

# Peculiar histopathologic findings of the salivary glands in patients with Sjögren's syndrome

## Ultrastructural and immunohistochemical studies on salivary gland duct and hyaline-like substance

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**和文抄録** : Sjögren 症候群における唾液腺の病理組織所見としては導管周囲を中心としたリンパ性細胞浸潤, 腺実質の退行性変化, 導管上皮細胞の破壊あるいは増生, いわゆる筋上皮島の形成などが挙げられる。これらの所見のうち, 導管周囲性のリンパ性細胞浸潤, 導管上皮細胞の増生と筋上皮島の形成が本症候群に特徴的な組織像とされている。また稀には硝子様物質の沈着をみることもあるが, このものの由来については未だ明らかではない。本研究では浸潤リンパ性細胞と導管上皮細胞との関連, ならびに硝子様物質を電顕的に観察するとともに, さらに硝子様物質についてはその中に補体が存在するか否かを蛍光抗体直接法にて検討した。結果は次の如くである :

リンパ性細胞は腺房部ならびに導管系の上皮細胞間に種々の程度に浸潤していたが, この所見は介在部導管において最も著明であった。したがって, Sjögren 症候群において唾液腺に浸潤したリンパ性細胞は介在部導管上皮細胞を標的としているものと推察された。

硝子様物質は導管周囲あるいは筋上皮島内外にみられ, 電顕的には不規則に配列した微細線維状を呈していた。この硝子様物質は上皮基底膜 (lamina densa) と連続してみられる部分もあり, この様な所見は SLE における腎糸球体病変に類似していた。また, FITC ラベル抗血清を用いた蛍光抗体直接法では硝子様物質中に Ig G, Ig M, C<sub>1q</sub>, C<sub>3</sub>が認められた。したがって, 硝子様物質の一部は免疫複合物よりなる可能性が示唆された。

**Key words** : Sjögren's syndrome, salivary gland, hyaline-like substance, lymphocytes, duct epithelia

Recent studies on Sjögren's syndrome have revealed that autoimmune basis may play an important role in its pathogenesis. Generally, Sjögren's syndrome consists of xerostomia and keratoconjunctivitis sicca which are caused by disorders of the salivary and lacrimal glands. And there is increasing evidence of a much higher frequency of Sjögren's syndrome in rheumatoid arthritis, in other connective tissue diseases, and also in certain

other disorders thought to be mediated by autoimmune reaction. The histopathologic changes of the salivary glands in Sjögren's syndrome are characterized by lymphoid cell infiltration in various degrees, atrophy of the acinar cells, destruction and/or proliferation of the duct epithelial cells, and formation of epimyoepithelial islands with or without deposition of the hyaline-like substance.

Ultrastructural changes of the salivary

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glands in Sjögren's syndrome have been described in several papers<sup>1-6</sup>, which mainly dealt with the origin of the epithelial elements in aggregations of the infiltrating lymphoid cells. The author has investigated the ultrastructural changes of the minor salivary glands in Sjögren's syndrome, with a particular attention to the relation between the duct epithelial cells of the salivary glands and infiltrating lymphoid cells, since an organ-specific antibody against the duct epithelial cells of the salivary glands has recently been demonstrated in patients with Sjögren's syndrome<sup>7-10</sup>. A report is made on the most peculiar histopathologic findings in the present study.

### Materials and Methods

The diagnosis of Sjögren's syndrome was based on the criteria of Sjögren's Disease Research Committee of the Ministry of Health and Welfare in Japan<sup>11</sup>. In two cases of definite Sjögren's syndrome, the biopsy specimens of the labial salivary glands which showed marked lymphoid cell infiltration and formation of epimyoeplithelial islands with deposition of hyaline-like substance in the light microscope were prepared for both electron microscopic investigation and direct immunofluorescent method using FITC-labeled specific antiserum (IgG, IgM, C<sub>1q</sub>, C<sub>3</sub>) to investigate the relation between the duct epithelia and infiltrating lymphoid cells, and the nature of the hyaline-like substance.

