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Case Report

Cutaneous Epitheliotropic T-Cell Lymphoma in a Marsh Rice Rat (*Oryzomys palustris*)

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Published reports of spontaneous neoplasia in marsh rice rats (*Oryzomys palustris*) are sparse. We report here a case of cutaneous epitheliotropic T-cell lymphoma in a 14-mo-old marsh rice rat that involved the ear pinnae, with dissemination to the liver and spleen. Histologically, the thickened ear pinnae showed diffuse infiltration of neoplastic lymphocytes into the epidermis, dermis, and adnexal skin structures, with Pautrier microaggregations present in the epidermis. In addition, neoplastic lymphocytes were observed infiltrating and disrupting the architecture of the liver and spleen. Neoplastic lymphocytes were strongly positive for the T-cell marker CD3 but were negative for the B-cell markers CD19 and CD20. These histologic and immunohistochemical features are consistent with an epitheliotropic T-cell lymphoma, as previously reported in other species, including humans. To our knowledge, this report represents the first published case of spontaneous cutaneous epitheliotropic T-cell lymphoma in a marsh rice rat.

Abbreviations: CETL, cutaneous epitheliotropic T-cell lymphoma; MF, mycosis fungoides.

Marsh rice rats (*Oryzomys palustris*) are a laboratory rodent belonging to the order *Rodentia* and family *Cricetidae*.[28] They are highly susceptible to the development of spontaneous periodontitis, and the disease can be accentuated by feeding a diet high in sucrose and casein.[1] More recently, rice rats have been used to develop a model for antiresorptive-related osteonecrosis of the jaw.[2] Published reports of spontaneous diseases in this species, especially spontaneous neoplasia, are sparse.

Cutaneous T-cell lymphomas are a rare and heterogeneous group of lymphoid neoplasms with primary cutaneous manifestations.[29] In human medicine, this group of lymphomas is divided into multiple distinct subtypes. Classification is based on the World Health Organization–European Organization for Research and Treatment of Cancer guidelines.[4,21] Mycosis fungoides (MF) is the subtype reported most commonly in humans. Classic MF is characterized by neoplastic lymphocytes with tropism for the epithelium and adnexal skin structures.[29]

In veterinary medicine, cutaneous epitheliotropic T-cell lymphoma (CETL) is a rare neoplastic disease that shares many features with human MF.[10] Although rare, CETL is most often diagnosed in dogs, with a prevalence ranging from 2 to 7 cases per 1000 dermatoses.[10,25] Histologic features of canine CETL are similar to those described for human MF.[11] Reports of CETL in noncanid species are uncommon but appear to be especially rare in rodents. In the order *Rodentia*, spontaneous CETL has been documented in 2 guinea pigs,[15,19] 6 Syrian hamsters,[26] an eastern chipmunk,[22] a squirrel,[12] a Sprague–Dawley rat,[23] and an ICR mouse.[17] We report here a case of spontaneous cutaneous epitheliotropic T-cell lymphoma in an experimentally naïve marsh rice rat.

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Case Report

A 14-mo-old, 122-g male marsh rice rat was reported for thickened ear pinnae. On physical examination, the rice rat was in good body condition but was moderately dehydrated. Both ear pinnae were diffusely thickened and mildly ulcerated. Bilaterally, white crusting debris obstructed the ear canals.

The rice rat was part of an IACUC-approved breeding colony that has recently been described in detail.[3] The rice rat was housed at the University of Florida in AAALAC-accredited facilities. At the time of diagnosis, the rice rat was singly housed in an autoclaved polycarbonate individually ventilated microisolation cage (Allentown Caging, Allentown, NJ), with pine shavings as bedding (J and D Wood, Fairmont, NC) in a temperature- (21 ± 2 °C) and humidity-(30% to 70%) controlled room with a 14:10-h light:dark cycle. Standard rodent chow (Teklad irradiated 7912 rat diet, Harlan Teklad, Madison, WI) and reverse-osmosis–purified water supplied by water bottle were available free choice. Rice rats were monitored quarterly by dirty-bedding sentinels, and were serologically free of coronavirus (sialodacryoadenitis virus, rat coronavirus), Kilham rat virus, lymphocytic choriomeningitis virus, mouse adenovirus, *Mycoplasma pulmonis*, pneumonia virus of mice, rat minute virus, rat parvovirus, reovirus type 3, Sendai virus, Theiler murine encephalomyelitis virus, and Toolan H1 virus. In addition, rice rats were free of any internal and external parasites.

