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Case Report

Von Hippel-Lindau's Disease, Syringomyelia and Multiple Endocrine Tumors: A Complex Neuroendocrinopathy

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Summary. A patient presenting with von Hippel-Lindau's disease, syringomyelia, bilateral pheochromocytoma and a multihormonal pancreatic tumor is described. We suggest that this syndrome results from a complex neuroendocrine disorder.

Key words: Von Hippel-Lindau's disease – Syringomyelia phaeochromocytoma – Pancreatic endocrine tumor – Complex neuroendocrinopathy.

Introduction

The occurrence of hyperplasia or tumors with inappropriate secretion of hormones from several endocrine glands in one individual is uncommon. However, it is important to recognize this disabling and life-threatening condition.

Three variants of the disease have been described by Wermer (1954, 1963, "Wermer's syndrome"), Sipple (1961, "Sipple's syndrome") and Ellenberg (1963, "Ellenberg's syndrome"). It has become customary to use the terms "multiple endocrine neoplasia" (MEN) "type 1" for the syndrome characterized by tumors of the pituitary, parathyroid glands and the endocrine pancreas ("Wermer's syndrome") and "type 2" for the entity characterized by the occurrence of pheochromocytoma (s), medullary thyroid carcinoma and parathyroid adenoma, often combined with mucosal neuromas ("Sipple's syndrome") (Steiner et al., 1968). The term "MEN 3" is assigned to the syndrome consisting of parathyroid adenomas and papillary thyroid carcinoma ("Ellenberg's syndrome"). It must be borne in mind that the term "multiple endocrine neoplasia" is not entirely correct, since both tumors and hyperplasia of cells of the pituitary, parathyroid glands or the adrenal medulla occur in this disease (De Lellis et al., 1976).

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From the pathogenetic point of view, diseases combining "endocrine" and "neurological" features are of special interest. The purpose of this paper is to describe clinical and morphological findings in a patient suffering from such a complex neuroendocrine syndrome.

Clinical Findings

The patient was first admitted at the age of 23 with a sudden loss of vision of the left eye, numbness and painful cramps in the right leg. Examination disclosed a bilateral angiomatosis retinae.

During the following years the patient's condition worsened steadily. At the age of 34, dysarthry, weakness and loss of stereognosis of the left hand appeared. Movements of the neck became painful and restricted. Subsequently, a spastic paraparesis and an ataxic gait developed. Vision on the right side became blurred because of repeated detachment of the retina.

At the age of 38, a vertebral angiogram disclosed a well vascularized and sharply circumscribed tumor in the medial and lower part of both cerebellar hemispheres, extending caudally as far as the first vertebral arch. Surgical exploration revealed a cerebellar hemangioblastoma which occupied the cerebellomedullary cistern and infiltrated the adjacent cerebellar vermis as well as the medulla oblongata. No attempt at excision was made. Immediately after surgery a sudden increase in blood pressure with a short peak (33.3/18.7 kPa) was recorded. This was the only documented instance of hypertension of the patient.

The patient's last 3 years of life until his death at 41 were marked by progressive muscle wasting, spasticity of legs and repeated urinary infections.

Post-Mortem Examination

The cause of death was a severe bronchopneumonia. The important pathologic findings were restricted to the eyes, to the central nervous system and to the endocrine organs.

Multiple hemangioblastomas were found in both retinae.

Central Nervous System. The cerebral hemispheres showed no gross lesions. The lower part of the pons and the medulla oblongata were considerably thickened and hard. The ventral part of the cerebellar vermis, the adjacent portions of both cerebellar tonsils, and the dorsal part of the medulla oblongata were infiltrated to a large extent by a partly cystic yellow tumor, measuring approximately $1.5 \times 3 \times 2$ cm (Fig. 1a). The first 5 segments of the spinal cord were thickened, measuring up to 23 mm in the transverse, 13 mm in the anteroposterior direction. Cross sections of the spinal cord disclosed multiple cystic spaces at all levels (syringomyelia) (Fig. 1b). They were most often localized in the center of the spinal cord, but extended to the posterior horns and to the dorsal columns. Moreover, multiple small compact yellow tumors were found at various levels of the spinal cord.

