



Pituitary Apoplexy and Idiopathic Thrombocytopenic Purpura: A New Case and Review of the Literature

J.C. Maïza¹, A. Bennet¹, M. Thorn-Kany²,
J. Lagarrigue³, and Ph. Caron¹

¹Department of Endocrinology, Centre Hospitalo-Universitaire Rangueil, Toulouse, France; ²Department of Neuroradiology, Centre Hospitalo-Universitaire Rangueil, Toulouse, France;

³Department of Neurosurgery, Centre Hospitalo-Universitaire Rangueil, Toulouse, France

Published online: 28 April 2005

Abstract. Pituitary apoplexy can occur as a complication of idiopathic thrombocytopenic purpura. We report here a new case of such association. A male patient aged 59 years, complaining of decreased libido for one year, was referred to the emergency department for purpura and severe thrombocytopenia (4000 platelets/mm³). 24 hours after the cutaneous rash the patient presented with clinical symptoms of bilateral cavernous sinus compression comprising ptosis, bilateral ophthalmoplegia and right supra-orbital hypoesthesia. Cranial CT scan showed an enlarged sella and a pituitary mass with signs of intrapituitary haemorrhage. Hormonal evaluation showed hyperprolactinemia (50 ng/mL) and hypopituitarism, and the patient needed substitution with hydrocortisone and levothyroxine. Immunoglobulins and corticosteroids were given to the patient to treat thrombocytopenia, then worsening of neurological and ophthalmological symptoms led to pituitary surgery. Histopathological examination found necrotical pituitary tissue. Immunostaining with an anti-prolactin antibody was positive in several groups of cells. Neurological symptoms subsided and thrombocytopenia was corrected by treatment. In conclusion, we report a case of pituitary apoplexy due to severe thrombocytopenia occurring as a complication of a preexisting macroprolactinoma.

Key Words pituitary apoplexy, macroprolactinoma, thrombocytopenia, idiopathic thrombocytopenic purpura

Introduction

We report a case of pituitary apoplexy occurring during severe thrombocytopenia due to idiopathic thrombocytopenic purpura in a patient with a prolactin-secreting pituitary macroadenoma. Pituitary apoplexy is a rare disorder, generally occurring as a complication of an underlying pituitary disease, such as a secreting or non-secreting pituitary adenoma, in most cases without an additional cause. To date, according to the review of the literature, there is only one previous report on the association of pituitary apoplexy and idiopathic thrombocytopenic purpura.

Observation

A 59-year-old male patient without any past medical history was referred to the Emergency Department because of occurrence of purpura. The initial clinical findings were ecchymotic purpura on the legs, without any other abnormality. Biological evaluation showed severe thrombocytopenia (4000 platelets/mm³) with normal haemoglobin level (14.2 g/dL) and no reduction of white blood cell count (10500/mm³). There was no biological inflammatory syndrome. Bone marrow cell count provided evidence for peripheral origin for thrombocytopenia; no abnormality of the bone marrow cell lines and no cellular invasion of the bone marrow was observed. Drug-induced thrombocytopenia, as well as thrombocytopenia occurring as a consequence of viral infections or inflammatory diseases were ruled out by anamnesis, clinical findings and biological evaluation. Serologies of HIV, EBV, VHB, VHC were negative and immunological evaluation was normal. It was concluded that thrombocytopenia was related to idiopathic thrombocytopenic purpura. During the next night the patient presented with right ophthalmoplegia and supraorbital headache. Neurological examination of the cranial nerves revealed total palsy of right oculomotor nerve and hypoesthesia in the territory innervated by the ophthalmic branch of the right trigeminal nerve, related to compression of the external wall of the right cavernous sinus. CT scan showed a pituitary mass with pituitary haemorrhage. On the next morning, the patient experienced worsening of clinical symptoms with palsy of the left oculomotor nerve. Then CT-scan revealed an increase in the size of intrapituitary hemorrhage. The patient was given immunoglobulins and corticosteroids in order to treat idiopathic thrombocytopenic purpura. Hormonal evaluation was performed because of the suspected

