

Hypophyseal pathology in AIDS

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Summary. One hundred and eleven pituitary glands of patients (93 males, 18 females; mean age 32 years, 5 months) who died of fully developed AIDS or ARC were examined under light microscopy with the aid of immunohistochemistry. On post mortem (p.m.) examination a wide series of multiorgan alterations was noticed. Microscopically various lesions in both adeno- and neurohypophysis were seen. These ranged from vessel damage to secondaries to systemic infections, neoplasms and functional derangements. Necrotic lumps due to recent infarction could appear in both parts of the gland, while old fibrous scars sustained a previously overcome necrosis. Different pathogens (mainly fungi) could be seen either within the gland or arising from its meningeal surroundings. Examples of tumour pathology were provided by microadenomas, gliosis/gliomas; the frequency of adenomas (11.7%) was similar to that typical of senility. The functional impairment was mainly connected with ACTH cell hyperplasia, which seems in keeping with corticoadrenal or ACTH-receptor damage.

Key words: Pituitary gland, Hypophysis, Pathology, AIDS, ARC (AIDS Related Complex)

Introduction

The pituitary gland pathology in acquired immune deficiency syndrome does not seem to have widely investigated. There is little literature on the subject, and few papers are based on a reliable number of samples (Ferreiro and Vinters, 1988; Giampalmo et al., 1988; Sano et al., 1989; Groll et al., 1990; Giampalmo et al., 1990; Amiot et al., 1990).

Our present study deals with a series of p.m. cases,

previously examined by clinicians who had followed the patients for varying lengths of time, from a few months to several years before death.

Materials and methods

One hundred and eleven pituitary glands were examined belonging to patients who were completely anergic to the multitest and who had a history of HIV infection lasting for various lengths of time which resulted in overt AIDS. There were 93 males and 18 females. The great majority (79 cases) were drug abusers, while others were homosexual (19 cases, especially the older ones), heterosexual (8 cases), or unknown (5 cases). The average age at death was 32 years, 5 months + 3.6 years (from 21 to 61).

The p.m. examination was performed between 5 and 48 hours after death, depending on the individual cases. The pituitary gland removed at the autopsy, was fixed in neutral formalin, then cut in five sections on four planes (Mosca and Baroni, 1963) and embedded in paraffin. These sections allowed us to observe the topography of the normal and pathological pictures much more reliably than on single (equatorial, midsagittal or coronal) cuts, as generally done by other investigators (Fig. 1).

On serial sections of each pituitary gland the following procedures were applied: hematoxylin and eosin, periodic acid-Schiff-orange G, PAP immunohistochemistry for ACTH, TSH, GH, PRL. Other special stainings were performed on single cases, when needed, while the typification of extrahypophyseal lymphomas and of some pathogens (e.g. *Toxoplasma* and *Pneumocystis Carinii*) was immunohistochemically achieved. The immunostains for four adeno-hypophyseal hormones were applied overnight using the peroxidase-antiperoxidase (Dako) method (1 : 100); rabbit anti-human GH (Lipshaw) and rabbit anti-human PRL (Lipshaw) both were already diluted in the commercial preparation); rabbit

anti-human ACTH (Biogenex Labs) (1:200); rabbit anti-human TSH (Dako) (1:100).

Results

A) Gross Pathology

At the p.m. examination the main pathological findings were usually multiple (see Table 1) (only five had only one type of lesion). There were also other lesions often associated with the aforementioned ones, such as pericarditis, pleuresy, abscesses in various organs, glomerulopathies, acute hepatitis, liver steatosis. The main pathogens found in various organs were: CMV (in 24 cases), Pneumocystis Carinii (in 8), Atypical Mycobacterium (in 7), Toxoplasma (in 9) other pathogens (tb, streptococci, cryptococci and cryptosporidiosis, candida, aspergilli; in 15).

Table 1. Frequency of main pathological pictures found at necropsy.

Site and Kind of alterations	Total No. of cases
Respiratory apparatus (bronchopneumonia, pneumonia, interstitial pneumonia, abscesses)	85
CNS typical HIV lesions, cerebral atrophy, gliosis, abscesses, meningitis)	76
Lymphatic system (systemic lymphadenopathy, lymphatic system depletion)	69
Hodgkin and non-Hodgkin lymphomas (either primary of the CNS or not)	8
Digestive tract (erosions in oesophagus, stomach, intestine)	26
Kaposi sarcoma	18
Liver cirrhosis	12
Adrenals (various pathogens and possible overt Addison's disease)	15

B) Pituitary Gland Findings

No gross pathology was generally detectable on each fixed and sectioned gland, but microscopically many alterations were seen ranging from actual anatomical lesions to functional impairment.

