Sialadenitis in IQI/Jic Mice: A New Animal Model of Sjögren's Syndrome

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(Received 17 April 1997/Accepted 12 June 1997)

ABSTRACT. Focal infiltration of lymphocytes with parenchymal destruction was noted in both salivary and lacrimal glands of IQI/Jic mice. The sialadenitis was found in more than 80% of female mice at all ages examined. The lesion progressed after 6 months and became more prominent with age. In contrast, male mice had slight and stable salivary lesions independent of age, though the incidence increased with age. Infiltrating lymphocytes consisted of both T and B cells. The dominant lymphocytes in small foci were CD4⁺ cells, but the majority of infiltrating cells were B cells (B220⁺), followed by CD4⁺ T cells in larger lesions. The ductal epithelium in the foci aberrantly expressed MHC class II antigen. Eight of 24 15-month-old female mice with sialadenitis produced speckled-type IgG antinuclear autoantibody. These findings are similar to those in patients with Sjögren's syndrome. IQI/Jic mice could be a novel animal model of Sjögren's syndrome. — **KEY WORDS:** animal model, IQI/Jic, sialadenitis, Sjögren's syndrome.

J. Vet. Med. Sci. 59(10): 897–903, 1997

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by lymphocyte infiltration of the lacrimal and salivary glands, resulting in dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) [3, 21, 26]. The disease may exist as a primary condition or as a secondary condition in association with other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis. It usually appears in women in their fourth and fifth decades in all races, with a female-to-male ratio of 9 to 1 [3, 26]. The lesion remains confined to salivary and lacrimal glands in the majority of the primary SS cases; however, B-cell lymphoma appears in some patients several years after onset [3, 21, 26].

Animal models resembling the human disease are helpful to clarify the important immune mechanism leading to exocrinopathy and development of tissue pathology. Spontaneous and experimental animal models of SS have been presented [4–6, 9, 10, 12, 16, 22, 25, 29, 31], but many models failed to produce the long-lasting lesions seen in human patients.

IQI/Jic is an inbred strain established from ICR mice in Japan [20]. This strain is a high responder to induce antinucleolar autoantibody by mercuric chloride [27]. Recently, we found that aged female mice of this strain had numerous B cells in their thymus [28]. During pathological studies on this strain, we often noticed focal accumulation of mononuclear cells in salivary glands of females. We started, therefore, chronological study on salivary and lacrimal glands in this strain. We found focal lymphocyte infiltration with parenchymal destruction in both organs. The sialadenitis progressed with age and was more prominent in females. These results suggest that this mouse strain could be a novel animal model of SS.

MATERIALS AND METHODS

Mice: Specific pathogen free IQI/Jic mice were originally obtained from the Central Institute of Experimental Animals

(Kawasaki, Japan) and maintained in the semi-barrier system of our animal facility. Four week old female BALB/c mice were purchased from CLEA Japan Ltd. (Tokyo, Japan). The animals were kept in polycarbonate cages and were given free access of standard laboratory pellets (CE-2, CLEA Japan Ltd., Tokyo, Japan) and tap water. The animal room was air-conditioned (temperature $22 \pm 2^\circ\text{C}$, relative humidity $55 \pm 5\%$) with a 12-hr light-dark cycle. Serological monitoring revealed that the animals used in this study were free from any infectious pathogens.

Histopathology: Both male and female IQI/Jic mice aged 3, 6, 9, 12 and 15 month and in good general condition were examined. In addition, 7- and 8-month-old females were examined. The mice were anesthetized with chloroform, bled by heart puncture and then autopsied completely. Tissues were fixed in 10% neutral-buffered formalin and embedded in paraffin. Sections cut at a thickness of 4 μm were stained with hematoxylin and eosin, and selected ones were also stained with periodic acid-Schiff, trichromatic or silver stains.

Longitudinal sections at central part of the mandibular glands were prepared and the severity of the lesions was scored as follows. Each inflammatory focus was graded by the number of infiltrating cells (IF) and focus points (FP); 1 FP=foci with less than 20 IF, 2 FP= foci with 20 to 200 IF and 3 FP=foci with more than 201 IF. The total FPs of tissue sections of left and right mandibular glands were calculated, and the severity of the mandibular lesion was evaluated as follows: slight=less than 15 FPs, moderate=16 to 40 FPs and severe=more than 41 FPs.

