Case Report

A Case Report of an Eyelid Amelanotic Malignant Melanoma in Ferret (*Mustela putorius furo*)

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Abstract

Amelanotic malignant melanoma is a rare subtype of melanoma that can occur in any part of the body, presenting in various forms and associated with a poor prognosis. Due to the absence of the pigment melanin, clinical diagnosis is challenging, often leading to delays in treatment. The primary treatment is early surgical intervention, which can be combined with radiotherapy, cryotherapy, and chemotherapy if necessary. To the best of the autho's knowledge, this is the first report of an eyelid amelanotic malignant melanoma in a ferret (*Mustela putorius furo*). A 5-year-old male ferret was presented with a small, irregular, protruding pinkish firm mass located in the medial of the left lower eyelid, extending to the palpebral conjunctiva of the left eye. The mass did not respond to medical treatment. Thoracic and abdominal radiographs revealed no abnormalities. Hematology and serum biochemistry results were within normal limits. The left eyelid mass was surgically removed using the H-plasty technique for biopsy. Histopathological examination and immunohistochemistry labeling with Melan-A confirmed a diagnosis of amelanotic malignant melanoma. A recurrent mass was observed 14 weeks after the initial surgery. Pre-operative computed tomography (CT) revealed that the left eyelid mass had extended into the left retrobulbar region, causing left ocular compression and exophthalmos. A second surgical excision and enucleation were performed. Histopathological evaluation confirmed the diagnosis of amelanotic malignant melanoma. Approximately 5 weeks after the second surgery, the tumor recurred and invaded the oral cavity, with bone lysis at the zygomatic arch and maxilla. The ferret was found dead at home approximately 8 months after the diagnosis. Amelanotic malignant melanoma appears to be a highly aggressive type of tumor in ferrets, and surgical removal alone is not effective in preventing metastasis or prolonging survival. Although uncommon, amelanotic malignant melanoma should be considered in the differential diagnosis of eyelid neoplasms in ferrets.

Keywords: Amelanotic malignant melanoma, Cancer, Eyelid, Ferret

รายงานสัตว์ป่วยมะเร็งเมลาโนมาชนิดไม่สร้างเม็ดสีที่บริเวณเปลือกตาในเฟอเรท (*Mustela putorius furo*)

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บทคัดย่อ

มะเร็งเมลาโนมาชนิดไม่สร้างเม็ดสีเป็นมะเร็งที่พบได้น้อยแต่มีความรุนแรงมาก สามารถเกิดขึ้นได้กับทุกส่วนของร่างกายในหลากหลายรูปแบบ เนื่องจากเป็นมะเร็งที่ไม่ผลิตเม็ดสี จึงยากต่อการวินิจฉัยหรืออาจวินิจฉัยผิดพลาดส่งผลให้เกิดการรักษาที่ล่าช้า การผ่าตัดเป็นวิธีการรักษาที่เป็นมาตรฐานโดยสามารถทำร่วมกับการให้รังสีบำบัด การบำบัดด้วยความเย็น และการให้ยาเคมีบำบัด รายงานสัตว์ป่วยนี้เป็นรายงานแรกของการเกิดมะเร็งเมลาโนมาชนิดไม่สร้างเม็ดสีที่บริเวณเปลือกตาในเฟอเรท เฟอเรทเพศผู้ อายุ 5 ปี ตรวจพบก้อนเนื้อสีชมพูขนาดเล็ก รูปร่างไม่สม่ำเสมอ บริเวณกลางเปลือกตาล่างจนถึงเยื่อบุตาขาวด้านในของเปลือกตาล่างซ้ายและไม่ตอบสนองต่อการรักษาทางยา ผลการตรวจเลือดและรังสีวินิจฉัยไม่พบความผิดปกติใดใด จึงพิจารณาผ่าตัดเอาก้อนเนื้อออกทั้งหมดและตัดเก็บชิ้นเนื้อเพื่อส่งตรวจทางพยาธิวิทยาด้วยวิธีเฮช พลาสที (H-plasty technique) ลักษณะเซลล์ที่พบทางพยาธิวิทยาและผลการตรวจทางอิมมูนฮิสโตเคมีวินิจฉัยได้ว่าเป็นมะเร็งเมลาโนมาชนิดไม่สร้างเม็ดสีที่บริเวณเปลือกตา หลังผ่าตัด 14 สัปดาห์พบว่ามีการกลับมาเป็นซ้ำ และก้อนเนื้อขนาดใหญ่ขึ้น เฟอเรทได้รับการตรวจเอกซเรย์คอมพิวเตอร์พบว่าก้อนเนื้อที่เปลือกตาซ้ายขยายเข้าไปในบริเวณหลังตาซ้ายส่งผลให้ตาซ้ายถูกดันออกจากเบ้าตา จึงทำการผ่าตัดก้อนเนื้อและควักตา ผลการตรวจทางพยาธิวิทยายืนยันว่าเป็นมะเร็งเมลาโนมาชนิดไม่สร้างเม็ดสีที่บริเวณเปลือกตา ประมาณ 5 สัปดาห์หลังจากการผ่าตัดครั้งที่ 2 พบการกลับมาเป็นซ้ำของมะเร็งและลุกลามไปบริเวณช่องปากส่งผลให้เกิดภาวะการสลายตัวของกระดูกโหนกแก้มและกระดูกขากรรไกรบน เฟอเรทเสียชีวิต ประมาณ 8 เดือนหลังจากได้รับการวินิจฉัย การศึกษาพบว่ามะเร็งเมลาโนมาชนิดไม่สร้างเม็ดสีเป็นมะเร็งชนิดร้ายแรงในเฟอเรท การรักษาด้วยการผ่าตัดเพียงอย่างเดียวไม่สามารถป้องกันการแพร่กระจายตัวของมะเร็งหรือเพิ่มอัตตราการรอดชีวิตในเฟอเรทได้ ถึงแม้จะเป็นมะเร็งที่พบได้น้อย แต่ควรพิจารณามะเร็งเมลาโนมาชนิดไม่สร้างเม็ดสีในการวินิจฉัยแยกโรคเนื้องอกที่เปลือกตาของเฟอเรท

