Cerebellar Hemangioblastoma and Primary Hyperparathyroidism

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The authors report the case of a 52-year-old woman presenting with cerebellar hemangioblastoma and primary hyperparathyroidism. It is the second reported case involving this new association. The relationship between these two tumors is discussed.

KEY WORDS: Cerebellar hemangioblastoma; von Hippel-Lindau disease; Primary hyperparathyroidism

Infratentorial hemangioblastoma is a rare, benign tumor occurring in middle-aged adults. Because of its localization, the clinical course is formidable and the diagnosis is often made only after the appearance of intracranial hypertension.

The prognosis can be further worsened by the tumor's tendency to be multifocal (spinal cord, brain stem, cerebral hemispheres) or to be associated with other, nonneurologic and sometimes vascular, tumors: kidney (cyst, angioma, adenoma, carcinoma), pancreas (cyst, cystadenoma, hemangioblastoma, cortical adenoma), epididymis (cyst, cystadenoma), liver (cyst, adenoma, superficial nevus, hemangioma, hamartoma, carcinoid, fibrosis), adrenal (pheochromocytoma, cortical adenoma), ovary, Fallopian tubes, bladder, prostate, stomach, mesocolon, spleen, bone, skin (café au lait spots, telangiectasias).

The association of a neurologic hemangioblastoma with a single or a number of these tumors with a retinal hemangioblastoma constitutes von Hippel-Lindau disease (VHL) [9]. A posterior fossa hemangioblastoma associated with primary hyperparathyroidism has recently been reported for the first time in a patient [7]. We report the second case involving this new association.

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Case Report

A 52-year-old woman was hospitalized on January 29, 1987, for recent onset of headaches and vomiting. Her past history included a liver tumor, which suggested a hemangioma on a computed tomography (CT) scan and two right kidney cysts. There was no history of hereditary disease. The patient was alert and cooperative. The blood pressure was 160/90 mm Hg. Clinical examination revealed discrete abnormalities in equilibrium, depressive reaction, and mild constipation. Laboratory investigations showed hypercalcemia (3.23 mmol/L), hypercalciuria (7.15 mmol/L), and hypophosphoremia (0.74 mmol/L). These abnormalities were verified a number of times, and three successive parathormone determinations were increased, respectively, 2.4, 2.1, and 2.2 ng/mL (normal: 0.40–2.0). Kidney function tests and the full blood count were within normal limits. The hemoglobin was 13.2 g/dL. Thyroid-stimulating hormone, thyrocalcitonin, prolactin, and ACTH were within normal limits. Gastroscopy and skull x-rays were normal, as was bone biopsy. The diagnosis of primary hyperparathyroidism was made. On February 4, 1987, her condition suddenly worsened; a vermian cerebellar syndrome appeared accompanied by intense headaches, unremitting vomiting, nuchal rigidity, and an alteration in her state of consciousness.

She was transferred to the neurosurgical department where an emergency CT scan showed a space-occupying lesion in the right side of the roof of the fourth ventricle, which was characterized by a hypodense, round, cystic center surrounded by a spontaneously hyperdense zone (Figure 1), markedly enhanced by intravenous contrast injection (Figure 2). Triventricular dilatation was noted. This picture suggested the presence of a macrocystic form of a vermian hemangioblastoma. An emergency ventriculostomy was performed and the patient was operated on on February 11, 1987. At that time, a cystic cavity in the superior vermis was found along with a reddish tumor, which was completely excised. The postoperative course was uneventful.

The histopathological study showed a cellular prolif-
Histopathology confirmed the presence of a parathyroid adenoma (Figure 4 A and B) and a benign thyroid adenoma (Figure 5). Serum calcium became normal the day following surgery (2.3 mmol/L). The patient was seen on follow-up in December 1987, and was asymptomatic.

Therefore, this patient has successively been operated on for a cerebellar hemangioblastoma, a parathyroid adenoma, and a benign thyroid adenoma, and had a hemangioma of the liver along with two right kidney cysts.

**Discussion**

Von Hippel-Lindau disease is an embryopathy that is familial in 20% of the cases [4,16]. It is an autosomal dominant with variable penetrance [3,6]. Nervous system hemangioblastoma has a dual embryologic origin: neuroectodermic, which corresponds to the intercapillary tumor tissue, and mesodermic, which explains the extensive neovascularization. Its late development can be explained by a persisting proliferative potential while the occasional multifocal character of associated lesions suggests an early disturbance in intrauterine differentiation (first month). Endocrine abnormalities are counted among these associated lesions. Consequently, the operation composed of irregular nuclei and pale cytoplasm lying in sheets separated by rich, capillary-like vascularization, typical of a hemangioblastoma (Figure 3, A-C).

At that point, the parathyroid gland work-up was resumed. The thallium scan discovered a small area of increased uptake outside the thyroid gland consistent with a parathyroid adenoma located in the upper left mediastinum. The thyroid echography revealed a normal size gland with a hypoechogenous area in the left lobe suggesting a cyst or an adenoma. The thyroid scan was normal.