### Results

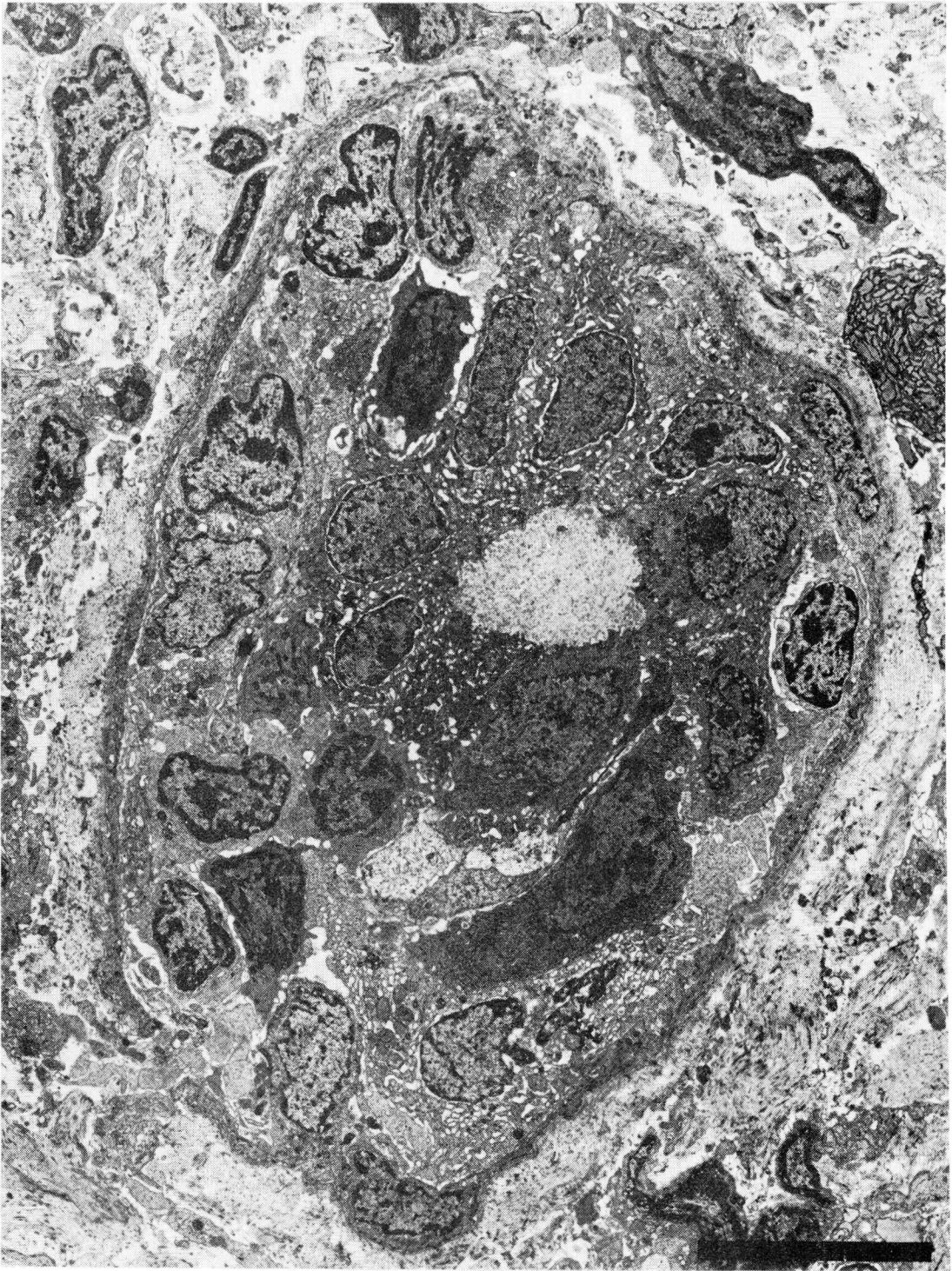
Small and medium sized lymphocytes and plasma cells appeared interspersed in the ducts and acini. The thickened duct wall seen in the light microscope could be identified at the ultrastructural level as epi-

thelial proliferation associated with infiltration of numerous lymphocytes and plasma cells. Infiltration of lymphocytes and plasma cells was more remarkable in the intercalated duct than in the acini or other parts of the duct system. Figs.1 and 2 showed a cross-section of the intercalated duct with early change. Many lymphocytes infiltrated between the duct epithelial cells and the basal lamina, and a plasma cell was also noted between them. A few myoeplithelial cells, which had long tapering cytoplasmic processes, were located in the basal portion of the duct. The basal lamina was well preserved. Many lymphocytes and plasma cells were scattered in the periductal area.

