Introduction

Management of Nelson’s syndrome has been a persistent challenge to clinicians since its initial description in 1958. Originally defined as the combination of a pituitary macroadenoma and elevated plasma ACTH levels in a patient with Cushing’s syndrome who had undergone bilateral adrenalectomy, it remains a serious, potentially life-threatening disease. Morbidity results from local invasion of surrounding structures, including the optic chiasm and cavernous sinus, and from excessive secretion of ACTH resulting in abnormal cutaneous pigmentation. Current treatment options include surgery, conventional external beam radiotherapy, focused irradiation (e.g. gamma knife radiosurgery or X-knife) and certain medical therapies, but morbidity and mortality remains high. We report a case of a patient with aggressive Nelson’s syndrome treated with temozolomide, a novel alkylating prodrug effective in the treatment of malignant melanoma and primary brain tumours. We use the case to illustrate the challenges associated with the management of Nelson’s syndrome and to highlight the requirement for a multidisciplinary approach in a centre of excellence. Recent cases have demonstrated successful use of temozolomide in the treatment of aggressive prolactinomas (1, 2) and pituitary carcinoma (3, 4), and led us to its use in a patient with an aggressive, life-threatening corticotroph tumour.

Case report

A 64-year-old woman originally presented in 2001 with Cushing’s syndrome. There was a loss of circadian rhythm with a sleeping midnight cortisol (954 nmol/l) and failure of suppression of serum cortisol following 0.5 mg q6 dexamethasone hourly for 24 h (653 nmol/l). Plasma ACTH was 24 pmol/l (reference range 11 pmol/l) and magnetic resonance imaging (MRI) revealed an intrasellar mass lesion suggestive of a macroadenoma. Trans-sphenoidal surgery was performed with macroscopic clearance of the pituitary fossa but was not curative; post-operative (0900 h) cortisol was 341 nmol/l. Histology showed a pituitary tumour with marked cellular and nuclear pleomorphism with conclusive ACTH immunopositivity and a high Ki-67 nuclear labelling index. Immunostainings were confirmed subsequently to be negative for O-6-methylguanine-DNA methyltransferase (MGMT), a predictor of responsiveness to temozolomide therapy (5). Following standard 25 fraction external beam pituitary radiotherapy (45 cGy), repeat MRI scan demonstrated good tumour clearance, with a small amount of residual tissue in the floor of the fossa. Despite 800 mg ketoconazole daily in divided doses, symptomatic and biochemical cortisol excess persisted and bilateral adrenalectomy was performed 5 months after her initial presentation. ACTH levels remained within the reference range until 36 months post-adrenalectomy, when she developed skin pigmentation...
in association with a plasma ACTH concentration (108 pmol/l), with no reduction in ACTH demonstrable post-hydrocortisone. In 2005, ACTH levels rose over 9 months to 565 pmol/l in association with left-sided headache and worsening skin pigmentation. MRI revealed extensive tumour in the clivus, involving the skull base and descending down to C1, with involvement of the occipital condyles and lateral masses of C1 (Fig. 1a). All areas of recurrence were within the original external beam radiotherapy field. A second trans-sphenoidal operation was performed with debulking of the tumour and removal of the infiltrated bone. Initial post-operative ACTH levels reached a nadir of 154 pmol/l but reverted to preoperative values within 2 weeks. Minimal ACTH suppression was noted with hydrocortisone (100 mg i.m. injection), dexamethasone (0.25 mg orally) and octreotide (100 mcg s.c. injection), but a 40% reduction in ACTH levels was demonstrated 2 h after a 2.5 mg bromocriptine test dose and so the patient commenced 0.5 mg cabergoline daily which she continues.

Eight weeks post-operatively, in 2005, the remaining tumour within the clivus and left occipital condyle was treated with gamma knife radiosurgery (20 Gy). The left-sided headache improved in association with a fall in plasma ACTH levels from 647 to 281 pmol/l. Plasma ACTH levels and follow-up MRI remained stable for 18 months, but she developed unsteadiness, left facial pain and left-sided hearing loss, preceded by several months of chronic middle ear effusion. Repeated imaging showed widely invasive tumour extending throughout the skull base and involving the occiput (Fig. 1b). A second dose (20 Gy) of gamma knife radiosurgery was administered to new areas of tumour not already treated: a lateral extension and inferior involvement of occipital condyle.

