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Abstract:

Background: Keratoacanthoma is a common cutaneous neoplasia in humans that most often occurs on sun exposed sites and is considered a rapidly growing pseudomalignancy, resembling squamous cell carcinoma (SCC), which most likely derives from the hair follicle cells [1]. Macroscopic changes can not differentiate the cause of the skin lesions, and histology is needed to differentiate the two tumors, although in some cases keratoacanthoma and squamous cell carcinoma have been used interchangeably in broiler chickens and parakeets [2,3,4].

Case description: Beak keratoacanthomas were diagnosed in two birds from two different households: in a 10-year-old male and in a 1-year-old male budgerigar
(Melopsittacus undulatus). The main clinical finding in both birds were hyperkeratotic lesions on and around the beak caused by Knemidocoptes spp mites and a mass formation on the side of the lesions. Both masses were solid red, ulcerated and would bleed easily.

Conclusions: Histology results revealed invasive epithelial neoplastic changes with centripetal keratin formation resembling epithelial keratoacanthomas that were formed due to the extensive epithelial damage. Both birds died from profuse hemorrhaging from the well-vascularized tumor. No keratoacanthoma formations were observed in the female cage mates.

Case relevance: In the two cases described in this report keratoacanthomas developed in animals with extensive skin lesions caused by Knemidocoptes spp infection. Further studies are warranted to confirm the association between these disorders.

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**Conclusions and Case relevance:** In the two cases described in this report keratoacanthomas developed in animals with extensive skin lesions caused by Knemidocoptes spp infection. Further studies are warranted to confirm the association between these disorders.

Key words: Keratoacanthoma; budgerigar; scaly face; Knemidocoptes spp; neoplasia; bird

**Introduction**

Keratoacanthoma is a common cutaneous neoplasia in humans that most often occurs on sun exposed sites and is considered a rapidly growing pseudomalignancy, resembling squamous cell carcinoma (SCC), which most likely derives from the hair follicle cells [1]. Macroscopic changes can not differentiate the cause of the skin lesions, and histology is needed to differentiate the two tumors, although in some
cases keratoacanthoma and squamous cell carcinoma have been used interchangeably in broiler chickens and parakeets [2,3,4].

**Case report**

Case 1: An estimated 10-year-old male and a 3-year-old female budgerigar (*Melopsittacus undulatus*) were brought to the Vet Piraeus Clinic, Athens, Greece. The birds were presented for white outgrowths around the beak, cere and legs. The lesions were more severe in the male bird, whose beak was also deformed (scissors beak) and resembled a honeycomb (Fig 1A). Neither of the birds had been previously examined by a veterinarian, and the owner’s main complaint was the males’ inability to eat properly.

During examination, both birds were alert and responsive. Their body condition score was 3 out of 5, with a body weight of approximately 28 g. Both birds were clinically examined, a fecal microscopic examination and skin scrapping from each of their beaks were undertaken. Whitish encrustations were observed on the sides of the females’ beak and on the legs, whereas on the male, lesions were mostly seen covering the whole beak, which had a porous, crusty appearance. The microscopic fecal examination was unremarkable (no pathogens observed by native microscopic examination and Diff Quick staining) while the skin scrapping revealed the presence of *Knemidocoptes* spp. Both birds were treated with ivermectin (10-15 mg/kg, on the dorsal part of the neck, Beaphar, Pulmosan, spot on) which was repeated 3 weeks later. The male’s beak was carefully trimmed down. One month later the male’s beak was free of encrustations, but the shape of the cere and nostrils remained deformed (Fig. 1B) The female had escaped, no follow up was possible. Two months later, the male budgerigar was handed over once again having a small mass at the right corner.
of the beak (angulus oris). The mass was small (1-2 mm), red, rod-shaped and solid in texture that did not affect the birds’ eating behavior but exhibited intermittent bleeding. Surgical removal and biopsy were offered but declined by the owners at that time. Trimethoprim-sulfamethoxazole (400 mg/L drinking water for 1 week, Tafarm, Aviomycine) and meloxicam (0.4 mg/kg, PO for 4 days, Boehringer Ingelheim, Metacam 0.5 mg/ml oral) on a small amount of feed were prescribed. A week later, the bird returned, the mass was ulcerated, and the owner described the bird often scratching its beak on the cages’ perches and bars. At that point, surgery was elected. The bird was premedicated with midazolam (0.3 mg/kg IM, Roche, Dormicum), butorphanol (0.3 mg/kg, SC, LeVet, Torphadine 1%) and meloxicam (0.3 mg/kg, SC, Boehringer Ingelheim, Metacam inj.). General anesthesia was induced by isoflurane (maintained at 2%) and oxygen (1.5 L/min) via face mask, and fluids (saline 0.9% at 30 ml/kg SC) were administered subcutaneously. The surgical area was aseptically prepared, and the mass was excised using electrocautery, but the defect could not be sutured, and the wound was left to heal by secondary intention. The mass was sent for histopathological analysis. The bird recovered uneventfully, returned home the same day and was prescribed trimethoprim-sulfamethoxazole (400 mg/L drinking water for 1 week, Tafarm, Aviomycine) and meloxicam (0.4 mg/kg, PO for 4 days, Boehringer Ingelheim, Metacam 0.5 mg/ml oral). Three weeks later, the owner reported that the mass had regrown, but they did not wish to pursue any further surgery. The bird died a week later of excessive bleeding from the ulcerated lesion. No necropsy was performed.