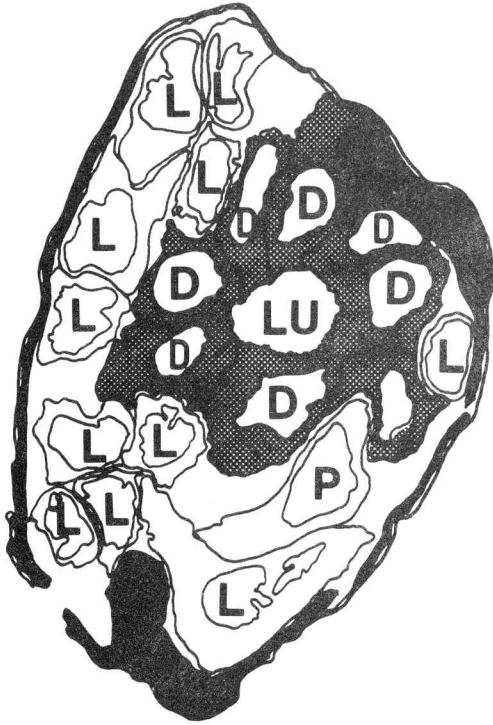
The hyaline-like substances were found light-microscopically in and around the epimyoeplithelial islands and the altered ducts, and were stained pink with hematoxyline and eosin (Fig.3A,B). By direct immunofluorescent method stained with FITC-labeled specific antiserum, IgG, C<sub>1q</sub> and C<sub>3</sub> were detected as granular fluorescences in some parts of the hyaline-like substance (Fig.4A,B). Electron microscopically the hyaline-like substance was shown to be an irregular and dense accumulation of fine fibrillar substances (Fig. 5A). In part, the hyaline-like substance was surrounded by basal lamina and was fused to the lamina densa (Fig.5B).

