An exceptional presentation of pituicytoma apoplexy: A case report

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Abstract. Pituicytomas are a rare form of indolent neoplasms, which typically present with visual disturbance and hypopituitarism. Complete resection by a trans-sphenoidal approach is the optimal treatment. Only 80 cases have been described thus far in the current literature and the present case is the first to describe the development of pituitary apoplexy in the context of a pituicytoma. A 77-year-old man presented with fatigue and clinical signs of hypogonadism and a sellar lesion was diagnosed at cerebral magnetic resonance imaging (MRI). A watch-and-wait management was initially decided and 1 year after the initial diagnosis, he presented with a thunderclap headache with images suggestive of pituitary apoplexy. A pituitary adenoma was suspected and an endoscopic resection was decided upon the development of a visual deficit. Pathological analysis established the correct diagnosis of a pituicytoma. Pituicytomas are characterised by dense vascularisation, thus ischaemic and haemorrhagic events may be common. When confronted with a hypervascularised pituitary lesion demonstrating strong contrast enhancement and no abnormal hormonal secretion, one must maintain a high index of suspicion for a pituicytoma. A wide range of differential diagnoses should thus be considered in the context of pituitary apoplexy.

Introduction

Pituicytomas are rare slow-growing tumours arising from the glial cells of the neurohypophysis and infundibulum (pituicytes). The histogenesis, natural history and prognosis of these lesions still need to be elucidated, as data in the current literature remain scarce.

Since the first reported case in 1955 (1), there has been a surge in the number of case reports and small case series describing this rare entity. There are no gender-specific differences in the incidence of pituicytomas, and the average age of presentation is 50 years of age (2). No specific risk factors were identified. These neoplasms generally present with headaches, visual disturbances and manifestations of hypopituitarism (typically sexual dysfunction). The clinical presentation is almost identical to other more frequent sellar lesions, therefore correctly diagnosing these lesions can be challenging. Of about 80 cases described in the literature up until now (3), only one previous case reported an abrupt onset of clinical features and this was due to an intraventricular haemorrhage (4).

On imaging, even if pituicytomas present with suspicious radiological peculiarities, their rarity often leads them to be misdiagnosed for more common lesions. Surgical resection represents the mainstay of treatment, and this is typically via an endoscopic endonasal approach (5). However, complete resection may be challenging due to the firm consistency and highly vascularised nature of these tumours.

We report a novel case of a pituicytoma presenting as pituitary apoplexy, with the aim to advance a hypothesis to explain this phenomenon. To our knowledge this is the first reported case in the literature that describes the development of pituitary apoplexy in the context of a pituicytoma.

Case report

A 77-year-old man presented to the University Hospital of Lausanne in October 2015 with fatigue and clinical signs of hypogonadism. The clinical presentation was suggestive of hypopituitarism and endocrine tests showed an anterior pituitary dysfunction. Investigation with cerebral magnetic resonance imaging (MRI) demonstrated a sellar lesion with suprasellar extension and no compression of optic structures. He was admitted at the neurosurgical department and initial management consisted of hormonal replacement therapy and a 'watch-and-wait' approach. One year after his initial presentation (October 2016), the patient returned to the emergency department with a thunderclap headache. A cerebral MRI demonstrated pituitary apoplexy (Fig. 1). There were no visual deficits on clinical examination and we decided to continue the regular monitoring and follow-up. Over 6 weeks of follow-up the patient started complaining of visual symptoms, secondary to a progressive growth of the pituitary lesion with compression of the optic chiasm (Fig. 2). Ophthalmological examination confirmed a right temporal quadrantanopia.