Microscopically, all tumors were made up of a network of thin walled blood vessels separated by large stromal cells with a foamy cytoplasm (Fig. 1c) and by a few larger arteriovenous channels. The intramedullary tumors

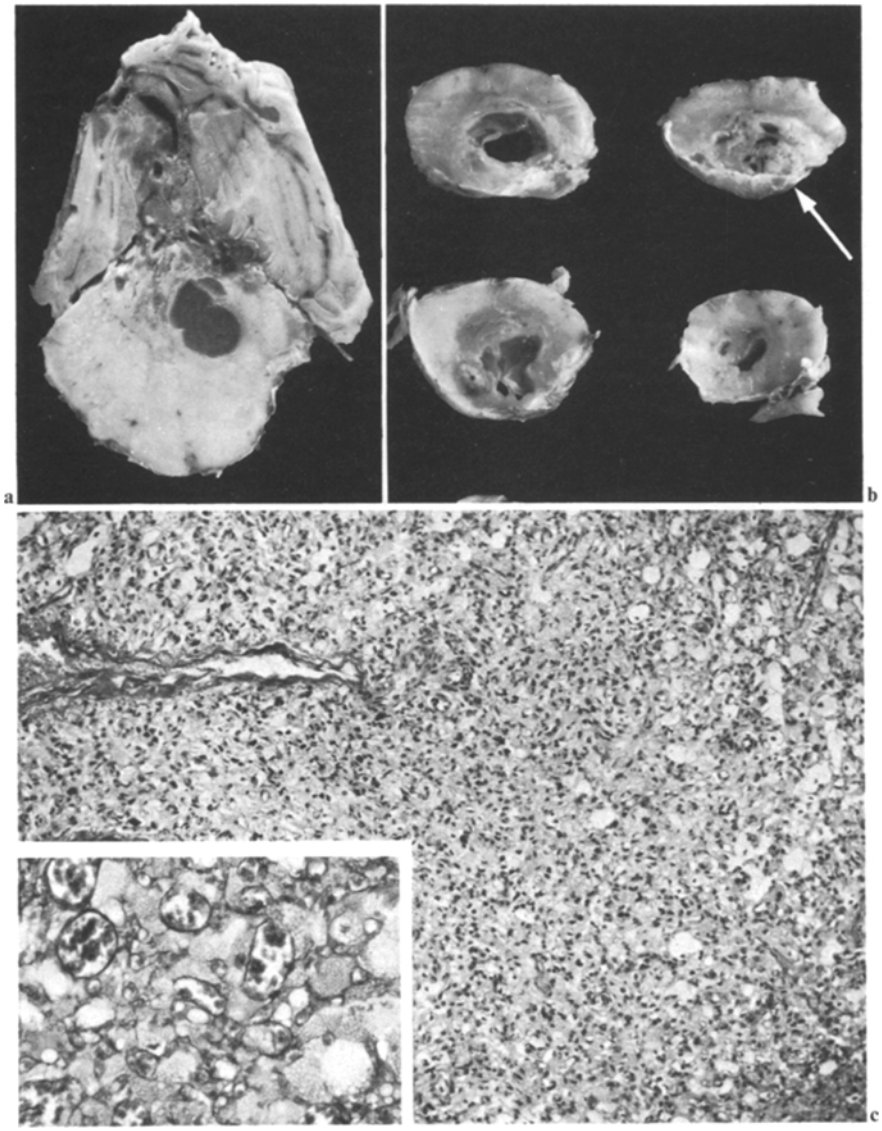

Fig. 1.a Cerebellar hemangioblastoma invading the cerebellar tissue and the floor of the 4 th ventricle (level of the area postrema). Confluent cystic cavities are present in the medulla oblongata (syringobulbia). **b** Transverse sections of spinal cord show syringomyelia. The arrow indicates an intramedullary hemangioblastoma. **c** Dense capillary network of cerebellar hemangioblastoma. Van Gieson (×125). *Inset:* Intercapillary large foamy cells. Gömöri's reticulin (×220)

of the spinal cord were all attached externally to the pia mater (Fig. 2a). The syringomyelic cavities were outlined by a thin connective tissue membrane rather than a layer of ependymal cells. The wall of the cavities was composed mainly of glial tissue, very rich in neuroglial fibrils and containing conspicuous Rosenthal fibers (Fig. 2b).