คำสำคัญ : มะเร็งเมลาโนมาชนิดไม่สร้างเม็ดสี มะเร็ง เปลือกตา เฟอเรท

Introduction

Neoplastic diseases are commonly diagnosed in domestic ferrets (*Mustela putorius furo*) (Williams and Wyre 2020). Ferrets can develop the same types of neoplasms that occur in other species. The age distribution with the highest tumor incidence is between 4 and 6 years (Williams and Wyre 2020). In ferrets, adrenocortical tumor is the most common, followed by lymphoma and pancreatic islet cell tumor (Shiga et al., 2021). Melanoma in ferrets has been reported in a limited number of cases over the years. Tunev and Wells documented a case of spontaneous cutaneous melanoma in a 4-year-old spayed female ferret in 2002. Additionally, d'Ovidio et al. (2016) described an oral malignant melanoma in a 3-year-old intact male ferret.

Melanocytic tumors are one of the most common neoplasms of the integumentary system in dogs but are rare in other domesticated species (Smedley et al., 2022; Abbate et al., 2023; Polton et al., 2024). Melanoma is a melanocytic tumor that arises from melanocytes in the skin, mucosa, and indigenous melanocytes of various internal organs (Long et al., 2023). Malignant melanoma accounts for 70% of all melanin-producing tumors and 7% of all malignant tumors (Polton et al., 2024). Amelanotic malignant melanoma is a rare subtype that constitutes approximately 2% to 20% of all melanomas in humans, that has little or no melanin pigment and can occur in any part of the body, presenting various manifestations related to the affected structure (Osama et al., 2023). Amelanotic malignant melanoma has a poor prognosis due to the absence of melanin pigment, which makes clinical diagnosis difficult, often leading to misdiagnosis and delayed treatment (Polton et al., 2024). Diagnosis of malignant melanoma with melanin pigment is straightforward, but the amelanotic form is much more challenging (Polton et al., 2024). Histopathological diagnosis may be difficult if the tumor does not contain melanin; therefore, immunohistochemistry is important for diagnosing amelanotic malignant melanoma (Mathewos et al., 2020; Pérez-Santana et al., 2024). Surgical resection with wide margins remains the primary treatment for local control of melanomas and is often supplemented by radiotherapy, immunotherapy, and chemotherapy, if necessary (Williams and Wyre 2020; Long et al., 2023; Kaminsky et al., 2023; Abbate et al., 2023). A limited number of melanoma cases in ferrets have been reported. Tunev and Wells (2002) documented a case of spontaneous cutaneous melanoma in a 4-year-old spayed female ferret. Additionally, d'Ovidio et al. (2016) described an oral malignant melanoma in a 3-year-old intact male ferret.

The aim of the present study was to describe the clinical manifestations and histological appearance of malignant amelanotic melanoma in ferrets. To date, there has been no documented evidence of amelanotic melanoma in ferrets (Mustela putorius furo) in the veterinary literature. This is the first published description of a clinical case and the histopathological findings of amelanotic malignant melanoma of the eyelid in this species.

Case description

A 5-year-old male ferret was presented to the Animal Space Pet Hospital with a history of left eye inflammation and ocular discharge for 2 weeks. Physical examination revealed a small, irregular, protruding pinkish firm mass located in the median area of the left lower eyelid, extending to the palpebral conjunctiva of the left eye (Figure 1). The remainder of the physical examination was unremarkable.