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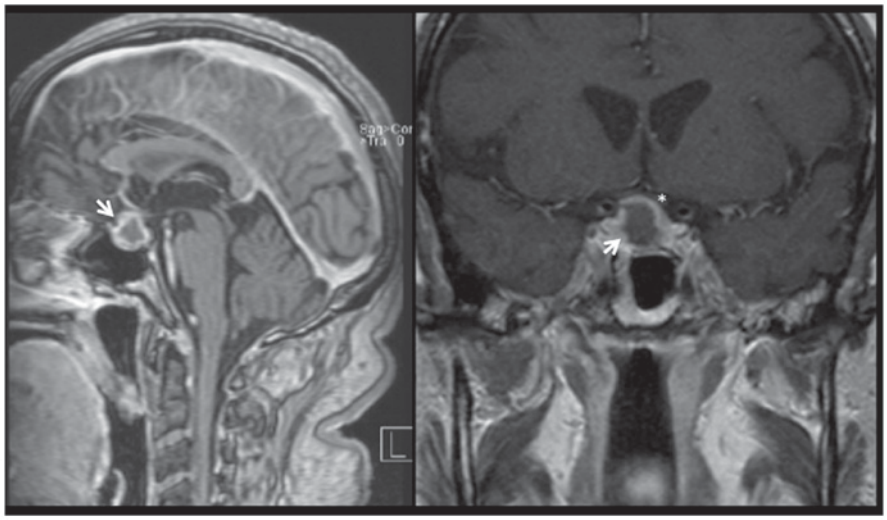

Figure 1. Sagittal (left panel) and coronal (right panel) views of a gadolinium enhanced T1-weighted cerebral magnetic resonance imaging. This shows a sellar lesion with peripheral contrast enhancement and a central hypointense core which is compatible with pituitary apoplexy (white arrow). The lesion provoked a sellar enlargement and presented an extension in the suprasellar space. The optic chiasm is visible immediately superior to the tumor, with no clear compression at imaging (the left optic nerve is marked with an asterisk).

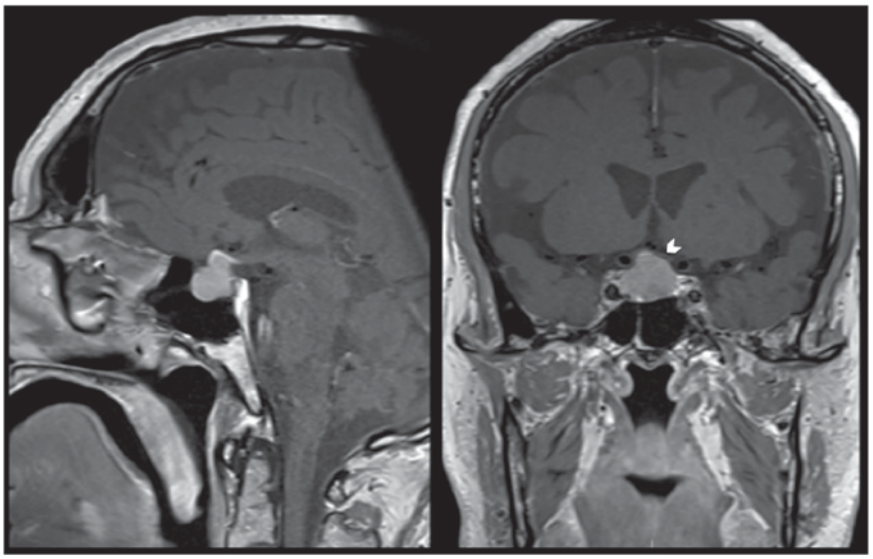

Figure 2. Sagittal (left panel) and coronal (right panel) views of a gadolinium enhanced T1-weighted cerebral magnetic resonance imaging revealing a sellar lesion with suprasellar extension, and intense homogeneous contrast enhancement. The pituitary stalk is not visible and the compression of the optic chiasm is evident (the left optic nerve is flattened just above the roof of the tumor and it is marked with an arrow head).

The patient underwent an uncomplicated endoscopic endonasal transsphenoidal resection of the tumour. Post-operatively the patient recovered well, with the right temporal quadrantanopia completely resolving. Endocrine function remained impaired, with a persistent anterior hypopituitarism but no diabetes insipidus. A post-operative MRI confirmed complete excision of the lesion (Fig. 3), and follow-up imaging at 15 months confirmed that the patient was still in remission.

