Environmental Effect on Eosinophilic Granulomatous Pneumonia (EGP) in Brown Norway Rats

Ryoichi Ohtsuka1,2 and Kunio Doi1

1Department of Veterinary Pathology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1–1–1 Yayoi, Bunkyo-ku, Tokyo 113–8657, Japan
2The Institute of Environmental Toxicology, 4321 Uchimoriya-machi, Mitsukaido-shi, Ibaraki 303–0043, Japan

Abstract: The prevalence of eosinophilic granulomatous pneumonia (EGP) is well known in Brown Norway (BN) rats. In this study, age-related changes in the incidence and severity of EGP in 4 to 20 weeks old BN rats were examined under two different housing conditions (isolator cages without woodchips and common cages with woodchips for bedding) in a SPF animal room in Charles River Japan Inc. A routine microbiological survey gave negative results to any specific pathogens tested. As a result of histopathological examination, there were no lung lesions observed at the age of 4 weeks. EGP developed at and after the age of 7 weeks, but the incidence and severity of EGP showed no age-related changes under both housing conditions. These findings suggest that EGP in BN rats may be a hypersensitivity response of strain-specific nature as reported by Albers and Clifford.

Key words: age-related change, Brown Norway rat, eosinophilic granulomatous pneumonia, housing condition

Brown Norway (BN) rats originate from several wild Norwegian rats captured by Helen Dean King in the suburbs of Philadelphia, and the strain has been established in 19791. BN rats have been widely used in various fields of investigation such as autoimmune nephritis2,3 and allergic asthma4–10.

There are reports that non-treated BN rats have eosinophilic granulomatous pneumonia (EGP) with high incidence11,12, and many histologists think that the existence of such lesions in BN lungs prevents correct evaluation of histological responses to allergens. Some researchers suppose that the cause of the lesion may be some pathogens11 while others consider that it is a hypersensitivity response and has no relation to infectious pathogens13. Some animal breeders suppose that dust originated from bedding may be one of the triggers of EGP in BN rats.

To clarify this point, 40 male BN/Crj (BN) rats were divided into two groups after birth. One group was kept in isolator cages without woodchips and the other group in common cages with woodchips for bedding in an SPF animal room of Charles River Japan Inc. (Kanagawa). And age-related changes in the incidence and severity of EGP were histopathologically assessed on 5 rats of each group at the age of 4, 7, 12, and 20 weeks, respectively (Table 1). The animals were fed a standard laboratory chow, MF pellet (Oriental Yeast Co., Ltd., Tokyo), and water ad libitum. A routine microbiological survey gave negative results to any specific pathogens tested in Charles River Japan Inc.

The animals were sacrificed by exsanguination under nembutal anesthesia and the lungs were fixed in 10% neutral buffered formalin and embedded in paraffin. Four-μm transverse sections of all lobes were cut and stained with hematoxylin and eosin (HE). Based on the number and extent of the lesion, the severity of EGP was graded as follows; –: no lesion, +: mild lesion (totally less than 10% of section area), ++: moderate lesion (10–30%), the severity was graded as follows; –: no lesion, +: mild, ++: moderate, +++: marked lesion (more than 30%).

No pulmonary lesions were observed at the age of 4 weeks (Fig. 1). EGP developed at the age of 7 weeks under

<table>
<thead>
<tr>
<th>Group</th>
<th>IC</th>
<th>CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (week)</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

IC: isolator cage without woodchips, CC: common cage with woodchips. Five rats of each group were examined at each time point. The severity was graded as follows; –: no lesion, +: mild, ++: moderate, +++: marked.
both housing conditions (Table 1). EGP was characterized by focal granulomatous lesion with severe infiltration of eosinophils in parenchyma, and the lesion include macrophages, histiocytes, and foreign body-type multinucleated giant cells (Fig. 2). The incidence and severity of the lesion showed no age-related changes under both housing conditions at and after the age of 7 weeks (Table 1). Taken together with the results of a routine microbiological survey undertaken in Charles River Japan Inc., EGP observed in the present study was considered to be a hypersensitivity response of strain-specific nature as reported by Albers and Clifford\textsuperscript{13}. They showed some evidences excluding the possibility of infection in the cause of EGP in BN rats; 1) Routine nasopharyngeal lavage cultures were consistently negative for bacteria and mycoplasma, and bronchial lavage cultures negative for bacteria, mycoplasma, and fungi, 2) HE and additional histochemical stains did not reveal etiological organisms, 3) Cesarean-derived BN rats raised in isolators developed EGP, and non-BN foster for cesarean-derived BN rats did not develop EGP, and 4) Outbred stocks and other inbred strains of rats housed with BN rats did not develop the lesion. From these findings, they suggested that it might be a hypersensitivity response, and morphologically resemble

Fig. 1. Lung of a 4-week-old BN rat showing no histological changes. HE, × 50.

Fig. 2. Lung of a 20-week-old BN rat kept in a common cage, showing eosinophilic granulomatous lesions. Inflammatory cell infiltration (mainly eosinophils) and multinucleated giant cells (arrow head) are seen. HE, a: × 40, b: × 100.
hypersensitivity responses in human, although they have no direct evidence to support this hypothesis. To clarify the real cause of EGP in BN rats, further studies should be done.

References