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Eosinophilic bronchitis-like lesion as the cause of death in a *Macaca mulatta*: a first case report

J.L. Christal¹, G.B. Hubbard², E.J. Dick Jr², K.M. Brasky², and J. Jagirdar¹

¹Department of Pathology, University of Texas Health Science Center, San Antonio, TX, USA

²Southwest National Primate Research Center at the Southwest Foundation for Biomedical Research, San Antonio, TX, USA

Abstract

Background—Eosinophilic bronchitis is a recently described, relatively benign condition in humans that is characterized by a corticosteroid-responsive chronic cough and sputum eosinophilia without the abnormalities of airway function seen in asthma. The exact cause of this condition is currently unknown, however has been associated with various occupational exposures in humans. It has also been reported to progress to irreversible airway obstruction. This disease has been reported in dogs and horses, but not in non-human primates.

Methods—Gross examination of an otherwise healthy 13-year-old, colony-born *Macaca mulatta*, which died of severe non-responsive respiratory distress revealed that the lungs were markedly inflated and moist.

Results—Hematoxylin and eosin-stained sections from the lungs contained widespread accumulation of eosinophils, sloughed epithelial cells, and mucus centered around bronchioles and adjacent airways. There was no evidence of mast cell infiltration of peribronchiolar smooth muscle, goblet cell hyperplasia, or basement membrane thickening.

Conclusions—This ruled out recurrent episodes as would be expected in asthma, favoring the diagnosis of an eosinophilic bronchitis-like lesion. We report a first case of eosinophilic bronchitis-like features in a *M. mulatta*.

Keywords

Eosinophilic airway disease; lungs; non-human primate

Introduction

Bronchopulmonary disease is rare in the non-human primate lung. To our knowledge, no reports of eosinophilic bronchitis in a *Macaca mulatta* or any other non-human primate exist. Only rare cases of eosinophilic bronchitis occurring in horses and dogs have been reported in the veterinary medicine literature [11,13,15]. This lesion has been described primarily in the adult human population, and the pathogenesis of this lesion is poorly understood. Clinically, the patient presents with chronic cough that, like asthma, shows increased airway eosinophils on sputum cytology, however, eosinophilic bronchitis differs from asthma in that clinical testing does not show the bronchoconstriction or bronchial hyperresponsiveness seen in asthma. The airway histopathology of eosinophilic bronchitis

and asthma are almost identical. Both show increased subepithelial eosinophils and variable thickening of the subepithelial collagen layer [7,9]. An increased number of mast cells in the peribronchiolar smooth muscle is seen in cases of asthma but not eosinophilic bronchitis [6]. Eosinophilic bronchitis has not been described in non-human primates. In this article, we describe a lesion in the lung of a *M. mulatta* that resembles eosinophilic bronchitis.

Materials and methods

An apparently healthy 9-kg, 3-year-old male, colony-born, *M. mulatta* was found experiencing extreme respiratory difficulty in an outdoor metal and concrete enclosure during a routine health check in an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) accredited facility. The monkey was treated in the emergency center and subsequently killed for failure to respond to therapy and for humane reasons. The monkey was fed commercially available monkey chow and water *ad libitum*. It had not been used experimentally. The *M. mulatta* was submitted for necropsy within 1 hour of death.

Results

No external gross lesions were identified at necropsy. Internal examination of the lungs revealed moist and well-inflated lungs bilaterally with no discrete lesions seen. No significant gross abnormalities were identified elsewhere. Lung tissues were collected and fixed in 10% neutral buffered formalin, embedded in paraffin, cut at 5 microns, and stained with hematoxylin and eosin. Microscopic examination of slides of lung tissue (Fig. 1) revealed a dense accumulation of inflammatory cells (primarily eosinophils) in the respiratory tract, centered on bronchioles and adjacent airways. Associated with the eosinophilic infiltrate were sloughed bronchial epithelial cells, macrophages, and mucus. The subepithelial collagen layer did not appear thickened. Peribronchiolar smooth muscle hyperplasia with associated mast cell infiltration of the smooth muscle, as would be expected in asthma, was conspicuously absent and this was confirmed with a Giemsa stain of the tissue. Careful examination of Giemsa-stained and Toluidine blue-stained tissue sections of greater than 50 high power fields of the peribronchiolar smooth muscle did not reveal any infiltration by mast cells. Microscopic examination of the other organ systems was unremarkable.

