Pituitary apoplexy following combination chemotherapy - a case report

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Abstract
We report a case of apoplexy of an undiagnosed pituitary adenoma in a patient treated with intravenous combination chemotherapy for squamous cell carcinoma of the penis. Apoplexy occurred while he was receiving a second cycle of vinblastine, cisplatin and methotrexate and he presented with classic neuro-ophthalmological signs. He made a full recovery following conservative management with steroids alone.

Introduction
Pituitary apoplexy is a rare but potentially fatal condition, with a spectrum of presentations ranging from an entirely silent picture (pituitary infarction) to marked neuro-ophthalmological symptoms and signs (Rolih & Ober 1993). Although recognised within the normal pituitary, apoplexy is more common in pituitary adenomas. Furthermore, apoplexy may be the initial presenting feature of a previously undiagnosed pituitary adenoma, with 65% of cases of apoplexy presenting in this manner (Wakai et al. 1981). Although rare, apoplexy must be diagnosed and treated urgently if significant morbidity and mortality are to be avoided. As such, the recognition of potential precipitants is important and reported causes include coronary artery bypass surgery (CABG) (Davies & Scanlon 1998), post-partum haemorrhage (Sheehan & Murdoch 1938), dopamine agonist therapy (Shirataki et al. 1988) and pituitary stimulation testing (Okuda et al. 1994).

We describe the hitherto unreported event of apoplexy of an undiagnosed pituitary tumour in a patient receiving intravenous chemotherapy for squamous cell carcinoma of the penis.

Case report
A 70-year-old man was referred for a surgical opinion after he noticed a nodular, ulcerated penile lesion and scrotal oedema. Squamous cell carcinoma of the penis with inguinal lymph node involvement was diagnosed and he elected to receive chemotherapy and radiotherapy. Initially he was treated with intravenous cisplatin (150 mg over 6 h), methotrexate (60 mg bolus) and vinblastine (8 mg bolus). However, during his second cycle, he developed a sudden, severe headache with associated nausea and vomiting. Later he was discharged, although he was subsequently readmitted to the Medical Unit complaining of persistent headache and diplopia. Examination revealed a partial, left third nerve palsy, although there were no visual field defects to confrontation. Plasma electrolytes and full blood count were normal. An MRI scan demonstrated a pituitary adenoma with suprasellar and left superior cavernous sinus extension (Fig. 1) within
which were areas of high signal intensity suggestive of haemorrhage. He made good progress on conservative management with steroids alone and the third nerve palsy gradually resolved. Subsequent endocrine assessment confirmed partial anterior hypopituitarism, with a sub-normal cortisol and growth hormone response to glucagon stimulation, and hypogonadotrophic hypogonadism, but normal thyroid function and prolactin concentrations. He was discharged on hydrocortisone (20 mg daily), although was not treated with testosterone in view of penile carcinoma.

**Discussion**

This report illustrates a classic presentation of pituitary apoplexy with neuro-ophthalmological symptoms and signs. The sequence of events strongly favours a causal effect of the chemotherapy though a casual relationship cannot wholly be excluded. Apoplexy developed within a previously undiagnosed pituitary adenoma, which was likely to be non-functional from endocrine investigations. Although surgery was considered, the case also demonstrates effective conservative management of apoplexy, which may be appropriate in certain patients where neurology is stable and sight is not threatened (Rohli & Ober 1993).

The pathogenesis of apoplexy is ill understood, although alterations in coagulation and blood flow may compromise the already tenuous pituitary vasculature. As such, anti-coagulation with non-pulsatile blood flow is implicated in apoplexy following CABG (Davies & Scanlon 1998), and hypotension may underlie the phenomenon in post-partum haemorrhage (Sheehan & Murdoch 1938). Furthermore, pituitary stimulation during dynamic function testing may impose further demands on the tenuous pituitary tumour blood supply producing ischaemia with infarction (Okuda et al. 1994). Such a mechanism has also been implicated in apoplexy following treatment with gonadotrophin-releasing hormone agonists (Masson et al. 1993, Morsi et al. 1996) and after thyrotrophin-releasing hormone administration where a direct vasoconstrictive effect may also be involved (Drury et al. 1982). Although chemotherapy may cause necrosis within tumour tissue, there are to our knowledge no reports of pituitary apoplexy following conventional chemotherapy.

All the chemotherapeutic agents given to this patient are individually capable of producing necrosis within both normal and tumour tissue, but necrosis is more common following combination therapy. This may be due to the combination of cytotoxicity and vascular occlusion, which is a feature of both vinblastine and cisplatin (Vogelzang et al. 1981) and the effect may be further exacerbated by cisplatin (Vogelzang et al. 1981). Furthermore, cisplatin may cause cerebral infarction (Icli et al. 1993) and myocardial infarction (Berliner et al. 1990, Icli et al. 1993) as a consequence of a vasculopathy. However, methotrexate may also produce ischaemic necrosis of certain tissues and organs, being implicated in pancreatic necrosis (Kolk et al. 1995), skin necrosis (Reynolds et al. 1989) and leukoencephalopathy with brain stem infarction when used with cisplatin (Watterson et al. 1993). In our patient, the sudden development of apoplexy while receiving chemotherapy would favour an acute vascular cause.

The mechanism underlying the vasculopathy induced by combined chemotherapy can be an early or delayed event (>63 days) (Vogelzang et al. 1981). Delayed events such as Raynaud’s phenomenon appear to be related to the induction of a hypomagnesaemia by induced renal losses, with nadir concentrations occurring after a median period of 63 days following cisplatin-based chemotherapy. However, early vascular events appear to be independent of magnesium concentrations and are due to direct endothelial toxicity (Vogelzang et al. 1981). Endothelial dysfunction may produce vascular occlusion by predisposing to platelet adhesion, aggregation and thrombosis (Cooke & Tsao 1994). This mechanism may underlie early myocardial and cerebral infarction following chemotherapy (Berliner et al. 1990, Icli et al. 1993). In our patient, this mechanism seems to provide the more likely explanation for pituitary apoplexy, although other factors, such as the promotion of a pro-coagulant state following chemotherapy may also contribute (Kuzel et al. 1990).

Although pituitary apoplexy appears to be a rare event, the incidence of pituitary adenomas is reported as between 10 and 30% (McCormick & Hami 1971, Burrow et al. 1981) and as such the true incidence of pituitary apoplexy/infarction may be under-diagnosed. With the improving therapeutic outcomes and expanding non-oncological indications of chemotherapeutic agents such as methotrexate, this report raises awareness of the potential of chemotherapy to precipitate apoplexy.

**References**


McCormick WF & Hani NS 1971 Absence of chromophobe adenomas from a large series of pituitary tumours. *Archives of Pathology and Laboratory Medicine* 92 231-238.


