Spontaneous Cure of an Apoplectic Somatotropinoma in the Setting of Coronary Angiography

Koroner Anjiyografi Sonrası Apoplektik Somatotropinomanın Spontan Kürü

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Abstract

Pituitary apoplexy, which results from spontaneous hemorrhage into a pituitary adenoma, may be associated with a number of clinical settings including head trauma, hypertension, diabetes mellitus, acute hypovolemic shock, contrast media usage, and anticoagulation therapy. Clinical manifestations are due to the mechanical compression of the optic apparatus and cavernous sinus content, and pituitary insufficiency. Pituitary insufficiency does not recover in most of the cases. Ophthalmoplegia may resolve spontaneously over time or after surgery. Rarely, pituitary apoplexy may be followed by an endocrinologic cure. We present an apoplectic somatotropinoma in the setting of coronary angiography and unstable angina pectoris, which was spontaneously cured after pituitary apoplexy. This is one of few reports of pituitary apoplexy in association with contrast medium and anticoagulant-antiaggregant drug administration. *Turk Jem 2008; 12:35-8*

Key words: Pituitary apoplexy; angiography; anticoagulants; platelet aggregation inhibitors

Özet

Pitüiter adeonomun içine spontan kanama sonucu gelişen pitüiter apopleksi;kafa travması, hipertansiyon, diyabetes mellitus, akut hipovolemik şok, kontrast madde kullanımı ve antikoagülasyon tedavisi gibi bir takım etkenlerle ilişkili olabilir. Klinik bulgular optik aparatusun ve kavernöz sinüs içeriğinin mekanik basısı ve pitüiter yetersizliğe bağlıdır. Pitüiter yetersizlik çoğu vakada düzelmez. Oftalmopleji ise zaman içerisinde kendiliğinden veya cerrahi sonrası düzelebilir. Nadiren pitüiter apopleksi sonrası endokrinolojik kür gelişir. Kararsız anjina pektoris nedeniyle koroner anjiyografi yapılan ve sonrasında apopleksi sonucu spontan kür oluşan bir somatotropinoma olgusunu sunuyoruz. Literatürde kontrast madde ve antikoagülan-antiagregan ilaç kullanımıyla ilişkili az sayıda pitüiter apopleksi olgusu bildirilmiştir. *Turk Jem 2008; 12: 35-8*

Anahtar kelimeler: Pitüiter apopleksi; anjiyografi; antikoagülanlar; platelet agregasyon inhibitörleri

Introduction

Pituitary apoplexy (PA), which complicates 1 or 2 in 100 pituitary adenomas, results from spontaneous hemorrhage into a pituitary adenoma or occurs in association with head trauma, hypertension, diabetes mellitus (hyperosmolarity), sickle cell anemia, or acute hypovolemic shock that may be related to cardiac and vascular surgery (1). There are also reports about PA associated with infection or abscess of the pituitary gland, anticoagulation therapy, idiopathic thrombocytopenic purpura, and gonadotropin releasing hormone therapy (2-20). Subclinical haemorrhage is evident in 10% of surgical specimens (19). Some reports suggest that corticotropic and somatotropic adenomas have a higher tendency for PA while others blame nonfunctioning adenomas (19).

Clinical manifestations include severe headache, neck stiffness, progressive cranial nerve damage, cardiovascular collapse, changes in consciousness, hypoglycemia, and fever [1]. Some of these manifestations are due to mechanical compression of the optic apparatus and cavernous sinus content, and some are due to damaged cells and resultant pituitary insufficiency. Pituitary insufficiency does not recover in most cases. Hormonal replacement therapy is given as needed (19). Ophthalmoplegia may resolve spontaneously over time or after surgery. Postoperative recovery of visual function correlates inversely with time elapsed since the acute hemorrhage (1). Subarachnoid haemorrhage and obstructive hydrocephalus are other complications. Complete or partial empty sella syndrome is a late onset complication of PA in many cases. Rarely, PA may be followed by an endocrinologic cure (8,19).

