\textit{\textbf{18}}F-FDOPA PET/CT accurately identifies MEN1-associated pheochromocytoma

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Summary

Pheochromocytoma (PHEO) in multiple endocrine neoplasia type 1 (MEN1) is extremely rare. The incidence is reported as less than 2%. We report a case of a 76-year-old male with familial MEN1 who was found to have unilateral PHEO. Although the patient was normotensive and asymptomatic, routine screening imaging with CT demonstrated bilateral adrenal masses. The left adrenal mass grew from 2.5 to 3.9 cm over 4 years with attenuation values of 9 Hounsfield units (HU) pre-contrast and 15 HU post-contrast washout. Laboratory evaluation demonstrated an adrenergic biochemical phenotype. Both \textit{\textbf{18}}F-fluorodeoxyglucose (\textit{\textbf{18}}F-FDG) PET/CT and \textit{\textbf{123}}I-metaiodobenzylguanidine (\textit{\textbf{123}}I-mIBG) scintigraphy demonstrated bilateral adrenal uptake. In contrast, \textit{\textbf{18}}F-fluorodihydroxyphenylalanine (\textit{\textbf{18}}F-FDOPA) PET/CT demonstrated unilateral left adrenal uptake (28.7 standardized uptake value (SUV)) and physiologic right adrenal uptake. The patient underwent an uneventful left adrenalectomy with pathology consistent for PHEO. Post-operatively, he had biochemical normalization. A review of the literature suggests that adrenal tumors >2 cm may be at higher risk for pheochromocytoma in patients with MEN1. Despite a lack of symptoms related to catecholamine excess, enlarging adrenal nodules should be biochemically screened for PHEO. \textit{\textbf{18}}F-FDOPA PET/CT may be beneficial for localization in these patients.

Learning points:

- \textit{\textbf{18}}F-FDOPA PET/CT is a beneficial imaging modality for identifying pheochromocytoma in MEN1 patients.
- Adrenal adenomas should undergo routine biochemical workup for PHEO in MEN1 and can have serious perioperative complications if not recognized, given that MEN1 patients undergo frequent surgical interventions.
- MEN1 is implicated in the tumorigenesis of PHEO in this patient.

Background

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant syndrome with a prevalence estimated around 2–3/100 000. Clinical manifestations include anterior pituitary adenomas, primary hyperparathyroidism, and duodenal/pancreatic neuroendocrine tumors \cite{1}. While the prevalence of adrenal tumors in MEN1 has been estimated to be as high as 45%, they are typically bilateral, non-functional cortical adenomas \cite{2}. Pheochromocytoma (PHEO) in MEN1 is a rare occurrence, estimated to occur in <2% of patients with MEN1 \cite{3}.

Once a biochemical diagnosis of PHEO/paraganglioma is established, anatomical and functional imaging is helpful to determine or confirm the location of PHEO or extra-adrenal paraganglioma, evaluate for multiplicity and determine if there is metastasis \cite{4}. Additionally, patients who present with bilateral adrenal nodules on anatomic
imaging may present diagnostic challenges. In patients with a known predisposition to bilateral PHEO, including those with von Hippel-Lindau (VHL), multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1) and myc-associated factor X (MAX) gene mutations, the utility of $^{18}$F-FDOPA PET/CT for identifying PHEOs has been previously demonstrated (4, 5, 6, 7). Here, we report a case of clinically silent PHEO in a patient diagnosed with MEN1 at an advanced age who presented with bilateral adrenal masses and highlight the diagnostic utility of $^{18}$F-FDOPA PET/CT over $^{123}$I-MIBG and $^{18}$F-FDG PET/CT scanning. We also present a review of the literature of MEN1 patients with PHEO.

