Virchows Archiv A Pathol Anat (1990) 417:353–356

Virchows Archiv A
Pathological Anatomy and Histopathology
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Case report

Cystic benign lymphoepithelial lesion of the salivary glands in HIV-positive patients

Report of two cases with immunohistochemical study

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Received December 18, 1989 / Accepted April 4, 1990

Summary. Two cases of cystic benign lymphoepithelial lesions (CBLL) of the submandibular and parotid glands occurring in HIV-positive patients are reported. The clinical and pathological criteria are defined and the differences from Sjögren's syndrome discussed. The presence, in the epithelial component, of T-cells labelled by the human mucosal lymphocyte antibody argues for a primary involvement of epithelial structures in CBLL, the lymphoid hyperplasia occurring secondarily.

Introduction

The salivary glands can be involved in a number of different ways in the acquired immune deficiency syndrome (AIDS) and its related disorders. Involvement of salivary gland lymph nodes as a part of persistent generalized lymphadenopathy syndrome (PGLS) (Helsper et al. 1986) is the most frequent phenomenon. Malignant lymphomas can also occur (Ioachim et al. 1987) and the sicca complex with characteristic clinical and histological features have been described (Couderc et al. 1987). Cystic benign lymphoepithelial lesions (CBLL), usually involving the parotid glands, have also been reported recently (Ryan et al. 1985) and we presenthere two new cases in HIV-positive patients that have been studied by immunohistochemical techniques with special reference to the human mucosal lymphocyte antigen (HML1).

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Case reports

Case 1. A 42-year-old homosexual man, who had suffered from widespread lymphadenopathy since 1984 associated since 1985 with positive HIV serology, presented in 1988 with massive, bilateral parotid gland enlargement. There was no history of dry mouth, dry eyes or arthritis. The right parotid gland (3×2 cm) was removed in August 1988 and the left (1.5×1 cm) in April 1989. The patient is alive on azidothymidine (AZT) therapy and has not progressed to AIDS (October 1989).

Case 2. A 48-year-old man presented in December 1988 with a herpes zoster. He gave a history of sexual contact with a HIV-positive Haïtian woman. Multiple, enlarged, peripheral lymph nodes were noted and HIV antibodies were detected in the serum. There was no evidence of the sicca syndrome. A right submandibular lymph node (2×1.5 cm) was biopsied. Three months later the patient presented with neurological manifestations and necrotizing leucoencephalitis was diagnosed on histological examination, reported to be due to a papovavirus infection. The patient was still alive in May 1989 but has subsequently been lost to follow-up.

Materials and methods

A portion of fresh tissue was frozen in liquid nitrogen and the remainder was fixed in Bouin's solution, embedded in paraffin and stained with haematoxylin and eosin and Gomori's silver impregnation.

Immunoperoxidase studies were performed on paraffin and on frozen sections using monoclonal antibodies directed against cytokeratin (KL1; Immunotech), epithelial membrane antigen (Dako), MB2 (pan-B; Clonab), L26 (pan-B; Dako), CDW75 and CD74 (pan-B LN1 and LN2 respectively; Miles), CD45RO (pan-T UCHL1, Dako), CD22 (pan-B, Dako), kappa and lambda light chains (Coultronics), IgM and IgD heavy chains (Becton-Dickinson), CD3, CD5, CD4, CD8 (Leu4, Leu1, Leu3, Leu2, respectively; Becton-Dickinson), dendritic reticulum cells (DRC, Dako), P24

HIV protein (Biosoft) and HML1 (courtesy of N. Cerf-Bensussan, Inserm U132, France).

Results

The biopsied tissues were firm. Numerous small, cystic cavities filled with clear gelatinous substance were found in case 2.

Histologically, the salivary glands showed both epithelial and lymphoid lesions. Cystic dilatations (Fig. 1) containing a homogeneous eosinophilic substance were present, lined by squamous metaplastic epithelium without keratin formation and with rare foci of oncocytic cells. Numerous small lymphocytes were intermixed with the epithelial cells. The cavities were surrounded by dense lymphoid tissue in which numerous epimyoepithelial islands (Fig. 2) and some normal residual acini and salivary ducts were found. The lymphoid infiltrate showed alterations similar to those observed in PGLS, occurring in HIV infection: florid follicular hyperplasia often associated with absent mantle-zones and containing numerous macrophages, follicular lysis and interfollicular hyperplasia with prominent vascularization.