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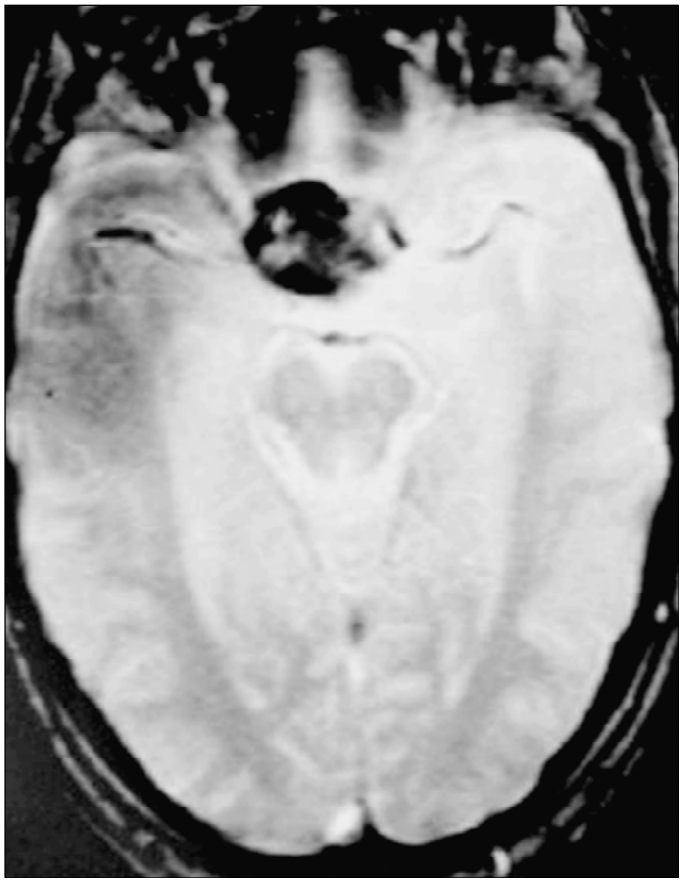
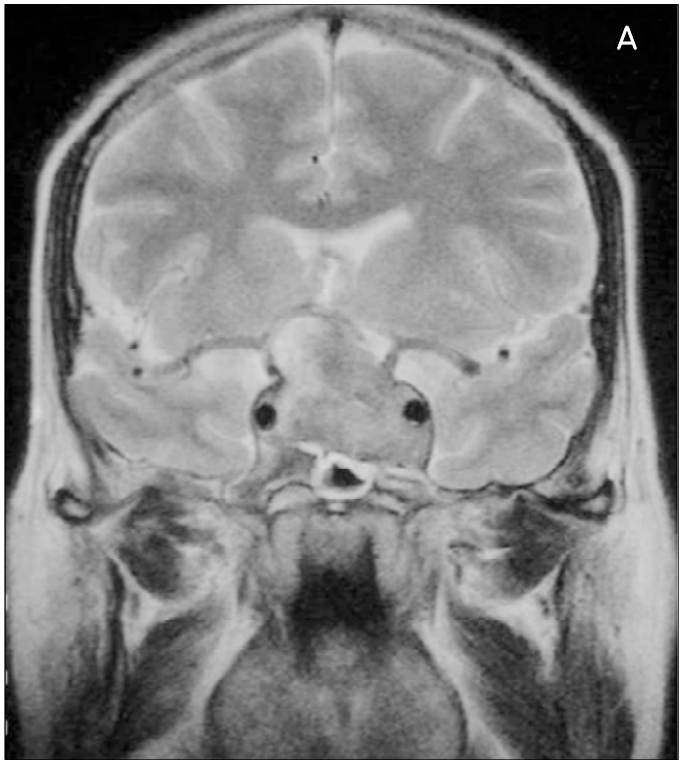


Figure 1. Abundant haemorrhage is evident on the transaxial plane (flask image).



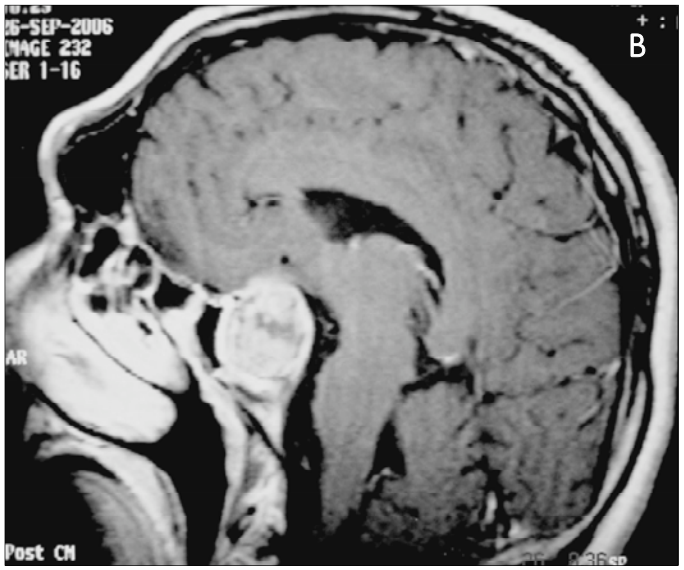


Figure 2. On the coronal (A) and sagittal (B) planes, bilateral sinus expansion and compression of the right optic nerve and the optic chiasm. Abundant contrast enhancement is evident within the lesion in the surrounding haemorrhagic area (B).