Address correspondence to: Ph. Caron, Department of Endocrinology and Metabolic Diseases, Centre Hospitalo-Universitaire Rangueil, TSA 50032 31059, Toulouse, France. E-mail: caron.p@chu-toulouse.fr

Table 1 Hormonal evaluation in the patient with pituitary apoplexy

| | D2 | M2 | M8 | M20 | Normal range |
|--------------|------|-----|-----|------|---------------|
| Prolactin | 50 | 34 | 34 | 2.40 | <20 ng/ml |
| LH | 0.9 | | | | 1.5–9.3 mU/ml |
| FSH | 1 | | | | 1.4–11 mU/ml |
| Testosterone | 24 | 125 | 325 | 232 | 240–820 ng/dl |
| TSH | 0.86 | | | | 0.2–4 mU/ml |
| T3l | 1.7 | 3.1 | 2.6 | 3.7 | 2–6 pg/ml |
| T4l | 5.1 | 14 | 6.3 | 9 | 6–15 pg/ml |
| Cortisol | 15 | | | | 4.3–22 µg/dl |
| ACTH | 12 | | | | 9–52 pg/ml |
| IGF1 | 169 | | | | 104–202 ng/ml |

D2: at time of diagnosis. M2 and M8: 2nd and 8th month, under thyroid and testosterone substitutive therapy. M20: 20th month, under dopamine agonist.

diagnosis of pituitary apoplexy (Table 1) and showed hyperprolactinemia and gonadotropin and thyrotropin deficiency. Anamnesis revealed that the patient had suffered from decreased libido and impotence for one year. The volume of the testes was normal. Substitutive treatment with levothyroxine (Levothyrox, Liplha-Santé) was started while the treatment with corticosteroids (which had been started for idiopathic thrombocytopenic purpura) was carried on. A MRI-scan of the pituitary was performed on the 5th day (Fig. 1). It showed an enlarged sella and a pituitary mass with suprasellar extension resulting in distortion of the optic chiasm, infrasellar extension and lateral extension into the right, and to a lesser extent, into the left cavernous sinus. Multiple hyperintense areas in T1-weighted imaging were observed, attesting for pituitary hemorrhage. Because of worsening of the clinical symptoms related to pituitary haemorrhage, transsphenoidal decompressive surgery was performed in order to reduce

the size of the pituitary mass (the platelets were 228 000/mm³ at the time of surgery). Histopathological examination led to the diagnosis of necrotical pituitary adenoma, and immunostaining with an anti-prolactin antibody was strongly positive on several groups of adenoma cells. Immunostaining for GH, β -LH, β -FSH and α -sub-unit was negative. Thus the histopathological diagnosis was necrotical prolactin-secreting pituitary adenoma.

After surgery the patient was treated orally for hypopituitarism with hydrocortisone 30 mg/day (Hydrocortisone Roussel, Aventis, Paris, France), levothyroxine 100 microg/day (Lévothyrox, Liplha Santé) and testosterone undecanoate 120 mg/day (Pantestone, Organon, Puteaux, France). The results were satisfactory and the patient totally recovered from the left oculomotor nerve dysfunction and the right facial hypoaesthesia while palsy of the right oculomotor nerve partially subsided. The MRI scan performed 2 months later (Fig. 2) displayed a residual pituitary mass, a marked reduction of the suprasellar extension, persistent lateral extension into both cavernous sinus with reduction of the right intracavernous part of the pituitary mass. Subsequent MRI-scans (performed 8 and 20 months after the initial symptoms) showed a reduction of the volume of the residual pituitary mass, with partial empty sella syndrome (Fig. 3). Hormonal evaluation performed at 2, 8, 20 months attested for correct hormonal substitutive therapy. Because of persistent hyperprolactinemia (34 ng/mL) at 2 and 8 months, treatment with a dopamine agonist (quinagolide) was started (Norprolac, Novartis, Rueil-Malmaison, France). Hormonal evaluation at 20 months showed normal prolactin levels. The course of haematological results was satisfactory. Recurrence of thrombocytopenia (with a count of 60 000 platelets/mm³) was observed one month after surgery but resolved spontaneously. Since this time, the platelets have remained above 150000/mm³ without any specific treatment.