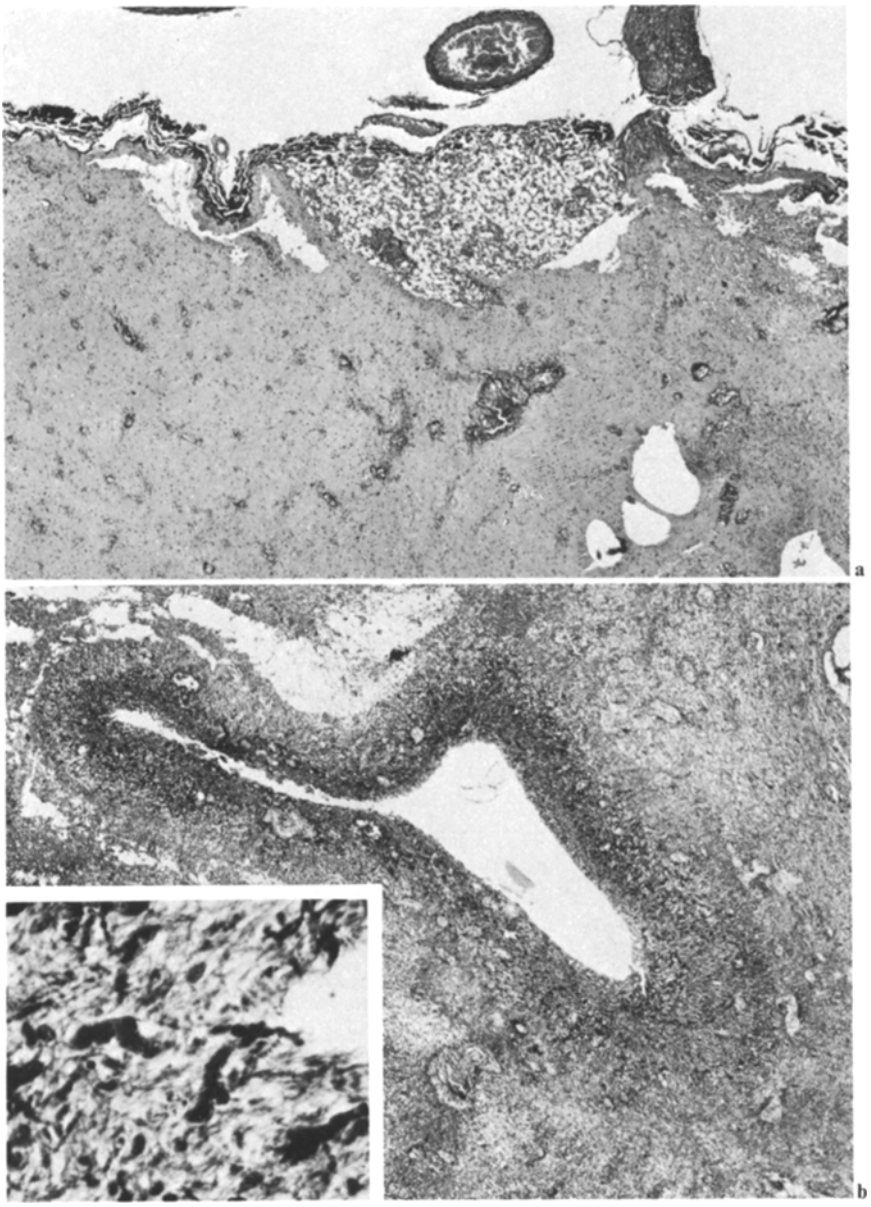

Fig. 2. a Small hemangioblastoma adjacent to pia mater of the spinal cord. Van Gieson-Luxol (×30). **b** Syringomyelia with dense gliosis surrounding the cavity. Microcavitation of the adjacent area. Van Gieson-Luxol (×34). *Inset:* Wall of syringomyelia showing several Rosenthal fibers (dark clubs). Mallory's phosphotungstic acid hematoxylin (×500)