Antibodies: Monoclonal antibodies (mAbs) to murine CD4 (clone GK1.5, rat IgG2b) and murine CD8 (clone 2.43, rat IgG2b) were obtained from Dr. S. Yamamoto at the Institute of Public Study (Tokyo, Japan). mAb to major histocompatibility complex (MHC) class II antigens, which reacts with I-A^{b,d,q} and I-E^{d,k} (clone M5/114.15.2, rat IgG2b), was supplied from Dr. S. Kyuwa at the Institute of Medical Science, the University of Tokyo (Tokyo, Japan). mAb to

murine B220 (clone RA3-6B2, rat IgG2a) with and without conjugation of phycoerythrin (PE), anti-mouse Fc γ II/III receptor (clone 2.4G2, rat IgG1) and biotinylated anti-mouse CD3 (clone 145-2C11, hamster IgG) were purchased from Pharmingen, California U.S.A. PE-conjugated anti-mouse CD4 (clone GK1.5, rat IgG2b), fluorescein-isothiocyanate (FITC)-conjugated anti-mouse CD8 (clone 53-6.7, rat IgG2a) and avidin-conjugated FITC were purchased from Becton Dickinson (California, U.S.A.). mAb to murine Mac-1 antigen (CD11b/CD18) (clone M1/70, rat IgG2b) was purchased from Boehringer-Mannheim (Tokyo, Japan). FITC-conjugated goat sera against mouse IgM or mouse IgG were purchased from Cappel (Pennsylvania, U.S.A.).

Immunohistology: Mandibular gland from 12- and 15-month-old female mice was examined by the avidin-biotin immuno-peroxidase method using the Vectastain ABC kit (Vector Laboratories, California, U.S.A.) to characterize infiltrating mononuclear cells. Mandibular tissue was embedded and frozen in O.C.T. compound (Miles Inc., Indiana, U.S.A.). Serial sections cut at a thickness of 4 μ m were incubated with mAbs to CD4, CD8, B220, Mac-1 and class II MHC in a refrigerator overnight. After antibody incubation, sections were incubated with biotinylated rabbit anti-rat IgG (Vector Laboratories) for 30 min and endogenous peroxidase activity was blocked by incubation with 0.3% H₂O₂ methanol solution for 30 min. Then, slides were incubated with avidin DH: biotinylated horseradish peroxidase H complex for 60 min and the peroxidase reaction was initiated in a solution of 0.05% diaminobenzidine (Wako Pure Chemicals, Tokyo, Japan) and 0.01% H₂O₂ in PBS. Sections were counterstained with methyl green. All reagent incubations were carried out at room temperature unless otherwise specified.

Flow cytometric analysis: To verify the results of immunohistology, lymphocytes from the mandibular gland from 12-month-old female mice were analyzed in two-color analysis by FACScan (Becton Dickinson). Single cell suspensions of lymphocytes were made from the mandibular gland of freshly killed mice in PBS containing 0.05% sodium azide, and were first incubated with anti-mouse Fc γ II/III receptor for 30 min to prevent non-specific binding of antibodies reacting later. After washing in PBS, an aliquot of the cell suspensions was incubated with biotinylated anti-mouse CD3 and PE-conjugated anti-mouse B220 for 30 min, washed with cold PBS, and then incubated with avidin-conjugated FITC for 30 min. Other suspensions were incubated with PE-conjugated anti-mouse CD4 and FITC-conjugated anti-mouse CD8 for 30 min. After washing with cold PBS, cell suspensions were applied to FACScan and 10,000 events were acquired from each sample. All reagent incubations were carried out on ice.

Autoantibodies: Mouse sera from 15-month-old mice were stored at -20°C until use. Antinuclear antibody and anti-salivary gland antibody were examined by indirect immunofluorescence using FITC-conjugated goat anti-mouse IgM or anti-mouse IgG. Sera diluted 1:10 with PBS were screened for their reactivity to nuclear antigens using

rat myoid cell line as substrate. Positive sera were further examined for their reactivity to SS-A and SS-B antigens prepared from human liver cell line (Hep-2) by double immunodiffusion using ENA-2 kit (MBL Ltd., Nagoya, Japan). Anti-salivary gland antibody was examined by indirect immuno-fluorescence using frozen tissue sections of normal salivary gland from 4-week-old female IQI/Jic and BALB/c mice.

RESULTS

Histopathology: There was focal accumulation of mononuclear cells in the salivary and lacrimal glands, while no gross abnormalities were noted. The infiltrates were prominent around the interlobular ducts in the central portion of the lobule (Fig. 1A). The acini and ducts were extensively replaced by these infiltrates in severe cases, but fibrosis was rare. Destruction of acinar cells and plasma cell infiltration were frequently seen at the periphery of large foci (Fig. 1B). These changes were prominent in the mandibular and extraorbital lacrimal gland (Fig. 1C). Similar lesions were often seen in the parotid gland (Fig. 1D); however, those in the sublingual and infraorbital lacrimal glands were rare.

