CAVERNOUS HAEMANGIOMA OF THE PITUITARY GLAND ASSOCIATED WITH PROLACTIN CELL MICROADENOMA
CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT : The authors present a case of a 27-year-old female with a nine-month history ofamenorrhea and galactorrhea. Although the neurological examination was normal, biological assays showed a high level of prolactinemia (1425 µUI/ml). Magnetic resonance imaging revealed a small and well demarcated lesion of the pituitary gland. No enhancement was observed after gadolinium infusion. The patient was operated on and a complete resection was performed via a transphenoidal approach. Prolactin level returned to a normal level subsequently to surgery. Histological examination showed a prolactin cell microadenoma associated with a cavernous hemangioma. To the best of our knowledge, this is the first report of a micro prolactinoma associated with a cryptic cavernous hemangioma.

Key words *: Crypticcavernous haemangioma, Pituitary gland, Prolactin cell microadenoma..*

INTRODUCTION

Cavernous haemangioma (CH) represent 5% to 13% of all the central nervous system vascular malformations [16]. Although they may develop throughout the central nervous system, they most commonly involve the cerebral hemispheres, the basal ganglia and the brain stem [3, 23, 24]. Even if a few case of intrasellar CHs have been reported, they have never been described as a cryptic lesion of the pituitary gland and to the best of our knowledge this is the first case of a cryptic pituitary CH associated with a prolactinoma [4, 5, 6, 20, 27].

CASE REPORT

A 27-year-old female, complained from a secondary amenorrhea and galactorrhea at the end of a 6-year period of an oral contraception. Her past medical history was unremarkable.

The patient's neurological and ophtalmological examinations were normal. Biological assay showed only an elevation of prolactin level to 1425 µUI/ml (normal range < 620µUI/ml). Magnetic resonance imaging (MRI) disclosed the presence of a 0,7 x 0,6-cm mass occupying the posterior right side of the pituitary gland. This mass was hypointense on T1 and isointense on T2 weighted images, and it did not enhance after gadolinium infusion (Fig.1). Owing to the radiological features and the biological results the diagnosis of prolactinoma was made. The patient declined the non-operative management by dopamine-agonist therapy and preferred to have the lesion resected via a selective adenomectomy.

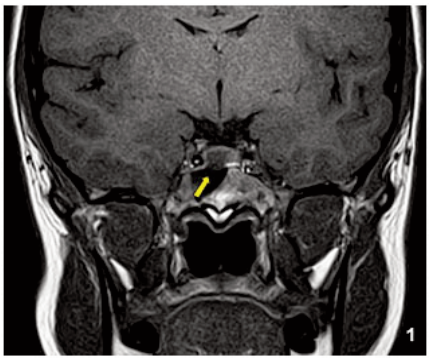

Fig. 1 : Coronal MRI : T1-Weighted image reveals a well circumscribed hypo intense lesion with non enhancement after gadolinium infusion (arrow).

Patient was operated on via a transphenoidal approach under optic magnification. At surgery the process appeared yellow-brown and a clear demarcation between the tumor and the pituitary tissue was observed allowing its total resection. The post-operative course was uneventful. The prolactine level returned to a normal level (40µUI/ml) within 2 days.

On macroscopic examination,surgical specimen corresponds to a yellow-brown fragment measuring 0,5 x 0,5 cm. After 4 % buffered formalin fixation, it was processed to paraffin, and serially sectioned into 4µm thin slides. Histological stains included haematoxylin, eosin and safran (H.E.S), periodic acid-Schiff (PAS), Gordon Sweet's reticulin and orcein. Microscopic examination showed two intertwined pathological

processes. The main process was composed of prominent anastomotic vascular network with multiple thin-walled vascular channels lined by a layer of regular endothelial cells. The interstitium was generally thin, sometimes showing fibro collagen thickening with rare associated mastocytes. Reticular silver impregnation disclosed a reticulinframework of capillaries; however no vascular spaces that resemble sinusoids were observed. No arteries have been identified with orcein stain. No mitosis or atypical cells were present. Histological features of this vascular network were consistent with cavernous haemangioma (Fig. 2, 3). The second pathological process was constituted by clusters of ante hypophysar cells with no nuclear or cytoplasmic pleomorphism.

Fig. 2 : The surgical sample is composed of variable sized capillary vessels lined with a single layer of flattened endothelial cells, with no nuclear atypia. (HES, original magnification X 100).