The diagnosis of a pituicytoma was confirmed by pathologic examination and immunohistochemistry performed on four-micron thick, formalin fixed and paraffin embedded sections, analysed with a Nikon Eclipse microscope and a Nikon DSFi1 camera (both from Nikon Corporation, Tokyo, Japan). Spindle-shaped cells with a fascicular growth pattern and heterogeneous nuclei were identified with hematoxylin and eosin stain (Fig. 4A and B). There was no evidence of atypical cellular features or mitotic figures and the detection of proliferation markers was performed on paraffin sections with anti-Ki67 (MIB-1; Immunotech; Beckman Coulter, Inc., Brea, CA, USA) with the cell count performed at high power (x400). Cellular proliferation resulted inferior to 1% (Fig. 4C). Immunohistochemical staining was performed through the Ventana platform and it revealed tumour cells positive for thyroid transcription factor-1 (TTF-1) (Fig. 4D), S-100, vimentin, B-cell lymphoma 2 (Bcl-2) and CD56. The cells were negative for synaptophysin, glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), signal transducer and activator of transcription (STAT)6, cluster of differentiation 34 (CD34), Melan-A, human melanoma

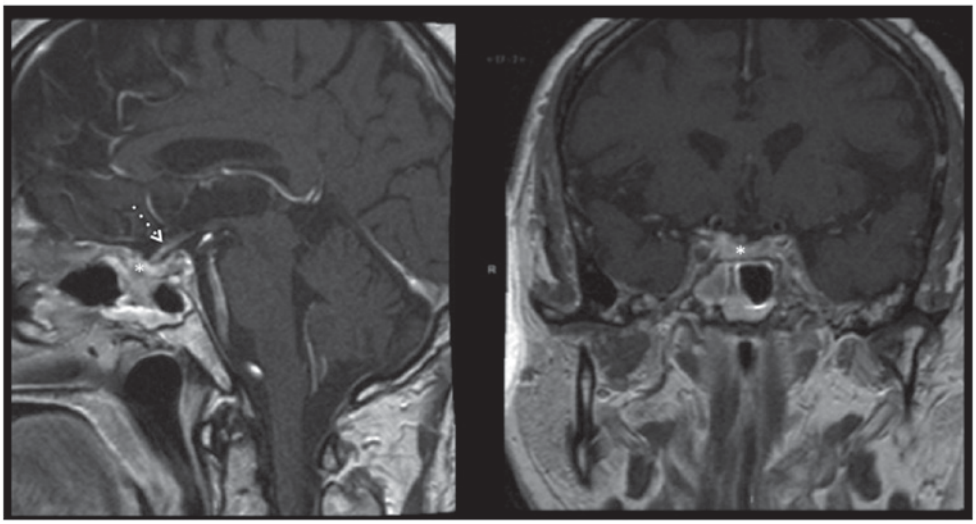

Figure 3. The postoperative cerebral magnetic resonance imaging with contrast confirms the complete resection of the lesion (sagittal view on the left panel and coronal view on the right panel). The lesion is no more present and the normal pituitary gland is visible (asterisk) in the sella. The pituitary stalk is well visualised in the sagittal plane (dotted arrow).