The squamous epithelium of the cyst was keratin-positive (Fig. 3) and also reacted strongly for epithelial membrane antigen. Intraepithelial lymphocytes were predominantly of B-cell type (Fig. 4, left) (CD22+, MB2+, LN1, LN2+ but L26−); a few were T-cells (UCHL1+ CD3+, CD4 or CD8+), which were labelled with HML1 antibody (Fig. 4, right). Some small B-lymphocytes and a few HML1+ T-cells were also found in the connective tissue. The surrounding lymphoid tissue showed the expected distribution of reactive lymphoid cells in PGLS, i.e. polyclonal follicles containing numerous CD8+ small T-lymphocytes and reduced numbers of CD4+ cells, very few IgD-positive, mantle-zone lymphocytes and disruption of the follicular dendritic reticulum cell network. Interfollicular areas were

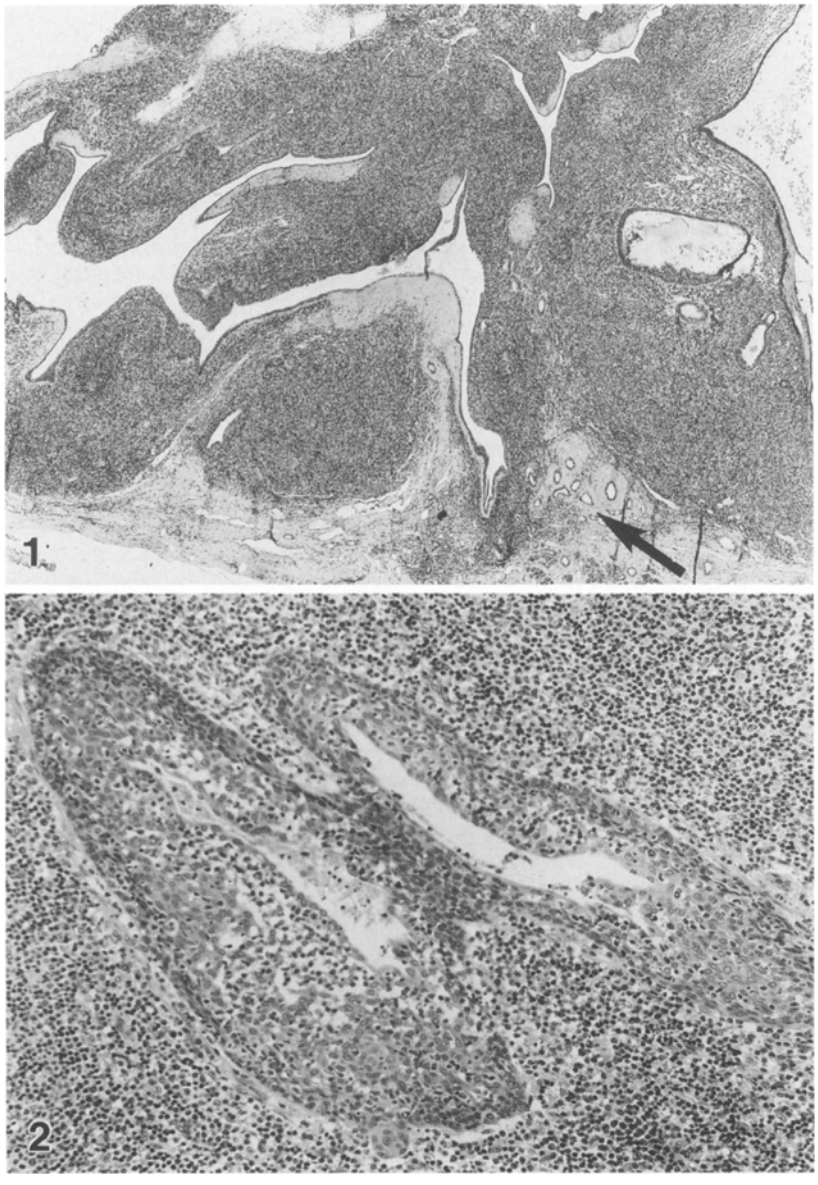

Fig. 1. Benign lymphoepithelial lesion of the right submandibular gland (case 2). Cystic ductal dilatation with dense peripheral lymphoid infiltrate. Persistance of small island of atrophic parenchyma (*arrow*). HE, ×22