Case 2: A pair of budgerigars (a male and a female) of approximately 1 year-old with progressive white encrustations around their beak and face were handed over. The male also had a large mass, originating from the left corner of the lower beak (angulus
orris), which was partly covered by encrustations (Fig. 2). The birds had no previous medical history. Both birds were active, stood upright and responded to verbal stimuli. The birds were in good body condition (3 out of 5) with a body weight of approximately 30 g. The female had minimal white encrustations, only visible at the corners of the beak, whereas the male had an elongated, crusty beak surrounded by whitish, hyperkeratotic and hyperplastic outgrowths on and around the cere, the corners of the beak and on the legs. Both birds had unremarkable fecal examinations (no pathogens observed by native microscopic examination and Diff Quick staining) while the skin scrapings revealed *Knemidocoptes spp*.

Both birds received a treatment with ivermectin (10-15 mg/kg, on the dorsal aspect of the neck, Beaphar, Pulmosan, spot on). Three weeks later, the birds were free of crusty lesions, but the mass on the left side of the males’ mandible remained. The owners did not want to proceed to further treatment at that time. A month later, the male was handed over again with bleeding of the mass. The mass had increased in size (1.5 cm diameter), and its capsule was ulcerated. Surgical excision and biopsy were elected. The bird was premedicated with midazolam (0.3 mg/kg IM, Roche, Dormicum), butorphanol (0.3 mg/kg, SC, LeVet, Torphadine 1%) and meloxicam (0.3 mg/kg, SC, Boehringer Ingelheim, Metacam inj.). General anesthesia with isoflurane (maintained at 2 %) and oxygen (1.5 L/min) was administered via face mask. Fluids (saline 0.9% at 30 ml/kg, SC) and enrofloxacin (10 mg/kg SC, Bayer, Baytril 5%) were administered. The surgical excision was difficult due to profuse bleeding of the mass despite the use of electrocautery. The bird recovered from anesthesia slowly. The following morning, the bird was alert but bled again from the surgical site. Despite the efforts to control the bleeding and reanimate the bird, it succumbed, presumably due to excessive blood
loss. Owners declined full postmortem examination, and only the mass was sent for histopathology.

**Histopathology**

The two biopsies (a mass of lentil size and a mass of 1.4x1.1x0.5 cm) were sent for histological analysis. The tissue samples were fixed in 10% neutral buffered formalin and submitted to the Department of Pathology, Faculty of Veterinary Medicine, Aristotle University of Thessaloniki, for histopathological evaluation. Cross and longitudinal sections through the masses were taken following immersion for 24h in decalcification solution. The tissue samples were embedded in paraffin following a routine procedure. Dewaxed, 3-5 μm-thick sections were stained with hematoxylin-eosin for viewing their histological architecture by light microscope.

The histological picture of both paraffin embedded masses was identical, showing focal ulceration of the epithelium and inflammatory reaction in the subcutaneous tissue, infiltrated by heterophils and lymphocytes (Fig. 3 A). Vascularization was well developed. The tumor parenchyma was formed by nests of stratified squamous epithelial cell areas, few of which contained centrally located keratin substance (Fig. 3 B). The neoplastic cell size did not display anisocytosis and had infrequent mitotic figures (3-5 per high power). No necrosis was identified. The capsule of the tumor was not invaded by the neoplastic cells. Based on the clinical signs and histological findings of the biopsies, the diagnosis was a keratoacanthoma.

**Discussion**

The histological picture of a keratoacanthoma differs according to its location (human lower lip, canine nail bed, avian beak) [5,6,7]. It is usually characterized by a central
core of keratin surrounded by centripetal keratinization of squamous epithelial cells, similar to that observed in the superficial epidermis, and rarely show verrucous plaque (or nodular) lesions without a central keratin–filled crater (crateridorm architecture) [5,6,7,8].

