Widely metastatic atypical pituitary adenoma with mTOR pathway STK11(F298L) mutation treated with everolimus therapy

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Practice points

- No therapy options exist for pituitary adenomas refractory to surgery and radiation.
- We present an ACTH-secreting pituitary carcinoma with an STK11(F298L) mutation.
- Everolimus monotherapy controlled and improved function for >6 months.
- Next-generation sequencing may detect actionable mutations for rare or advanced tumors.
- Early and personalized molecularly targeted therapy may improve outcomes.

Pituitary adenomas are the commonest intracranial tumor, but metastases are rare (0.2% yearly incidence) and portend poor prognosis. CAPECITABINE and TEMOZOLOMIDE improved outcomes for neuroendocrine tumors. However, no chemotherapy is approved for refractory pituitary carcinomas. Next-generation sequencing revealed an actionable mTOR pathway *STK11* mutation in a woman with adrenocorticotrophic hormone-secreting pituitary carcinoma refractory to six resections, radiation and CAPECITABINE and TEMOZOLOMIDE. Given efficacy in preclinical pancreatic cancer models with *STK11* mutations, she received radiation and everolimus leading to clinical improvement and stability on MRI and PET for >6 months. She ultimately expired from widely metastatic disease. Next-generation sequencing can identify actionable mutations in rare or treatment refractory tumors. Earlier targeted therapy may improve outcomes.

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Background

Pituitary adenomas are the most common intracranial tumor, present in $\leq 20\%$ of imaging or autopsy series [1]. While most are benign, atypical adenomas or carcinomas behave aggressively. Pituitary carcinomas, defined by systemic or CNS metastases, have a yearly incidence of 0.2%. Prognosis is poor with median survival of <4 years but varies by subtype, corticotroph secreting tumors and systemic metastases with survivals of <1 year [1–3].

Treatment of atypical or metastatic pituitary adenoma remains a challenge. Surgery followed by radiation is standard. For prolactinomas, only cabergoline is indicated for treatment of residual

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disease. Corticotroph secreting tumors causing Cushing's disease can be treated with steroid synthesis inhibitors. CAPecitabine and TEMozolomide (CAPTEM) have been shown to improve control of aggressive pituitary adenomas and carcinomas [2–8]. For metastatic pancreatic neuroendocrine tumors, CAPTEM resulted in median progression-free survival (PFS) of 14 months. Overall response and clinical benefit rates were 61 and 83.2% [9]. The RADIANT4 trial of advanced, progressive, differentiated, nonfunctional, GI tract or lung neuroendocrine tumors revealed significantly increased PFS from everolimus versus placebo (11 vs 3.9 months) [10]. No approved or proven therapies exist for atypical or metastatic adenomas refractory to CAPTEM [11]. We present a metastatic adrenocorticotrophic hormone (ACTH)-secreting atypical pituitary adenoma with an *STK11* (serine threonine protein-kinase 11) mutation detected by next-generation sequencing (NGS). Everolimus monotherapy stabilized disease and improved function for >6 months.

Case presentation

In 2006, a 46-year-old woman presented with diabetes mellitus, central obesity and hypothyroidism. Endocrine testing and MRI revealed an ACTH-secreting pituitary adenoma. By 2007, she was diagnosed with Cushing's disease at an outside institution. She presented to our institution initially in January 2008 with progressive hypertension. MRI at that time showed a 6.0 × 7.0 mm enhancing sellar mass with asymptomatic optic apparatus compression. Labs were consistent with a diagnosis of Cushing's disease with cortisol 48.6 µg/dl (normal range [8 am] 5–25 µg/dl); ACTH 195 pg/ml (normal range 6–58 pg/ml); and positive dexamethasone suppression test (cortisol 41.4 µg/dl at 4 pm [normal range: 2–12 µg/dl] and 49.5 at 8 am the following morning). She then underwent trans-sphenoidal resection. The pathology showed a 1 × 1 × 0.6 cm pituitary adenoma with focal ACTH, but no prolactin (PRL) or growth hormone (GH). Her diabetes and hypertension improved. She clinically stabilized for 3 years. Serial computed tomography (CT) and MRI are shown in [Figure 1](#).