We present an apoplectic somatotropinoma in the setting of coronary angiography and unstable angina pectoris, which was spontaneously cured after PA. This is one of few reports of PA in association with contrast medium and anticoagulant-antiaggregant drug administration.

Case

A 40-year-old male was hospitalized for retrosternal chest pain extending to both arms, accompanied by excess sweating. His past medical history was unremarkable despite two operations; one for hydatid cyst in the liver and one for gastric ulcer. His family history was also unremarkable. He was not on any medication before hospitalization. Resting electrocardiogram revealed ST segment depression in V5-6 precordial leads. Echocardiogram was normal. He was diagnosed with unstable angina pectoris. This was medicated with metoprolol 100 mg daily, rosuvastatin 10 mg daily, cilazapril 1 mg daily, acetylsalicylic acid 300 mg daily, enoxaparin 120 mg daily, and clopidogrel 75 mg daily. Coronary angiography (CAG) was done on the 8th day of hospitalization. There was no stenosis but thrombosis was present in the right coronary artery. Two days following angiography, the patient developed severe unremitting headache and sudden loss of vision. Ophthalmic examination was found normal despite visual acuity of counting fingers close to face in the right eye. His neurologic examination was otherwise normal. Cranial computed tomography (CT) was done initially to delineate the underlying pathology. CT showed a heterogeneous mass filling the sella and extending into the suprasellar cistern. Thereafter, magnetic resonance imaging (MRI) was done. MRI showed a haemorrhagic hypophyseal mass invading the cavernous sinuses and displacing the optic chiasm (Figure 1, 2). At this point, our endocrinology department became involved in the sequence of events. The patient was noticed to have enlarged hands and feet, coarse facies, prognathism, and deepened voice. These features suggested acromegaly. The initial examiner of the patient failed to

notice these features until the patient developed sudden loss of vision and the CT was obtained. Though anticoagulant-aggregant therapy and percutaneous intervention were perhaps inevitable in terms of risk-benefit ratio, perhaps if the acromegalic features had been noticed before unstable angina pectoris and coronary artery thrombosis ensued, the patient would not have been prone to the risky cascade of events that followed.

The patient's blood pressure and clinical status remained stable. Hormonal evaluation done on an emergent basis showed low levels of free T3 (FT3), thyroid stimulating hormone (TSH), luteinizing hormone (LH), total testosterone, and cortisol. Tests for partial adrenocorticotropic hormone (ACTH) deficiency were inconclusive. Random growth hormone (GH) was within the normal range. There was not enough time for an oral glucose tolerance test (OGTT) to determine GH response. Therefore, steroid coverage during operation for a suspected ACTH deficiency was proposed. Transnasal sphenoidal adenomectomy was performed. The early postoperative sella MRI showed subtotal resection of the tumour, residual tumour in the upper left part invading the cavernous sinuses, and postoperative changes. Forty-eight hours after steroid coverage, ACTH and cortisol levels were reevaluated. The hypothalamopituitary adrenal axis was sound so steroid replacement therapy was not resumed. The pathologic specimen was almost totally necrotic. Intact tumour cells constituted 10% of the specimen. Ki-67 was positive in 2% of the tumour cells. Immunohistochemical staining was positive only for somatotropin. One month later, the patient was reevaluated for hormonal status. Free T4 was low. LH and total testosterone remained low during follow-up. GH measurement during 100 g OGTT was not done since random GH was below 0.4 ng/mL and insulin like growth factor-I (IGF) was normal. Preoperative and postoperative test results are shown in Table 1. He was diagnosed with postadenomectomy partial hypopituitarism (central hypothyroidism and hypogonadotropic hypogonadism). Testosterone and levothyroxine replacement therapy was initiated.

Discussion

PA has no predilection for any gender. It can occur at any age with a peak in the fifth decade. It is defined in association with a variety of medical disorders, medications, and procedures, with no common pathologic explanation. Arteriosclerosis and tumour blood vessel fragility of the pituitary vasculature and ischemia of the pituitary gland are speculated to be involved in the apoplectic process (20).