### Discussion

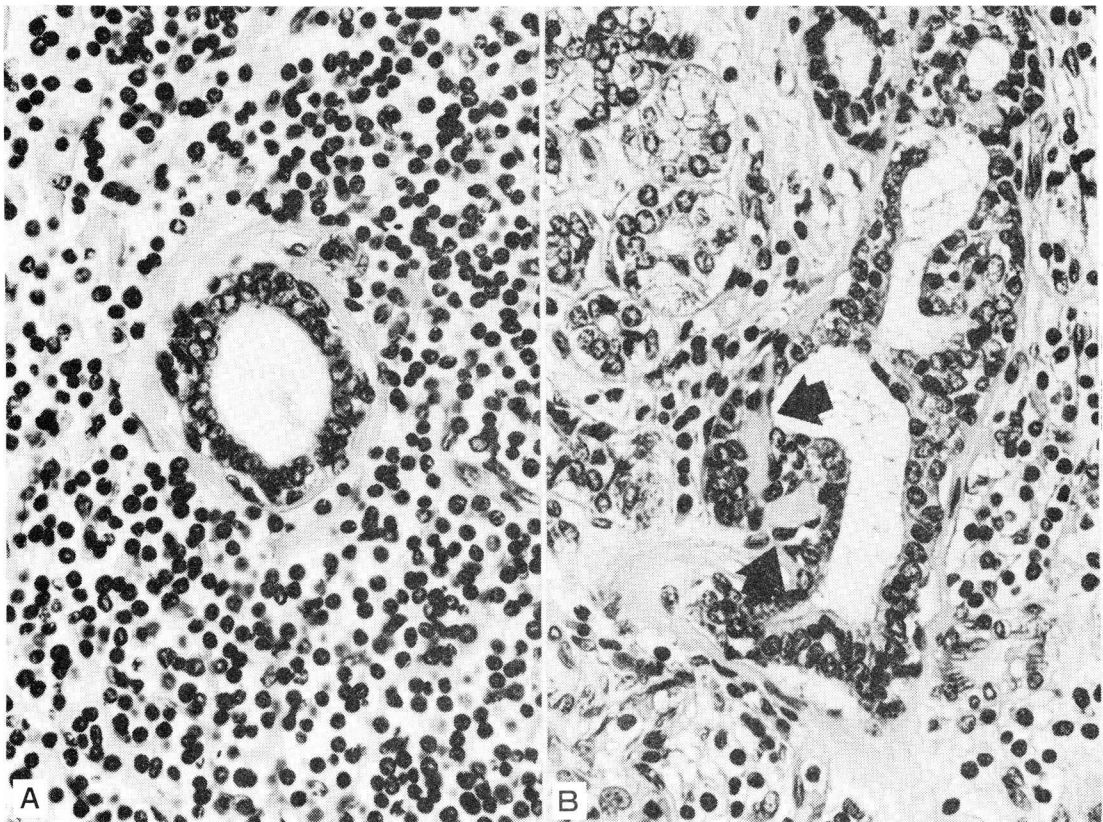
Although the cause of Sjögren's syndrome remains unknown, it seems likely that a combination of genetic, immunologic, latent viral and/or environmental factors may play an important role in the pathogenesis<sup>12</sup>. Taking into account the pathologic and laboratory findings in Sjögren's syndrome, it is reasonable to learn toward the immunologic basis



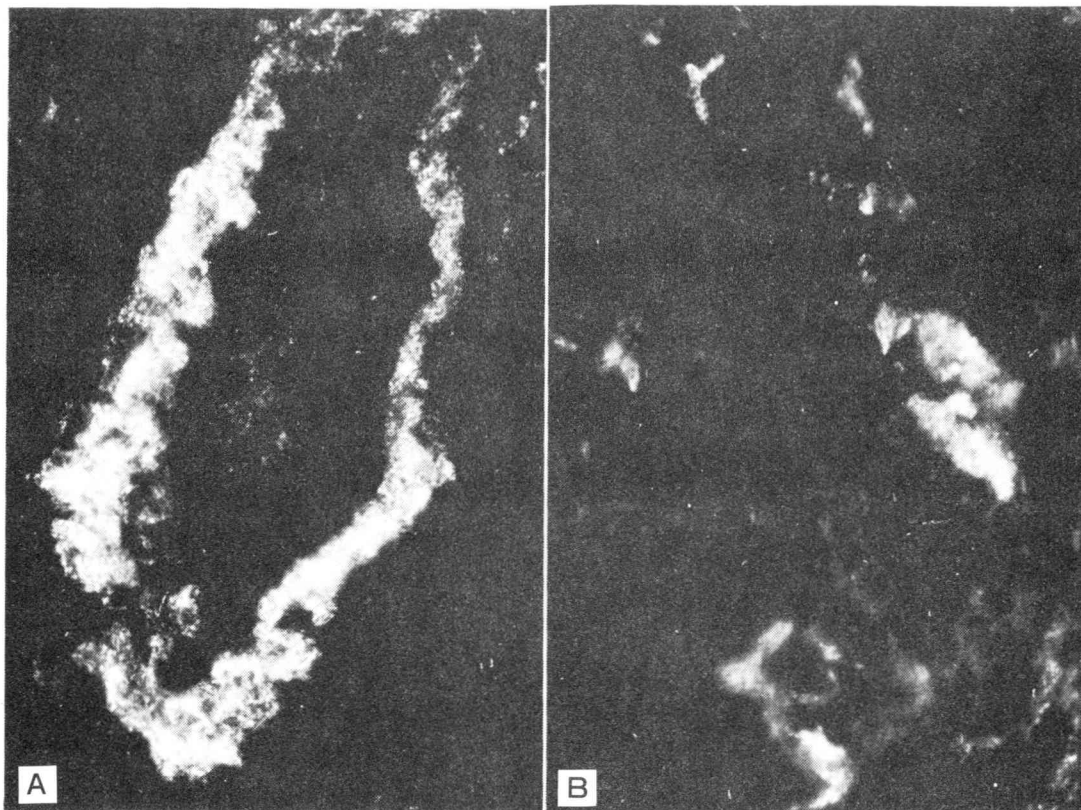
**Fig. 1** Electron photomicrograph of a cross-section of intercalated duct. Many lymphocytes infiltrate between the duct epithelial cells and the basal lamina. Bar = 10 $\mu$ m. (X 3,530)