In March 2011, she developed striae and acne with recurrent hypertension and diabetes mellitus. A second trans-sphenoidal resection showed a 0.7 × 0.5 × 0.2 cm adenoma, diffusely ACTH and synaptophysin positive, but PRL and GH

negative ([Figure 2A & B](#)). Postsurgical cortisol (14 µg/dl) and ACTH (47 pg/ml) suggested residual disease. Postsurgically, she required thyroid supplementation and intermittent desmopressin (ddAVP) for diabetes insipidus. Rising cortisol (118 µg/dl), ACTH (591 pg/ml) and urine free cortisol (3000 µg, normal range <45 µg/day) suggested recurrent Cushing's disease. In July 2011, she developed refractory hypokalemia requiring bilateral adrenalectomy, pathology revealed cortical hyperplasia. Postoperative cortisol (5.4 µg/dl) normalized; however, ACTH (645 pg/ml) remained elevated. Initially, she was started on prednisone 10 mg daily and by August she was changed to hydrocortisone 20 mg b.i.d., tapered to 10 mg b.i.d. by September 2011. In late September 2011, she developed significant hyperpigmentation and rising ACTH, while MRI revealed recurrent tumor.

By January 2012, she developed headache, left eye vision loss and diplopia, epistaxis, hyperpigmentation, weight gain and ACTH elevation (45,754 pg/ml). MRI showed growth with left optic chiasm impingement. She underwent a third trans-sphenoidal resection, pathology showed Ki-67 index of 19%, consistent with WHO atypical pituitary adenoma classification. She underwent involved field radiation to 5040 cGy ending April 2012. By August 2012, improved ACTH (3257 pg/ml) and stable MRI suggested controlled residual tumor.

By May 2013, she developed left jaw pain progressing to hemifacial pain. MRI showed growth (2.1 × 2.1 × 2.2 cm) with cavernous sinus invasion and left preorbital optic nerve and lateral optic chiasm impingement. Visual fields were normal, but acuity decreased in her left eye. ACTH was elevated (10,788 pg/ml). An octreotide scan was moderately positive with uptake in the sella turcica. She received octreotide LAR 30 mg monthly, but headaches and cranial nerve palsies worsened within 1 month. In July 2013, MRI again showed growth so she underwent a fourth trans-sphenoidal resection, pathology revealed rare mitoses and diffuse cytoplasmic granular ACTH immunoreactivity, but no follicle-stimulating hormone (FSH), growth hormone (GH), luteinizing hormone (LH), prolactin (PRL), or thyroid stimulating hormone (TSH). Octreotide LAR was maximized to 60 mg/month with continued progression on MRI and worsening imbalance.

By November 2013, she developed worsening left facial numbness, eye pain, oculomotor

Figure 1. Imaging findings. Head CT scan with contrast prior to trans-sphenoidal resection in 2008 shows a circumscribed, 6 × 7 mm enhancing lesion in the sella (A). Brain MRI with gadolinium in March 2011 shows recurrence limited to the sella and suprasellar space (B). Gadolinium enhanced brain MRI in January 2012 reveals recurrent disease involving the left sphenoid sinus and impinging on the optic chiasm (C). Brain MRI with gadolinium in November 2013 shows tumor progression further involving the optic apparatus and encasing the carotid artery (D). Partial response to CApecitabine and TEMozolomide after re-resection was seen in February 2014 (E). By November 2014, while on treatment hold, she had tumor progression with direct brain invasion (F). Stable to slightly improved disease was seen on brain MRI with gadolinium in March 2015 after starting everolimus (G). Clear disease progression was seen on the brain MRI with gadolinium in July 2015 (H).

and trigeminal palsies, and rising ACTH (18,167 pg/ml). Tumor encased the left internal carotid artery with optic chiasm compression. She underwent a fifth trans-sphenoidal resection. Pathology revealed a highly cellular neoplasm growing in sheets and infiltrating dense connective tissue, with mild-to-moderate pleomorphism, mitoses and Ki-67 elevation to 15% (Figure 2C–E). Weak-to-moderate nuclear p53 was expressed by rare cells.