The ADENOHYPHYSIS was affected by infarctions with lumps of recent or old necrosis (10 cases), where the ACTH cells retained their secretory granules for a long time and were immunohistochemically detectable (Fig. 2a). Some old scars were also present (Fig. 2c) with typical vasodilations, while microcalcific follicles were rarely visible (4 cases). In some instances of meningitis the pathogen organisms were detectable around but seldom inside the gland; e.g. cryptococci in 2 cases (Fig. 3a). Cells affected by CMV could appear here and there, especially among ACTH cells (Figs. 3b, c, d). An inflammatory reaction

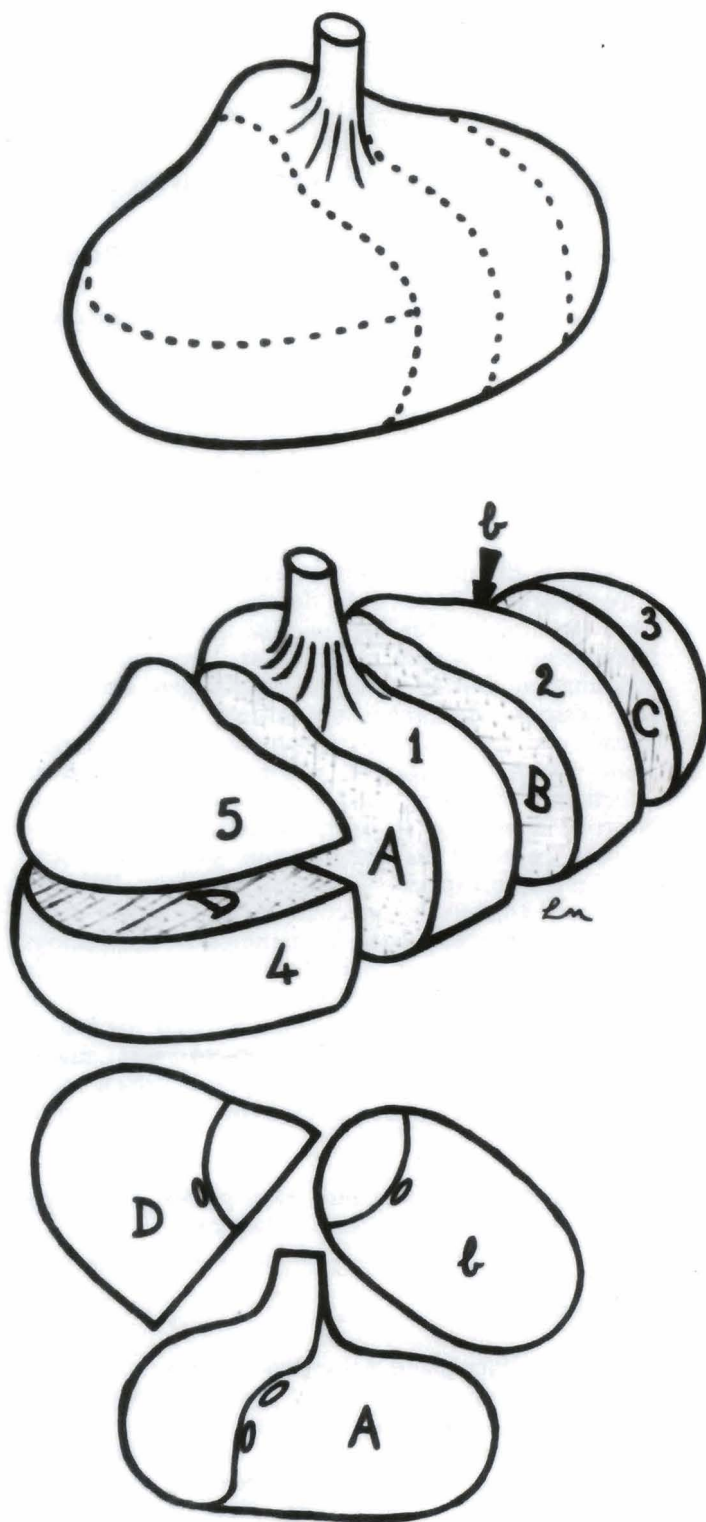


Fig. 1. Human pituitary as seen from above and right side (above). The sections along dotted lines permit the splitting of the gland into five specimens. A single paraffin block (bottom) gives serial midsagittal, laterosagittal and equatorial sections for processing with various techniques. (According to Mosca and Baroni, 1963).

