Comparative Medicine
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Vol 73, No 3
June 2023
Pages 242–247

Case Reports

Spontaneous Vitiligo in a Captive Rhesus Monkey (*Macaca mulatta*)

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Vitiligo affects a significant portion of human and animal populations. The disease causes irregular and multifocal progressive loss of fur, skin, and mucous membrane pigmentation due to the loss or absence of melanocytes. While etiopathogenesis is not completely understood, autoimmunity, environmental, and genetic factors are implicated We present a case report on a 16-y-old female rhesus macaque (*Macaca mulatta*) with depigmented areas that are progressively increasing on the skin and coat and are distributed on the head and back. Histopathology revealed alterations compatible with vitiligo characterized by the absence of melanocytes in the epidermis and dermis. The clinical history and complementary exams support this diagnosis.

DOI: 10.30802/AALAS-CM-22-000091

Introduction

Vitiligo is a commonly acquired hypomelanosis in humans.[11,29] The disorder is responsible for irregular and multifocal progressive loss of skin and mucous membrane pigmentation due to the absence of melanocytes.[4,17] Hair pigmentation loss can follow or precede skin depigmentation.[14] The pathogenesis of vitiligo involves multiple components such as environmental factors, autoimmunity, and genetic factors.[4,35] The worldwide prevalence of human vitiligo has been estimated at approximately 0.5% to 2.0% of the world population,[37] however, it has been reported to reach 8.8% in India and approximately 1% in the United States and Europe.[2] Adults and children of both genders are affected.[41] About 7% of those affected reported that the depigmentation started with some emotional stress.[43]

The etiopathogenesis is not fully understood, but the condition is characterized by the absence of melanin pigment due to the destruction of melanocytes.[4,11,32,49] Familial cases occur in a non-Mendelian pattern that suggests complex inheritance.[21,31,44] Genome-wide scans have provided strong support for vitiligo susceptibility genes on chromosomes 4q13-q21, 1p31, 7q22, 8p12, and 17p13. Previous linkage studies have identified sequences supporting the involvement of at least 50 susceptibility loci of vitiligo. Genes that are important in melanocyte function (for example, tyrosinase, OCA2, and MC1R), cellular stress response (for example, XBP1), in innate immunity (for example, NLRP1, IFIH1, and TICAM1), and adaptive immunity (for example, GZMB, HLA-A, FoxP3, and CD80)[20,42,45] are related.

Vitiligo is associated with autoimmune diseases such as autoimmune thyroid disease, rheumatoid arthritis, psoriasis, adult-onset autoimmune type 1 diabetes mellitus, pernicious anemia, Addison's disease, and systemic lupus erythematosus.[13,17,45,46] The main environmental factors precipitating vitiligo are nutritional deficiency, emotional stress, trauma, drugs, infections, exposure to UV radiation (UV), and chemicals.[15,41,50] Patients with vitiligo have increased tissue and serum levels of proinflammatory mediators such as interleukin (IL)-1, IL-6, granulocyte-macrophage colony-stimulating factor, interferon-γ, and tumor necrosis factor (TNF) -α.[16,22] Antimelanoma therapies sometimes lead to the development of vitiligo because healthy melanocytes are also destroyed by CD8+ cytotoxic cells.[3,28,34] This melanocyte loss is associated with a positive clinical response to melanoma treatment.[38]

Vitiligo has been reported in a variety of species, but to date has not been reported to develop spontaneously in nonhuman primates (NHP). The most common characteristic of vitiligo in animals is the progressive whitening of the fur, extending to the nose and mucous membranes. Vitiligo is not common in dogs, with autoimmune factors being the predominant cause of onset. Canine vitiligo has also been associated with hypoadrenocorticism and treatment of subcutaneous mast cell tumors with tyrosine kinase inhibitors.[7,9,24] In cats, the skin lesions and depigmentation appear first occur in the nasal plane, periocular area, and paw cushion, progressing later through the body with no report of associated systemic disease.[1,23] In pigs, vitiligo is related to the regression of melanocytic tumors in several different areas of the body.[6] In chickens, depigmentation occurs after vaccination for lymphoma. As in humans, the immune response in these species is mediated by CD8 T cells.[10] Transgenic AAD+ C57BL/6 mice whose cells have a high affinity for tyrosinase also develop vitiligo. Histologic examination of these mice revealed a loss of melanocytes in the affected hair follicles and T cell infiltration.[10] Other transgenic C57BL/6 retain melanocytes in the epidermis, and then after induction of CD8 T cells, specific melanocytes develop depigmentation in the skin, similar to human cases.[36] Some horse breeds develop vitiligo spontaneously in the face, perianal, perioral, and perigenital areas in association with the regression of melanomas. In buffalo, vitiligo occurs in scattered areas of the body, progresses slowly, and is associated with low intake of copper sulfate.[26] A giraffe with progressive depigmentation was considered to have developed vitiligo as a result of a skin infection.[27] A black rhino was reported with

