrophilic foci ((d) asterisk, HE 40×).

Certain portions of the lesion displayed loss of epithelial polarity and disruption of normal maturation, with neoplastic cells infiltrating the submucosal layers. The cancerous component formed trabecular, papillary, and nest-like structures containing pleomorphic cells with visible nucleoli, dyskeratinization, and an increased mitotic count (4–9 per high-power field). Keratin pearls and localized neutrophilic infiltrates surrounded the malignant areas. Acantholytic cells, koilocytes, and cells containing eosinophilic intranuclear inclusions were identified along the tumor margins and among carcinoma cells **(Figure 4).**

Conclusion

In horses, both primary and secondary ocular tumors may occur, with squamous cell carcinoma (SCC) representing the most frequent and clinically significant type. This neoplasm often arises in regions such as the limbal bulbar conjunctiva**,** third eyelid**,** and palpebral margins, which are all highly exposed to ultraviolet radiation [3]. Early epithelial abnormalities—including squamous plaques**,** papillomatous lesions, and carcinoma in situ—can act as precursors that precede the full development of malignancy [8]. It is also well established that equine penile and preputial papillomas may progress into SCC at a relatively high rate [9].

Among benign epithelial proliferations, inverted papilloma represents a variant of the classical papillomatous pattern that has occasionally been linked to SCC. In human medicine, approximately 9.1% of patients with inverted papilloma exhibit malignant transformation [10]. Although such an association is recognized, the pathogenetic relationship between the two entities remains incompletely understood. SCC may arise in connection with inverted papilloma in three possible scenarios**:** (1) as microscopic malignant foci within the papillomatous structure, (2) as an independent synchronous carcinoma adjacent to the benign lesion, or (3) as a metachronous malignancy developing at the previous excision site of an inverted papilloma [11–13].

The link between papillomavirus infection and the emergence of epithelial neoplasia has been widely documented. Papillomas induced by viral agents are typically recognized through their papillary architecture and cytopathic features, in addition to the identification of viral particles by supplementary diagnostic methods [14, 15]. In the current case, both the gross morphology and microscopic profile were highly suggestive of a viral origin**,** although no molecular confirmation was obtained.

Recently, the progression from papilloma to SCC has gained attention as a notable issue in canine oral papillomas [16]. However, a similar association involving inverted papilloma has not previously been reported. The findings presented here—documenting an inverted papilloma with malignant transformation in an equine conjunctival site—suggest that this pathological connection should also be considered in other species susceptible to papillomatous growths. Consequently, the present report emphasizes the importance of including inverted papilloma in the differential diagnosis of conjunctival tumors, and provides valuable insights for refining the therapeutic approach to papillomatous lesions in veterinary ophthalmology.

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Conflict of Interest: None

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Ethics Statement: None

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