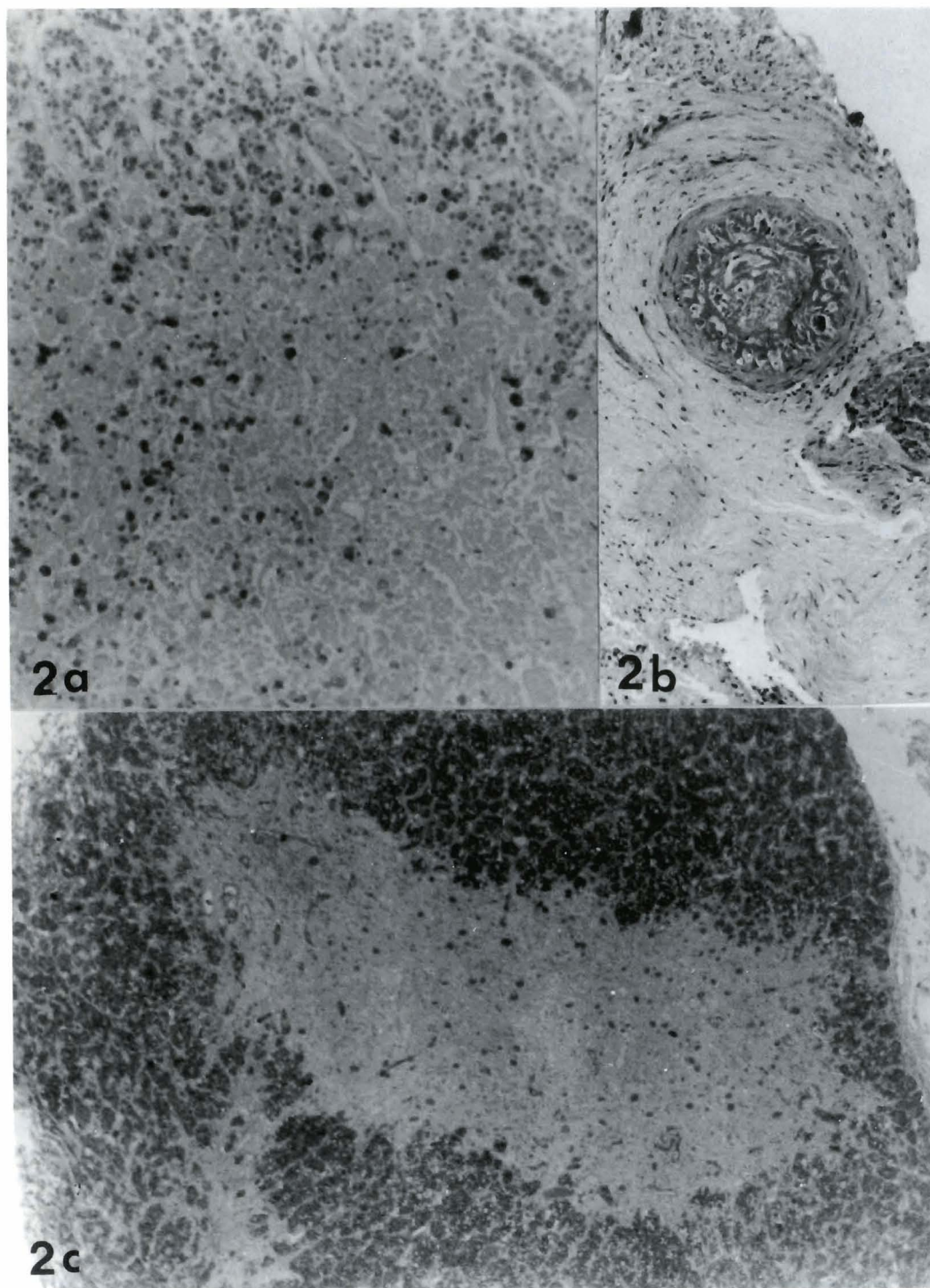


Fig. 2. Aspecific lesions. Recent necrotic lumps. **a.** PAP-immunoperoxidase-hematoxylin ($\times 200$) in which immunostained ACTH cells still retain secretory granulations. Thrombotic involvement of a hypophyseal artery close to an aspergillary lesion in neurohypophysis. **(b.)** H + E $\times 150$. **c.** a large adenohypophyseal scar (postinfarction?) (H + E $\times 150$).

never appeared. In three cases of cerebral lymphoma the gland showed peripheral involvement (Fig. 4a, b).

The incidence of microadenomas containing secretory granulations of different types was very high (Fig. 4c). Thirteen microadenomas (11.7%) were detected, only two of which were present in old patients (60 and 61 years old). These adenomas started

as foci of hyperplasia and, when they increased in size, still being intrasellar, they could undergo haemorrhages strictly circumscribed to the adenoma (Fig. 5a).

From the functional point of view, a clearcut increase of ACTH cells could be found not only in their normal midsagittal area (central wedge), but