A liver scan performed with marked red cells identified a hemangioma of that organ. The intravenous pyelogram demonstrated a calcium-like density in the right distal ureter.

Both CT scan and echography failed to demonstrate any tumor-like area in the adrenal glands. In addition, three separate determinations of catecholamine metabolism products were normal. Finally, the ocular fundi were within normal limits.

The parathyroid adenoma was excised on June 24, 1987. At surgery, the tumor was easily located and removed and the other parathyroid glands were of normal size and consistency; however, the left thyroid lobe contained a 1 cm nodule, which was extirpated.

![Figure 1. CT scan without contrast demonstrating a cystic vermian tumor.](image1)

![Figure 2. CT scan with intravenous administration of contrast demonstrating intense contrast enhancement of the tumor.](image2)
Simultaneous existence of a pheochromocytoma and phakomatosis (neurofibromatosis or VHL) is well known [1,3]; the adrenal glands also have a neuroectodermic origin [20]. In addition, it can be associated with hyperparathyroidism. The presence of multiple cancers, including renal cell carcinoma, can also be observed in patients with VHL syndrome. This condition is characterized by the development of several distinct tumors, including both benign and malignant lesions, that can affect various organs and systems. The coexistence of these conditions underscores the importance of early detection and multidisciplinary management to improve patient outcomes.

Figure 3. (A–B) Cerebellar hemangioblastoma: proliferation of large pale cells with high chromatic and irregular nuclei, separated by numerous capillaries lined by plump endothelial cells (H&E, safran × 250).
Figure 3. (Continued).

with a pheochromocytoma and with other lesions at the same time; in 1961, Sipple [19] then several authors [11,12] reported associations between a pheochromocytoma and a thyroid tumor containing amyloid stroma, while Ljundberg et al [10] showed in 1967 that important histologic similarities were present in these two tumors. Once again, it is likely that they have a common embryologic origin.

These disseminated lesions in the endocrine system have been termed “multiple endocrine neoplasia” [11,12] and the association of primary hyperparathyroidism with Sipple’s syndrome has been called “Type II multiple endocrine neoplasia” by Steiner [20]. The latter brings up the question of the significance of the hyperparathyroidism, since these glands are classically considered to have a different origin, the entoblast.

These different explanatory hypotheses are important because they might explain the association of hyperparathyroidism with VHL disease [17], which is also significantly associated with pheochromocytomas. We don’t have the answer to this question yet. According to Steiner et al [20], Schimke et al [18], and Castelman and Mallory [2], the thyroid tumor could lower serum calcium by secreting thyrocalcitonin, resulting in parathyroid hyperplasia or even adenomas. However, the existence of parathyroid adenomas along with a pheochromocytoma in the absence of any obvious thyroid tumor [5,13,17,20] should suggest other diagnoses, namely, a thyroid tumor without any clinical symptomatology [20] or a coincidental occurrence. Finally, Pages and Marty-Double [14] have suggested that the thyroid tumor may be induced by chronic hypercalcemia secondary to a parathyroid adenoma. Lamont et al [7] consider that the embryologic theory should not be excluded. Accordingly, Pearse and Takor in 1976 [15] have suggested that, contrary to classical theory, the parathyroids might be of ectodermic origin, although this theory has not been accepted or expanded upon since. In 1982, Le Douarin [8] attempted a synthesis of recent acquisitions on this question, and has concluded that only parathyroid mesenchymal cells and not glandular cells are of neuroectodermic origin. In conclusion, hyperparathyroidism and VHL’s disease can be encountered in three different circumstances.

The first is in the context of a hereditary, embryologic disease in which they could be associated with a pheochromocytoma, or a thyroid tumor with amyloid stroma. The presence or absence of one and/or the other of these associated lesions might be explained by the variable penetrance involved. However, as we have previously mentioned, the embryologic theory has not been generally accepted by experts.

The second circumstance is during the course of an embryologic disease in which the thyroid tumor would
appear as the result of a preexisting parathyroid adenoma; hypercalcemia induced by the adenoma would produce a thyrocalcitonin-secreting thyroid tumor, thereby lowering the serum calcium. As a conse-

Figure 4. (A) Chief cell parathyroid adenoma. The cells were arranged as a solid mass on formed acini and follicles. On the left, a rim of normal parathyroid tissue containing fat (H&E safran × 250). (B) Chief cell parathyroid adenoma. Absence of normal parathyroid gland (H&E safran × 250).
Figure 5. Colloid thyroid adenoma. The follicles contained large colloid masses. Fibrous reshaping is observed (H& E safran × 250).

sequence, unremitting high calcitonin levels from the thyroid tumor with an amyloid stroma would cause secondary parathyroid hyperplasia or even a parathyroid adenoma as a result of the lowered serum calcium. One could explain the more frequent appearance of a thyroid as opposed to a parathyroid tumor by the embryologically ectodermic origin of thyroid C cells.

The final circumstance is as a coincidental association. This possibility must be considered due to its rarity and, in that context, the publication of cases such as ours is indispensable.

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References