She started CAPTEM (CApecitabine 1500 mg b.i.d. days 1–14; TEMozolomide 200 mg b.i.d. days 10–14) in December 2013. Her course was complicated by severe thrombocytopenia due to unintended overdose. MRI showed a mixed response by February 2014. CAPTEM restarted in March at 50% temozolomide dose then increased to 75% by April. She developed progressive left ophthalmoplegia. By May, she developed epigastric pain radiating to her back. Body MRI and PET-CT revealed spine and pelvic bony metastases. Bone scan demonstrated uptake in the ribs and pelvis. MRI showed sellar and cavernous sinus progression

with new enhancement along the left planum sphenoidale.

By August 2014, her left ptosis and back pain worsened followed by severe radicular arm pain. She remained off treatment for toxicity until November. She presented with severe left eye proptosis, blindness and ACTH elevation (>125,000 pg/ml). She came to our practice for second opinion. She underwent a sixth trans-sphenoidal resection, pathology showed an atypical pituitary adenoma with increased mitoses, Ki-67 index to 40–50% and weak ACTH immunoreactivity (Figure 2F–H). NGS revealed an *STK11*(F298L) mutation in the mTOR pathway, plus *NOTCH1*(R1672H), *FGFR2*(P443A) and *PDGFRFB*(A713T) mutations. PET-CT in January 2015 revealed progression of her sellar and bony metastases. She underwent palliative radiation (30 Gy) to the sacrum and pelvis ending February 2015. Given preliminary efficacy in pancreatic cancer harboring *STK11* mutations, she started concurrent everolimus at 7.5 mg/day then adjuvant everolimus at 10 mg/day. Her course was complicated by

Figure 2. Pathology. (A & B) Pituitary adenoma resected in March 2011 (100×). Hematoxylin and eosin stained sections (A) show sheets of monomorphic cells. No mitotic figures or necrosis is seen. ACTH immunostain (B) shows diffuse, strong positivity. (C–E) Atypical pituitary adenoma resected in November 2013 (100×). Hematoxylin and eosin stained sections (C) show sheets of tumor cells with increased nuclear pleomorphism. Scattered mitotic figures are seen (*indicates mitotic figures). ACTH immunostain (D) shows diffuse, moderate positivity. Ki-67 immunostain (E) shows elevated proliferation, with up to 10–15% of tumor cells staining positive. (F–H) Atypical pituitary adenoma resected in November 2014 (100×). Hematoxylin and eosin stained sections (F) show sheets of tumor cells with increased nuclear pleomorphism. Scattered mitotic figures are seen (*indicates mitotic figures). ACTH immunostain (G) shows weak positivity. Ki-67 immunostain (E) shows markedly elevated proliferation, with up to 40–50% of tumor cells staining positive.

multifocal herpes zoster despite prophylactic valaciclovir 1000 mg/day and involving her

left arm and left eye, requiring enucleation and titration of valaciclovir to 2000 mg/day.

By June 2015, MRI showed generally stable sellar tumor, while PET showed stable systemic metastases (**Figure 3**). She presented with weight loss and new severe back and sternum pain. MRI revealed progressive spine metastases with T9–10 vertebral body compression. She underwent palliative IMRT (30 Gy) ending July 2015 with good transient pain control. She resumed everolimus 7.5 mg/day with addition of capecitabine 1000 mg/m² b.i.d. for 14 days every 21 days; neutropenia led to dose interruptions. By September 2015, she presented with severe low back pain and systemic progression. She died shortly after admission to hospice.