Additional diagnostics and treatment were declined by the principal investigator. The rice rat was euthanized and immediately submitted for necropsy. On gross examination, both ear

pinnae were diffusely thickened and had patchy ulceration of the skin. White debris obstructed both ear canals. Mild hepatosplenomegaly was apparent.

Multiple sections from the ear pinnae, heart, lungs, liver, spleen, kidneys, and gastrointestinal tract were fixed in neutral-buffered 10% formalin. Tissues were trimmed and routinely processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Sections from the ear pinnae, liver, and spleen also underwent immunohistochemical staining.

Immunohistochemistry was performed on formalin-fixed paraffin-embedded tissue sections. Slides were deparaffinized with xylene and rehydrated through decreasing concentrations of ethanol to water, including an intermediate step to quench endogenous peroxidase activity (3% hydrogen peroxide in methanol). Slides were transferred to 1× TBS. For heat-induced antigen retrieval, sections were submerged in Trilogy (Cell Marque, Rocklin, CA) and heated in a steamer for 25 min. Slides were rinsed in 1× TBS and incubated with a universal protein blocker (Sniper, Biocare Medical, Walnut Creek, CA) for 15 min at room temperature. Slides were rinsed in 1× TBS and coincubated in primary antibody (CD3, Dako, Carpinteria, CA) for 1 h at room temperature. Alternatively, slides were rinsed in 1× TBS and coincubated in primary B-cell antibody (CD19 or CD20, Dako) for 1 h at room temperature. All slides were rinsed in 1× TBS followed by application of conjugated secondary antibody (Mach 2 goat antirabbit, horseradish peroxidase-conjugated; Biocare Medical) for 30 min at room temperature. Detection of uncoupling protein 1 was achieved by incubating slides in 3′3′ diaminobenzidine (Biocare Medical) at room temperature for 1 min for CD3 or 2 min for CD19 and CD20. Slides were counterstained with hematoxylin (Vector Laboratories, Burlingame, CA) for 40 s and mounted with Cytoseal XYL (Richard–Allen Scientific, Kalamazoo, MI). Positive and negative tissue controls for both T- and B-cell subsets were examined. Immunostained rice rat lymph node and spleen were compared with murine lymph node and spleen.

Histopathologic analysis showed that the dermis of both ear pinnae was diffusely thickened and infiltrated by dense bands of large to medium size lymphocytes, which also infiltrated the epidermis and adnexal structures (Figure 1). The lymphocytes had hyperchromatic, convoluted nuclei and scant cytoplasms. Multiple, small, intraepithelial aggregates of lymphocytes were present throughout the epidermis, consistent with Pautrier microaggregations. In addition, neoplastic lymphocytes infiltrated and disrupted the architecture of the spleen and liver. Neoplastic lymphocytes infiltrating both ear pinnae and the liver and spleen were strongly positive for the T-cell marker CD3 but were negative for the B-cell markers CD19 and CD20. No other noteworthy histopathologic findings were present in the tissues examined. The combined findings supported a diagnosis of cutaneous T-cell lymphoma with epitheliotropism and dissemination to the spleen and liver.