Ophthalmic examination showed that the dazzle reflex, menace response, palpebral reflex, and pupillary light reflexes (both direct and consensual) were present in both

eyes. The intraocular pressure (IOP) in both eyes was within the reference range, and both eyes were negative for corneal fluorescein staining. Nuclear sclerosis was present bilaterally. There was mild conjunctivitis in the left eye. A protruding, solitary, well-defined, firm, pinkish mass measuring 0.5 x 0.3 x 0.2 cm in the palpebral conjunctiva and lower eyelid region of the left eye was noted. The ferret was started on topical eye ointment (MAXITROL® Ophthalmic Suspension, Novartis Pharma AG, Basel, Switzerland) in a 0.5 cm strip, applied to the left eye (OS) every 8 hours, marbofloxacin at 5 mg/kg orally (PO) every 24 hours, and prednisolone at 0.5 mg/kg PO every 12 hours for 2 weeks. The ferret did not respond to the treatment.

A presurgical clinical assessment of the patient's health status was performed for an excisional surgical biopsy. While anesthetized, blood was collected from the cranial vena cava, and full-body radiographs were performed. The complete blood count and serum biochemical profile were unremarkable. Radiographic evaluation did not reveal any evidence of distant metastasis.

The ferret was premedicated with ketamine at 7 mg/kg intramuscularly (IM), midazolam at 0.5 mg/kg IM, and atropine at 0.04 mg/kg IM. An endotracheal tube was placed and maintained with isoflurane gas. Reconstructive surgery was performed using the H-Plasty technique, which involves an "H"-shaped incision to reconstruct tissue. This approach successfully removed the mass from the lower palpebral conjunctiva and eyelid margin (Figure 2). Monofilament suture material (7-0) was used for intradermal closure. The mass was fixed in 10% neutral buffered formalin for histological examination at Vet Central Lab. The tissue was embedded in paraffin, sectioned into 3 μm thick slice, and stained with hematoxylin and eosin (H&E). Additionally, immunostaining was performed using antibodies specific to Melan-A proteins to immunohistochemical evaluation.

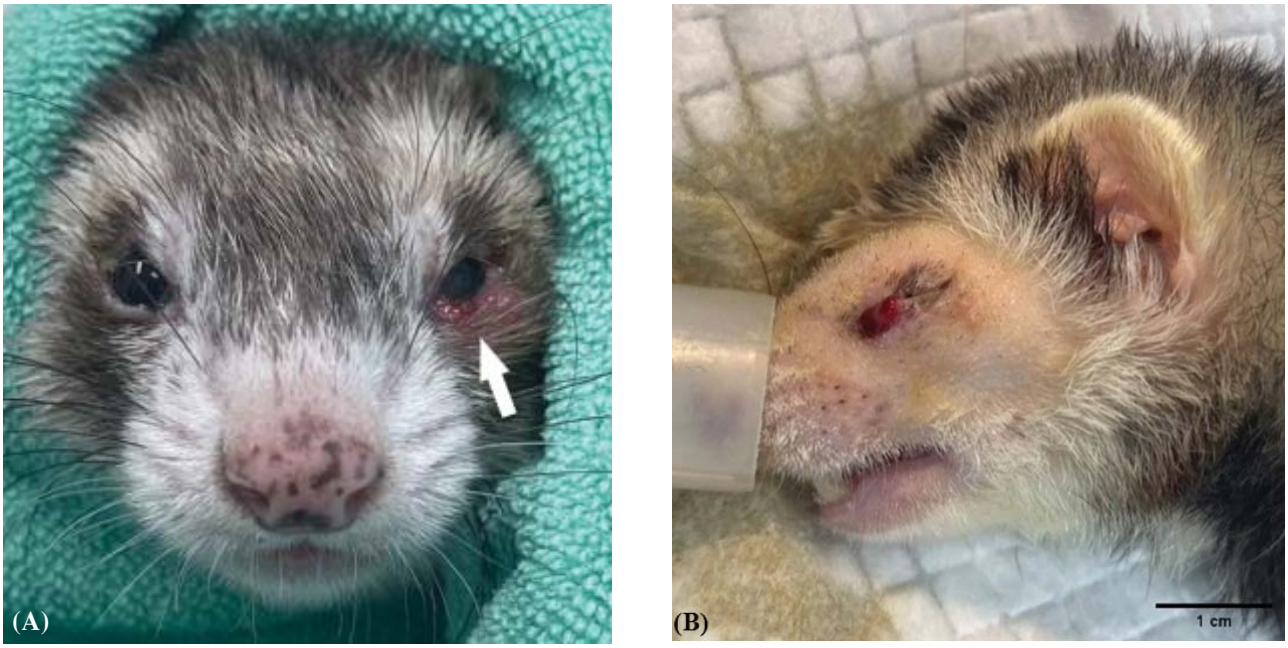

Figure 1. A 5-year-old male ferret was presented with a small, irregular, protruded pinkish firm mass located in the median left lower eyelid area to the palpebral conjunctiva of the left eye (arrow) (A). The same mass in lateral view. Bar = 1 cm (B).