An acute increase in blood flow to the gland, as occurs in hypertensive attacks, can lead to PA. Acute changes in intracranial blood pressure may be associated with angiography and other imaging modalities using contrast material, anesthesia, lumbar punction, minor head trauma, and positive pressure ventilation as well as with physiologic actions including coughing and sneezing. Another mechanism proposed is reduced blood supply due to degenerated vasculature as in DM. Systemic hypotension can also decrease the blood flow to the gland [20]. A third mechanism is concomitant administration of antiaggregant and anticoagulant drugs (8-20).

The contrast media reportedly associated with PA are ioxaglate (HexabrixR), iohexol (OmnipaqueR), and gadolinium (15). OmnipaqueR is a nonionic iodinated contrast agent and HexabrixR is an ionic dimer. Both belong to the low-osmolality group. Their osmolality still exceeds that of the blood (280 mosm/kg) (21, 22). Gadolinium solutions comprise another contrast media group with an osmolality two to seven times that of plasma [23]. Although the exact mechanism by which they induce PA is unknown, increased endothelial permeability and intravascular pressure are implicated. One hundred milliliters of HexabrixR 320 was used for CAG. One hundred milliliters of HexabrixR contains 39.3 g meglumine salt and 19.6 g sodium salt of ioxaglic acid. The agent has an osmolality of 580 mosm/kg.

Despite these precipitating factors, most patients lack any identifiable trigger.

Our patient had neither hypertension nor a documented hypotensive attack. He was not at an age that was closely related to high

Table1. Laboratory tests before and after hypophyseal adenomectomy

	Preoperative	Immediate postoperative evaluation	1 month after operation
ACTH (pg/mL)	Not available	28.40	16.40
Cortisol (µg/dL)	14.70	28.75	16.60
GH (ng/mL)	1.71		0.12
FT4 (ng/dL)	1.14		0.75
FT3 (pg/mL)	1.43		1.75
TSH (IU/mL)	0.05		
PRL (ng/mL)	3.64		9.08
LH (mIU/mL)	0.48		1.08
FSH (mIU/mL)	0.68		2.27
Total testosterone (ng/dL)	<20.00		101
Glucose (mg/dL)	99	89	73
Na^+ (meq/L)	140	135	139
K^+ (meq/L)	4.0	4.1	4.0
IGF-I* (mg/mL)			73

* upper normal limit of IGF-I is 210 ng/mL. Abbreviaitons: ACTH, adrenocorticotropic hormone; GH, growth hormone; FT4, free T4; FT3, free T3; TSH, thyroid stimulating hormone; PRL, prolactin; LH, luteinizing hormone; FSH, follicle stimulating hormone; Na+, sodium; K+ , potassium; IGF-I, insulin-like growth factor-I.

incidence of arteriosclerosis. CAG showed no signs of atherosclerosis but did show signs of thrombosis. Acetylsalicylic acid, enoxaparin, and clopidogrel were used. Our patient's symptoms occurred two days after CAG. Therefore, we believe that concomitant usage of antiaggregant and anticoagulant agents in the presence of macroadenoma and contrast medium resulted in PA.

PA presents as hyperdensity in CT images in the acute phase and as decreased signal intensity on T1 and T2 weighted planes in MRI in the subacute phase. MRI is superior in showing haemorrhage within the hypophysis. It is estimated that the diagnosis can be missed in approximately 50% of the cases if CT is used as the diagnostic modality (8,15,24).

Pituitary masses can become endocrinologically silent after PA as was the case in our patient [8, 19]. GH response to both oral glucose and IGF-I following surgery was normal. However, preoperative random GH was not very high and unfortunately neither the IGF-I level nor the GH response to OGTT could be elucidated due to the emergent operation. Since our patient had signs and symptoms that can be ascribed to acromegaly, the GH positive adenoma was less likely to be a nonsecreting one.

Antiaggregant and anticoagulant drugs and contrast medium can interact to give rise to haemorrhagic complications, including PA, in an undiagnosed pituitary tumour. Despite the fact that the annual incidence of pituitary neoplasms is less than 1%, severe unremitting headache and visual disturbances should alert the physician to this possibility.