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symmetrical depigmentation in various areas of the body. Skin histopathology revealed a reduction in melanocytes and the presence of macrophage and lymphocyte infiltrates.[47] Serum from affected of chickens, dogs and horses contains antibodies against melanocytes.[10,12,25,40]

This case report describes the clinical and histopathologic features of spontaneous vitiligo in a female rhesus macaque.

Case Report

A 16-y-old female rhesus macaque (*Macaca mulatta*) presented with depigmented areas on the skin and coat distributed on the head and back. The macaque belonged to the NHP colony of The Institute of Science and Technology in Biomodels (ICTB)/ Fiocruz-RJ, Brazil, and was living with 27 other individuals including males and females of different ages. The subject animal's clinical and family history were evaluated. Blood, cytogenetic, and histopathologic tests were performed to study the possible causes of the depigmentation.

Materials and Methods

The NHP colony houses about 500 *Macaca mulatta* reared in a closed mating system distributed in 18 family groups in outdoor enclosures with an area of 63 m^2, covered areas of 7 m^2, and height 3,5 m^2 each. This colony receives filtered water ad libitum. Animals receive commercial primate feed (NuvilabPrimatas Velho Mundo, Quimtia, Colombo, PR, Brazil) in the morning. In the afternoon, they are, supplemented with fruits and vegetables that have been immersed in 2% sodium hypochlorite solution before being offered to provide parasitologic and bacteriologic control.

The floor of the enclosure is concrete with autoclaved wood shavings. It is cleaned daily with brooms to remove solid residue and washed with pressurized water. Environmental enrichment items (such as frozen fruit, seeds, boxes, tree trunks, and bamboo mobiles) and shelters for protection from the weather are offered. Outdoor enclosures have a natural lighting environment without controlled ambient temperature. Sanitary monitoring is carried out twice a year based on FELASA (Federation of European Laboratory Animal Science Associations) guidelines. Health management includes a physical exam (cardiac and pulmonary auscultation, abdominal and lymph node palpation, fur and skin assessment, body score assessment, mucosal assessment, and body temperature), hematologic examination, deworming (ivermectin 0.2 mg/kg + secnidazole 30 mg/kg), stool analysis for parasites and pathogenic microbiologic agents), tuberculosis skin testing, and tartar cleaning with dental ultrasound. The colony is currently free of ectoparasites based on microscopic examination of fur samples. The absence of antibodies for the following agents was confirmed by the ELISA with blood serum.: retrovirus (SRV), rabies virus, simian immunodeficiency virus (SIV), and simian T-cell lymphotropic virus (STLV). Bacterial culture from rectal swabs provided no evidence of *Salmonella* sp., *Shigella* sp.or *Yersinia* sp. Blood smears howed no evidence of *Plasmodium* sp. The following parasites were not detected in stool samples: *Trongyloides* sp., *Prosthenorchis* sp., *Tritrichomonas* sp., *and Giardia* sp. The absence of *Mycobacterium tuberculosis* was confirmed with molecular testing (GeneXpert), bacterial culture, and tuberculosis skin test. The breeding colony is maintained in compliance with Brazilian laws and approved by the Animal Experimentation Ethics Committee Oswaldo Cruz Foundation under protocol number LW5/16.

For clinical examination and measurement of the affected area, chemical restraint was performed with 10 mg/kg of ketamine and 0.1 mg/kg of IM midazolam. Blood was collected for a thyroid panel (TSH, T4) and hematologic and biochemical analysis (sodium, potassium, chlorine, calcium, glucose, CK, triglyceride, cholesterol, bilirubin, ALKP, ALT, AST, creatinine, and urea). For chromosome analysis, blood was collected in heparinized syringes and transported to the laboratory in polystyrene foam with ice. Chromosomes were examined using a cytogenic technique in which peripheral blood lymphocytes were cultured in RPMI 1640 with 20% fetal bovine serum and phytohemagglutinin as mitogen. They were then analyzed for number and structure using conventional giemsa staining.

A biopsy was performed with a 6-mm punch and infiltration of 2% lidocaine (6 mg/kg) intradermally around the collection sites. The biopsy material corresponded to the visually depigmented region, pigmented area, and the margin between depigmented and pigmented areas. After collection, the biologic material was fixed in 10% formalin and sent for histopathologic processing. Slide preparation was performed at the Institute of Science and Technology in Biomodels and samples were analyzed at the Laboratory of Cellular Biology, which are both located near the NHP colony.

