Prevalence of Lymphocytic Infiltrate in 1400 Pituitary Adenomas


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Abstract. To evaluate the prevalence of lymphocytic infiltrate in a large series of pituitary adenomas, we retrospectively studied tumor tissues from 1400 patients. Based on immunocytochemical data, tumors were classified as PRL (n=411), multihormonal (n=310), immunonegative (n=275), ACTH (n=166), GH (n=137), alpha subunit (n=44), FSH and/or LH, (n=42), and TSH (n=15) adenomas. The lymphocytic infiltrate was diagnosed on histological examination and investigated by immunostaining with anti LCA (human leukocyte common antigen), anti CD45RO (human T cell) and anti CD20 (human B cell) antibodies. Lymphocytic infiltrate was present in 40 adenomas (2.9%), 26 females and 14 males, aged 18 to 77 years (mean ± SD, 37 ± 14 years). The tumors were 19 PRL, 8 multihormonal, 4 GH, 4 alpha subunit, 3 ACTH, and 2 immunonegative adenomas. In PRL adenomas, the sex ratio (female/male) and the age were similar in patients with and without lymphocytic infiltrate (2.8 vs. 4.6 and 29 ± 6 years vs. 32 ± 11 years, respectively). The frequency of lymphocytic infiltrate was similar in PRL, GH, ACTH and multihormonal adenomas, but lymphocytic infiltrate was significantly more frequent in PRL adenoma than in immunonegative adenoma, and in alpha subunit adenoma than in immunonegative, ACTH and multihormonal adenomas. The lymphocytic cells were almost exclusively T cells. We conclude that lymphocytic infiltrates are rare in pituitary adenomas. Their frequency is not statistically different in major categories of secreting adenomas (PRL, GH, ACTH, multihormonal). Their pathophysiological significance remains to be established.

Key words: Lymphocytic infiltrate, Pituitary adenomas, Autoimmunity, Prevalence

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LYMPHOCYTIC infiltrate has been found in a variety of tumors, including intracranial neoplasms [1, 2]. Its presence may be considered as an expression of local cellular immune response of the host to the existing tumor [3]. Data on lymphocytic infiltrate in pituitary adenomas are scarce [4].

The aim of this study was to evaluate the prevalence of lymphocytic infiltrate in a large series of pituitary adenomas.

Materials and Methods

Patients

A consecutive series of 1400 pituitary adenomas, operated on in 2 centers (Pitié Hospital, Paris, and Foch Hospital, Suresnes, France), during a 7-year period (January, 1985 to January, 1992), was
retrospectively studied. Patients included 908 females and 492 males, aged 6 to 79 years (mean ± SD, 41 ± 15 years). Based on preoperative clinical and/or hormonal data, patients were initially classified as having PRL (n=484), non-functioning (n=337), GH (n=301), ACTH (n=186), PRL + GH (n=22), TSH (n=8), and FSH and/or LH (n=4) adenomas. In 58 subjects, because of the relative urgency of visual symptoms, preoperative evaluation and diagnosis were not available (undetermined adenomas). After surgery, based on immunocytochemical data, patients were finally classified as having PRL (n=411), multihormonal (n=310), immunonegative (n=275), ACTH (n=166), GH (n=137), alpha subunit (n=44), FSH and/or LH (n=42), and TSH (n=15) adenomas. In this immunocytochemical classification, multihormonal adenomas corresponded to the presence of immunoreactivity to at least 2 different hormones (e.g., PRL + GH) or a non-glycoprotein hormone and alpha subunit (e.g., GH + alpha subunit). Also, glycoprotein hormone adenomas (FSH/LH, TSH) corresponded to the presence of immunoreactivity to the beta subunit of each hormone with or without an alpha subunit. The procedures followed for these subjects were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Histological study

The tumor tissues were obtained during surgery, fixed in Gerard’s fluid, and embedded in paraffin. Studies were performed on deparaffinized 4 μm-thick sections of each tumor. The histological diagnosis was established by light microscopy with Herlant’s tetrachrome, PAS-orange G reaction, and Wilder’s technique. The immunocytochemical study was performed by the indirect peroxidase method. Antisera were used against pituitary hormones and subunits of glycoprotein hormones, and helped to classify the pituitary adenomas. These antisera were against PRL (polyclonal antibodies, Institut Pasteur, Paris, France), GH (polyclonal antibodies, Faculté de Médecine, Lyon, France), ACTH (polyclonal antibodies, INSERM, Lille and INRA, Nouzilly, France), beta-FSH, beta-LH and beta-TSH (monoclonal antibodies, Immunotech S.A., Marseille, France), and alpha subunit of human chorionic gonadotropin (monoclonal antibodies, Serotec Ltd., Kidlington, UK). The lymphocytic infiltrate was first diagnosed on histological examination (presence of at least 1 to 20 lymphocytes at 400 magnification by counting the nucleus of lymphocytes on the whole section of the tumor) and further investigated by immunostaining with anti LCA (human leucocytic common antigen), anti CD45RO (human T cell) and anti CD20 (human B cell) antibodies (monoclonal antibodies, Dako S.A., Trappes, France). The lymphocytic infiltrate was diagnosed in at least out of 13 sections examined for each tumor (sections for routine staining, 7 sections for pituitary hormone immunostaining, and 3 sections for lymphocyte immunostaining).

