Spontaneous sialoadenitis and dacryoadenitis in MRL/1 mice A model for human Sjögren's syndrome

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Introduction

NZB and NZB/WF1 mice have been extensively used as experimental models for human SLE, and also develop spontaneous sialoadenitis and dacryoadenitis which bear such close resemblance to those in human Sjögren's syndrome. Hence, it is accepted that they provide an excellent disease model for Sjögren's syndrome¹⁻²⁾. The same kind of sialoadenitis was described by Takeda *et al.*³⁾ as occurring in SL/Ni mice which also develop spontaneous PN-like arteritis and SLE-like glomerulonephritis, and they proposed SL/Ni mice as a good model of Sjögren's syndrome.

Recently, Murphy *et al.*⁴⁾ developed a MRL/Mp-lpr/lpr (MRL/1) strain which occurred as a by-product of a series of crosses involving strains AKR/J, C57BL/6J, C3H/D and LG/J. MRL/1 mice have an autosomal recessive mutant gene, *lpr*, which is responsible for massive generalized lymphadenopathy and early onset of autoimmune diseases. MRL/1 females die at around 4 months and males at around 5 months due to immune complex glomerulonephritis.

Concerning sialoadenitis and dacryoadenitis in MRL/1 mice, detailed histopathological changes have never been described. Hence, we have examined the salivary and lacrimal glands of MRL/1 mice and reported the results here.

Materials and Methods

Twelve MRL/1 virgin females aged 3

months obtained from the Jackson Laboratory (Bar Harbor, Marine, USA) were housed for a month under pathogen free condition and fed sterilized commercial pelleted food with free access to sterilized tap water. The mice were sacrificed by bleeding and specimens of the parotid, submandibular and sublingual salivary glands, exorbital lacrimal glands and cervical lymph nodes were fixed in 95% ethyl alcohol. Four-micron serial sections were stained with hematoxylin and eosin.

Results

The histopathological changes which characterize sialoadenitis and dacryoadenitis spontaneously occurring in MRL/1 mice was the dense infiltration of lymphoid cells replacing the acinar and ductal structures but the lobular architectures were usually preserved.

Multifocal lymphoid cell infiltrates were seen in all of the submandibular glands examined. The severity of the infiltrate foci varied from only a minor degree without appreciable glandular destruction to a more advanced, severer one followed by extensive destruction and disappearance of the glandular tissues (Fig. 1). There were differences in the infiltrating lymphoid cell types between minor and the advanced foci. The minor infiltrate foci consisted mainly of plasma cells. On the other hand, predominant cell types of the advanced one were small to large-sized lymphocytes and only at the periphery of such foci were seen the aggregation of plasma cells, some of which were

accompanied by various sized Russell's corpuscles. Some infiltrate foci were seen in the intralobular regions and others in the interlobular connective tissue, being closely related to ducts and blood vessels. The duct and an adjoining blood vessel were constricted by the proliferating lymphoid cells (Fig. 2). The epithelial cells constituting the duct underwent degenerative changes and two such cells were pushed out into the lumen of the duct (Fig. 3). The walls of small blood vessels were occasionally infiltrated by lymphoid cells with an admixture of small amount of neutrophils (Fig. 4). Within some of the advanced infiltrate foci, there were epimyoe epithelial islands which were composed of large polyhedral epithelial cells with vesicular nuclei and abundant eosinophilic cytoplasm whose cell walls were sometimes ill-defined (Fig. 5). Infiltration of the islands by lymphoid cells was constantly seen. Some of the islands had central spaces resembling to those of the ducts.

The histopathological changes in the ex-orbital lacrimal glands were also identical with those in the other glands and also identical with those in the other glands and also characterized by lymphoid cell infiltrates. Each infiltrate focus in the exorbital glands was commonly less severe than that occurring in the submandibular glands, but the foci of infiltration were more intensively distributed per one exorbital gland (Fig. 7). The

epimyoe epithelial islands were less frequently seen in the exorbital glands. The infiltrates appeared to arise from the interacinous regions rather than from the scanty interlobular connective tissues. The lobular architectures rarely disappeared because of the extension of infiltration over the adjoining lobules.