The biopsy region was sutured. After that, a topical antibiotic was applied (Penicillin G Benzathine, Zoetis) and subcutaneous meloxicam (0.1 mg/kg) and intramuscular tramadol (2 mg/kg) were administered for anti-inflammatory and analgesic effect.

Results

During the daily assessment of the NHP colony, a macaque was noticed to have depigmentation of the fur on the head. This initial change in fur color was observed when the animal was 8 y old. Until about the age of 14, the change consisted of a small whitish area of about 4 cm in diameter on the left side of its forehead (Figure 1 A and C). By the time this animal was 16 y old, the size of the affected area had increased, extending to both sides above the forehead and in a large band on the right side of the shoulder and back (approximately 8 cm in diameter) (Figure 1 B and D).

Histopathologic changes were consistent with vitiligo. Samples collected from the margins of the depigmented area had hydropic degeneration of keratinocytes (including in the basal layer and skin appendages) and predominantly perivascular lymphocytic infiltrates in the dermis and epidermis (Figure 2 A). The depigmented area had no melanocytes in the epidermis or dermis, few mopholgic alterations in the epidermis and dermis, and a discreet perivascular infiltrate in the dermis (Figure 2 B, C and D). Normal skin had normal numbers of melanocytes and no lymphocytic infiltrate (Figure 2 E).

The subject animal's parents, 8 brothers, and son were born in the colony (3 generations), but this condition had not been documented in related individuals. The animal's history includes a miscarriage and a stillbirth, both without a known cause. The clinical record does not report any physical injury. No numerical or structural changes in chromosomes were observed under the optical microscope. Hematology and serum biochemistries were standard for the species. The total concentration of T4 was 5.1 ug/dL (reference ranges 3.9 to 14.7 ug/dL[39]) and TSH 1.50 mcIU/mL (reference ranges 0.25 to 2.09 mcIU/mL[30]).

Discussion

The standard coat coloring of rhesus macaques ranges from light brown to dark brown with lighter and more vivid color in the arms, waist, thigh, and legs while the back is darker. Females and males develop red skin coloration on their face, genitalia, and hindquarters during the reproductive period.[5,8,18]

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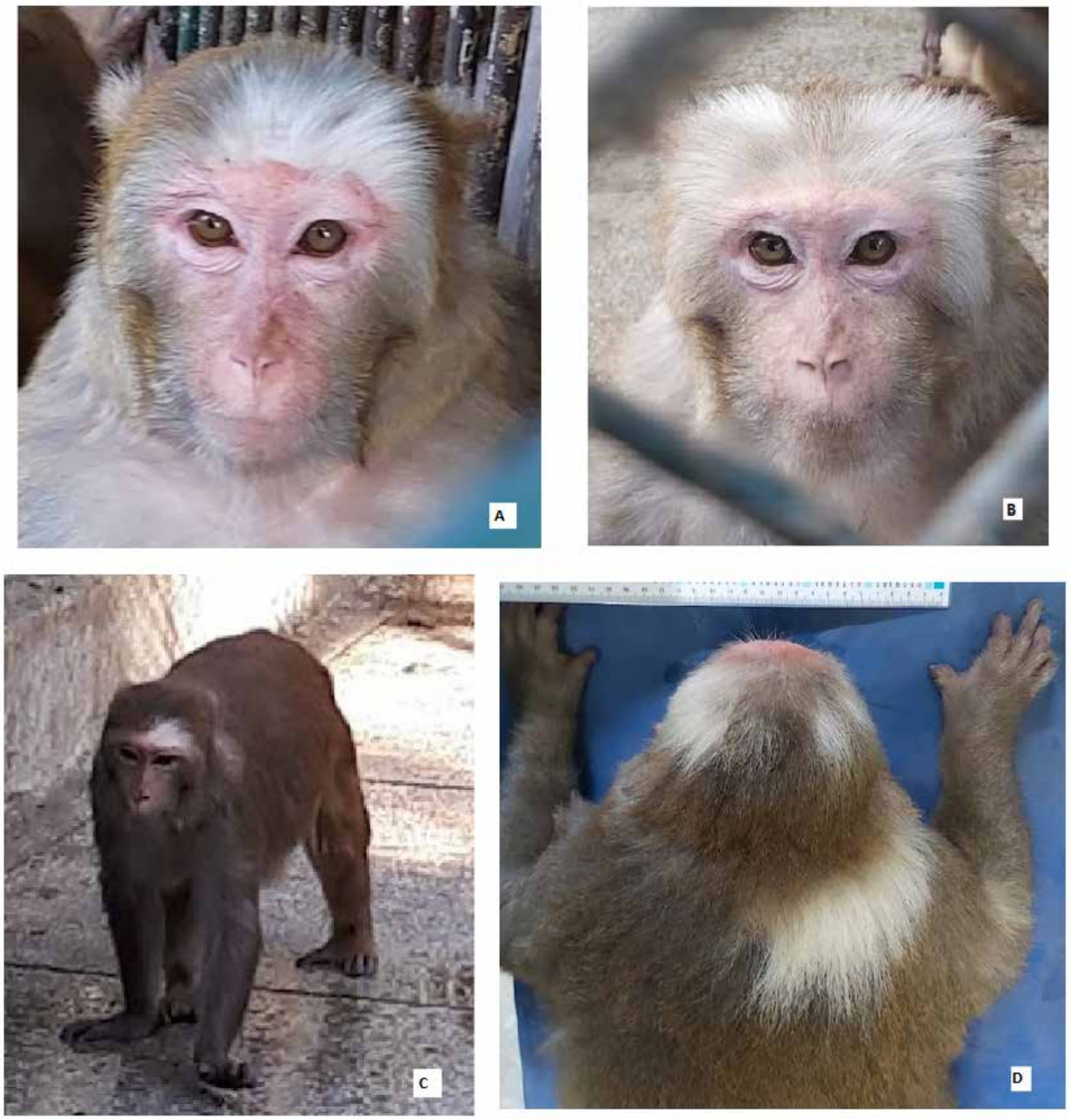