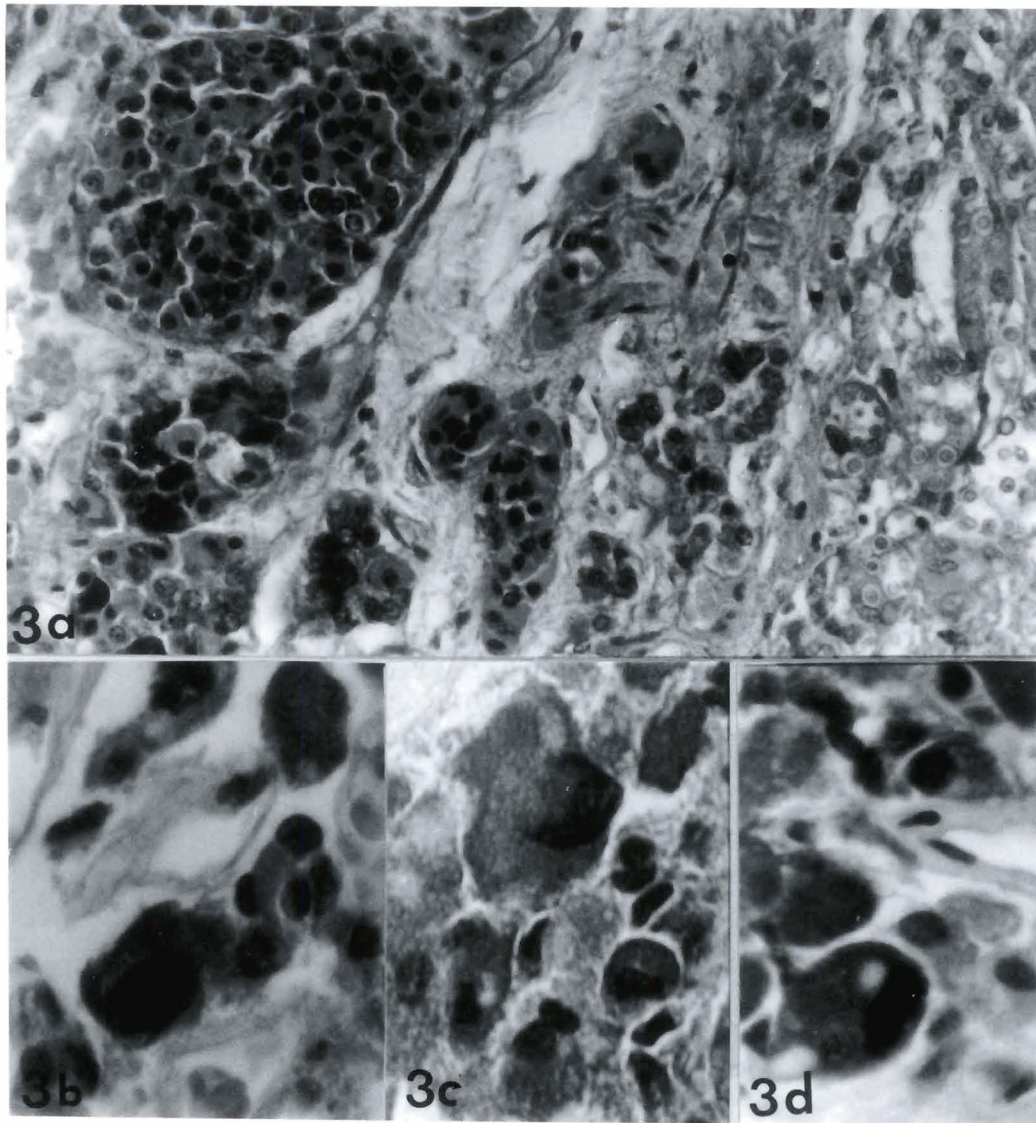


Fig. 3a. Cryptococcal involvement of anterior pituitary from synchronous meningitis. (H + E \times 450). **b, c, d.** ACTH cells affected by CMV in anterior pituitary (H + E \times 1,000).

even in lateral wings, where they were mixed with the other cell types which are usually located in these regions. Their number appeared to be about three to five times greater than normal (25 cases; only two in people of 51 and 57).

The NEUROHYPOPHYSIS also showed a variety of lesions: necrotic foci to wide coagulation areas, sometimes connected to vessel thrombosis; giant cell granulomata; spotted gliosis or true microscopic glioma; lymphoma involvement (Fig. 4a); large cysts as remnants of the intermediary part or true small Rathke's pouch cyst (in a female of 33 and in two males of 31 and 33). Specific pathogens were detected in some instances (Cryptococci, Aspergilli, Toxoplasma, Pneumocystis Carinii) (Fig. 6). Circumscribed vacuolation areas in five neurohypophyses were investigated with immunohistochemistry, but no specific virus involvement could be detected.

The most remarkable functional finding was the

prominent basophilic invasion of the neurohypophysis (usually close to the anterior part) (Fig. 7). This was present in 56 cases (7 in patients of over 50).

If our cases, in which ACTH cells increased in the anterior part or invaded the posterior or both, are considered, we can see that out of all the 111 cases, in 9% the ACTH cell increase was limited to the adenohypophysis, in 12.6% there was an increase in adeno- and basophilic invasion of neuro, while 37.8% showed consistent basophilic neurohypophyseal invasion.

Discussion

Within the wide range of multiorgan or systemic alterations (Reichert et al., 1983; Guarda et al., 1984; Costanzi et al., 1990; Joshi, 1990; Racz et al., 1990) the pituitary gland cannot escape from viremias or bacteremias, and this can explain many of its

