A previously undescribed cutaneous paraneoplastic syndrome in a cat with thymoma

Abstract

Background– Exfoliative dermatitis is a well-recognized cutaneous paraneoplastic syndrome (PNS) associated with thymoma in cats, of which the clinical and histopathological presentation has been well characterized.

Objectives – To describe a novel clinical skin manifestation associated with thymoma in a cat

Animal – A 14-year-old neutered female domestic short haired cat

Methods – Physical, abdominal ultrasonographic, thoracic radiographic, ultrasonographic and computed tomographic examinations, histopathologic assessment of the skin and mediastinal mass.

Results – The cat was presented with non-inflammatory alopecia, with a dorsal multifocal distribution. Examination of the alopecic areas using a dermascope indicated an apparent lack of follicular ostia. Histopathological assessment of alopecic areas confirmed follicular and epidermal atrophy, trichilemmal keratinization and mild orthokeratotic hyperkeratosis. Diagnostic imaging revealed a mediastinal mass, which was surgically removed. Histopathological and immunohistopathological examination of the mass was consistent with a thymoma, associated with multiloculated cyst formation and multifocal cholesterol granulomas. Following surgery, hair re-growth was noted in the previously alopecic areas. The cat was euthanized 3.5 months later because of recurrent chylothorax, suspected to be a post-operative complication. The alopecic lesions had markedly improved.

Conclusions and clinical importance – Thymoma-associated PNS might not always manifest as an exfoliative dermatitis, and should be considered in the differential diagnosis of multifocal non-inflammatory alopecia.

A 14-year old neutered female domestic shorthair cat was presented for investigation of alopecic patches of skin on the back that the owner noticed the day before presentation. The cat showed no signs of pruritus nor over-grooming. In hindsight, the owner reported that the cat had developed progressive lethargy over the previous 9 months. The cat lived strictly indoors without any other pets and was fed a complete diet. The last vaccine was given 2 years prior to presentation, and regular antiparasitic treatment was not administered.

General physical examination was unremarkable. Dermatological examination showed multifocal small, well demarcated, areas of hair loss over the dorsum, extending from 0.5 cm to 3 cm in diameter. The areas showed no evidence of inflammation, and the skin had a slightly shiny appearance (Figure 1.a). Throughout the hair coat there was fine scale and the hair was slightly greasy to touch. Dermascopic assessment of the alopecic areas showed fewer follicular ostia than expected in the area and compared to surrounding skin, suggesting a loss of some follicles. The main differential diagnoses considered included immune-mediated follicular diseases such as pseudopelade and alopecia areata, endocrine diseases such as hyperadrenocorticism and hypothyroidism, demodicosis, dermatophytosis and a paraneoplastic syndrome (PNS).

A complete blood count and serum biochemistry panel including serum thyroxin concentration did not reveal any significant abnormalities. Trichograms, deep skin scraping, Wood's lamp test, and a fungal culture were normal or negative. Skin biopsy samples of the alopecic lesions were performed. On histopathological assessment, the epidermis was thinner than normal, consistent with atrophy. There was mild to moderate orthokeratotic hyperkeratosis, with very mild segmental parakeratosis around the ostia of the hair follicles. Most hair follicles were atrophic and in telogen phase of the growth cycle, with absent or small and distorted hair shafts. Trichilemmal keratinization was also present (Figure 2). These histological findings were not characteristic of any differentials considered, and a medical evaluation was pursued.

On abdominal ultrasound, a few well-defined hyperechoic splenic nodules were considered typical of myelolipomas. Thoracic radiographs revealed a cranio-ventral mediastinal mass (Figure 3), which was also noted on thoracic ultrasound. Ultrasound-guided fine-needle aspirates of the mediastinal mass were performed. Cytology was compatible with a thymoma, although a definitive diagnosis could not be reached. A pre-operative computed tomographic examination of the thorax did not reveal any sign of infiltration, vascular invasion or metastasis.