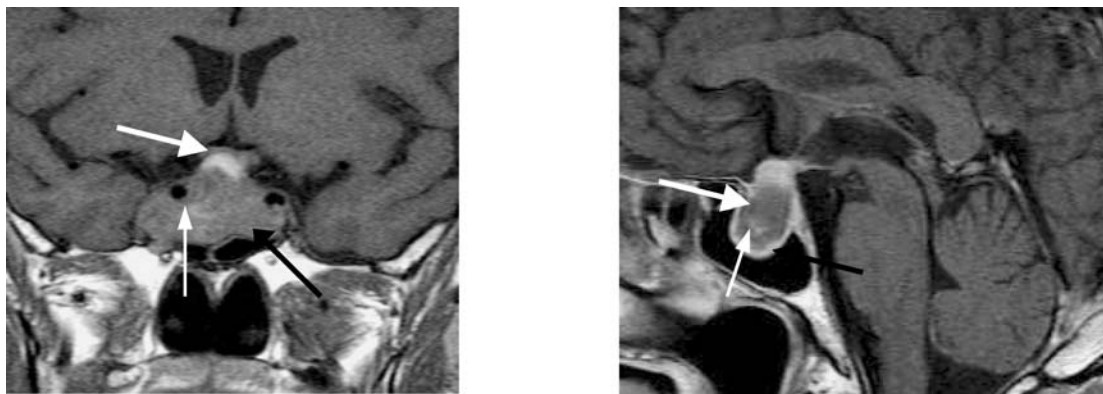


Fig. 1 First IRM revealed a voluminous intrasellar mass syndrome with supra and laterosellar extension, associated with hemorrhage components: ⇒: hemorrhagic or necrotic components. →: solid components.

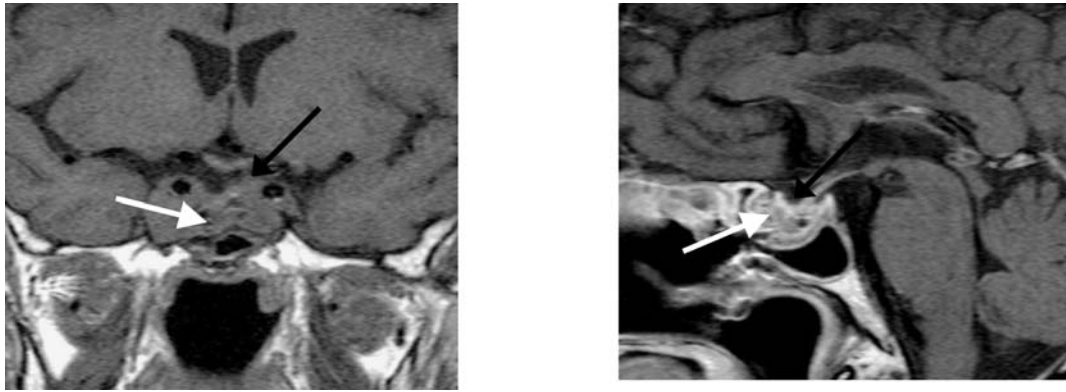


Fig. 2 IRM at 2nd month revealed a marked reduction of tumoral mass.

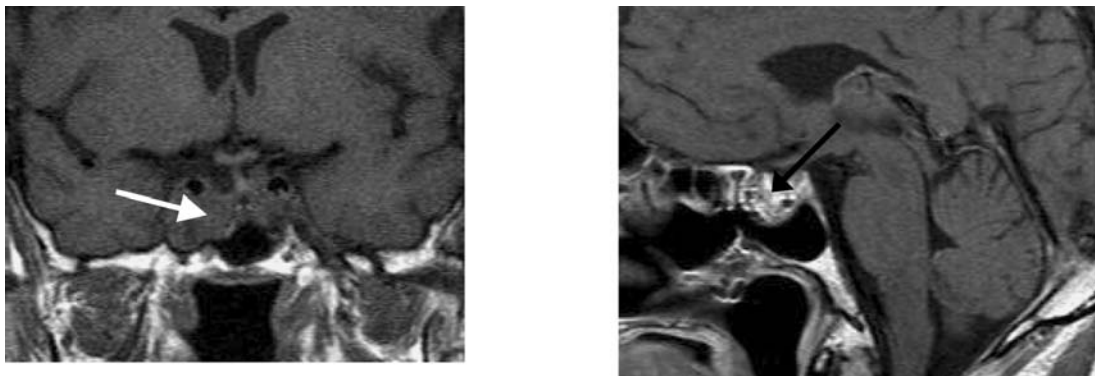


Fig. 3 IRM at 20 months revealed a progression of reduction of tumoral mass with partial empty sella syndrome.