Fig. 2. Islands of myoepithelial cells in a dense lymphoid tissue, HE, ×160

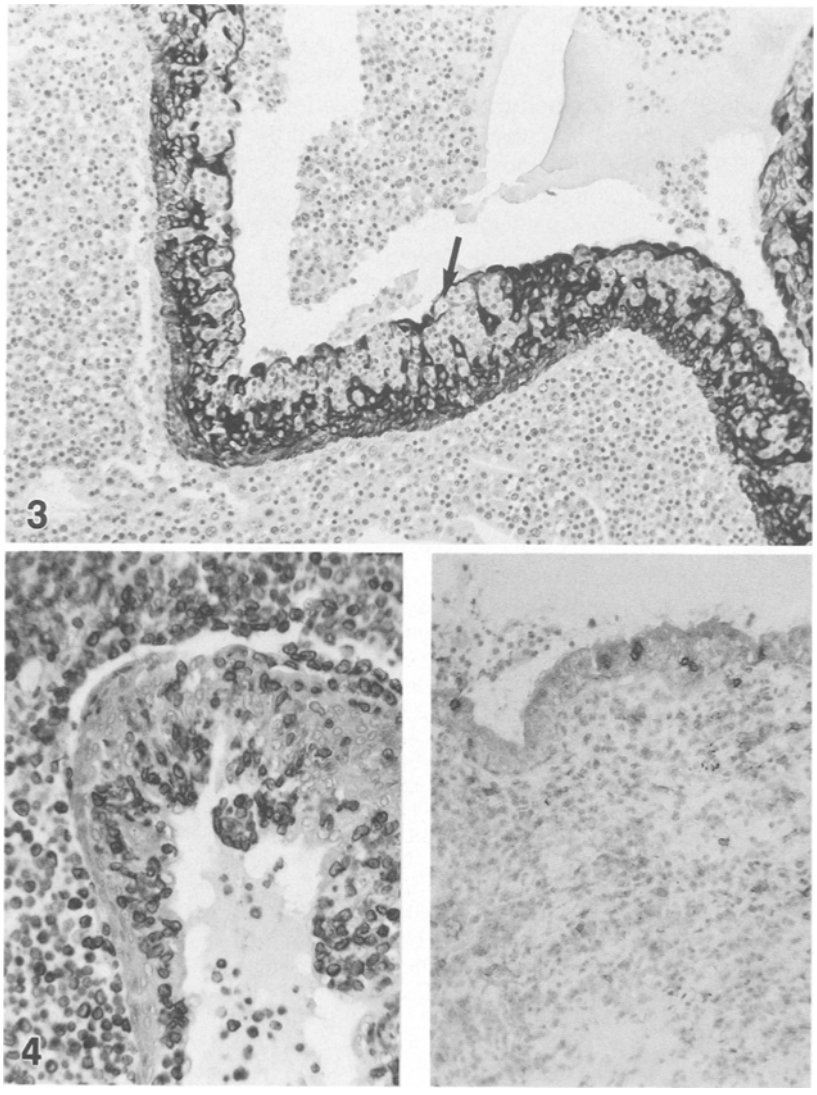

Fig. 3. Epimyoepithelial hyperplasia of the lining epithelium containing numerous unstained lymphoid cells (*arrow*). Cytokeratin staining, ×250

Fig. 4. *Left*, Numerous B-cell infiltrating the lining epithelium and the surrounding area. LN2 antibody on paraffin section, ×400. *Right*, Presence of T HML1-positive cells in the lining epithelium. HML1 antibody on frozen section, ×160

rich in polyclonal plasma cells. No positivity was obtained with the antibody directed against the HIV p24 protein.

Discussion

Manifestations of HIV infection are often evident in the head and neck region, frequently as the initial clinical feature (Helsper et al. 1986), but they usually involve cervical lymph nodes and oral mucous membranes rather than the salivary glands themselves.

When salivary glands (usually parotid) are involved, several patterns are seen. Most frequently, there are modifications of intraparotid or peri-submaxillary lymph nodes showing either explosive follicular hyperplasia as a part of PGLS, high-grade B-cell malignant lymphoma or Kaposi's sarcoma (Ioachim et al. 1987). The sicca syndrome can occur during the PGLS phase of the disease. However, it differs from the usual Sjögren's syndrome by its occurrence in young men, the absence of autoantibodies, the decrease in CD4 cells and the intense lymphoplasmocytic infiltrate in the glandular parenchyma without epithelial lesions (Couderc et al. 1987).