Statistical analysis

Data were analyzed with the non-parametric Mann-Whitney U test and the Fisher’s exact test. A P value lower than 0.05 was considered significant. All reported values represent the mean ± SD.

Results

Lymphocytic infiltrate was present in 41 adenomas (2.9%), 26 females and 14 males, aged 18 to 77 years (mean ± SD, 37 ± 14 years). The sex ratio (female/male) was similar in patients with and without lymphocytic infiltrate (1.9 vs. 1.8), but the age was lower in patients with lymphocytic infiltrate (37 ± 14 years vs. 41 ± 15 years, P<0.05). The tumors were 19 PRL, 8 multihormonal, 4 GH, 4 alpha subunit, 3 ACTH, and 2 immunonegative adenomas (Table 1). In PRL adenomas, the sex ratio and the age were similar in patients with and without lymphocytic infiltrate (2.8 vs. 4.6 and 29 vs. 32 ± 11 years, respectively). Comparison of the frequency of lymphocytic infiltrate in different types of adenomas showed no significant difference between PRL, GH, ACTH and multihormonal adenomas. But lymphocytic infiltrate was significantly more frequent in PRL adenoma than in immunonegative adenoma (P<0.003), and in alpha subunit adenoma than in immunonegative (P<0.004), ACTH (P<0.04) and multihormonal (P<0.05) adenomas.

The cellular infiltrate was either perivascular (n=25), interstitial (diffuse, n=8; nodular, n=5) or
mixed (n=2) (Table 2). Routine microscopic examination showed that lymphocytic cells belonged usually to the small lymphocyte type. No germinal center was ever found when cells were clustered. All lymphocytic cells were immunostained with LCA antibodies. Lymphocytes were almost exclusively T cells (Fig. 1).

No autoimmune disease was found clinically in the patients with lymphocytic infiltrate.

**Discussion**

The present study is the first report of the prevalence of lymphocytic infiltrate in a large series of pituitary adenomas. Our results show that the lymphocytic infiltrate has to be considered as a rare finding in pituitary adenomas. Its incidence is not affected by gender, but has a tendency to be higher in younger patients. Its frequency is similar in PRL, GH, ACTH and multihormonal adenomas, but lymphocytic infiltrate is significantly more frequent in PRL adenoma than in immunonegative adenoma, and in alpha subunit adenoma than in immunonegative, ACTH and multihormonal...
Lymphocytic infiltrate has been reported in a non-tumorous pituitary disease called lymphocytic hypophysitis which is characterized by destruction of the anterior pituitary and resultant hypopituitarism of various degrees [5-8]. Most cases have been observed in women during late pregnancy or in the postpartum period [7, 8], and variously associated with other autoimmune disorders such as thyroiditis [7], adrenalitis [9], atrophic gastritis [10] and parathyroiditis [11]. The pathologic pattern is lymphocytic infiltration with B and T cells, various numbers of neutrophils, eosinophils and macrophages, edema and fibrosis. Lymphocytic infiltrate has also been described in combination with a pituitary adenoma (clinically silent GH adenoma), in a young woman without a previous pregnancy [12].

The significance of lymphocytic infiltrate in pituitary adenomas is presently unknown. Several hypotheses may be proposed: the effect of pituitary hormone hypersecretion on the immune system, expression of a local autoimmune reaction, index of a general autoimmune disorder, and others. Pituitary hormones, especially PRL and GH, play a role in immune function [13, 14]. At physiologic levels, a trophic function predominates. At very low or very high levels, lymphocyte proliferation may be altered. In a series of 28 pituitary adenomas, the study of mononuclear cell infiltrate and HLA-DR expression suggests a low degree of cellular immune response to the adenomas [4]. In hyperprolactinemic patients, natural killer cell activity is reduced when compared to bromocriptine-treated prolactinoma patients and healthy control subjects [15]. Tumor antigens may include normal self proteins produced in abnormally large quantities. These proteins can induce an autoimmune reaction to the tumor cell by activating anergic T cells [16]. In some tumors, the presence of lymphocytic infiltrate may represent an active antitumor response and thus, be of prognostic value by reducing the abnormal cell population. This has been reported in a variety of tumors such as parathyroid adenoma [17], malignant melanoma [18], endometrial carcinoma [3] and esophageal cancer [19].

In our study, since tumor samples were never allowed to be frozen, no other antibodies could be used to investigate T and B lymphocytes in greater detail. In view of the great preponderance of T cell lymphocytes, this retrospective study should be considered as the first step in a more extensive analysis of T cell subpopulations. Such studies would require systematic frozen samples of rare pituitary tumors with lymphocytic infiltrates.

In conclusion, lymphocytic infiltrates are rare in pituitary adenomas. In contrast with lymphocytic hypophysitis, the infiltrate involves the tumor parenchyma instead of the normal pituitary tissue and the lymphocytes are almost exclusively T cells instead of B and T cells. The frequency of lymphocytic infiltrate in this series is not statistically different in major categories of secreting adenoma (PRL, GH, ACTH, multihormonal). The pathophysiological significance of lymphocytic infiltrate in pituitary adenomas remains to be established.

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References