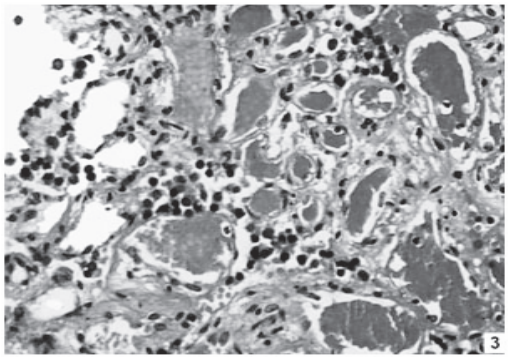

Fig. 3 : The disease interstitium is thin with clusters of hypophysartumorcells. (HES, original magnification X 400).

These areas of antehypophysar cells revealed a strong cytoplasmic immuno peroxydase staining for prolactin (Fig. 4) and negative staining for growth hormone, thyroid stimulating hormone, adrenocorticotrophic hormone, follicle stimulating hormone and luteinizing hormone. These aspects were in concordance with biological and clinical behaviours of hyperprolactinemia and the diagnosis of a prolactin cell microadenoma associated with a CH was made.

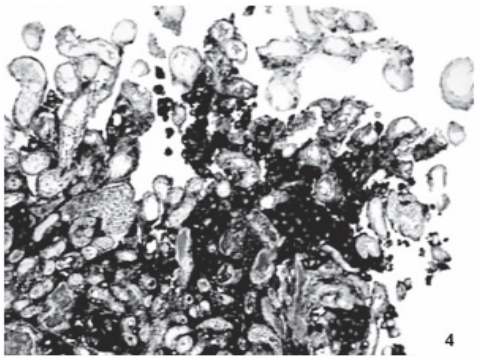

Fig. 4 : Immunostaining for prolactin shows a strong and diffuse cytoplasmic positivity in all hypophysar cells favouring the diagnosis of prolactinoma. (Hematoxylin counterstain, original magnification X 400).

DISCUSSION

Brain vascular lesions are relatively common and the nomenclature for classifying these lesions is sometimes complicated and confusing. Various classification systems have been used in both the central nervous system [19, 25, 31] and the soft tissue [9, 21]. Traditionally, cerebral non tumoral vascular lesions are divided into four categories: arteriovenous malformations, venous haemangioma, cavernous haemangioma and capillary telangiectasias. Moreover, in spite of the problem regarding nomenclature of the vascular lesions, controversy still exist regarding the nature of these lesions.

Herein we report an unusual vascular lesion developed within a prolactinoma and discuss the differential diagnosis with particular attention to its histopathological aspect.

At pathologic analysis, vascular lesions can be classified as capillary, venous and arteriovenous malformation depending on the predominant anomalous vascular channels. [9, 19] Although the histological features of the present lesion were that of capillary lesion,the exact diagnosis was uneasy because of the smallness of the pathological process. Indeed, in the present case, microscopic examination revealed a vascular lesion composed of nests and lobules of variable size capillary channels lined by flattened endothelial cells. These tightly packed and variably thickened capillaries channels, lacking elastic fibers and smooth muscle, were separated by a thin connective tissue. No mitoses were identified and no evidence of cytological atypia was seen. The presence of a little intervening brain tissue represented by small scattered clusters of hypophysar cells and the presence of areas of inconspicuously hyalinized vascular walls favour the diagnosis of cavernous haemangioma rather than capillary telangiectasia [11]. The presence of occasional intervening brain parenchyma is admitted in the diagnosis of CH, and according to Rigamonti and

al., intervening brain parenchyma was found within the cavernous lesions in 35% of the cases [24].

Furthermore, clear distinction between CH and capillary telangiectasia remains uncertain because these lesions share many similarities and this distinction has been source of debates and controversies although, many authors have outlined the inaccuracy of this distinction [1, 24]. Smaller vascular malformations most likely represent an early transitional form 24 while cavernous haemangioma are considered to be a more developmentally mature form of capillary telangiectasias. So that cavernous malformations and capillary telangiectasia are not distinct and separate histological entities but are variations of the same type of vascular malformations [24].

The absence of arteries and veins allowed us to rule out arteriovenous malformation and venous hemangioma. The lack of some specific histological features helped us to eliminate other vascular tumors diagnoses. So, histological examination failed to demonstrate the presence of foamy stromal cells characteristic of hemangioblastomas. Absence of highly cellular areas and lack of intracytoplasmic lumens allowed us to exclude hemangioendothelioma. The tumor failed to show the storiform architecture and pericellular reticulin staining characteristic of hemangio pericytomas. The lack of papillary formations ruled out the diagnosis of intravascular papillary endothelial hyperplasia.

However, it is well known that some authors have also reported intracranial capillary or mixed capillary lesions that could not be distinguished in a specific category of vascular neoplasm [18].