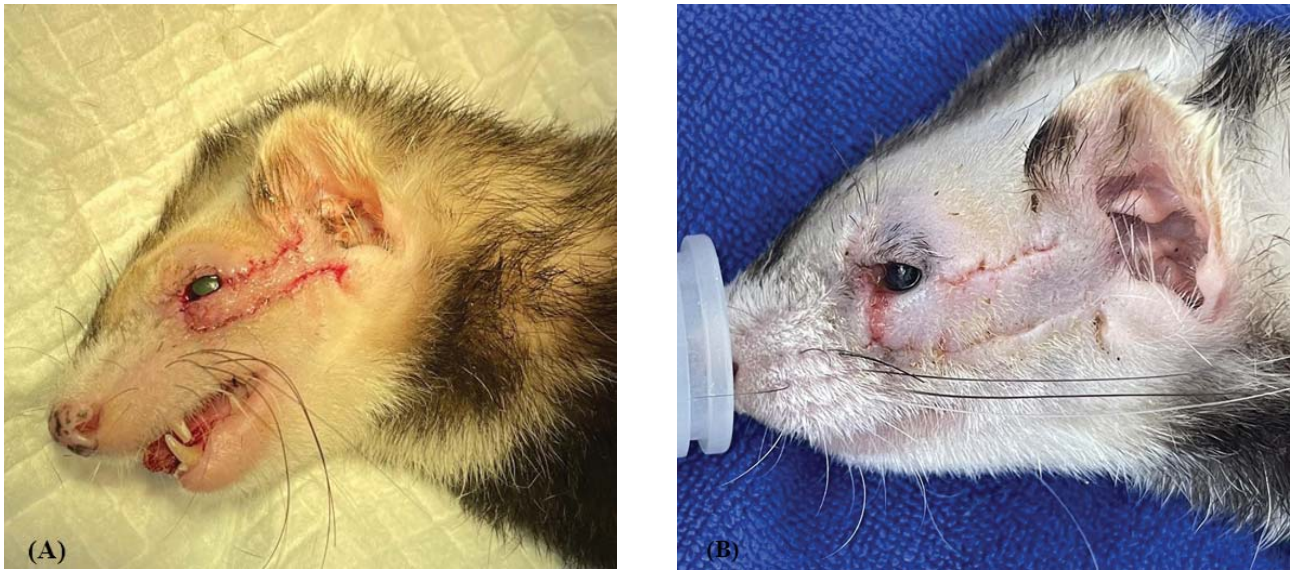

Figure 2. The H-plasty reconstructive surgery was performed to completely remove the mass in lower palpebral conjunctiva and eyelid margin of the ferret (A). Seven days after surgery, the sutures were removed (B).

The ferret was discharged with chloramphenicol eye ointment (1%) in a 0.5 cm strip OS every 12 hours, marbofloxacin at 5 mg/kg PO every 24 hours, and meloxicam at 0.5 mg/kg PO every 24 hours. The sutures were removed 2 weeks after surgery, with no complications noted at the surgical site. Approximately 14 weeks after surgery, the ferret was presented with a recurrent raised, ulcerated, reddish, irregular, firm mass measuring 1 x 1 x 0.5 cm displacing the left eye laterally (Figure 3). Pre-operative computed tomography (CT) was recommended for surgical planning of the invasive mass. Skull CT showed the left eyelid mass extended into the left retrobulbar region, causing left ocular compression and exophthalmos. The left eye was smaller compared to the right. No evidence of bone reaction or destruction was detected. Mild swelling of the left medial retropharyngeal lymph node was present; the approximated size is 4.4 x 3.3 mm. (figure 4). Thoracic CT revealed an unremarkable tracheal diameter and alignment, with no evidence of airway collapse. The pulmonary parenchyma and vasculature were also unremarkable.

An extended enucleation of the left eye globe was performed and submitted for histopathologic evaluation. However, the protruding pinkish, firm tumor measuring 2 x 2 x 2.5 cm recurred 5 weeks after enucleation and invaded the oral cavity (Figure 5). Radiographs of the skull revealed a large soft tissue opacity on the left side of the head, resulting in the loss of the left zygomatic arch and bone lysis in the body of the mandible (Figure 6). The owner requested palliative care, and the ferret was found dead at home approximately 8 months after the diagnosis.

Figure 3. The ferret was presented with the recurrence mass displacing the left eye laterally approximately 14 weeks after surgery. Bar = 1 cm.