Case presentation

A 70-year-old Caucasian gentleman presented for a workup for MEN1 at our institution because his son had been recently diagnosed with MEN1. Written informed consent to a long-standing natural history hyperparathyroidism protocol (NCT00001277) was obtained prior to study enrollment. At the time of initial presentation, the patient was asymptomatic. Clinical features of PHEO, including sustained or paroxysmal hypertension, sweating, pallor, palpitations, constipation, headaches or weight loss, were notably absent. He had documented normocalcemia until age 60 when he was identified to have hypercalcemia on routine screening and subsequently underwent a single gland parathyroidectomy. A second parathyroidectomy was performed 5 years later due to recurrent hyperparathyroidism. Other pertinent past medical history includes gastrointestinal reflux disease, ischemic stroke, prostate cancer, melanoma, squamous cell skin cancer and type 2 diabetes mellitus. Social history was unremarkable. The patient had a 20 pack/year tobacco history but quit smoking cigarettes at the age of 55. In a review of the family history, it is unknown if either parent had MEN1 (Fig. 1). On physical exam, the patient was normotensive and had a resting heart rate of 94. Skin exam revealed lipomas on the trunk. Initial screening with computerized tomography (CT) scan demonstrated two cysts in the uncinate process of the pancreas and qualitatively similar bilateral adrenal nodules measuring 2.5 cm on the left (9 HU pre-contrast and 15 HU post-contrast contrast washout) and a multinodular right adrenal, with the dominant nodule measuring 2.7 cm (23 HU pre-contrast- and 25 HU post-contrast). MRI confirmed 2.5 cm left and right adrenal nodules, and the largest right adrenal nodule measured 2.5 cm. MRI characteristics showed left adrenal hyperintense activity on T2 and hypointense activity on T1, while the right adrenal was isointense on T1. Pituitary MRI was negative.

Investigation

Initial labs demonstrated slightly elevated ionized Ca (1.38 mmol/L; range: 1.12–1.32 mmol/L), PTH (72.3 pg/mL; range: 15–65 pg/mL) and low phosphorus (2.2 mg/dL; range: 2.5–4.8 mg/dL). Gastrin was elevated (302 pg/mL; normal <100 pg/mL), while on 20 mg of omeprazole by mouth daily, and hemoglobin A1c was 7%. Prolactin and all other biochemical tests were within normal limits. Screening evaluation of adrenal function was notable for a seven-fold increase in plasma metanephrine (432 pg/mL; range: 12–61 pg/mL), three-fold increase in normetanephrine (291 pg/mL; range: 18–112 pg/mL) and two-fold increase in epinephrine (126 pg/mL; range: 0–57 pg/mL). Aldosterone was normal (<4 ng/dL; normal <21 ng/dL). Chromogranin A was 2443 ng/mL (normal <93 ng/mL) (Table 1).

Germline mutation testing by the Next Generation Sequencing (NGS) method revealed a heterozygous pathogenic variant $\text{MEN1}$ c.249_252delGTCT causing a frameshift mutation, also known as rs587776841. Germline mutation testing for known pathogenic genes associated with PHEO/paraganglioma by NGS was negative for $\text{RET}$, $\text{NF1}$ and $\text{VHL}$. In addition, all succinate
Dehydrogenase subunit mutations were negative by sequencing and deletion analysis, including succinate dehydrogenase complex flavoprotein subunit A (SDHA), succinate dehydrogenase complex assembly factor 2 (SDHAF2), succinate dehydrogenase complex subunit B (SDHB), succinate dehydrogenase complex subunit C (SDHC), transmembrane protein 127 (TMEM127), MAX, egl-9 family hypoxia inducible factor 1 (EGLN1), fumarate hydratase (FH) and kinesin family member 1B (KIF1B).

During a workup for Zollinger–Ellison Syndrome (ZES), the patient unexpectedly developed a perforated duodenal ulcer requiring prolonged hospitalization and multiple surgeries. Due to these complications, the adrenal nodule was monitored, and over the course of 4 years the right adrenal nodule remained stable while the left increased from 2.5 cm to 3.9 cm by CT (Fig. 2A).

Functional adrenal imaging with $^{123}$I-mIBG scintigraphy demonstrated mild abnormal bilateral uptake (Fig. 2B), similar to $^{18}$F-FDG PET/CT (6.4 SUVmax on the left and 4.4 SUVmax on the right; Fig. 2C). However, $^{18}$F-FDOPA PET/CT clearly demonstrated an avid uptake in the left adrenal with SUVmax of 28.7 (Fig. 2D), with physiologic uptake on the right adrenal. Gallium-68 ($^{68}$Ga) DOTATATE PET/CT was not available at the time.

**Treatment**

The patient underwent a successful laparoscopic left adrenalectomy for PHEO (Fig. 2E, F and G) without complications. Pathology revealed positive staining for chromogranin A and S100 highlighted sustentacular cells (Fig. 2E, F and G). Tumor DNA sequencing and analysis of markers near the MEN1 locus demonstrated loss of heterozygosity (LOH), consistent with the Knudson’s two-hit hypothesis (Fig. 3).

**Outcome and follow-up**

Post-operatively, the patient had normalization of previously elevated plasma metanephrines (27 pg/mL; range 12–61 pg/mL), normetanephrine (107 pg/mL; range 18–112 pg/mL) and plasma epinephrine (<20 pg/mL; range 0–57 pg/mL). As expected, chromogranin A remains elevated due to the presence of known duodenal and pancreatic neuroendocrine tumors. Additionally, he is normotensive, has no biochemical evidence of recurrence and continues yearly follow-up for MEN1 at our institution for the past 8 years.