Sialadenitis was found in more than 80% of female mice at all ages examined, and the severity increased with age (Table 1). Although only slight lesions were observed in most females younger than 6 months, severe lesions suddenly appeared in 10 of 25 (40%) 9-month-old female mice. Thus we studied an additional 10 females of 7 and 8 months of age. Two and 3 mice 7- and 8-month-old, respectively, suffered from severe lesions. These results indicated that the lesion of the female mice might be progressive after 6 months. In contrast, male mice had slight and stable salivary lesions independent of age, though the incidence increased with age (Table 1).

In addition to the lesions in the salivary and lacrimal glands, no specific lesions could be found in either male or female mice younger than 6 months. Systemic lymphadenopathy with plasmacytosis was apparent in female mice with severe sialadenitis. Lymphoid hyperplasia of the thymic medulla was frequent, and segmental glomerular sclerosis and necrotizing vasculitis involving small- to medium-sized arteries were not uncommon in females older than 9 months. However, these extraglandular lesions were not always correlated with the severity of the sialadenitis.

Immunohistology: The infiltrating lymphocytes in salivary lesions consisted of B cells (B220⁺) and T cells (CD4⁺ and CD8⁺). The dominant lymphocytes in small foci were CD4⁺ cells. However, the majority of infiltrating cells were B cells (B220⁺), followed by CD4⁺ cells in larger lesions (Fig. 2). A few CD8⁺ and Mac-1⁺ subsets were scattered in the foci (Fig. 2C). MHC class II antigen was expressed on most infiltrating mononuclear cells and on the ductal epithelial cells in the foci (Fig. 2D).

Flow cytometric analysis: Two color analysis of

Fig. 1. Sialadenitis in a 12 month-old female IQI/Jic mouse. (A) Multiple focal infiltration of mononuclear cells around interlobular ducts in mandibular gland (Bar=500 μ m). (B) Infiltration of lymphocytes and destruction of acini and granulated ducts in mandibular gland. Note infiltration of plasma cells at periphery of the lesion (Bar=50 μ m). (C) Infiltration of lymphocytes replacing the acinar cells in extraorbital lacrimal gland (Bar=100 μ m). (D) Lymphocyte infiltration in parotid gland (Bar=100 μ m). Hematoxylin and eosin stain.

Table 1. Incidence and severity of submandibular adenitis in IQI/Jic mice

Sex	Age (months)	positive/ examined (%)	No. of cases with the lesion ^{a)}		
			Slight	Moderate	Severe
female	3	16/17 (94)	16	0	0
	6	20/25 (80)	19	1	0
	7	9/10 (90)	4	3	2
	8	10/10 (100)	4	3	3
	9	24/25 (96)	6	8	10
	12	30/31 (97)	8	6	16
	15	24/24 (100)	1	7	16
male	3	2/15 (13)	2	0	0
	6	13/23 (57)	13	0	0
	9	14/21 (67)	10	4	0
	12	15/18 (83)	12	3	0
	15	22/23 (96)	18	4	0

a) Each focus was graded by the number of infiltrating cells (IF) and focus point (FP). 1 FP=foci with less than 20 IF, 2 FP=foci with 21 to 200 IF, and 3 FP=foci with more than 201 IF. The total FPs of the lesion from both sides are calculated and the severity of the lesion is evaluated by the total FPs of tissue sections from both sides. Slight=less than 15 FPs, moderate=16 to 40 FPs, and severe=more than 41 FPs.

lymphocytes from the salivary gland revealed that a large population of the infiltrating lymphocytes was B cells (Fig. 3) and that the ratio of B (B220⁺)/T (CD3⁺) cells was from 1 to 2. CD4⁺ cells were dominant in T cells, and the ratio of CD4⁺/CD8⁺ cells was from 5 to 10. These results were in agreement with the immunohistological observations.

Autoantibodies: Speckled-type antinuclear IgG antibody was detected in 8 of 24 females and 1 of 23 males at 15 months of age, but no positive reaction to SS-A or SS-B was obtained by double immunodiffusion. Anti-salivary gland antibody was not detected.