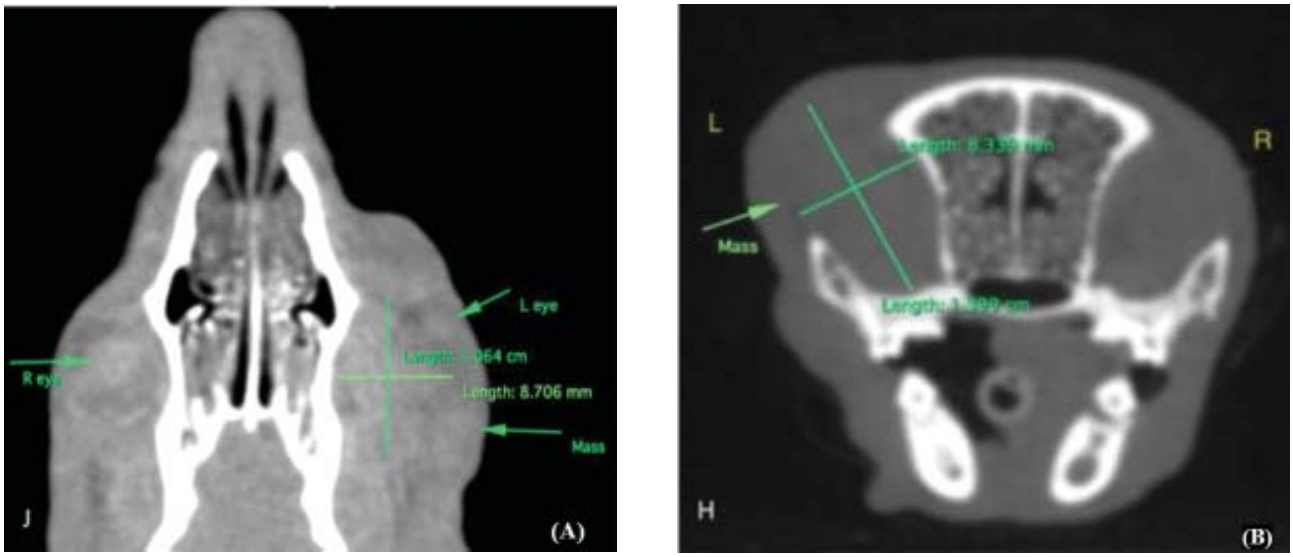

Figure 4. Soft tissue window of dorsal view skull CT scan showed left eyelid mass extended into the left retro bulbar region caused the left ocular compression and exophthalmos. Small size of left ocular (smaller compared to the right ocular). No evidence of bone reaction and bone destruction was detected. Mild reactive of left medial retropharyngeal lymph node (regional lymph node) (A). The same mass in transverse view skull CT scan (B).

Figure 5. The tumor was recurrent at 5 weeks after enucleation and invaded the oral cavity. Bar = 1 cm.