Discussion

The current case is characteristic of cutaneous epitheliotropic $CD3^+$ T-cell lymphoma with dissemination to the liver and spleen. To our knowledge, this report represents the first published case of CETL in a marsh rice rat. In particular, histologic features including epitheliotropism, adnexal structure invasion, and Pautrier microaggregations resemble those seen with MF in humans and CETL in other species.[11,29]

MF is the most common type of primary cutaneous T-cell lymphoma in humans, accounting for nearly 50% of all cases.[24] MF is a slowly progressive disease that is characterized by infiltration of small to medium-size neoplastic T cells with a specific tropism for the epithelium and adnexal skin structures. Infiltration of neoplastic lymphocytes into the upper dermis often occurs as well.[14] Pautrier microaggregations are a specific but insensitive characteristic seen only rarely in early stages of the disease but in as many as one third of cases as the disease progresses.[4] In later stages, lymphocytes become larger, and blasts may be present. The terminal stage occurs with dissemination to the visceral organs, particularly the liver, spleen, bone marrow, lungs, gastrointestinal tract, and kidneys.[5] Immunologically, MF is typically $CD4^+CD8^-$, however $CD8^+$ cases have been described.[29]

The clinical course of CETL in other species is often reported to be acute, with fulminating disease present at the time of diagnosis.[15] The findings in the current case are consistent with this clinical picture. Our rice rat had a good body condition at the time of diagnosis, yet concurrent dissemination to the spleen and liver was present. This pattern may indicate an acute course similar to that reported in other species.[15]

In humans, early stages of MF that are confined to the skin can be treated with topical corticosteroids, nitrogen mustard, UV-based photochemotherapy, interferon α, and retinoids such as bexarotene.[13] With these skin-directed therapies, the prognosis is typically favorable, but curing the disease remains unlikely.[31] Advanced stages with dissemination to visceral organs require systemic doxorubicin-based multiagent chemotherapy with or without total-skin electron-beam therapy.[13] The prognosis in cases with dissemination to visceral organs is poor.[29]

Systemic therapy with lomustine (CCNU) is the treatment of choice in dogs.[7,30] The response to treatment is variable, however, and side effects such as bone marrow suppression and liver damage are common.[30] Due to the acute nature of CETL, most rodents have a poor prognosis at the time of diagnosis, and euthanasia is often elected over treatment.[15,19,26] In one case, surgical resection of a solitary CETL skin lesion in a squirrel was performed. Despite incomplete resection, local recurrence was not observed 10 mo later.[12]

Few animal models of MF have been described in the literature. Spontaneous CETL in dogs has been reported to be immunophenotypically similar to human MF, but most canine cases have a $CD4^-CD8^+$ cytotoxic phenotype.[20] Several studies have evaluated canine CETL as an animal model of the disease.[8,9,18] One study concluded that dogs may prove useful for elucidating etiologic factors of spontaneous MF.[18] Mouse xenograft models of MF have been described as well. Athymic nude, NOD.Cg-Prkdc^{scid} B2m^{tm1Unc}/J, and CB17 SCID mice have all shown promise for studying disease dissemination and evaluating novel approaches for the treatment of MF.[6,16,27]

In conclusion, the current report describes the histopathologic and immunohistochemical characterization of CETL in a marsh rice rat with dissemination to the spleen and liver. This case of spontaneous CETL in a marsh rice rat shares many of the features observed in cases of CETL in other species and of MF in humans. This report appears to be the first published case of CETL— or of any cutaneous T-cell lymphoma—in a marsh rice rat.