Our two patients presented another type of salivary gland lesion, first reported by Ryan et al. (1985), and called later "benign lymphoepithelial lesion" (BLL) by Smith et al. (1988). Both parotid glands were involved in one case, the right submandibular gland alone in the other. The sicca syndrome was absent. The epithelial component consisted of cystic dilatations lined by squamous epithelium associated with numerous epimyoepithelial islands; normal acini and salivary ducts persisted in variable number. A dense lymphoid infiltrate surrounded the epithelial structures in an organoid pattern, with follicles and interfollicular areas; this lymphoid tissue presented the same histological and immunological features as the lymph nodes of PGLS: large secondary follicles, without mantle-zones, infiltrated by small lymphocytes, many of them being of the CD8 type and follicular lysis.

After the first two cases reported by Ryan et al. in 1985, several other cases of BLL, often cystic, have been published. The parotid gland is usually involved and

more rarely the submandibular gland (Ioachim et al. 1987; Smith et al. 1987; Poletti et al. 1988; Shugar et al. 1988; Kornstein et al. 1988; Vaillant et al. 1989). The three cases reported by Ulirsch and Jaffe (1987) under the title of "Sjögren's syndrome-like illness" are confusing, since they present neither the clinical nor the pathological criteria of Sjögren syndrome as discussed by Ioachim and Ryan (1988), and the pathological findings in these three patients appear, in fact, compatible with benign lymphoepithelial lesions (Jaffe and Ulirsch 1988).

The histogenesis of CBLL is unknown. For many authors, the primary phenomenon in this disease is a lesion of the lymph nodes included in salivary glands. Because of its organoid pattern, the lymphoid component of CBLL is interpreted as hyperplasia of intrasalivary gland lymphoid tissue and the epithelial component as salivary duct inclusions within peri-submaxillary and intraparotid lymph nodes, related to the embryology of the salivary glands (Ryan et al. 1985; Ioachim et al. 1987; Smith et al. 1987; Poletti et al. 1988; Shugar et al. 1988).

However, epithelial alterations could be the primary lesion in CBLL, the lymphoid tissue proliferation having been induced secondarily by the epithelial component. Epithelial proliferation and cyst formations surrounded by reactive lymphoid cells occur in inflammatory states as well as in altered immune states (Poletti et al. 1988). As discussed by Jaffe and Ulirsch (1988), myoepithelial islands are considered the hallmark of autoimmune lesions in the salivary glands and their presence argue against a primary lymph node lesion within the salivary lymph node. In Warthin's tumour, Ruco et al. (1987) considered the possibility that the accumulation of lymphoid tissue is modulated by the epithelial cells, perhaps through a pecular pattern of vascularization. A similar hypothesis has been proposed by Vaillant et al. (1989) about CBLL in two HIV-positive patients.

Numerous small lymphocytes were intermixed with epithelial cells in BLL. The majority were B-cells, but we also found many T-cells which were labelled by the HML1 antibody. This antibody, specific for a membrane molecule on human mucosal lymphocytes (Cerf-Bensussan et al. 1987), stains most intra-epithelial lymphocytes and some lymphocytes of the lamina propria in different mucosae but stains very few cells in peripheral lymphoid organs. The presence of HML1-positive lymphocytes in our two patients is a strong argument for primary involvement of epithelial structures in CBLL, the lymphoid hyperplasia occurring secondarily, after antigen stimulation through the epithelial component (Vaillant et al. 1989). According to this hypothesis, the presence of lymphoid tissue in the salivary glands could occur through the same mechanism as that leading to the development of mucosa-associated lymphoid tissue in the intestine, the lung or the breast.

HML1 antibody did not react with intra-epithelial lymphocytes of one Warthin's tumour (personal observation). This negativity, if confirmed on other adenolymphoma cases, would be a supplementary argument for adenolymphoma being a true epithelial tumour and not a reactive process.

Does the HIV itself play a direct antigenic role in the occurrence of CBLL? The p24 HIV protein (Gelderblom et al. 1987), was absent in our two cases but HIV structural proteins need to be sought in similar cases. It is possible, as suggested by Vaillant et al. (1989), that an opportunistic infection occuring in the state of HIV-induced immunodeficiency such as Epstein-Barr virus or cytomegalovirus in the saliva could be responsible for the epithelial hyperplasia and constitute the initial step in the histogenesis of CBLL.

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