DISCUSSION

The present study showed that IQI/Jic mice developed focal lymphocytic infiltration with parenchymal destruction in both salivary and lacrimal glands. The glandular inflammation was more pronounced in females than in males. Sialadenitis in females was progressive with age and long-lasting, becoming prominent after 9 months. Immunohistological and flow cytometric analyses revealed that the infiltrating lymphocytes consisted of both T and B cells, and CD4⁺ cells were dominant among T lymphocytes. The ductal epithelium in the foci showed aberrant expression of MHC class II. Some mice with the sialadenitis produced speckled-type antinuclear antibody. Mice with prominent lesions developed systemic lymphadenopathy with plasmacytosis, suggesting hypergamma-globulinemia. These syndrome observed in IQI/Jic mice fulfil the basic features of SS [3, 21, 26], indicating that this mouse strain could be a novel animal model of SS.

Immunohistological study of lymphocyte subsets

indicated that CD4⁺ cells were the major population in T lymphocytes. This result is in agreement with infiltrating cells in small salivary glands of SS patients [2, 3, 13, 21, 24, 26, 28, 32]. Similar observations were reported in other mouse models of SS [4, 6-10, 14, 16, 18, 19, 25, 29, 31]. It also revealed that the dominant infiltrating lymphocytes were T cells in small foci, but those were B cells in larger lesions. This observation suggested a progression from T cell-dominant foci with later accumulation of B cells. Similar results were reported in the studies on human SS [1, 13, 24], therefore, this mouse strain might make it possible to study the early events and the identification of potentially important immune reactions in the pathogenesis of SS.

Recently, examination of the B cells in the lesion was emphasized [11, 17, 23]. Salivary glands in SS patients are suspected to be a major site of activation of B cells which might secrete large amounts of immunoglobulins with rheumatoid factor activity [11, 17]. In this study, plasma cell infiltration was often found at the periphery of large foci, indicating active immunoglobulin production. This strain, therefore, may be useful to elucidate the characteristics of autoantibodies produced in salivary glands and their roles in the pathogenesis of SS.

We detected MHC class II antigen on ductal epithelial cells in inflammatory lesions but not in normal epithelial cells of salivary gland in this study. Similar results were obtained in MRL/lpr mice [12, 16, 19]. Epithelial cells of salivary glands from SS patients express HLA DR molecules whereas those of normal salivary glands do not [21, 24]. The induction of aberrant expression of MHC class II molecules is suspected to be due to local production of interferon γ by T cells [15, 24]. Since CD4⁺ T cells interact with peptide antigen presented by class II MHC molecules, aberrant induction of this molecule on the epithelial cells may cause CD4⁺ T cells to generate an autoimmune response against the epithelium.

It is well known that antinuclear antibody which usually give a speckled pattern is present in 40 to 50% of primary SS patients [3, 21, 26]. Speckled-type antinuclear antibody was detected in 33% of 15-month-old female mice with sialadenitis in the present study. However, this autoantibody did not react with SS-A or SS-B antigens prepared from human liver cell line Hep-2. Since the immuno-diffusion techniques were not sensitive enough [10], we might have failed to detect the autoantibody. St Clair *et al.* [30] reported anti-La autoantibody production in MRL/lpr mice by ELISA, although the pattern of recognition of recombinant human La antigen differed between mice and human patients, suggesting the epitopes on human cells are different from those on murine cells. Spontaneously occurring antinuclear autoantibody in IQI/Jic mice may recognize different epitopes from human SS-A or SS-B antigens; therefore, murine nuclear antigens should be prepared to identify the antigen of antinuclear autoantibody produced in this mouse. Anti-salivary gland autoantibody was not detected in this study, while its production was reported in aged mice with sialadenitis [7-9]. Organ-specific

Fig. 2. Immunostain of infiltrating lymphocytes of a relatively large lesion in mandibular gland from a 12 month-old female mice. (A) B220⁺ (B) lymphocytes, (B) CD4⁺ lymphocytes and (C) CD8⁺ lymphocytes. (D) Expression of MHC class II antigen. Most infiltrating cells and interstitial dendritic cells are positive. Ductal epithelial cells (arrow) in the lesion aberrantly express the MHC class II antigen. ABC stain.

Fig. 3. Two color analysis of infiltrating lymphocytes in mandibular gland from a 12 month-old female mouse. Analysis of T cells (CD3⁺) and B cells (B220⁺) ratio (left) and CD4⁺ and CD8⁺ T cells subsets (right). Percentage of each gated cells are shown at upper right corner.

autoantibody is absent in most SS patients [3, 21, 26], indicating that the antibody may not play a primary role in pathogenesis.

In conclusion, sialadenitis in IQI/Jic mice coincide with the features of human SS in many respects. This mouse strain may be a novel animal model to clarify the pathological mechanism of SS.

ACKNOWLEDGEMENT. We particularly wish to thank Dr. A. Yasuda at the Laboratory of Experimental Toxicology in this institute for his technical support in flow cytometric analysis.

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