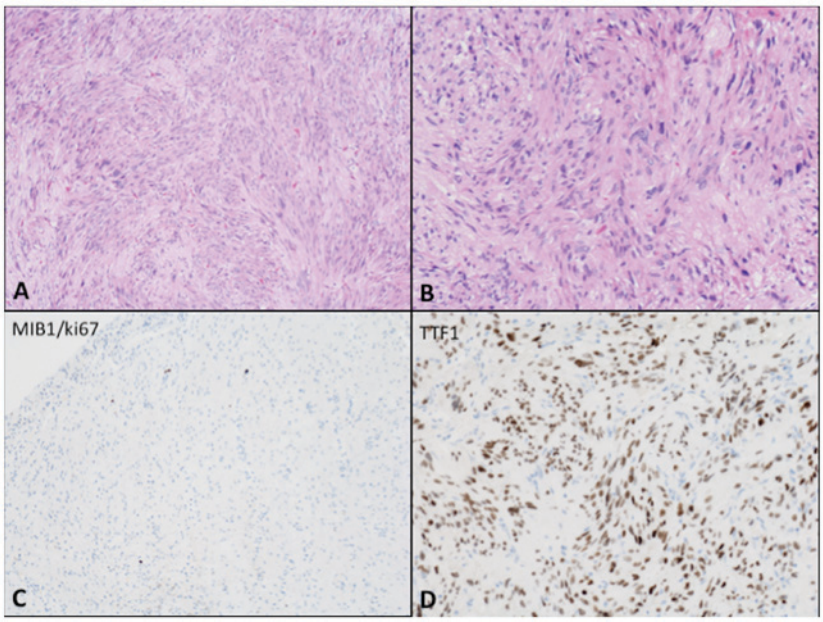

Figure 4. A hematoxylin and eosin stain [initial magnification x10 in (A) and x20 in (B)] shows fascicules of spindle-shaped cells with an absence of cellular atypia and mitotic figures. The proliferative index marked with the MIB-1/Ki67 was <1% [initial magnification x10 in (C)]. Immunohistochemical staining was performed with the Ventana platform and it revealed tumour cells positive for TTF-1 (Nitrogen antibody, ref 18-0221), which is specifically expressed in pituicyte lineage [initial magnification x20 in (D)].

black 45 (HMB45), (tumor) protein 63 (P63), calretinin and neurofilament (NF). The details for each antibody and for the methodology used to perform immunohistochemistry were reported in Table I. The entire sections on the stained slides were evaluated. Electron microscopy was not performed.

Discussion

Pituicytomas are defined as indolent World Health Organization (WHO) grade 1 tumours involving the posterior lobe of the pituitary and/or the pituitary stalk. They are solid tumours, generally well circumscribed and composed of spindle cells derived from pituicytes (6,7).

Pituicytomas are slow growing and they may often go unnoticed until clinical signs and symptoms secondary to mass effect start to develop. These lesions are known to compress the pituitary gland and the optic system, thus provoking more frequently hypopituitarism and visual disturbance. We describe here the first reported case of pituitary apoplexy secondary to a pituicytoma. The primary goal of the management was to mitigate the consequences of apoplexy through urgent hormonal substitution and to monitor for visual deficits. Surgical management was decided upon following the development of a visual deficit.

Pituicytomas have similar radiological features to pituitary adenomas, thus distinguishing these diagnoses from one another

Table I. Antibodies used to perform the immunohistochemistry with the Ventana platform.

Antibody	Clone	Fabricant	Reference	Dilution	Incubation
Antibodies that stained positively					
TTF-1	8G7G3/1	Invitrogen	18-0221	1:30	32 min 37˚C
S-100	Polyclonal	Novocastra Laboratories, Ltd.	NCL-S100P	1:400	24 min 37˚C
Vimentin	VIM3B4	Progen Biotechnik GmbH	61013	1:3,200	32 min 37˚C
Bcl-2	Bcl2/100/D5	Novocastra Laboratories, Ltd.	NCL-Bcl-2	1:30	92 min 37˚C
CD56/NCAM	CD564	Novocastra Laboratories, Ltd.	NCL-L-CD56-504	1:25	60 min 37˚C
Antibodies that did not stain tissue					
Synaptophysin	27G12	Novocastra Laboratories, Ltd.	NCL-Synap-299	1:100	32 min 37˚C
GFAP	G-A-5	Sigma-Aldrich	G3893	1:15	92 min 37˚C
EMA	E29	DAKO	M0613	1:100	32 min 37˚C
STAT-6 (S-20)	Polyclonal	Santa Cruz Biotechnology, Inc.	SC-621	1:400	60 min 37˚C
CD34	Qbend-10	DAKO	M7165	1:25	32 min 37˚C
Melan-A	A-103	DAKO	M7196	1:50	32 min 37˚C
HMB45	HMB45	DAKO	M0634	1:50	32 min 37˚C
P63	DAC-P63	DAKO	M7317	1:100	32 min 37˚C
Calretinin	CAL2	Dianova GmbH	DIAL-CAL-250	1:20	32 min 37˚C
NF	2F11	DAKO	M0762	1:1,000	37˚C

Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA; Novocastra Laboratories, Ltd., Newcastle, UK; Progen Biotechnik GmbH, Heidelberg, Germany; Sigma-Aldrich, St. Louis, MO, USA; DAKO; Agilent Technologies GmbH, Waldbronn, Germany; Santa Cruz Biotechnology, Inc., Dallas, TX, USA; Dianova GmbH, Hamburg, Germany. Bcl-2, B-cell lymphoma 2; CD34, cluster of differentiation 34; CD56/NCAM, cluster of differentiation 56/neural cell adhesion molecule; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; HMB-45, human melanoma black 45; NF, neurofilament; P63, (tumor) protein 63; STAT-6 (S-20), signal transducer and activator of transcription 6; TTF-1, thyroid transcription factor-1.