Left mastoidectomy was performed due to persistent otitis media with effusion with initial improvement in symptoms. However, tumour burden continued to progress with the invasion of the left ear canal forming a polypoid mass in the auditory meatus with persistent discharge. MRI showed increased lateral extension into extracranial soft tissues including the left pterygoid and the right petrous bone. There was extensive involvement of the right cavernous sinus, an occipital soft tissue mass and replacement of normal occipital bone (Fig. 1c). Plasma ACTH rose to 2472 pmol/l.

Figure 1 Series of MRI scans performed, demonstrating the initial progression of the aggressive corticotroph tumour and subsequent reduction in tumour bulk following treatment with temozolomide. (a) MRI brain (2005); extensive tumour in the clivus, involving the skull base and descending down to C1, with involvement of the occipital condyles and lateral masses of C1. (b) MRI brain (2006); progression of the widely invasive tumour extending throughout the skull base and involving the occiput; this was treated with a second course of gamma knife radiosurgery. (c) MRI brain (2007); extensive tumour evident within the occiput, replacing normal occipital bone. Temozolomide was subsequently commenced. (d) MRI brain (2008); reassessment post-fourth cycle of temozolomide, with marked shrinkage of tumour evident in the occipital region.
On account of its recent demonstration of efficacy in the treatment of aggressive prolactinomas (1, 2) and pituitary carcinoma (3, 4), temozolomide therapy was commenced in November 2007 at a dose of 320 mg (200 mg/m² per day) orally for 5 days of a 28-day cycle. Symptomatic response was noted following the first month of treatment, with the resolution of the persistent ear discharge and significant improvement in the severity of headaches. Persistent nausea was experienced 5 days after treatment but without vomiting. Repeated MRI imaging, post-fourth cycle, has confirmed marked shrinkage of tumour, most evident in the occipital area (Fig. 1d). Plasma ACTH levels have fallen from 2472 to 389 pmol/l (Fig. 2). Treatment has been complicated by leakage of cerebrospinal fluid from both ears and nostrils resulting from tumour shrinkage; this abated following an episode of bacterial meningitis. Routine haematology and biochemistry parameters remain normal. She has now completed six cycles of temozolomide therapy with ongoing control of symptoms, tumour burden and plasma ACTH levels.

Discussion

Nelson originally described a case of pituitary macroadenoma with elevated plasma ACTH levels occurring in a patient as a possible late complication of bilateral adrenalectomy (6). It is reported to occur in 8–38% of patients with Cushing’s disease post-bilateral adrenalectomy (7); the variability in rates probably reflects the variation in diagnostic criteria used. It remains controversial whether the development of Nelson’s syndrome is purely due to loss of negative feedback of cortisol at the pituitary or whether it reflects a subset of pituitary tumours pre-programmed to behave aggressively. Neither the presence of mitoses nor a high percentage of Ki-67 immunopositivity in the nuclei have so far been found to be predictive of corticotroph tumour progression (8).

Clinical features of Nelson’s syndrome range from increased cutaneous pigmentation secondary to excessive ACTH production to local mass effects including visual disturbance and cranial nerve palsies. Our patient demonstrates the destructive nature of these aggressive corticotroph adenomas with extensive involvement of the clivus and occiput, extending to the auditory canal. The invasive nature of these tumours often demands an aggressive approach to management with the intention to reduce tumour bulk and reduce ACTH secretion. Current treatment options include surgery, radiation therapy and medical management. The success of pituitary surgery is dependent on the location of the tumour in relation to surrounding anatomy; the aim of surgery is total hypophysectomy with an accepted high risk of hypopituitarism and diabetes insipidus. Success rates vary from 10 to 70% (9, 10) in some series although there is variability in the criteria used and duration of follow-up. External beam radiotherapy has long been demonstrated to be an effective tool, both in reducing ACTH production in established Nelson’s syndrome and also in its prevention (11). Tumours may also show evidence of regression although persistent growth has been documented (12). There is an increase in hypopituitarism with the use of external beam radiotherapy. Gamma knife - radiosurgery has also proven to be beneficial, with reduction in tumour size noted in 12 out of 22 patients with a further 8 out of 22 patients demonstrating no tumour growth in a recent series (13). Previous external beam radiotherapy does not preclude subsequent gamma knife radiosurgery although the cumulative dose of radiation to the optic chiasm must be closely observed. Delayed hypopituitarism and cranial nerve palsies are reported complications of gamma knife radiosurgery.