All of the mice examined developed massive enlargement of the cervical lymph nodes of 70 or 80-fold increase in size, so that the adjoining submandibular glands as well as the parotid and sublingual glands were displaced and distorted, sometimes atrophied (Fig. 8). The bulk of the enlarged lymph nodes consisted predominantly of small to large lymphocytes, which proliferated monotonously or with formation of numerous well-developed lymphoid follicles accompanied by a derangement of the nodal architectures. In some cases, there were aggregations of plasma cells, some of which contained Russell's corpuscles, with an admixture of various amounts of histiocytes around the sinuses. The proliferating lymphocytes frequently extended across the fibrous capsules of the nodes but never reached insides of the adjoining salivary glands.

Discussion

MRL/1 mice also developed spontaneous

Explanations of figures

- Fig. 1 Extensive lymphoid cell infiltrate focus. Submandibular gland. Orig. Mag. $\times 40$.
 Fig. 2 Proliferating lymphoid cells constrict adjoining duct and blood vessel. Submandibular gland. Orig. Mag. $\times 100$.
 Fig. 3 Ductual epithelial cells are attacked by lymphoid cells and two epithelial cells are pushed out into the lumen of duct. Submandibular gland. Orig. Mag. $\times 400$.
 Fig. 4 Wall of small blood vessel is infiltrated by lymphoid cells with admixture of small amount of neutrophils. Submandibular gland. Orig. Mag. $\times 200$.
 Fig. 5 Epimyoe epithelial island consisting of large polyhedral epithelial cells with infiltration of lymphoid cells. Submandibular gland. Orig. Mag. $\times 200$.
 Fig. 6 Lymphoid cell infiltrate in parotid gland. Orig. Mag. $\times 100$.
 Fig. 7 Multifocal lymphoid cell infiltrates, one of which contains an epimyoe epithelial island (upper right). Exorbital lacrimal gland. Orig. Mag. $\times 40$.
 Fig. 8 Low power view of extremely enlarged cervical lymph nodes (1) showing a number of well-developed lymphoid follicles. Adjoining submandibular (Sm), parotid (P) and sublingual (Sl) glands are pressed by lymph nodes. Orig. Mag. $\times 6$.

sialoadenitis and dacryoadenitis characterized by lymphoid cell infiltrates like other SLE mice such as NZB, NZB/F1 and SL/Ni mice. The lesions of MRL/1 mice appeared to be more rapidly progressive and severer than the NZB and SL/Ni mice at least. The infiltrating cell types which predominated in the minor foci and the advanced foci respectively were morphologically very similar to those of NZB mice. As described in the previous report⁵⁾, the predominant cells of the advanced foci in NZB mice were T lymphocytes and they were considered to play an important role in the progressive destruction of salivary and lacrimal glands.

Also in MRL/1 mice, it is possible that the lymphoid cells which contribute to glandular destruction are T lymphocytes. However, it is suspected that the etiopathogenesis which underlies the glandular destruction by the those infiltrating cells is not common to all kinds of SLE mice. All SLE mice share various immunologic, virologic and other abnormalities, but there were some differences among the strains. This is considered to depend upon different genetic backgrounds. Especially, MRL/1 mice possess an unique characteristic being an excessive proliferation of T lymphocytes, genetically determined by a mutant gene, *lpr*⁴⁾. This proliferation of T lymphocytes probably contributes not only to massive generalized lymph nodes enlargement but also development and progress of SLE, RA and vasculitis as well as sialoadenitis and dacryoadenitis in MRL/1 mice.

Finally, comparison among sialoadenitis and dacryoadenitis seen in some kinds of

SLE mice is very useful to clarify the different etiopathogenesis among them, and this may be helpful in order to further understand the entity of human Sjögren's syndrome.

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