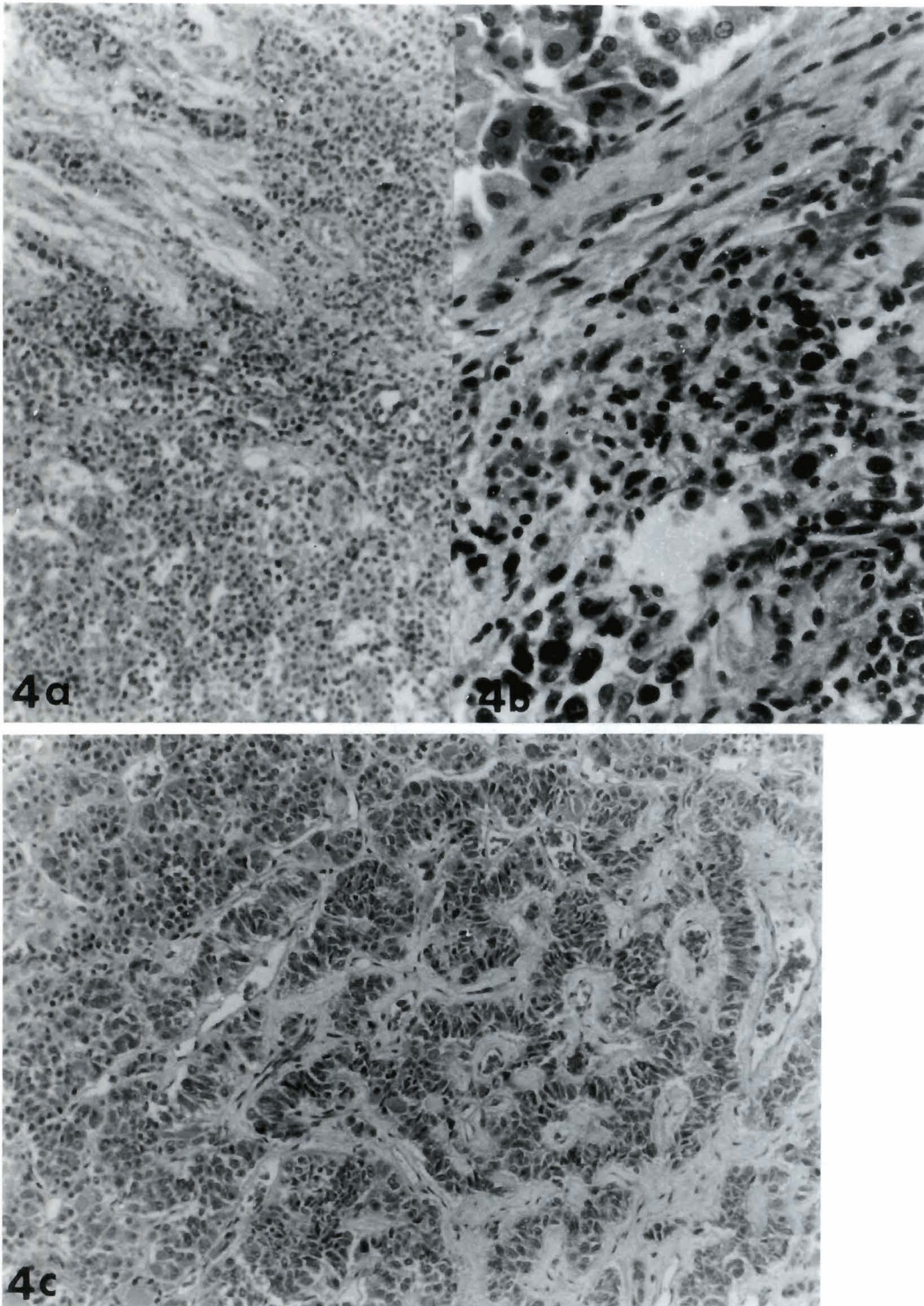


Fig. 4. **a.** Lymphocytic lymphoma involving adeno- and neurohypophysis. ($\times 200$). **b.** Perihypophyseal invasion by a Burkitt's lymphoma ($\times 400$). **c.** Subclinical chromophobe microadenoma in a patient aged 26 years. (H + E $\times 200$).

regressive lesions. As a matter of fact the manifold pituitary gland pathology results from different types of involvement (Sano et al., 1989): direct HIV lesions; secondaries to systemic infectious diseases; neoplasias; and morphological pictures of functional impairment. Moreover, the impairment of vascular supply (either primary or secondary to other local lesions)

contributes to tissue breakdown, necroses and scars. A direct damage transmission from surrounding organs is conceivably shown in cases of meningitis or brain abscesses. The same mechanism seems likely for the peripheral hypophyseal involvement by CNS lymphomas. Since they are normally due to immune deficiency of whatever origin, even in hypophysial