Medical therapies for Nelson’s syndrome are generally ineffective with minimal effect on tumour size and variable effects on ACTH production. Valproate shows variable and often minimal response rates (14, 15) and despite initial reports, use of even high doses of rosiglitazone has failed to produce a significant clinical and biochemical response (16). Dopamine agonists (e.g. cabergoline) have been used with variable success (15, 16). There is a theoretical risk of cardiac valvular fibrodysplasia with cabergoline, although the doses used in the treatment of Nelson’s syndrome are one-sixth of the stated at risk dose (17). Glucocorticoids such as hydrocortisone and dexamethasone may also be used in patients with maintained negative feedback on ACTH production.

While there are limited data assessing the efficacy of traditional somatostatin analogues, such as octreotide in Nelson’s syndrome, they are generally perceived to be ineffective due to their high affinity for the sst2 receptor.

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rather than the sst5 receptor, which are predominant in corticotroph adenomas (18, 19). The multireceptor ligand somatostatin analogue pasireotide (som230) binds with high affinity to the ss5 receptor, and in vitro studies have demonstrated reductions in ACTH production and variable effects on cell proliferation (19, 20) clinical trial data are awaited.

Temozolomide is a novel alkylating prodrug that depletes MGMT, a DNA repair enzyme, which methylates DNA and exerts an antineoplastic effect. It is administered orally at a dose of 150–200 mg/m² for 5 days per 28-day cycle and easily crosses the blood–brain barrier, thereby proving a useful tool in the treatment of neurological tumours, such as gliomas and metastases from malignant melanoma. Its use in aggressive pituitary tumours has been documented with prolactinomas and pituitary carcinoma (1–4). Its use in Nelson’s syndrome is so far limited, with one preliminary report in a patient with MEN1 (21).

There appears to be some variability in responsiveness of tumours to temozolomide: this has been demonstrated in gliomas but there is speculation that similar mechanisms are relevant for other tumour types. Tumours possessing a methylated MGMT gene promoter appear to be more responsive (22); this is associated with epigenetic inactivation of the gene and loss of the MGMT protein that is important for repair of DNA damage, including damage induced by alkylating agents such as temozolomide (23, 24). Significantly longer survival times have been documented in patients with a hypermethylated MGMT gene promoter, compared with unmethylated MGMT gene promoters (22, 25). A recent report postulated that response to temozolomide may be predicted by the level of MGMT immunostaining within the tumours; low levels result in improved response while higher levels are associated with resistance (5). Our case supports this hypothesis with confirmed negative immunostaining for MGMT in our patient and a good clinical response to temozolomide (Fig. 3).

Temozolomide is generally well tolerated; commonly reported side effects include nausea, vomiting and fatigue. Myelosuppression occurs in a minority of patients and there is a theoretical concern, as with other alkylating agents, of the development of myelodysplasia and secondary haematological malignancies (1).

In summary, we present a case demonstrating the aggressive and destructive nature of Nelson’s syndrome that proved refractory to standard multimodality treatment including surgical resection, gamma knife radiosurgery and high-dose dopamine agonist therapy. Although the duration of response remains unknown, we wish to alert clinicians to the potential beneficial effect of temozolomide in this clinical situation, and to highlight the requirement for a multidisciplinary approach to the management of aggressive corticotroph tumours.

**Declaration of interest**

All authors have nothing to declare.

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**References**


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