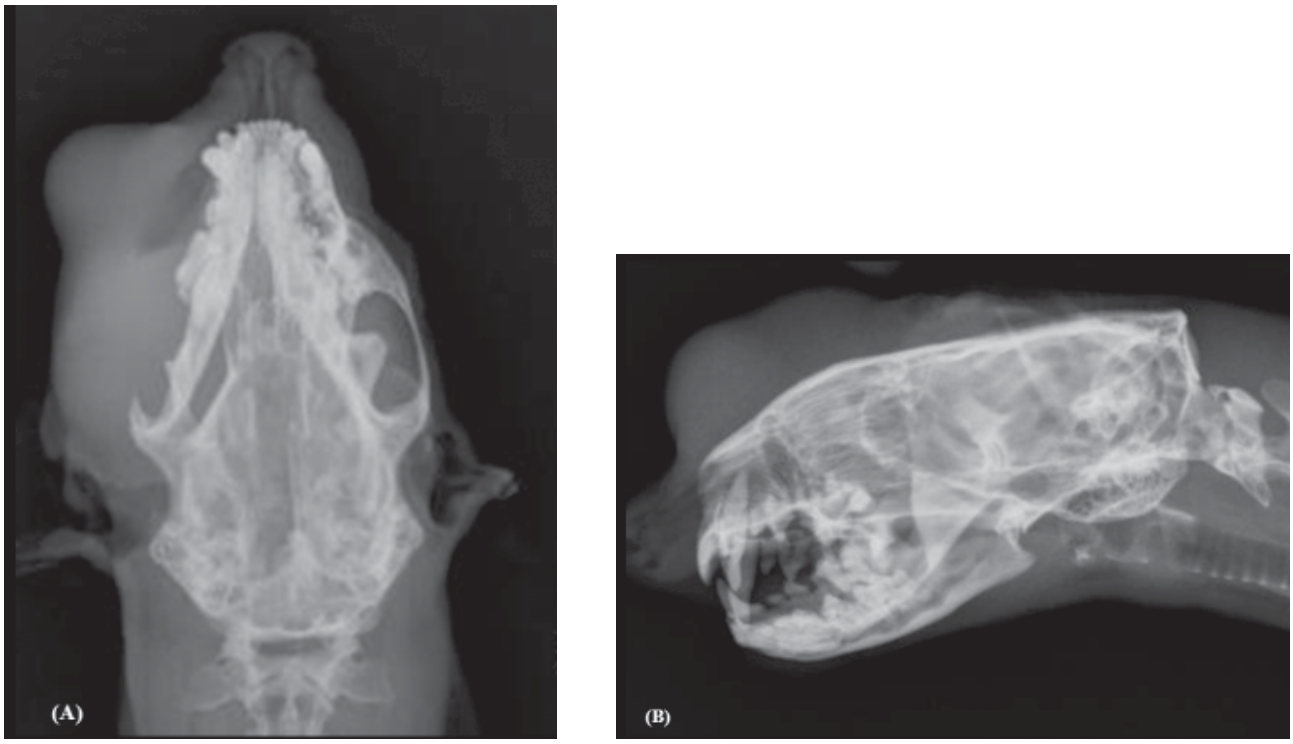

Figure 6. Radiographic examination of the skull dorsoventral view showing a large soft tissue opacity mass at left side of head affected to loss of left zygomatic arch (A). Right lateral view showing a soft tissue opacity mass at the rostro dorsal area with a bone lysis at rostal part of mandibular (B).

Results

The surgically removed mass was fixed in 10% neutral-buffered formalin and sent to Vet Central Lab, the standard laboratory procedures, for histopathological examination. The tissue sections were stained with Hematoxylin and Eosin (H&E). Histopathological examination revealed a section measuring 1 cm in size, with a soft consistency and pink coloration, from the left eyelid mass. It exhibited a well-demarcated, unencapsulated melanocytic neoplasm within the upper and deep dermis, dense palisading pattern of the epithelioid cell type of melanocytic tumor cells supported by a fibrovascular stroma. The neoplastic cells were pleomorphic, spindle and epithelioid shaped to ovoid, with variably distinct cell borders and moderate volume of pale basophilic cytoplasm. Some neoplastic cells contained scant brown pigment (melanin). The nuclei exhibited moderate anisokaryosis and large pleomorphic ovoid nuclei with prominent nucleoli. The histopathological diagnosis was amelanotic malignant melanoma of the left eyelid mass (Figure 7a). Immuno-histochemistry was recommended to confirm the tentative diagnosis. Immunopositivity for Melan-A was characterized by brown coloured staining in the cytoplasm of neoplastic cells (Subapriya 2021). Immunohistochemical labeling with Melan-A revealed that all tumor cells exhibited mild light brown cytoplasmic expression of Melan-A. The failure to demonstrate strong immunoreactivity of Melan-A was caused by incompatibility of epitope antigen of ferret species (Figure 7b).

Histopathological examination of the second surgical mass showed the section of measuring 1-2 cm in size, firm consistency, oval shape, pink to red in color, lower eyelid mass with a suppurative lesion revealed a nonencapsulated, dense palisading pattern of the epithelioid cell type of melanocytic tumor cells supported by a fibrovascular stroma. The neoplastic cells were pleomorphic, spindle and epithelioid shaped to ovoid, with variably distinct cell borders and moderate volume of pale basophilic cytoplasm. A few neoplastic cells contained brown pigment (melanin). Nuclei were large pleomorphic ovoid with prominent nucleoli. Pathological diagnosis was amelanotic malignant melanoma of the lower eyelid mass (Figure 7c).

