

## Concurrent occurrence of metastatic cutaneous melanoma and early feline diffuse iris melanoma in a cat

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### Abstract

This report presented a case of the concurrent diagnosis of early feline diffuse iris melanoma (FDIM) and metastatic cutaneous melanoma in a tricolored mixed stray cat. Histopathological examination of biopsy samples identified melanoma on the nasal planum, lips along with metastasis to the submandibular lymph nodes. The initial treatment included surgical resection of the primary nasal planum neoplasm and the metastatic lesions in the submandibular lymph nodes. The necropsy, performed 40 days after the surgery, revealed the metastatic nodules in multiple organs including the liver, lungs, thyroids, pericardium, pleura, peritoneum, kidneys, and numerous lymph nodes. Histopathological examination revealed a biphasic neoplastic tissue composed of a mixture of epithelioid and spindle cells in primary and metastatic tumors. Additionally, the anterior surface of the iris contained 4 - 5 rows of melanocytic interstitial infiltration indicative of early FDIM. Immunohistochemical analysis revealed that the neoplastic cells showed positive immunoreactivity for Melan-A. To the authors' knowledge, this case represented the first reported case of concurrent FDIM and cutaneous melanoma in a feline patient.

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### Introduction

Melanomas represent malignancies originating from melanocytes, a distinct type of cell derived from neuroectodermal melanoblasts. Melanocytes act as specialized dendritic cells, distributed throughout the skin and various anatomical locations, where they produce melanin pigment. The transformation of melanocytes into melanomas involves complex genetic alterations and environmental factors leading to uncontrolled growth and metastasis.<sup>1</sup> Their migratory activity during embryogenesis results in their distribution predominantly within the basal layer of the epidermis, pilosebaceous units, mucosal membranes, meninges and the uveal tract of the eye.<sup>2</sup> The distribution pattern of melanocytes plays a role in determining the susceptibility to melanomas across different animal species.<sup>1,3,4</sup> The progression of malignant melanoma involves distinct stages: Initiation, promotion, transformation and metastasis.<sup>1</sup> Some specific breeds of cats exhibit a genetic tendency towards melanoma suggesting a familial clustering and potential vulnerability.<sup>1,2,4</sup> Nevertheless, the exact risk factors for

feline cutaneous melanoma remain uncertain likely due to its rarity.<sup>4</sup> Cutaneous melanoma arises from genetically altered epidermal melanocytes influenced by complex interactions between genetic and environmental factors. It progresses rapidly from localized to advanced stages, posing a significant threat to feline health. Compared to feline dermal melanoma counterpart, they are more prevalent in dogs, white horses and specific miniature pig breeds.<sup>3</sup> Feline melanomas typically occur on the head similar to dogs with fewer instances on extremities. However, unlike in canines, histological evaluations of feline melanomas inconsistently predict clinical outcomes.<sup>1,3,4</sup>

Feline ocular melanomas including atypical melanoma, limbal melanoma and feline diffuse iris melanoma (FDIM), are notably more common and aggressive compared to other types of feline melanomas. FDIM, in particular, is characterized by a higher prevalence and greater malignancy. In this case study, a stray cat was diagnosed with both metastatic cutaneous melanoma and early FDIM highlighting the severity and complexity of such conditions in felines.<sup>5,6</sup>

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## Case Description

An 8-year-old intact female calico mixed-breed stray cat, recently adopted, was presented to the veterinary hospital of veterinary medical school. The cat exhibited a mass extending from the nasal planum to the upper lip, whisker pad and nostrils (Fig. 1A). Bilateral lymphadenomegaly (Fig. 1B) in the submandibular lymph nodes indicated possible metastasis, although radiological examinations showed no metastasis in other organs.