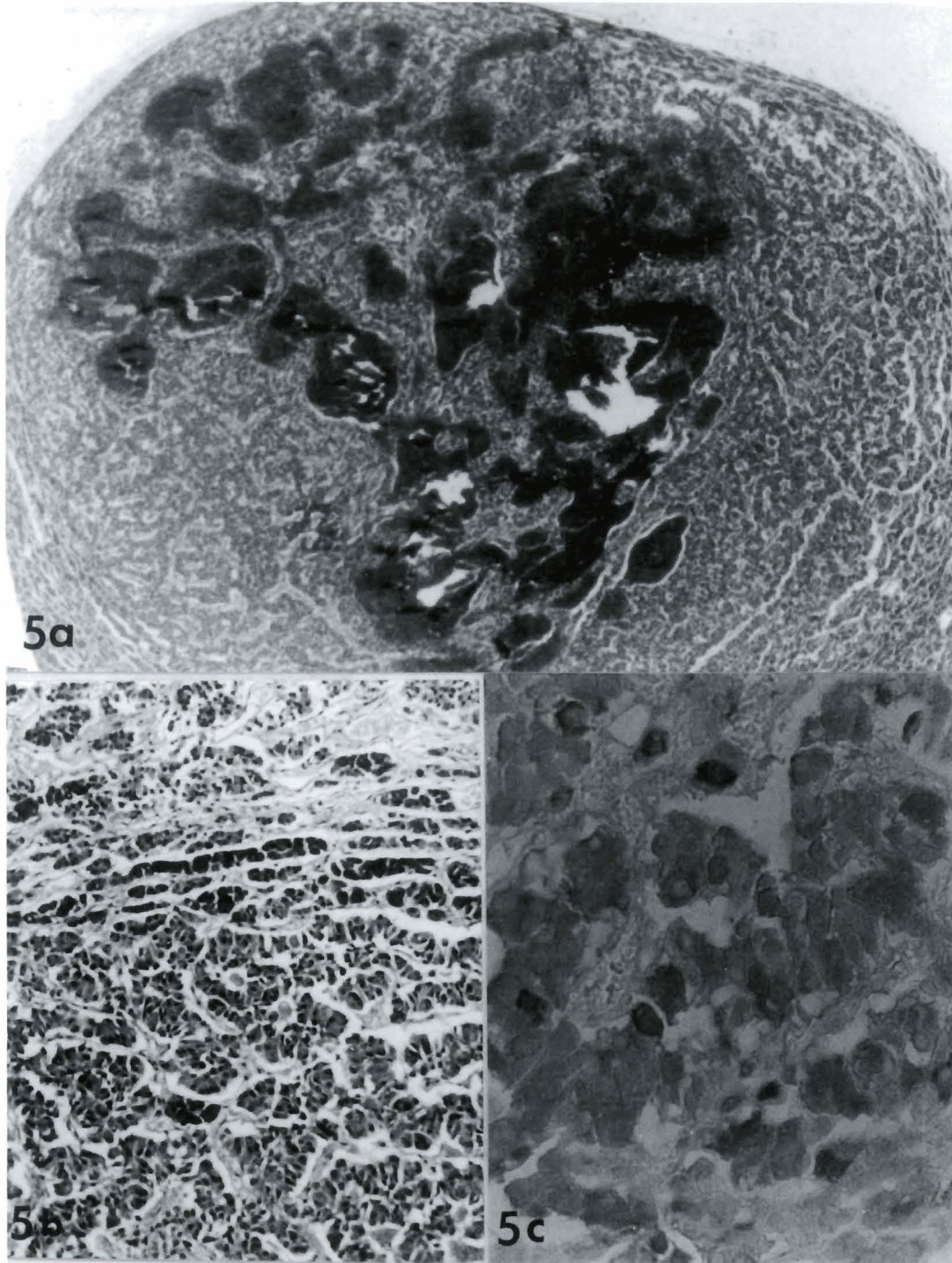


Fig. 5. A TSH-cell adenoma in a 29-year-old male with prominent hemorrhages, as seen with H + E. **a.** $\times 100$, PAS, **b.** $\times 200$, TSH immunostaining. (**c.** $\times 450$).

inflammatory reaction neutrophils, lymphocytes and plasmacells are almost completely lacking, while histiocytes and multinucleated giant cells gather in granulomatous reactions.

Adeno- or neurohypophyseal necrotic lumps could have developed in the majority of cases during the last stage of life, since they showed the features of recent coagulation damage. Still, the onset of some regressive alterations must be back-dated, as suggested by well-

constituted scars in a few instances. These collagen areas in the anterior part certainly replaced previous lesions which have been overcome in spite of the bad potential reactivity of single patients.

The high incidence of subclinical pituitary gland microadenomas of various cell types (Mosca et al., 1975, 1980a,b, 1984) in unselected autopsy cases has been repeatedly quoted in the literature (Costello, 1936; Mosca and Vassallo, 1970; Rewcastle, 1986;