based on radiological imaging remains challenging. They are often described as sellar lesions with frequent suprasellar extension and sellar enlargement (and/or bone remodelling). They generally present as isointense lesions on T1-weighted MRI and the posterior lobe of the pituitary gland is generally not identifiable, while they appear as hyperintense lesions on T2-weighted images (2,8). T1-weighted MRI sequences with gadolinium contrast enhancement may prove useful in diagnosis, as pituicytomas may appear brighter than classical adenomas due to their dense vascularisation (4). A recent paper reports the usefulness of flow voids at the MRI to differentiate pituicytomas from pituitary adenomas. Flow voids represent signal loss due to rapidly flowing blood, and thus indirectly equate to increased vascularity (9). Angiography may also be a useful tool, with a vascular blush typical of pituicytomas (2). Despite these differences, radiological distinction from other more common sellar lesions, such as pituitary adenomas and meningiomas, is not always easy.

Considering this, the diagnosis of a pituicytoma strongly relies on pathological analysis and immunohistochemical investigations, as pituicytomas demonstrate a characteristic immunohistochemical profile with a strong positive staining for S-100 and TTF-1, a focal positivity for GFAP, and an absence of staining for synaptophysin, p53 or pericellular reticulin (6,10,11).

The mainstay of treatment for symptomatic pituicytomas is surgery, with gross total resection considered curative. Unfortunately, due to the dense vascularity and the firm consistency of these tumours, the extent of resection is often limited. Precise surgical planning is necessary, with a focus on the extension of the tumour itself and its radiological characteristics. The development of endoscopic surgery has led to an endonasal approach being the preferred procedure.

Our case had a peculiar clinical presentation and we suggest that apoplexy was most likely due to the haemorrhagic transformation or to the intralesional ischemia secondary to the rupture or the occlusion of pathological vessels arising directly from the internal carotid artery or from its branches. We put forth the hypothesis that the incidence of pituicytoma apoplexy might actually be underestimated, as with pituitary apoplexy, surgery and tissue diagnosis is performed only in cases complicated by visual disturbance.

We assert that pathologists, endocrinologists and neurosurgeons should be mindful of pituicytoma as a possible differential diagnosis when dealing with pituitary apoplexy.

Recommendations and future directions. Over the last few years there has been substantial advancement regarding the definition and classification of pituicytomas (7). However, the histogenesis of these lesions remains controversial, and the natural history of progression of this disease is yet to be elucidated. Understanding the natural history of these tumours is difficult, because all of the cases described so far have been diagnosed retrospectively following surgical management and pathological confirmation.

Treatment is mainly empirical, and when gross total resection is possible, management is relatively straightforward. In cases where only subtotal resection is possible, the use of adjuvant therapies is highly debated, and there is no existing evidence to recommend specific management.

Further work to clarify the optimal management of patients with pituicytomas still needs to be undertaken, and we hope that future studies will help to standardise treatment strategies.

To conclude, pituicytomas are rare and indolent lesions. However, atypical presentations may be challenging and should not be underestimated. Due to the vascularised nature of these lesions, haemorrhagic or ischaemic events are potential serious consequences. We assert that a wider range of differential diagnoses should be considered when clinicians encounter pituitary apoplexy in the context of hypervascularised pituitary lesions not associated with abnormal hormonal secretion.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

GC, JD, RTD and MM contributed to the design and conception of the study. GC and JD proceeded with the acquisition of data, GC performed a literature review and JPB performed the pathological analysis and provided the necessary material. All the authors contributed substantially to the drafting of the manuscript and revised it critically for important intellectual content. They all gave final approval of the version to be published.

Ethics approval and consent to participate

Informed consent was obtained from the patient.

Consent for publicationv

The patient has consented to the submission of this case report for publication.

Competing interests

The authors declare that they have no competing interests.

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