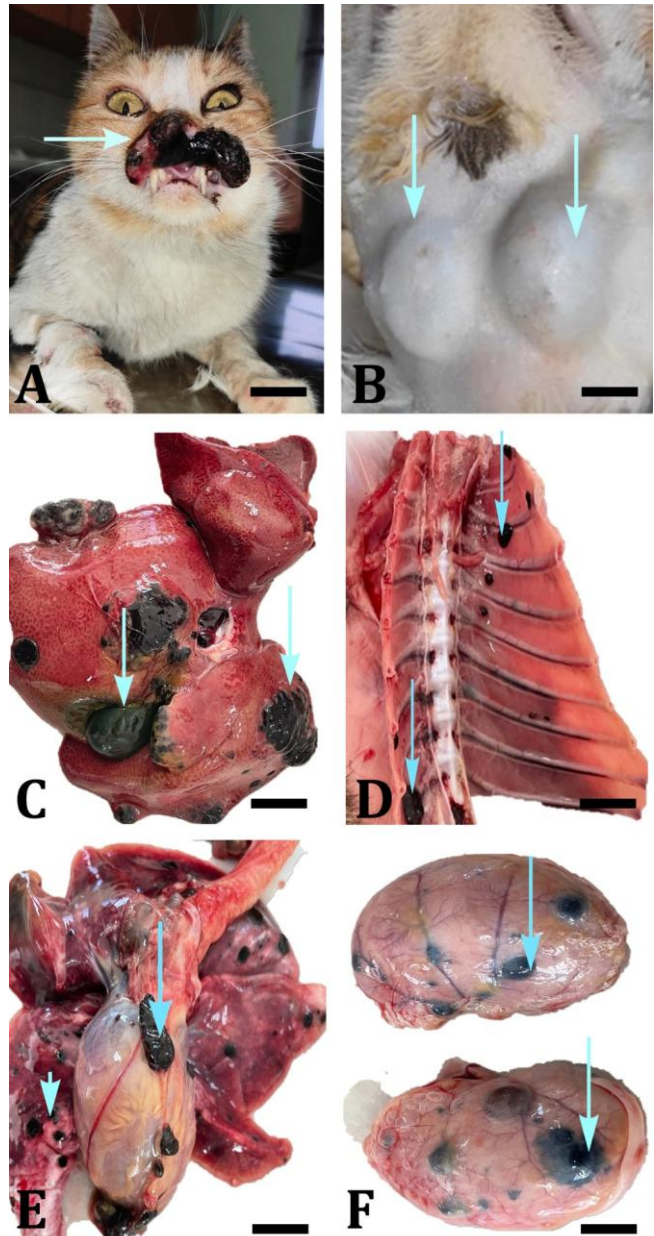
The cat was diagnosed with nasal obstruction and associated dyspnea leading to surgical intervention. The procedure included excision of the tumor from the upper lip, realignment of the nostrils to alleviate obstruction and complete excision of the submandibular lymph node. Post-surgery, tissue samples were histopathologically examined and the cat received 10 days of supportive care with lactated Ringer's solution (Polifarma, Tekirdag, Türkiye), dextrose (Trendvet, Istanbul, Türkiye) and penicillin (Vetas, Istanbul, Türkiye). The cat resumed normal eating and daily activities 30 days post-surgery, however, her condition deteriorated and she died on the 40<sup>th</sup> day. An autopsy was conducted at the pathology laboratory of veterinary medicine of Firat University under protocol number 5721. Tissue samples from the tumor tissues, lungs, cardiac muscle, pericardium, liver, brain, kidneys, thyroid, eyes, large and small intestines were collected and fixed in 10.00% formalin. The samples were paraffin-embedded and sectioned at 4.00 - 5.00 µm thickness and stained with Hematoxylin and Eosin as well as Masson's trichrome.

Immunostaining involved the avidin-biotin complex method. Initially, the tissue sections were deparaffinized and rehydrated using xylene and graded ethanol. Subsequently, endogenous peroxidase activity was inhibited through a 10-min treatment with 3.00% hydrogen peroxide in methanol. Antigen retrieval was achieved by microwave treatment in citrate buffer (pH = 6.00; Thermo Scientific, Waltham, USA). To prevent non-specific binding, sections underwent a 30-min wash with 1.00% bovine serum albumin (BSA; Sigma Aldrich, St. Louis, USA) in tris buffered saline (TBS, pH= 7.60; Sigma Aldrich). Finally, sections were incubated overnight with an immunohistochemistry-specific rabbit antibody for melan-A (diluted 1/25, Novocastra Laboratories; Leica Biosystems, Deer Park, USA).

Black nodules were present in multiple tissues and organs including the liver (Fig. 1C), pleural and peritoneal surfaces (Fig. 1D), lungs, pericardium (Fig. 1E), kidneys (Fig. 1F), retropharyngeal and mesenteric lymph nodes, thyroid and gastric mucosa. These nodules varied in size from 2.00 mm to 4.00 cm in diameter.