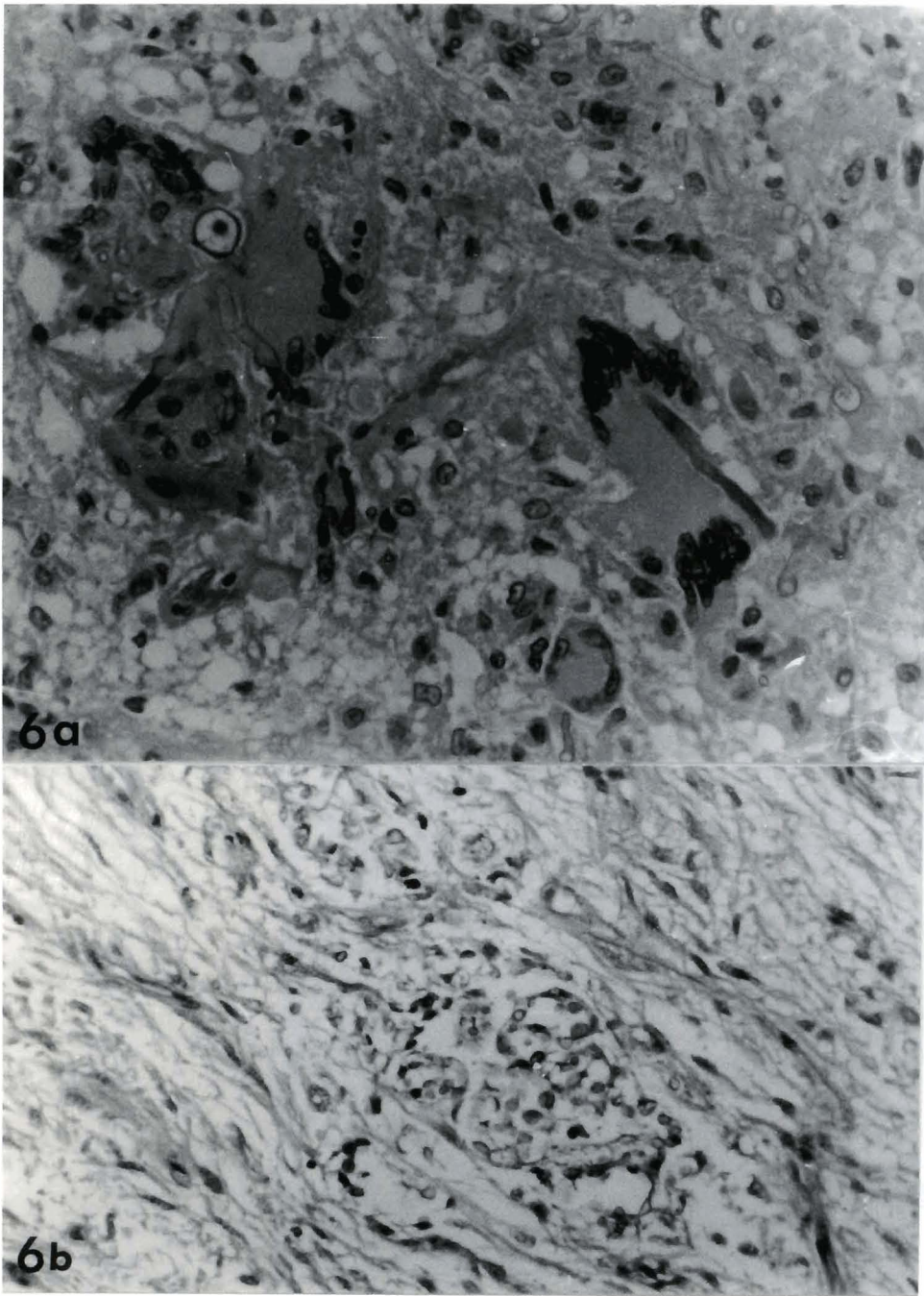


Fig. 6. (a) Deep neurohypophyseal lesions in a case of brain abscesses due to aspergilli (H + E \times 400) and (b). in a case of cryptococcal meningitis (PAS + H. \times 300).

Ribeiro et al., 1989), and the great majority of such adenomas are unanimously reported in older subjects. However, in the present series, only two microadenomas belonged to people of 60 and 61, while the other 11 are all in young patients. No correlation exists in our cases between the length (as far as has been detected by laboratory tests) of the HIV-positive, or overt AIDS period (the beginning of which can be more reliably stated) and the presence of such adenomas, the cellularity of which was mainly chromophobe on various stainings. Four of them were

sparsely granulated PAS positive, and one of these was a TSH cell adenoma. Unavoidable p.m. deteriorations often hinder a precise classification; nevertheless an impairment of feed-back mechanisms is likely to be at the base of their development in young people. Moreover, the possibility exists that, since immunodeficient people are prone to develop tumours in general, they could also be able to develop pituitary gland tumours.

On the other hand, the agents which are noxious to the pituitary gland as a whole, seem to enhance either