**Fig. 2** Schematic presentation of Fig. 1. Duct epithelial cells (D), duct lumen (LU), lymphocytes (L), plasma cell (P) and myoepithelial cells (black shading areas) are indicated.



**Figs. 3A,B** Light photomicrographs of hyaline-like substance. Fig. A showing that hyaline-like substance surrounds the duct. Fig. B showing that hyaline-like substances are also found in proliferated duct wall (arrows). (Hematoxyline and eosin stain. Original magnification, X 400)



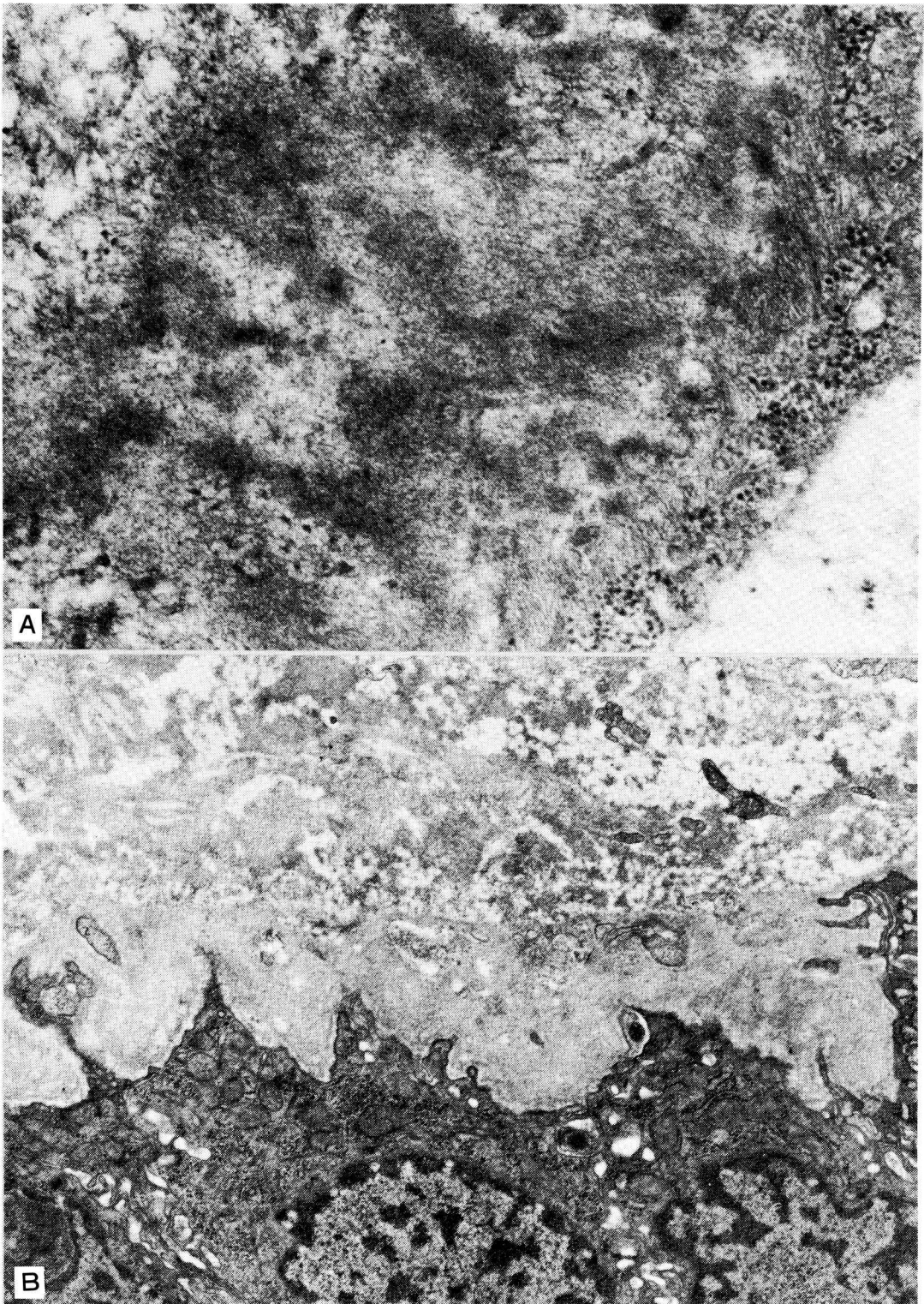
**Figs. 4A,B** Fluorescence photomicrographs of hyaline-like substance. Fig. A showing IgG-positive hyaline-like substance in periductal area, and Fig. B showing C<sub>1q</sub>-positive hyaline-like substance in epimyoe epithelial island. (Original magnification, X 400)