In skin, there was complete loss of the epidermis together with infiltration of inflammatory cells and necrotic material, along with a mixture of melanin-

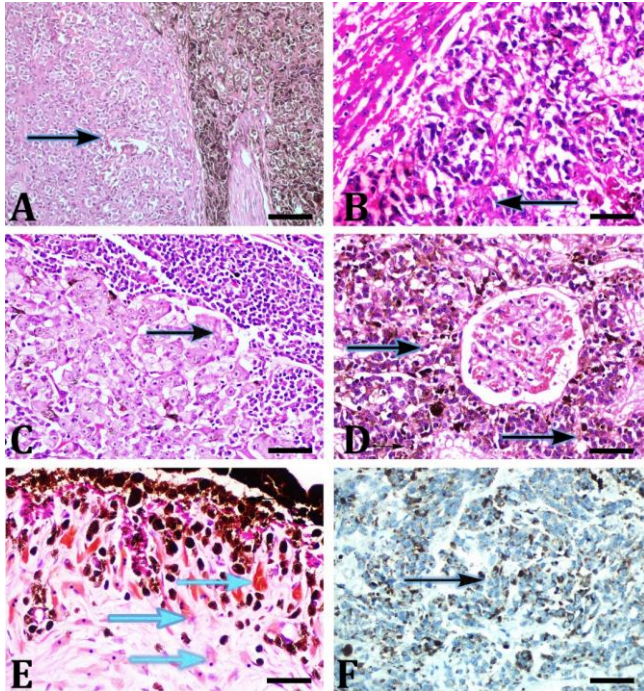
containing and amelanotic neoplastic cells within the dermal layer (Fig. 2A). The neoplastic cells formed nests or sheets displaying a biphasic morphology either rounded epithelial-like structures or spindle-shaped formations.



**Fig. 1.** Illustration of the progression of primary melanoma and its metastatic spread. **A)** The primary tumoral mass arising from the nasal planum extended into the upper lip (arrow), (Bar = 3.00 cm). **B)** Bilateral enlargement of submandibular lymph nodes (arrows), (Bar = 0.50 cm). **C)** Multifocal well-defined black nodules, slightly protruding and located subcapsularly, indicate the presence of metastatic nodules (arrows) in liver (Bar = 2.00 cm). **D)** Multifocal metastatic foci in subpleural and sub-peritoneal regions (arrows), (Bar = 4.00 cm). **E)** Multifocal metastatic nodules in both the pericardium (arrow) and subpleural regions of the lungs (arrow head), (Bar = 1.00 cm). **F)** Bilateral multifocal black bulging nodules (arrows) in the kidneys, (Bar = 2.00 cm).

Furthermore, they demonstrated extensive infiltration throughout the dermis. The morphological features of neoplastic cells included prominent cytoplasm, vesicular chromatin pattern of nuclei, and well-defined nucleoli. Anisocytosis and anisocariosis were also evident. Additionally, multifocal areas of necrosis and moderate dysplastic alterations were observed. Bacterial clusters, comprising cocci and rods were present in the necrotic debris in the epidermis. Multiple metastatic lesions were identified in the liver (Fig. 2B), lungs, lymph nodes (Fig. 2C) and kidneys (Fig. 2D) characterized by their lack of encapsulation and exertion of compressive forces on the surrounding parenchyma. In lungs, diffuse alveolar edema was present accompanied by the infiltration of melanophages in the alveolar septum. In the submandibular lymph nodes, approximately 90.00% of lymphatic tissue was replaced by neoplastic cells, necrosis, fibrosis and the accumulation of melanophages.

Metastatic neoplastic cells had polygonal or spindle morphology organized in nests, packets, and cords and all



**Fig. 2.** Histopathologic and immunohistochemical features of the melanomas (Bars = 40.00  $\mu$ m). **A)** Melanotic and amelanotic features of dermal melanoma also showing biphasic nature, rounded epithelial-like structures (arrow) or spindle-shaped formations, Hematoxylin and Eosin (H&E). **B)** Epithelioid form of melanoma forming nest with scant cytoplasmic melanin in metastatic focus in the liver, (H&E). **C)** Neoplastic melanocytes forming nests (arrow) in retropharyngeal lymph node, (H&E). **D)** Melanocytes forming nests in renal parenchyma (arrow; H&E). **E)** Neoplastic melanocytes deeply infiltrated the iris parenchyma, forming 4 - 5 layers of cells (arrows), indicative of the feline diffuse iris melanoma, (H&E). **F)** Positive cytoplasmic immunoreaction in neoplastic cells (arrow) in dermis, (Masson's trichrome staining).

embedded within a delicate fibrovascular stroma. They had well-defined borders and granular eosinophilic cytoplasm. Nuclei predominantly were oval to round shapes exhibiting clumped chromatin and a singular nucleolus. Anisocytosis and anisokaryosis were present. The mitotic rate ranged from two to four *per* 40 $\times$  field. Surrounding the tumor, the adjacent parenchyma showed signs of compression and infiltration by a few lymphocyte aggregates. Multifocal necrotic foci were frequently present in all the metastatic neoplastic masses. In both eye globes, the early stage of FDIM was diagnosed. A hyperpigmented neoplastic cell population, arranged in 4 - 5 rows, was observed covering the anterior surface of the iris and infiltrating a limited extent into the anterior iris stroma (Fig. 2E). These cells exhibited variably pigmented cytoplasm with indistinct cell borders and had round to fusiform nuclei characterized by finely stippled chromatin and inconspicuous nucleoli. Clusters of neoplastic cells were present in the supleural, sub-peritoneal and subpericardial surfaces. Immunohisto-chemical examinations revealed medium-intensity cytoplasmic staining for Melan-A in both primary (Fig. 2F), metastatic and FDIM.