References

1. Melmed S, Kleinberg D. Anterior pituitary. Williams textbook of endocrinology. 10th ed. (Ed: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS) Saunders Company Elsevier Science, 2003; 177-280.
2. Colli ML, Migowski W Jr, Czepielewski MA, Ferreira N, Gross JL. Pituitary abscess simulating apoplexy. Arq Bras Endocrinol Metabol 2006; 50: 1122-6.
3. Salinas-Lara C, Rembao-Bojorquez D, de la Cruz E, Marquez C, Portocarrero L, Tena-Suck ML. Pituitary apoplexy due to mucormycosis infection in a patient with an ACTH producing pulmonary tumor. J Clin Neurosci 2007 Apr 24; [Epub ahead of print].
4. Maiza JC, Bennet A, Thorn-Kany M, Lagarrigue J, Caron P. Pituitary apoplexy and idiopathic thrombocytopenic purpura: a new case and review of the literature. Pituitary 2004; 7: 189-92.
5. Davis A, Goel S, Picolos M, Wang M, Lavis V. Pituitary apoplexy after leuprolide. Pituitary 2006; 9: 263-5.
6. Blaut K, Wisniewski P, Syrenicz A, Sworczak K. Apoplexy of clinically silent pituitary adenoma during prostate cancer treatment with LHRH analog. Neuro Endocrinol Lett 2006; 27: 569-72.
7. Deogaonkar M, De R, Sil K, Das S. Pituitary tuberculosis presenting as pituitary apoplexy. Int J Infect Dis 2006; 10: 338-9.
8. Audia S, Popitean L, Camus A, Pfitzenmeyer P, Petit JM. An unusual complication of anticoagulation therapy in an elderly patient: Pituitary apoplexy with remission of acromegaly. J Am Geriatr Soc 2006; 54: 1798-1800.
9. Imo O, Castells I, Recasens A, Yetano V. Pituitary apoplexy following treatment for acute coronary syndrome. Med Clin (Barc) 2006; 127: 477.
10. Nagarajan DV, Bird D, Papouchado M. Pituitary apoplexy following anticoagulation for acute coronary syndrome. Heart 2003; 89: 10.
11. Korotinsky S, Smadja P, Goland S, Somin M, Attali M, Zhornicky T, Malnick SD. Pituitary apoplexy after administration of heparin and isosorbide dinitrate. South Med J 2002; 95: 469-70.
12. Fuchs S, Beeri R, Hasin Y, Weiss AT, Gotsman MS, Zahger D. Pituitary apoplexy as a first manifestation of pituitary adenomas following intensive thrombolytic and antithrombotic therapy. Am J Cardiol 1998; 81: 110-1.
13. Oo MM, Krishna AY, Bonavita GJ, Rutecki GW. Heparin therapy for myocardial infarction: an unusual trigger for pituitary apoplexy. Am J Med Sci 1997; 314: 351-3.
14. Willamowicz AS, Houlden RL. Pituitary apoplexy after anticoagulation for unstable angina. Endocr Pract 1999; 5: 273-6.
15. Skljarevski V, Khoshyomn S, Fries TJ. Pituitary apoplexy in the setting of coronary angiography. J Neuroimaging 2003; 13: 276-9.
16. Slaughter TF, Mark JB, Reves JG. Pituitary apoplexy and the conflicting perioperative goals of anticoagulation and hemostasis. Anesth Analg 1993; 76: 470-1.
17. Cooper DM, Bazaral MG, Furlan AJ, Sevilla E, Ghattas MA, Sheeler LR, Little JR, Hahn JF, Sheldon WC, Loop FD. Pituitary apoplexy: a complication of cardiac surgery. Ann Thorac Surg 1986; 41: 547-50.
18. Slavin ML, Budabin M. Pituitary apoplexy associated with cardiac surgery. Am J Ophthalmol 1984; 98: 291-6.
19. Thapar K, Kovacs K, Horvath E. Morphology of the pituitary in health and disease. Principles and practice of endocrinology and metabolism. 3rd ed. (Ed: Becker) Lippincott Williams and Wilkins, 2001;103-29.
20. Biousse V, Newman NJ, Oyesiku NM. Precipitating factors in pituitary apoplexy. J Neurol Neurosurg Psychiatry 2001; 71; 542-5.
21. The comprehensive source for physicians, drug and illness information: HexabrixR. Available from http://www.rxmed.com/b.main/b2.pharmaceutical/b2.prescribe.html. Accessed 20 May 2007.
22. The comprehensive source for physicians, drug and illness information: OmnipaqueR. Available from http://www.rxmed.com/b.main/b2.pharmaceutical/b2.prescribe.html. Accessed 20 May 2007.
23. Nyman U, Elmståhl B, Leander P, Nilsson M, Golman K, Almén T. Commentary on the viewpoint of Spinosa et al. Radiology 2002; 223: 326-7.
24. Elsasser Imboden PN, De Tribolet N, Lobrinus A, Gaillard RC, Portmann L, Pralong F, Gomez F. Apoplexy in pituitary macroadenoma: eight patients presenting in 12 months. Medicine (Baltimore) 2005; 84: 188-196.