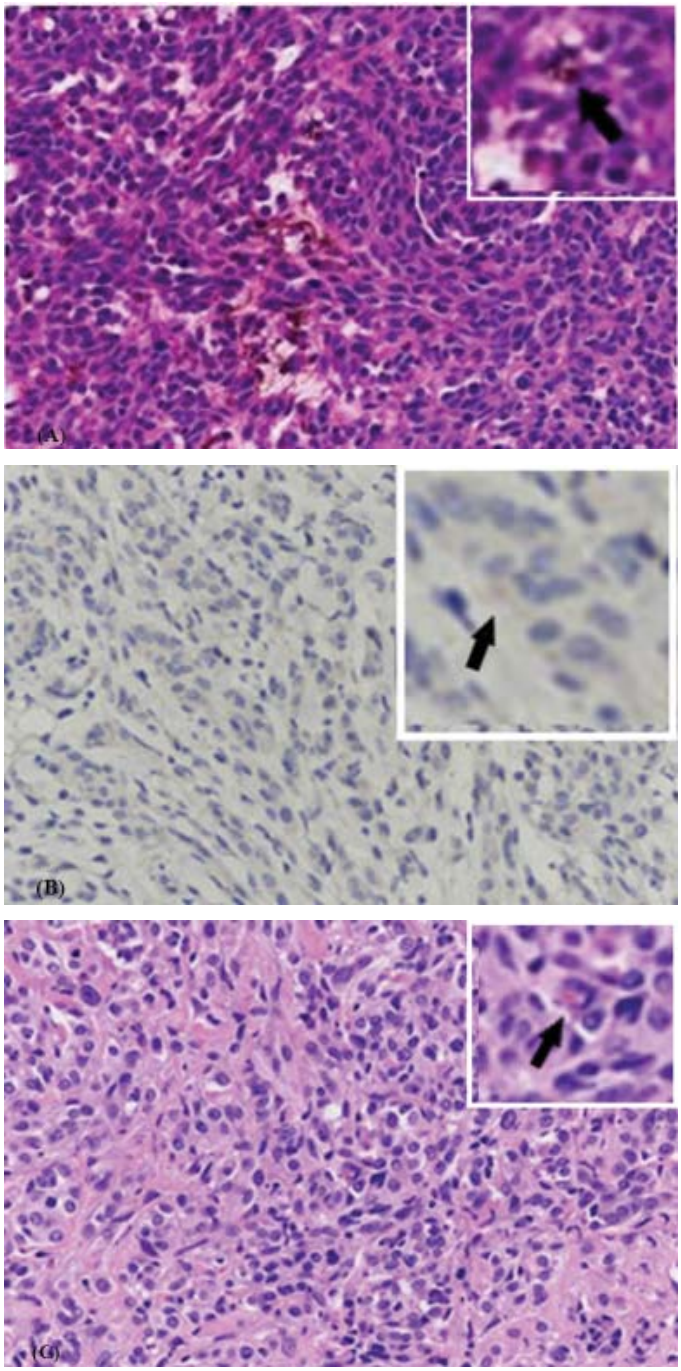

Figure 7. The eyelid; ferret. Amelanotic malignant melamona. The dense palisading pattern of the epithelioid cell type of melanocytic tumor cells supported by a fibrovascular stroma. The neoplastic cells were pleomorphic, spindle cell and epithelioid shaped to ovoid, with variably distinct cell border and moderate volume of pale basophilic cytoplasm. A few neoplastic cells contained brown pigment (melanin) (Arrow). Nuclei were large pleomorphic ovoid with prominent nucleoli (H&E stain, 40x) (A). All of tumor cells showed mild light brown cytoplasmic expression of Melan-A (Arrow) (IHC Melan-A stain 40x) (B). The second surgical mass showed a dense palisading pattern of the epithelioid cell type of melanocytic tumor cells supported by a fibrovascular stroma. The neoplastic cells were pleomorphic, spindle and epithelioid shaped to ovoid, with variably distinct cell borders and moderate volume of pale basophilic cytoplasm; some neoplastic cells contained scantly brown pigment (Arrow). The nuclei exhibited moderate anisokaryosis and large pleomorphic ovoid nuclei with prominent nucleoli (H&E stain, 40x) (C).

Discussion

Amelanotic malignant melanomas have been described in various animals, including dogs (Oliveira Júnior et al., 2022), cats (Jajou 2020), rabbits (Brandão et al., 2015), guinea pigs (Allnoch et al., 2020), and goats (Patel et al., 2020). However, melanomas are uncommon in ferrets and eyelid amelanotic melanoma is extremely rare. A few cases of melanoma in ferrets have been reported. Tunev and Wells (2002) documented a case of spontaneous cutaneous melanoma in a 4-year-old spayed female ferret. d'Ovidio et al. (2016) described an oral malignant melanoma in a 3-year-old intact male ferret. In dogs, malignant melanoma of the eyelid margin is reported in less than 1% of cases (Grahn 2023). In horse, eyelid melanomas are less commonly affected than other typical sites such as the perineum, ventral tail, and prepuce (Rose and Mair 2023). A survey of the literature found no documented evidence of amelanotic melanoma in ferrets. This is the first published case of amelanotic malignant melanoma of the eyelid in this species.

Neoplasia is commonly diagnosed in middle-aged to older ferrets, between 4 and 6 years old, with the average age of affected ferrets being 4.6 years (Otrocka-Domagala et al., 2022). Similarly, in this report the ferret was 5 years old. Clinical signs of eyelid margin neoplasia can lead to ocular complications including ocular pain, ocular discharge, conjunctivitis, and even corneal ulceration. As the size of the mass increases, clinical symptoms may be apparent including eyelid movement may be affected, making blinking difficult and leading to discomfort (Ahn et al., 2023). In this case, the eyelid tumor showed mild conjunctivitis and a protruding pinkish mass in the palpebral conjunctiva and lower eyelid region; however, clinical symptoms were not apparent.

Diagnosis is based on detailed ophthalmological exams and supported by pathological evaluation. The differential diagnosis is neoplasms and inflammatory skin diseases. Biopsy of the eyelid mass revealed the potential utility of the diagnostic method in differentiating diagnosis (Shiga et al., 2021; Long et al., 2023; Polton et al., 2024). Due to the location and size of the mass in this case, complete surgical removal with H-plasty for eyelid reconstruction was the procedure of choice for both diagnostic and therapeutic purposes. In this case, the left medial retropharyngeal lymph node (regional lymph node) showed mild reactivity; however, a lymph node biopsy was not performed due to the deep location and the small size of the retropharyngeal lymph node, which complicates access and increase the risk of damaging surrounding structures, such as blood vessels, nerves, and the trachea during the procedure (Evans and An 2014).