Discussion

Gibson et al. [8] first described non-asthmatic eosinophilic bronchitis as a cause of chronic cough in 1989. They identified a group of non-smoking patients with corticosteroid-responsive chronic cough who had sputum eosinophilia-like asthmatic patients, but did not show abnormalities of airway function that characterize asthma. These patients had no objective evidence of variable airflow obstruction or bronchial hyperreactivity. Studies have since shown that eosinophilic bronchitis is the cause of chronic cough in 10–20% of patients being referred to respiratory specialists for treatment. No cases of sudden death attributed to eosinophilic bronchitis have been reported to date.

The airway histopathology of eosinophilic bronchitis and asthma are almost identical, both showing increased epithelial and subepithelial eosinophils and no increase to variable increase in the thickness of the subepithelial collagen layer [7,9]. The fundamental difference in the pathology of these two entities has been reported to be an increase in the number of mast cells within the airway smooth muscle layer, which is seen in asthma and not in eosinophilic bronchitis [6]. Brightling et al. observed mast cell infiltration of a smooth muscle, with a median of 5.1 mast cells per square millimeter (range 0–33.3) in asthma

patients vs. a median of 0 per square millimeter (range 0–4.8) in eosinophilic bronchitis patients.

Although the prevalence of eosinophilic bronchitis is far lower than asthma, its identification as an important cause of chronic cough that is responsive to corticosteroid therapy has an important implication in the management of patients [2,4,5]. Treatment with inhaled corticosteroids is associated with a short-term improvement in cough and reduced sputum eosinophil counts, but the long-term outcome of eosinophilic bronchitis is uncertain. Studies have shown that the most common outcome in eosinophilic bronchitis is continuing disease and that complete resolution is quite rare [1]. Cases have also been reported in which development of irreversible airflow obstruction has developed in patients with eosinophilic bronchitis, suggesting that eosinophilic bronchitis may progress and be a prelude to chronic obstructive pulmonary disease in some patients [3,14].

The exact cause of eosinophilic bronchitis remains unclear in most cases; however, cases have been reported which implicate occupational and/or environmental exposures as the cause [10,12,16]. With no known allergic conditions or previous asthma-like response in the current subject, the exact cause for the histologic findings remains unclear. Pulmonary function testing was not performed, so reversible airflow obstruction could not be evaluated. An acute allergic response to an unknown environmental exposure remains possible.

We report a rare case of eosinophilic bronchitis-like disease in the lungs of a rhesus macaque. The histologic findings are similar to those reported in cases of eosinophilic bronchitis in human patients. The case further promotes the *M. mulatta* as a model of human disease for its similarities in respect to physiology, anatomy, immunophenotype, genetics, and shared neoplasia.

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Fig. 1.

(A) Hematoxylin and eosin (H&E)-stained slide (original magnification, 10 $\times$) showing airway-centered inflammation. (B) H&E-stained slide (original magnification, 100 $\times$) showing bronchitis with excess mucus within the bronchial lumen. (C) H&E-stained slide (original magnification, 400 $\times$) showing eosinophilic infiltrate of bronchial epithelium and subepithelium. Note the lack of increased thickness of the subepithelial collagen layer and no increase in goblet cells. (D) Giemsa-stained slides (original magnification, 100 $\times$) showing no increase in the number of airway smooth muscle mast cells. (E) Toluidine blue rhesus case tissue with no mast cell granules recognized (600 $\times$). (F) Toluidine blue of control tissue with one mast cell with metachromatic granules in circle (600 $\times$).