Discussion

The 2004 WHO classifies pituitary adenomas as typical, atypical and carcinomas. Atypical adenomas are characterized by Ki-67 index >3%, mitoses and extensive nuclear p53 staining [12]. This classification inconsistently predicts clinical behavior, so several revised classifications were devised [11,13]. Accurately identifying aggressive pituitary adenomas with potential to transform into pituitary carcinomas is imperative [4]. Even without transformation, adenomas can cause significant morbidity and mortality, in our case adrenal axis dysfunction and cranial neuropathies and blindness. Prognosis is linked to histology (pleomorphism, Ki-67 index,

mitoses), radiographic features and behavior (e.g., early recurrence), while invasiveness does not accurately predict aggressiveness [4].

For refractory adenomas, treatment is challenging. ACTH secreting behave most aggressively [2]. For adenomas failing surgery, radiation and/or pharmacotherapies, novel targets and effective treatments are crucial. Recent trials include mTOR, VEGF and tyrosine kinase inhibitors [4]. A prior case showed no response to everolimus and octreotide in an ACTH-secreting adenoma. mTOR pathway activation was low versus 17 other tumors, likely explaining treatment failure [14]. NGS focused on key cancer genes increases the ability to identify actionable mutations – those conferring sensitivity to targeted agents [15,16]. In a Vanderbilt series of 103 metastatic or stage III tumors, 83% had ≥1 actionable mutation, 21% receiving targeted therapy, primarily via trials. Several cases dramatically benefited from targeted treatment [17]. While there is a role for NGS in all disease stages, it may particularly benefit patients with advanced disease and limited or no approved therapies.

NGS revealed an actionable mutation in *SKT11* in the mTOR pathway in our case. The PI3K/Akt/mTOR pathway is a major promoter of cancer cell growth and proliferation. mTOR pathway mutations can confer sensitivity to mTOR inhibitors [18]. Rapamycin is an antifungal

Figure 3. Body FDG-PET from January 2015 (left) and June 2015 (right) demonstrates improvement in bony metastases after starting everolimus with focal external beam radiation to lower spine and sacrum (A). Brain FDG-PET from January 2015 (top) and March 2015 (bottom) demonstrates stable disease after starting everolimus (B).

drug with antineoplastic and immunosuppressive functions. Rapamycin analogs (e.g., everolimus) inhibit growth and proliferation of tumor cells in *STK11* mutant mouse models, suggesting this may be a potential target pathway [19,20]. Everolimus decreased cell viability for GH pituitary adenomas [21] and nonfunctioning adenomas [22]. Given NGS and preclinical data, our patient underwent everolimus monotherapy with >6 months PFS and overall survival despite years of failed surgery, radiation and hormone and antineoplastic therapy. Typical life expectancy for ACTH-secreting pituitary carcinoma with systemic metastases is <1 year. While everolimus resulted in only stable disease, outcomes may improve with earlier identification of actionable mutations, preferably while tumor is restricted to the sella and/or concurrent with radiation given the added radiation sensitization attributed to everolimus. Ultimately, our patient succumbed to her widely metastatic disease.

Conclusion

Our case highlights the utility of NGS in identifying potential treatments for resistant atypical adenomas or pituitary carcinomas. Adenomas refractory to resection, radiation and/or hormone therapy prove difficult to treat, with only one studied antineoplastic therapy, combination CAPTEM. Until pathogenesis is better elucidated, NGS can readily identify potential therapeutic targets for further investigation in these extremely rare, but fatal refractory tumors.

Author contributions

LE Donovan and AV Arnal reviewed the medical record

and existing literature and authored the manuscript. SH Wang reviewed pathology and contributed to the manuscript. Y Odia provided clinical care for the patient, conceptualized the project and critically revised the entire manuscript.

Note

This report includes off-label use of chemotherapy.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved. Retrospective review medical records, pathology and imaging did not require IRB approval. The patient provided consent for report of her data.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the family member of the patient for the inclusion of their medical and treatment history within this case report.

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