and, indeed, recent immunologic studies agree that Sjögren's syndrome may be derived from autoimmune disorders. It has been thought that salivary gland is one of the target organs in Sjögren's syndrome, and auto-antibody to the cytoplasm of the salivary duct epithelial cells (antisalivary duct antibody, ASD) has been demonstrated<sup>7-10</sup>, though pathologic significance of ASD is unknown and its existence has been doubted by some investigators<sup>13</sup>. It seems reasonable to assume that the epithelial cells of the intercalated ducts represent the target cells for the infiltrating lymphoid cells in Sjögren's syndrome, since early glandular infiltration by lymphoid cells surrounded the small ducts, and marked infiltration of the lymphoid cells

was detected ultrastructurally in the duct walls, especially in the intercalated region.

From materials obtained at labial salivary gland biopsy, Talal et al.<sup>14</sup> have demonstrated a greater synthesis of immunoglobulins, especially IgG and IgM, in Sjögren's syndrome compared with controls, while Anderson et al.<sup>15</sup> have demonstrated that the local synthesis of rheumatoid factor in labial salivary gland tissue is distinctive for Sjögren's syndrome. Then immune deposits may be also found in the salivary gland in Sjögren's syndrome. Pirsig und Donath<sup>5</sup> compared the parotid glands taken before and after the immunosuppressive therapy in the same patient with Sjögren's syndrome. Following the immunosuppressive therapy, the hyaline-like





**Figs. 5A,B** Electron photomicrographs of hyaline-like substance. Fig. A showing an irregular and dense accumulation of fine fibrillar substances. Fig. B showing hyaline-like substance is fused to the lamina densa. (Fig. A, X 50,100 and Fig. B, X 11,700)

substance disappeared, and they concluded that the hyaline-like substance represented a form of antigen-antibody reaction. The results of the present study also suggest that the hyaline-like substance in the salivary gland in Sjögren's syndrome contains the antigen-antibody complex, since IgG, C<sub>1q</sub> and C<sub>3</sub> were detected by immunofluorescent method in some parts of the hyaline like substances. And the hyaline-like substance was shown to be an accumulation of fine fibrillar substances closely resembling the immune deposits in various tissues and organs in

other autoimmune diseases ultrastructurally. The detailed nature and pathologic significance of the hyaline-like substance in salivary gland in Sjögren's syndrome present an intriguing field for research.

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**Abstract :** The ultrastructural and immunohistochemical studies were made on the labial salivary glands in patients with Sjögren's syndrome, and peculiar histopathologic findings were reported. As the results of present investigation a hypothesis is put forward that the epithelial cells of the intercalated ducts represent the target cells for the infiltrating lymphoid cells. The hyaline-like substance in and around altered ducts and epimyoeptithelial islands may contain antigen-antibody complex in part.

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