Discussion

The prevalence of pituitary apoplexy is highly variable in the literature, depending on the definition of pituitary apoplexy. If the definition is clinical (sudden occurrence of symptoms related to necrosis and/or hemorrhage in a pituitary adenoma), the prevalence is 1% of pituitary adenomas. If the definition is based on histopathology (necrotical and/or haemorrhagical areas in pituitary tissue) the prevalence is much greater and reaches 15–20% of all cases of pituitary adenomas. The mean age of the patients with pituitary apoplexy is the 5th decade. There is no sex ratio and the odds for occurrence of pituitary apoplexy do not depend on the histological type of pituitary adenoma [1–3].

Our patient underwent pituitary apoplexy in a previously undiagnosed pituitary prolactin-secreting adenoma. When hyperprolactinemia was found, it could be related to 3 different diagnoses: prolactin-secreting adenoma, hyperprolactinemia consecutive to compression of the infundibulum or destruction of the lactotrophs resulting in prolactin release. The histopathological findings with the results of immunostaining finally confirmed the diagnosis of prolactinoma, leading

to medical treatment with a dopamine agonist. The initial relatively moderate level of hyperprolactinemia is probably due to the necrosis of the prolactin-secreting adenoma. This may explain that prolactin levels were only 50 ng/ml, a lower than expected level of prolactin for a macroprolactinoma.

The pituitary gland has dense vascularization. The anterior pituitary is vascularized by the superior hypophysial artery, originating from the internal carotid artery, following the infundibulum to enter the anterior pituitary. Vascularization of the anterior pituitary is also provided by the portal vessels, that come out of the hypothalamus, start within the infundibulum and run along the infundibulum. Vascularization of the posterior pituitary is supplied by the inferior hypophysial artery, which also comes from the internal carotid artery. Anastomoses link the hypothalamic portal vessels system to the inferior pituitary artery [4,5].

Several pathophysiological mechanisms have been described in pituitary apoplexy. On the one hand, pituitary macroadenomas may compress branches of the superior hypophysial artery, leading initially to ischemic necrosis of the tissue, then to haemorrhage due to the reappearance of the blood flow in this necrotical

tissue after cessation of the compression of the artery. On the other hand, direct compression of the infundibulum by the pituitary tumor may hamper vascularization of the pituitary gland by the portal vessels, which may also result in ischemic necrosis, also followed by an intrapituitary haemorrhage. Such "macrovascular" theories may appear satisfactory to explain pituitary apoplexy in huge pituitary adenomas, but it is now well known that pituitary apoplexy may occur in patients with pituitary microadenomas, or even with non adenomatous pituitary glands. A microvascular theory has been advocated, pituitary apoplexy occurring as a consequence of intratumoral or intrapituitary frailty of the capillaries.

Several factors liable to hasten pituitary apoplexy have been described [3,6]:

- factors involved in growth of pituitary adenomas: estrogens, pregnancy [7] LHRH [8] or TRH employed for in vivo evaluation of pituitary functions
- factors that may hamper microcirculation: radiotherapy, hypertension, diabetes mellitus [9]
- factors that alter intracranial pressure and result in hypoperfusion of the pituitary: cranial traumas, rachiocentesis, spinal anesthesia
- factors that lead to systemic hypoperfusion, thereby to hypoperfusion of the pituitary: cardiac surgery, haemodialysis
- factors liable to alter the clotting of the blood : multiple myeloma, Von Willebrand's disease, anticoagulants (heparine) [10,11], antithrombotic agents (fibrinolytic agents) [12,13], thrombocytopenia.