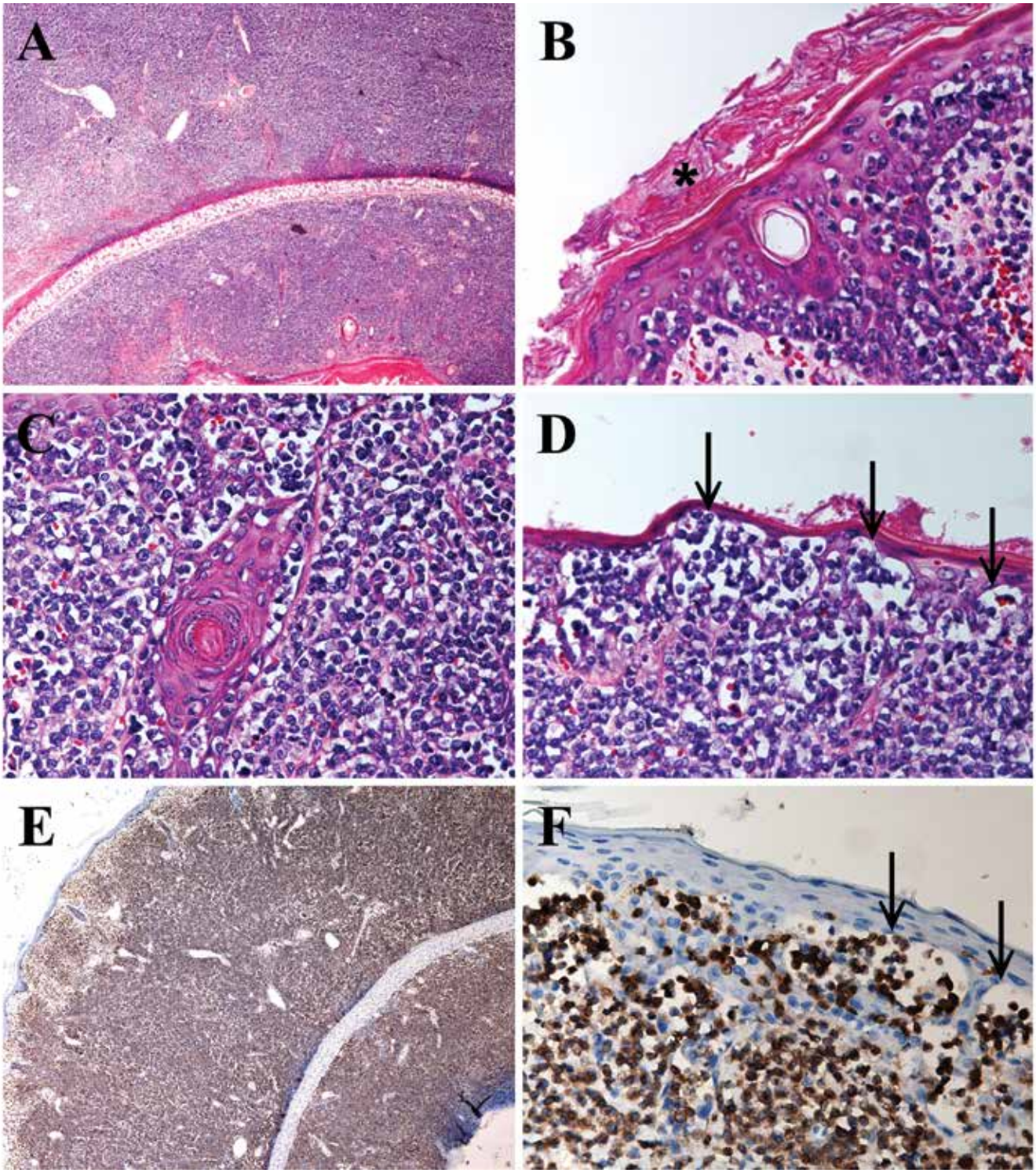

Figure 1. Histopathology and immunohistochemical features of CETL affecting the ear pinnae. (A) The dermis of the pinna is diffusely thickened due to infiltration of lymphocytes. Hematoxylin and eosin stain; magnification, 40×. (B) The epidermis is infiltrated by medium to large lymphocytes. Hyperkeratosis (*)is present. Hematoxylin and eosin stain; magnification, 400×. (C) Neoplastic lymphocytes are invading a hair follicle. Hematoxylin and eosin stain; magnification, 400×. (D) Pautrier microaggregations (arrows) are present in the epidermis. Hematoxylin and eosin stain; magnification, 400×. (E) Infiltrating neoplastic lymphocytes are strongly immunopositive for CD3 (brown). Immunohistochemistry stain for CD3; magnification, 40×. (F) Neoplastic $CD3^+$ lymphocytes and Pautrier microaggregations (arrows) are present in the epidermis. Immunohistochemistry stain for CD3; magnification, 400×.

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