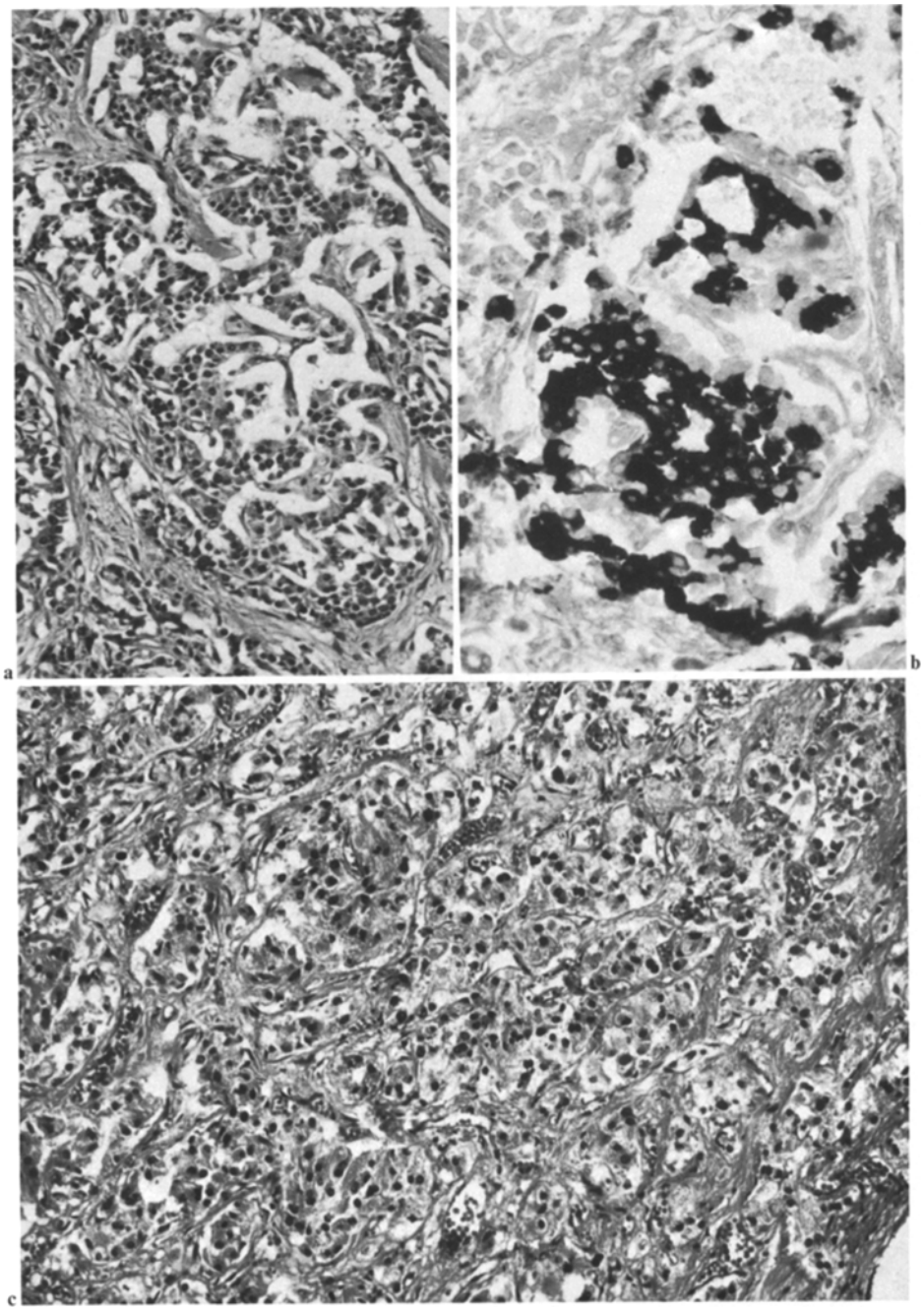

Fig. 3.a Endocrine pancreatic adenoma. HE (×133). **b** Group of B-cells in the endocrine pancreatic adenoma. Indirect immunoperoxidase method for insulin (×133). **c** Pheochromocytoma of the left adrenal gland. HE (×133)

Endocrine Organs. The *adrenals* were greatly enlarged (left gland 39 g, right gland 50 g). The cut surface displayed gray, partly hemorrhagic tumors of the adrenal medulla. Histologic examination confirmed the macroscopic diagnosis of bilateral pheochromocytoma (Fig. 3c).