A median sternotomy was performed. A 5 cm x 3 cm x 3 cm cranial mediastinal mass was extirpated, and the sternal lymph node was removed. Most of the centre of the mass comprised a multiloculated cyst like cavity lined by slender trabeculae of fibrovascular connective tissue. Cystic spaces were approximately 1cm in diameter, sometimes slightly larger. Some pre-existing thymic structure was evident, with a capsule, cortex, medulla and Hassall's corpuscles was noted. However, the distinction between cortex and medulla was ill-defined and the parenchyma was expanded by a population of lymphoid cells (predominantly small),

numerous tingible body macrophages, and an increased number of plump oval epithelial cells with approximately 1-2 mitotic figures per high-power field (400X magnification). Multiple cholesterol granulomas were also present. Immunohistochemically, a diffuse and strong CD3 and pan-cytokeratin (CK) labelling was present throughout the parenchyma, and small numbers of scattered Pax5 positive cells were noted. The lining of the cystic spaces also included CD3 and CK positive cells but no ciliated epithelial cells were evident. Based on the 2015 World Health Organization (WHO) human classification of tumors of the thymus, the histopathological findings were consistent with a type B2 thymoma.[1] Some clusters of epithelial cells had breached the capsule, but no metastasis was detected within the sternal lymph node. The clinical and histopathological findings were consistent with a stage IIa thymoma, based on the Masaoka-Koga human staging system.[2] It was suspected that the multifocal alopecia was a PNS associated with the thymoma, although these features have never been reported previously.

The cat was discharged from the hospital three days after the surgery. Three weeks later (day 25), the demeanor of the cat had improved. Physical examination was unremarkable, except for unchanged alopecic patches on the dorsum. Thoracic radiographs and ultrasound revealed a moderate amount of bilateral pleural effusion, which was drained. Fluid analysis was consistent with a chylous effusion, and was suspected to be a post-operative complication. A month later (day 58), the hair was regrowing on the dorsum (Figure 1.b), supporting the diagnosis of thymoma-associated cutaneous PNS. Although the pleural effusion initially resolved, the cat was presented a month later (day 87) with a moderate expiratory dyspnea. Recurrence of the bilateral pleural effusion was confirmed and the thoracic cavity drained. The cat was presented again two weeks later (day 103) for progressive dysorexia and lethargy, and an acute onset of dyspnea. A second recurrence of the pleural effusion was confirmed and the cat was euthanized. Necropsy was declined by the owners.

Discussion

Thymic epithelial tumors represent a complex group of neoplastic diseases, with variable clinical behavior and histopathological appearance.[1,3-5] Their classification is controversial in humans, and the WHO classification of thymic tumors aimed to unify the previous systems.[1] Cystic thymomas have previously been described in cats,[6] but the cystic spaces were unusually large in our case. This was reminiscent of the cystic degeneration commonly described in humans, which may be mistaken for a non-neoplastic thymic cyst.[7]

Cats with thymoma often present with respiratory signs,[4,5 6,7] however, skin lesions are occasionally the presenting complaint.[8,9] Multiple cases of thymoma-associated cutaneous PNS have been reported, and the clinical presentations were all consistent with exfoliative dermatitis.[8,9] Cats typically present with generalized desquamation, alopecia, crusting, scaling, and sometimes erythema. The lesions usually start on the head, but progressively become generally distributed in an asymmetrical pattern. Histopathological features include orthokeratotic and

parakeratotic hyperkeratosis with extensive desquamation. In the epidermis and follicular infundibula, there are variable degrees of keratinocyte apoptosis, CD3+ lymphocytic exocytosis, and hydropic degeneration of basal cells (interface dermatitis). Follicular changes can extend to infiltrative mural folliculitis, with only a few or no remaining sebaceous glands.[8,9] The pathophysiology is not clearly understood, but it is suspected that autoreactive cytotoxic T-cells activated by the abnormal thymus could aberrantly target epithelial cells.[9] The clinical and histopathological presentation of the cat in this report did not correlate with the exfoliative dermatitis typically reported in cats with thymoma.

Although uncommon in humans, thymoma-associated cutaneous PNS have been reported. Reported dermatological changes are characteristic of alopecia areata or paraneoplastic pemphigus.[10,11] Alopecia areata is a non-scarring inflammatory alopecic disease with no overt epidermal changes. It is a clinical entity that manifests as patchy areas of hair loss on the scalp and other parts of the body. It is suspected to be an autoimmune disease that results from selective T-cell mediated damage to anagen follicles.[11,12] The histopathologic appearance varies depending on disease duration.[11,12] Based on the clinical presentation of the cat, alopecia areata was considered, but not supported by the histopathological appearance of the skin. Based on the history, the alopecic patches had developed recently and no bulbitis could be seen histologically to suggest any underlying alopecia areata. Although a late stage alopecia areata could still be considered, the lack of inflammatory infiltrate in the histological sections was less consistent with this disease. Paraneoplastic pemphigus is an immune-mediated blistering disorder characterized by vesicobullous changes affecting the head, trunk and extremities. Erythema and inflammation are always associated with maculae, papules and plaques, and oral erosive lesions are often severe. Acantholysis, keratinocyte necrosis, and vacuolar interface dermatitis are typical histopathological features. The clinical and histopathological presentation of the cat herein was not consistent with this PNS.