In our patient, pituitary apoplexy occurred in a pre-existing and undiagnosed prolactin-secreting pituitary adenoma consecutively to thrombocytopenia due to idiopathic thrombocytopenic purpura. There is one report about the association of thrombocytopenia and pituitary apoplexy in a patient suffering from acute myeloid leukemia [14]. To our knowledge, there is only one previous report on the association of pituitary apoplexy and thrombocytopenia related to idiopathic thrombocytopenic purpura [15]. Thus thrombocytopenia, whatever its cause may be, appears to be a predisposing factor liable to result in pituitary apoplexy in a patient with a pituitary disease such as a secreting or non secreting pituitary adenoma. Regarding the treatment of pituitary apoplexy, some authors advocate a conservative management in some patients in particular in the absence of consciousness abnormalities or visual loss. For these authors, systematic neurosurgery may be discussed if neurological problems are limited to unilateral oculomotor palsy [16]. In our patient, persistent bilateral oculomotor nerves palsy af-

ter one week warrants decompressive neurosurgery after recovery of a normal platelets count. After treatment, the haematological and neurological disorders subsided; the only persistent abnormalities were hypopituitarism, which required hormonal therapy, and hyperprolactinemia, which was controlled by treatment with dopamine agonist.

References

1. Mohr G, Hardy J. Hemorrhage, necrosis and apoplexy in pituitary adenomas. *Surg Neurol* 1982;18:181–189.
2. Wakai S, Fukushima T, Teramoto A, Sano A. Pituitary apoplexy: Its incidence and clinical significance. *J Neurosurg* 1981;55:187–193.
3. Vidal E, Cevallos R, Vidal J, et al. Twelve cases of pituitary apoplexy. *Arch Intern Med* 1992;152:1893–1899.
4. Rolih Ca, Ober P. Pituitary apoplexy. *Endocrinol Metab Clin North Am* 1993;22:291–302.
5. Reid R, Quigley M, Yen S. Pituitary apoplexy, a review. *Arch Neurol* 1985;42:712–719.
6. Biousse V, Newman N, Oyesikbu N. Precipitating factors in pituitary apoplexy. *J Neurol Neurosurg Psychiatry* 2001;71:542–545.
7. Freeman R, Wezenter B, Silverstein M, et al. Pregnancy-associated subacute hemorrhage into a prolactinoma resulting in a diabetes insipidus. *Fertil Steril* 1992;58(2):427–429.
8. Chanson P, Schaison G. Pituitary apoplexy caused by GnRH-agonist treatment revealing gonadotroph adenoma. *J Clin Endocrinol Metab* 1995;80:2267–2268.
9. Sussman E, Porro R. Pituitary apoplexy: the role of atheromatous embolus. *Stroke* 1974;5:318–323.
10. Nourzaden A, Pitts F. Hemorrhage into pituitary adenoma during anticoagulant therapy. *JAMA* 1965;623–625.
11. Oo M, Krishna A, Bonavita G, Rutecki G. Heparin therapy for myocardial infarction; an unusual trigger for pituitary apoplexy. *Am J Med Sci* 1997;314:351–353.
12. Hyer S, Soo S, Taylor W, Nassey S. Spontaneous hemorrhage into pituitary tumor after streptokinase therapy. *Postgrad Med J* 1993;69:244.
13. Fuchs S, Beerli R, Hasin Y, et al. Pituitary apoplexy as a first manifestation of pituitary adenomas following intensive thrombolytic and antithrombotic therapy. *Am J Cardiol* 1998;81:110–111.
14. Wongpraparut N, Pleanboonlers, et al. Pituitary apoplexy in a patient with acute myeloid leukemia and thrombocytopenia. *Pituitary* 2000;3:113–116.
15. Lenthall R, Jaspan T, Gonugunta V. Pituitary apoplexy with optic tract oedema and haemorrhage in a patient with idiopathic thrombocytopenic purpura. *Neuroradiology* 2001;43:156–158.
16. Maccagnan P, Macedo C, Kayath M, et al. Conservative management of pituitary apoplexy: a prospective study. *J Clin Endocrinol Metab* 1995;80:2190–2197.