In the tail of the *pancreas* a gray soft nodule (diameter 1 cm) was found. Light microscopic examination revealed an endocrine adenoma. Immunohistochemical examination by an indirect immunoperoxidase method for insulin and the unlabelled antibody enzyme method (Sternberger, 1974) for glucagon, somatostatin and human pancreatic polypeptide revealed the presence of insulin-producing B-cells, of glucagon-producing A-cells and pancreatic polypeptide-producing PP-cells (Fig. 3a, 3b).

In spite of close inspection no medullary carcinoma of the thyroid, no pituitary and no parathyroid adenoma or hyperplasia could be detected.

Discussion

The salient features in this case are multiple hemangioblastomas of the central nervous system and both retinae ("von Hippel-Lindau's disease"), syringomyelia and syringobulbia, bilateral pheochromocytoma and a multihormonal pancreatic endocrine adenoma.

We are thus dealing with a neuroectodermal dysplasia and two endocrine tumors. The question arises whether the association of the various lesions is fortuitous or whether these lesions are part of a complex disorder. We favour the latter hypothesis for the following reasons:

On a statistical basis, a pure coincidence of these conditions does not seem probable, since pheochromocytoma, pancreatic endocrine tumors, hemangioblastoma of the central nervous system and syringiomyelia are all uncommon. Moreover, pheochromocytomas associated with other endocrinopathies are most often bilateral (Funyn et al., 1973; Carney et al., 1976; De Lellis et al., 1976), whereas isolated pheochromocytomas are, in general, unilateral (Pusterla and Hedinger, 1975).

The association of bilateral pheochromocytomas together with medullary carcinoma of the thyroid is now firmly established as MEN 2a (Sipple, 1961; Steiner, 1968) and the association of these two endocrinopathies with multiple neuromas as MEN 2b (Williams and Pollock, 1966; Gorlin et al., 1968; Schimke et al., 1968; Bartlett et al., 1971; Carney and Hayles, 1977). Pheochromocytoma combined with hemangioblastomas of the central nervous system or with angiomatosis retinae have been repeatedly described (Mandeville and Sahyoun, 1949; Glushien 1953; Chapmann and Diaz-Perez, 1962; Melmon and Rosen, 1964; Illingworth 1967; Nibbelink, 1969; Wise and Gibson, 1971; Andersson and Bergdahl, 1975).

Of particular interest of the case reported here is the combination of features of MEN 1 (endocrine pancreatic tumor) and MEN 2 (bilateral pheochromocytoma) with those of the combined form of von Hippel-Lindau's disease as well as with syringomyelia. To our knowledge, only one similar, though not identical case has been hitherto described (Andersson and Bergdahl, 1975).

Despite the fact that the association of lesions found in this case is apparently very uncommon, it might be explained by the common embryological origin of neural and endocrine cells. The cells of the adrenal medulla are of proven neural crest origin (Pearse, 1975, 1977), and endocrine cells of the pancreas are probably of neurally programmed epiblastic origin (Pearse, 1977; Welbourn, 1977). All these cells are part of the APUD series and tumors arising from these cells are named APUDomas (Pearse, 1969; Sziji et al., 1969). Although the neural origin of endocrine cells of the pancreas and of the gut is not yet proven, there is already much evidence to support this view. Several peptides, e.g. somatostatin, vasoactive intestinal peptide, gastrin- and cholecystokinin-like peptides and substance P are common to both nervous tissue and endocrine peptide producing cells of the APUD series (Heitz et al., 1976; Pearse, 1976; Dockray, 1977). Moreover, APUD cells were shown to share some electrophysiological properties with neurons (Tischler et al., 1977). On the basis of these findings we propose that the association of angiomatosis retinae, hemangioblastoma of the central nervous system, bilateral pheochromocytoma and of a pancreatic endocrine tumor is one particularly rare variant of the complex neuroendocrine disorders.

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