Differential diagnosis for non-pigmented or minimally pigmented neoplasms can be challenging. In this case, histopathological investigation of the excised mass confirmed the diagnosis of eyelid amelanotic malignant melanoma. A study on canine cytology showed a sensitivity and specificity of 100% for diagnosing pigmented melanocytic neoplasms; however, both sensitivity and specificity decrease for amelanotic melanocytic neoplasms (Smedley et al., 2022). Immunohistochemistry is recommended for poorly differentiated tumors and positive staining for melanocytic markers such as S-100, tyrosinase and Melan-A can help distinguish melanoma from other neoplasms (Smedley et al., 2022; Polton et al., 2024). In canine studies, immunocytochemistry for Melan-A may be useful in differentiating between non-melanocytic tumors and diagnosing amelanotic melanocytic neoplasms; Melan-A has been demonstrated in more than 80% of primary or metastatic canine oral melanomas (Smedley et al., 2011). Immunohistochemical

staining with Melan-A was used in the presented case to confirm the diagnosis of amelanotic malignant melanoma.

Melan-A is a specific marker for melanocytes that targets a cytoplasmic protein of melanosomal differentiation recognized by cytotoxic T-cells (Ohsie et al., 2008). In canine studies, immunocytochemistry for Melan-A may be useful in differentiating between non-melanocytic tumors and diagnosing amelanotic melanocytic neoplasms; Melan-A has been demonstrated in more than 80% of primary or metastatic canine oral melanomas (Smedley et al., 2011). Additionally, the use of Melan-A markers to confirm the amelanotic melanocytic origin in felines has also been reported (Pittaway et al., 2019). Therefore, Immuno-histochemical staining with Melan-A was used in the presented case to confirm the diagnosis of amelanotic malignant melanoma in this study.

Tunev and Wells (2002) reported on cutaneous melanoma in a ferret, the mass was characterized by closely packed large, atypical cells that were polygonal to spindle-shaped, arranged in sheets, poorly formed nests, and short bundles. Some cells contained varying amounts of granular, brown to black intracytoplasmic pigment. Nuclei were large, round to oval, and with a vesicular pattern of chromatin dispersion. Most nuclei contained one and rarely two large and round magenta nucleoli. The atypical cells of the mass stained negatively Melan-A. In the case of amelanotic melanoma in the rabbit, the cells exhibited densely cellular neoplasm with cells arranged in sheets and nests supported by a fine, fibrovascular stroma, a round epithelioid morphology, characterized by abundant, homogeneous, amphophilic cytoplasm. The nuclei were round to oval, finely stippled, and centrally located, with one to two prominent nucleoli. The neoplastic cells in this case stained strongly positive for Melan-A (Brandão et al., 2015). In this study, the neoplastic cells were arranged in a palisading pattern, while other reports described them as being organized in nests. The neoplastic cells exhibited pleomorphism, varying from spindle to epithelioid shapes and ovoid forms, with variably distinct cell borders and a moderate volume of pale basophilic cytoplasm. The nuclei demonstrated moderate anisokaryosis and large pleomorphic ovoid nuclei with prominent nucleoli, resembling findings in the amelanotic melanoma of the rabbit, although the neoplastic cells stained only mildly positive for Melan-A. The lack of strong immunoreactivity for Melan-A may be attributed to the incompatibility of the epitope antigen specific to the ferret species.

A melanocyte containing melanin can be distinguished from a melanophage by the latter's distinctive solitary distribution around the papillary dermal capillaries. Melanophages are typically larger than melanocytes and have a bright, granular cytoplasm with a coarser texture, whereas melanocytes tend to have a more uniform appearance and are smaller in size (Busam et al., 2001).

In veterinary medicine, there are no established clinical guidelines for treating amelanotic malignant melanoma of the eyelid. Therapeutic plans are based on the clinician's judgment, the patient's health, and the owner's financial considerations (Guerra Guimarães et al., 2021). In this case, due to local recurrence after surgical excision, it was concluded that eyelid amelanotic malignant melanoma may have a high risk of recurrence and distant metastasis. Consultation with an oncologist for adjunctive therapies such as cryotherapy, radiotherapy, or laser therapy was recommended. However, the owner declined due to the long distance to the university clinic. Therefore, enucleation was considered following the first recurrence of the neoplasm for invasive tumors, with frequent monitoring for further recurrence. A poor prognosis was given.

Conclusion

This report describes a case of eyelid amelanotic malignant melanoma in a 5-year-old ferret presenting with a rapidly growing mass on the eyelid. The case presentation describes the clinical and histopathological features of an eyelid amelanotic malignant melanoma in a ferret. A presumptive clinical diagnosis of an eyelid tumor was formulated based on history and clinical signs, but a definitive diagnosis was confirmed through histopathological and immunohistochemical examination of the mass after surgical excision. A study indicated that surgical removal alone in ferrets with eyelid amelanotic malignant melanoma is not effective in preventing metastasis or prolonging survival. Although uncommon, amelanotic malignant melanoma should be considered in the differential diagnosis of eyelid neoplasms in ferrets.

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