Figure 1. A) Frontal view of the face, highlighting the depigmented area on the left side above the eyes in macaque with vitiligo at 14 y of age. B) Frontal view of the face with highlighting of depigmented areas on both sides above the eyes in macaque with vitiligo at 16 y of age. C) Frontal view of the whole body showing depigmentation only on the left side above the eyes in macaque with vitiligo at 14 y of age. D) Dorsal view of head and back showing depigmentation on both sides above the head and a large band on the side of the right shoulder in macaque with vitiligo at 16 y of age.

The progression of the depigmented fur coincided with a change in a nearby enclosure and the COVID-19 pandemic between the years 2020 to 2021, which led to changes in the animal husbandry routine and turnover of the animal care team members. More specifically maintenance was performed in the enclosure a few meters from this animal. At the time, the animals were moved to another area to provide access for the maintenance team, who painted and replaced gates, perches, feeders, railings, and roofs. The pandemic directly affected the team that had access to the colony and required a delay in completion of the work, which took several months for full completion. We speculate that these stressful situations may be related to the progression of the condition, although no other clinical, laboratory, or behavioral changes were observed. The animal was not subjected to any experimental procedure.

The diagnosis of vitiligo is based on the clinical history along with histopathologic examination of the depigmented areas. Complementary tests can help with the diagnosis. In animal species, the histologic feature of vitiligo is the loss of melanocytes from the epidermis and/or hair follicle. The