Hypophyseal pathology in AIDS

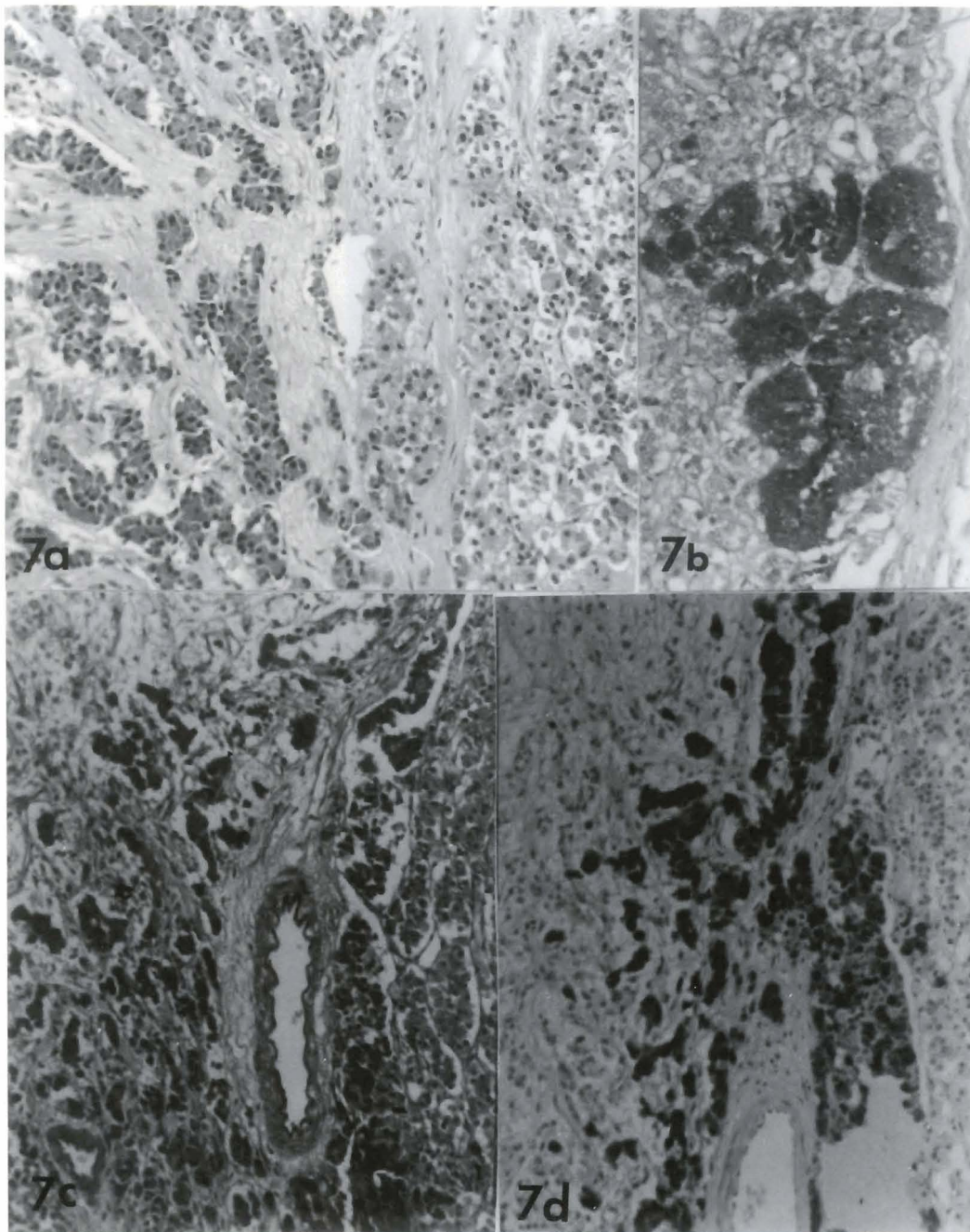


Fig. 7. Basophilic invasion of the neurohypophysis
a. H + E. $\times 200$. A hyperplastic ACTH cell nest in the anterior pituitary.
b. PAS + H $\times 150$. Two serial sections of another case showing basophilic invasion.
c. PAS + H $\times 200$.
d. (ACTH-immunoperoxidase + H $\times 200$

adenomas in the pars glandularis or gliosis/gliomas in the pars nervosa. However, the survival of pars intermedia cystic remnants or the presence of a true small Rathke's cleft cyst (Baldini et al., 1980) seems utterly independent of specific lesions.

An interesting finding is the actual numerical increase of ACTH cells in many cases, and this is in keeping with the common clinical observation of corticoadrenal deficit (Dluhy, 1990; Ruttimann et al., 1991) in many terminal AIDS patients. The hypothesis of a possible ACTH-receptor derangement is actually under investigation (Galli et al., 1991 a, b). Indeed,

about 79% of our cases showed ACTH cell increase (in the pars anterior, or as a basophilic invasion of neurohypophysis, or both) in comparison with the usual 15% of total ACTH cells in the normal adult pituitary gland (Lloyd, 1990). On a tentative interpretation, this means that when an adrenal impairment occurs (Verges et al., 1989; Villette et al., 1990), the hypothalamic-pituitary axis still functions to meet the requirements of the feed-back mechanism in spite of severe CNS damage (Budka et al., 1987; Raffi et al., 1991). However, hypothalamic neurosecretory nuclei should be better investigated in AIDS.

The peculiar phenomenon of basophilic invasion of the neurohypophysis has been known for a long time and is characteristic of senility (Mosca et al., 1966; Mosca, 1973). The invading basophils (as first shown by Mosca and Baroni, 1963) and now immunohistochemically confirmed) are ACTH cells. The reason for this migration, and perhaps also for subsequent local reproduction, does not seem to be clearly understood. The hypothesis can be put forward that, owing to a primary impairment (either because of old age, or local damage enhanced by AIDS) of vessel structure and function of the hypophyseal portal system, the delivery to the anterior pituitary gland of hypothalamic neurosecretory stimuli is comprised (Merenich et al., 1990), and subsequently the ACTH cells can find a more reliable and direct nervous stimulation in neurohypophysis.

The way of sectioning the whole gland before embedding must be briefly discussed. It is well known that the different cell types are preferably located in some areas of the pituitary gland (Mosca and Baroni, 1963; Lloyd, 1990), while even microadenomas of various cell composition tend to develop in the same places (Mosca and Vassallo, 1970; Hardy, 1980). So, if the gland is microscopically observed on a single (equatorial, midsagittal or coronal) section, it seems quite probable that some relevant pictures can escape detection.

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Hypophyseal pathology in AIDS

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