## Discussion

This report represented the first document of the simultaneous occurrence of FDIM and cutaneous melanoma in a tricolor, stray cat. While this coexistence in cats or other veterinary species has not been reported in the literature, the diagnosis of uveal and cutaneous melanomas concurrently reported in four out of 104 human cases suggesting a potential genetic predisposition.<sup>7</sup> In addition research suggests that multiple primary cutaneous melanoma constitutes a significant proportion comprising up to 10.00%, of malignant cutaneous melanoma in human cases.<sup>8</sup> However, the simultaneous occurrence of uveal and dermal melanomas is reportedly associated with genetic alterations in humans.<sup>6</sup> Notably, approximately seventy-five percent of malignant melanomas result in feline mortality within two years post-tumor excision, while dogs typically have an average survival duration of around one year following excision.<sup>3</sup>

Dermal melanomas in red-haired and tricolor cats have been previously documented.<sup>9</sup> While it would be speculative to suggest a higher susceptibility of red-haired or tricolor-colored cats based on a single case, there is a potential association between hair color genetics and melanoma predisposition. The susceptibility of humans with red hair to cutaneous melanomas reportedly stems from the presence of pheomelanin, a pigment associated with melanoma progression.<sup>10</sup> Also, research utilizing mutant mice has demonstrated that pheomelanin contributes to an increased susceptibility to melanoma.<sup>11</sup> Tricolor cats with red hair as in presented case, may possess a predisposition linked with pheomelanin, similar

to humans with red hair. The importance of pheomelanin and its related pathways in predisposition to melanoma, irrespective of ultraviolet exposure, is highlighted by investigations carried out in genetically characterized models like red-coated rodents.<sup>11</sup> However, further research is necessary to test the relationship among red-colored or tricolor cats, pheomelanin and melanoma susceptibility. The environment and lifestyle of a stray cat, characterized by uncertain care and feeding might contribute to its vulnerability to melanoma development.<sup>12</sup> Further research is needed to understand the relationship between red-colored or tricolor cats, pheomelanin and melanoma susceptibility considering factors like environment and lifestyle. When considering feline nasal planum tumors, the differentials includes hemangiosarcoma, melanocytoma and squamous cell carcinoma due to their documented occurrence in this anatomical location.<sup>11</sup> Histopathologically, melanoma variants include epithelioid, spindle cell or mixed types.<sup>4,9</sup> Nonetheless, epithelioid-dominated melanomas are more frequently reported.<sup>3</sup> Surgical excision is the preferred method of treatment for feline cutaneous melanoma.<sup>13</sup> The overall prognosis for affected cats is poor. The recurrence rate for melanoma is reported at 5.00%, while metastasis occurs in 50.00% of cases indicating significant variability in clinical outcomes.<sup>12,14</sup> Iris melanosis, characterized as precursor lesion, is typically benign and localized to a limited anterior portion of the iris. It may display different behaviors including stability or rapid advancement. Dysplastic melanocytes within the iris stroma show various characteristics.<sup>5</sup> The FDIM originates from hyperpigmented spots on the iris due to abnormal melanocyte proliferation, progressing into early FDIM detectable histologically.<sup>15</sup> This precursor lesion can evolve into FDIM as pigmented cells infiltrate the anterior iris stroma, often displaying morphological alterations.<sup>5,13</sup> Melanomas, originating from the malignant transformation of melanocytes, typically present as skin tumors. However, they can also arise in areas where melanocytes exist.<sup>2</sup> In dogs, melanomas account for 6.00 - 20.00% of all skin tumors.<sup>1</sup> Despite arising from the same cellular origin, melanocytes in uveal and cutaneous melanomas display considerable differences in tumorigenesis, metastatic dissemination and genetic mutations.<sup>5,7</sup> In conclusion, it is necessary to evaluate the mechanisms underlying tumor development from melanocytes in various tissues, necessitating an examination of genetic factors, environmental influences and the intrinsic bio-logical characteristics of melanocytes. An ophthalmologic examination may be useful for cats diagnosed with cutaneous melanoma to detect the presence of any concurrent uveal melanoma.

#### Conflict of interest

The authors declared no conflict of interest.

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