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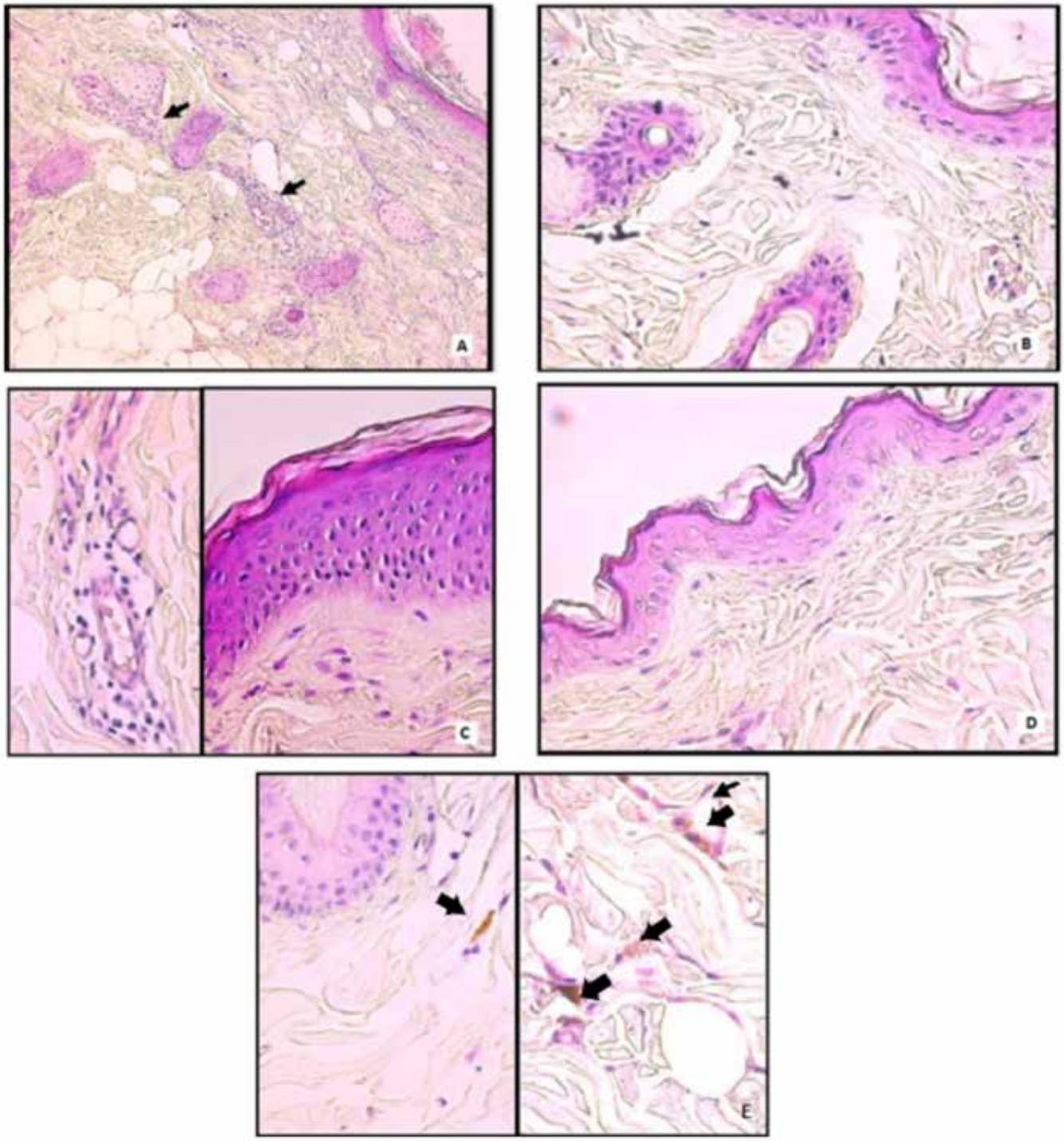

Figure 2. Histologic section stained with hematoxylin and eosin (HE) of macaque with vitiligo at 16 y of age, optical microscopy at 40× magnification. A) Margin of the lesion with the presence of perivascular lymphocyte infiltrates (arrow). B) Inside the lesion, absence of melanin and melanocytes in the dermis and epidermis and depigmented fur. C) Lesion margin with lymphocytic perivascular infiltrate and epidermal hydropic degeneration. D) Epidermis without structural changes, absence of melanin and melanocytes in dermis and epidermis. E) Normal skin showing dermal melanocytes indicated by an arrow.

epidermal architecture is normal, but keratinocytes lack pigment granules. Minimal numbers of lymphocytes are often present in the basal epidermal layer, especially near the border of pigmented and nonpigmented epidermis. The presence of mild dermal or epidermal-dermal mononuclear infiltrates at the margin of lesions with ongoing loss of melanocytes indicates active disease.[33,48]

In this reported case, in addition to the progression of depigmentation, the histopathologic analysis confirmed the loss of melanocytes in the epidermis and the dermis possibly due to their destruction, with perivascular lymphocytic infiltrate in the dermis. Vitiligo patients are at elevated risk of developing other concomitant autoimmune diseases, mainly autoimmune thyroid disease.[11] However, this animal had no hematologic or hypothyroid condition associated with the presence of vitiligo.

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We did not identify any other autoimmune condition in the tests performed, although perivascular lymphocytic infiltrates were found in the marginal region, which suggests autoimmune destruction of melanocytes. Constant exposure to UV light is also a risk factor as the enclosures are outdoors. However, no other cases have been reported in the colony.

The rhesus macaque has phylogenetic proximity to humans and the spontaneous development of vitiligo in this animal suggests the potential for studying causative factors such as genetic influences and potential environmental triggers. Comparison of animals and humans is a powerful approach to determining the pathogenesis of and new treatments for vitiligo. To our knowledge, ours is the first report of spontaneous vitiligo in *Macaca mulatta.*

Acknowledgments

We are grateful to the technical team of the primatology service of the Institute of Science and Technology in Biomodels/Fiocruz who take care of nonhuman primates with great professionalism.

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