The etiology of keratoacanthoma is not well known. The most important etiologic factor associated is the chronic irritation of the skin, especially the actinic damage, which can be related to trauma, burns, tar exposure, human papillomavirus, immunosuppression and genetic factors [9,10]. In an unpublished study on broiler chickens, 363/1,373,989 (0.02%) carcasses had evidence of cutaneous ulcerative lesions. Of those 363 carcasses with ulcerative lesions, keratoacanthoma was diagnosed in 169 (46.6%). This condition was more often found in springtime and more often presented in broilers with multiple skin lesions. The type of bedding also tended (P=0.12) to alter the incidence of keratoacanthomas (birds reared on sawdust, 100%; wood shavings or sawdust, 67%; only savings, 42%) [11]. Other factors, such as the stress encountered at the peak of egg production, do seem to be involved in 30-week-old broilers, in which leg toe keratoacanthomas spontaneously regressed 28 weeks later [12]. Neoplastic lesions of the avian beak have been infrequently reported in various bird species, out of which very few cases were distinguished as keratoacanthomas [7,11,13,14,15,16]. Budgerigars are referred to in the literature to be more likely to develop neoplastic lesions than other psittacine species [17]. A case of beak keratoacanthoma has also been previously reported in a male budgerigar that suffered from extensive beak malformation, of which no causative factor was identified [7].

Although keratoacanthoma has not been related to a specific causative factor in birds, other neoplastic lesions in the avian organism have been related to some well-known
viral diseases (avian pox-virus, Marek’s disease, avian leukosis virus). In contrast, parasitic infections have not been clearly proven to do so in birds, as it has been reported in humans and dogs [18,19]. In birds, the coexistence of viral-induced neoplasia has been linked to acceleration by parasitic infestations; on the other hand, very few cases of neoplasia in avian species have been linked to parasites [20,21]. Chronic diffuse typhlitis caused by *Heterakis gallinarum* and *Heterakis isolonche* in golden pheasants associated with neoplastic nodules in the muscular and submucosa layers is one of these rare cases [22]. The proposed mechanism of carcinogenesis from parasitic pathogens seems to be a) inflammation, b) oxidative stress caused by parasite-derived molecules and c) cell proliferation [18].

*Knemidocoptes pilae* mite infection, also known as “scaly face/scaly leg” disease, occurs commonly in budgerigars. Its burrowing nature can lead to extensive hyperkeratotic lesions in the face, beak and legs that resemble a honeycomb [23].

To the authors’ knowledge, searching on PubMed and Google Scholar using the keywords: Keratoacanthoma, budgerigar, *Knemidocoptes* spp, neoplasia, bird, no published studies were found demonstrating that *Knemidocoptes* mite infection can lead to or is correlated with neoplastic changes. In these two cases, both birds of the same sex suffered from extensive beak lesions and developed neoplasia. The histology results revealed the same crater-like architecture, suggesting a keratoacanthoma neoplasia. The tumors were highly vascularized, a finding that led to diffuse and uncontrollable hemorrhaging leading to the birds’ deaths. Unfortunately, none of the owners agreed to have a postmortem performed, a restriction that might have shed more light on the affected area or the assumption of possible metastasis. Interestingly, both birds reported here and a previously published case that developed keratoacanthomas were males [4,7]. In broiler chickens, the male-female ratio of the
carcasses examined with avian keratoacanthoma (dermal SCC) was 1.5: 1 [3]. In human medicine, keratoacanthoma has a peak incidence between the sixth and seventh decades of life, with male preponderance [9].

The treatment of choice is complete excision of the tumor, as it allows histopathological evaluation of the lesion and the exclusion of a keratoacanthoma-like SCCs or keratoacanthomas with an SCC component [9]. Complete excision was the only treatment approach significantly associated with complete or partial response and increased survival time in birds with SCC [24].

Despite its variable observed effectiveness, radiation therapy has been used as a method for neoplasia treatment, with or without the combination of chemotherapeutic drugs in different bird species [25, 26, 27, 28, 29]. Promising results were also found after a successful treatment of a keratoacanthoma in a human patient with electrochemotherapy [30]. The results suggest that intralesional bleomycin injection combined with electroporation could represent a valid alternative therapeutic approach for the treatment of keratoacanthomas [30].

In conclusion, we described two cases of keratoacanthoma originating from skin lesions from two different budgerigars that were infected by the skin parasite *Knemidocoptes spp*. Further studies are needed to investigate the potential correlation of the ectoparasites and keratoacanthoma, including risk factors, gender predisposition and potential metastatic extension.
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Figure 1A: Case 1 budgerigar, before treatment, showing characteristic, extensive upper and lower beak lesions due to Knemidocoptes spp infection.
Figure 1B: Case1 budgerigar after treatment, with malformed and shortened beak. No mass had yet developed.
Figure 2: Case 2 budgerigar with porous, hyperkeratotic lesions due to Knemidocoptes spp infection and a solid, ovoid mass formation on the left side of its lower beak.
Figure 3A: Histology picture from the keratoacanthoma of Case 1 budgerigar, showing focal ulceration of the epithelium, nests of stratified squamous epithelial cell areas, and inflammatory reaction in the subcutaneous tissue, infiltrated by heterophils and lymphocytes.

Figure 3B: Histology picture from the keratoacanthoma of Case 2 budgerigar, showing nests of stratified squamous epithelial cell areas containing centrally located keratin substance. Vascularization is well developed.