Cavernous haemangioma as other vascular malformations are considered by many authors as hamartomas or malformations of the microcirculation rather than true vascular neo plasms [28]. They may occur throughout the central nervous sytem but are more frequently demonstrated in the cerebral hemisphere. Intrasellar cavernous hemangiomas are very rare with only five cases reported in the literature (Table 1). They often present as a sellar mass and mimic a non-functional pituitary adenoma [5, 6, 27].

Authors / year	Sex, Age	Clinical Presentation	Associated lesion	Neuroradiological Findings	Mass Size	Localization
Sansone et al. [27] / 1980	F, 72 y	None	Metastatic breast adenocarcinoma	None	PME: 4,5 x 4 cm	Sella turcica and left hypothalamic area
Buonaguidi et al. [4] / 1984	M, 42 y,	Headache, seizure, hypopituitarism weakness, loss of vision	None	CT: contrast enhancing	Unknown	Sella turcica and chiasma
Mitsuhashi et al. [20] / 1991	F, 45 y	headache, nausea, Loss of vision,	Type 1 Neurofibromatosis	CT: contrast enhancing	CT: 7 x 5 cm	Sella turcica and left middle cranial fossa
Cobbs et al. [6] / 2001	M, 41 y	None	Orbital hemangioma	MRI: gadolinium-enhancing	MRI: 1,4 x 1,3 cm	Sella turcica
Chuang, et al. [5] / 2006	F, 62 y	Ptosis, inferolateral deviation of the eye, anisocoric pupils	None	MRI : gadolinium-enhancing	MRI: 2,4 x 1,5 cm	Sella turcica and cavernous sinus
Present case	F, 27 y	amenorrhea and galactorrhea following 6 years period of oral contraception	Prolactin cell microadenoma	MRI: no enhancement	MRI : 0,7 x 0,6 cm	Intra hypophysar

Y= year; F female; M male;
CT = CT scanning; MRI = magnetic resonance imaging; PME = Postmortem examination

Table 1 : Reported cases of intrasellar cavernous hemangioma

The association of pituitary adenoma with other diseases is well known [14] and the co-occurrence of cavernous haemangioma with nervous system lesions is not unusual. [10, 13, 17] Although the pathogenesis of CH is still not fully understood, genetic alterations have been incriminated for the familial form [7, 8, 26]. Nonetheless, the underlying mechanism of the association of cavernous malformation within tumors and its dynamic behaviour is unknown although, it has been suggested that cavernous malformation within tumors may occur as part of neoplastic growth which might be related to tumor angiogenic factors involving the proliferative and angiogenic capacities of the endothelium [17]. It has also been suggested that co-occurrence of cavernous malformation with nervous system tumors might be related to a common genetic pathway such as hyperactivation of the Rasoncogene [10]. Therefore these hypotheses should remind us whether or not such association indicates any related link. If these lesions share any common basis the incidence of their combination should be high, otherwise the combination is only fortuitous [13].

Furthermore, no histological features can differentiate between the disease's dormant state and the proliferating state [2]. CH increases in volume gradually, although a rapid evolution might be due to thrombotic occlusion,hormonal influence during pregnancy [23] or chronic encapsuled hematomas suggesting that minor recurrent bleeding from newly vascularized and fragiles vessels results in expansion of these lesions [15]. Recent studies of pituitary adenoma's angiogenesis have demonstrated that pituitary adenomas display a lower vascular density compared to non neoplasticadenohypophysis [29, 30]. Moreover, in pituitary adenomas, those presenting the lower microvessel density are usually the prolactin cell adenomas [22] and macroprolactinomas are significantly more vascular than macro-prolactinomas [12].Thus we can deduce and speculate that the growth of a micro-prolactinoma may favour the growth of a cryptic CH.

This case also highlights the pitfall or inaccuracy of our radiological diagnosis. Recent MRI images study reported a classification of cavernous angioma on the basis of MRI imaging features [31].

This classification includes four types differentiated by means of spine echo (SE) and gradient echo (GRE) MR imaging findings. The type 4 is not visible both on T1 and T2 weighted images and appears as punctate hypo intense lesion on GRE and the histological features was that of tiny lesion or telangiectasia. In our case the lesion was not visible on both T1 and T2 although GRE sequences were not performed.

CONCLUSIONS

The unusual localization of the present cavernoma, as well as its cryptic form and occurrence within a microprolactinoma make this case interesting. Furthermore our observation underlines the necessity to perform GRE sequence in the radiological cheek up of micro adenoma even if these vascular entities remain exceedingly rare.

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