Feline paraneoplastic alopecia is another cutaneous PNS that has been associated with pancreatic and biliary carcinomas.[8] Hair loss is typically symmetrical, starts over the ventrum, but can progress to the head and extremities. The alopecic skin is often shiny and thin. Foot pads are often dry, crusted and fissured when involved.[8] On histopathology, marked follicular telogenization, miniaturization and atrophy are characteristic. Other findings include mild epidermal acanthosis and hyperplasia, and patchy parakeratosis with a mild perivascular, mainly mononuclear, inflammatory dermal infiltrate.[8] Follicular telogenization and atrophy were also noted in this case. However, the distribution of the lesions was very different from the typical feline paraneoplastic alopecia, and there was no mononuclear inflammatory infiltrate in the dermis.

In conclusion, we report a presumptive thymoma-associated cutaneous PNS, for which the clinical and histopathological presentation is not entirely consistent with previously reported PNS in cats or other species.

References

1. Marx A, Chan JK, Coindre JM, *et al*. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. *J Thorac Oncol* 2015;10:1383-1395.
2. Koga K, Matsuno Y, Noguchi M, *et al*. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. *Pathol Int* 1994;44:359-367.
3. Burgess KE, DeRegis CJ, Brown FS, *et al*. Histologic and immunohistochemical characterization of thymic epithelial tumours in the dog. *Vet Comp Oncol* 2016;14:113-121.
4. Garneau MS, Price LL, Withrow SJ, *et al*. Perioperative Mortality and Long-Term Survival in 80 Dogs and 32 Cats Undergoing Excision of Thymic Epithelial Tumors. *Vet Surg* 2015;44:557-564.
5. Zitz JC, Birchard SJ, Couto GC, *et al*. Results of excision of thymoma in cats and dogs: 20 cases (1984-2005). *J Am Vet Med Assoc* 2008;232:1186-1192.
6. Patnaik AK, Lieberman PH, Erlandson RA, *et al*. Feline cystic thymoma: a clinicopathologic, immunohistologic, and electron microscopic study of 14 cases. *J Feline Med Surg* 2003;5:27-35.
7. Suster S, Rosai J. Cystic thymomas. A clinicopathologic study of ten cases. *Cancer* 1992;69:92-97.
8. Turek MM. Cutaneous paraneoplastic syndromes in dogs and cats: a review of the literature. *Vet Dermatol* 2003;14:279-296.
9. Rottenberg S, von Tscharner C, Roosje PJ. Thymoma-associated exfoliative dermatitis in cats. *Vet Pathol* 2004;41:429-433.
10. Barbetakis N, Samanidis G, Paliouras D, *et al*. Paraneoplastic pemphigus regression after thymoma resection. *World Journal of Surgical Oncology* 2008;6:83-83.
11. McElwee KJ, Boggess D, Olivry T, *et al*. Comparison of alopecia areata in human and nonhuman mammalian species. *Pathobiology* 1998;66:90-107.
12. Alkhalifah A, Alsantali A, Wang E, *et al*. Alopecia areata update: part I. Clinical picture, histopathology, and pathogenesis. *J Am Acad Dermatol* 2010;62:177-188, quiz 189-190.

Figures captions

Figure 1. Feline thymoma: Multifocal non-inflammatory alopecia, with dorsal distribution.

Close-up of the largest alopecic patch located on the mid-dorsum at the initial visit (day 0). (b) Follow-up after the surgery showing re-growing shorter hairs in an area of previous hair loss (day 58).

Figure 2. Feline thymoma: Histopathological features of the skin (alopecic area over the dorsum).

The epidermis is composed of only one to two layers of cells, consistent with epidermal atrophy (black arrowhead). There is mild to moderate orthokeratotic hyperkeratosis (black asterisk). Most hair follicles are atrophic and in telogen phase of the growth cycle (black arrow), with hyalinisation of keratin consistent with trichilemmal keratinisation (white arrowhead); Haematoxylin and eosin (H&E).

Figure 3. Feline thymoma: Thoracic radiographic features

Ill-defined rounded soft tissue mass extending from the thoracic inlet to the 4th intercostal space, associated with marked dorsal displacement of the thoracic trachea; left latero-lateral view.