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**Table 1** Biochemical evaluation of blood and 24-h urine.

| Parameters               | Normal values | Patient values |
|--------------------------|---------------|----------------|
| Blood chemistry          |               |                |
| 1 mg DST, µg/dL          | <1.8          | 2.8            |
| Aldosterone level, ng/dL | <21           | <4             |
| Metanephrine, pg/mL      | 12–61         | 432 (7× ULN)   |
| Normetanephrine, pg/mL   | 18–112        | 291 (3× ULN)   |
| Epinephrine, pg/mL       | 0–57          | 126 (2× ULN)   |
| Norepinephrine, pg/mL    | 84–794        | 198            |
| Chromogranin A, ng/mL    | <93           | 2443 (26× ULN) |
| Gastrin, pg/mL           | <100          | 302 (3× ULN)   |
| PTH, pg/mL               | 15–65         | 72.3           |
| Ionized Calcium, mmol/L  | 1.12–1.32     | 1.38           |
| 24-h urine* analysis     |               |                |
| Urine free cortisol      | 3.5–45        | 41.8; 61.6 (1–1.5 ULN) |
| Urine metanephrine       | 44–261        | 1616 (6× ULN)  |
| Urine normetanephrine    | 148–560       | 787 (1.5× ULN) |
| Total metanephrine       | 246–753       | 2403 (3× ULN)  |

*Urine creatinine and volume within normal limits. DST, dexamethasone suppression test.

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**Figure 2** Imaging studies and surgical pathology of the pheochromocytoma. (A) CT demonstrating the left adrenal mass measuring 3.9 cm (15 Hounsfield unit (HU) post-contrast) and right adrenal mass measuring 2.5 cm. (B) $^{123}$I-mIBG demonstrating abnormal uptake corresponding to the right and left adrenal masses. (C) $^{18}$F-FDG-PET/CT demonstrating bilateral adrenal uptake (6.4 SUVmax on the left and 4.4 SUVmax on the right). (D) $^{18}$F-FDOPA PET/CT demonstrating increased uptake in the left adrenal gland (SUVmax 28.7) compared to the right. (E) S100 highlights sustentacular cells, 20×. (F) Hematoxylin and eosin staining, 60×. (G) Chromogranin A staining, 20×.
Table 2). LOH was detected at two markers, D11S4945 and D11S449, in the patient's tumor DNA compared to his blood DNA (PCR products resolved in 1× TBE 6% polyacrylamide gels).

Discussion

In this report, we describe a patient with a confirmed germline MEN1 mutation and a clinically silent PHEO. Because of the bilateral adrenal masses demonstrated on CT and MRI, 18F-I-mIBG scintigraphy, 18F-FDG PET/CT and 18F-FDOPA PET/CT were performed to localize the tumor. Only 18F-FDOPA PET/CT identified the left PHEO. These results suggest that 18F-FDOPA PET/CT may be a sensitive tool to capture biochemically-confirmed PHEO, especially in cases with bilateral adrenal hyperplasia/nodules in patients with MEN1.

The incidence of adrenal nodules in patients with MEN1 is reported to be up to ~40% depending on the series, radiological methods and criteria used to characterize adrenal enlargement (2). The majority of these tumors are bilateral, hyperplastic and non-functional. A large multicenter database analysis of patients with MEN1 and adrenal nodules demonstrated increased prevalence of primary hyperaldosteronism and adrenocortical carcinoma compared to sporadic incidentalomas. This cohort series described 4/146 cases of hyperaldosteronism, which were more common in patients with unilateral adrenal lesions. This paper may have overestimated the prevalence of endocrine hypersecretion, as 50% of asymptomatic patients with adrenal lesions were not biochemically screened and therefore were not included in the prevalence calculation. Only one case of MEN1-associated PHEO was identified in this cohort (1/144) (2), and this patient had bilateral PHEOs with obvious clinical features of NF1 (yet no genetic analysis was performed). Similarly, a patient with a germline mutation in MEN1 was reported with clinical findings of both MEN1 and MEN2, including a PHEO (8). This patient had a negative RET gene analysis of pathogenic variants but did have germline RET polymorphisms Gly691Ser and Arg982Cys. It remains unclear if either of these variants, individually or in combination, were working in synergy with the MEN1 germline mutation in that patient (1132delG) or with another gene to produce features of MEN2, including pheochromocytoma and thickened corneal nerves. Nevertheless, our current patient had no detected variants detected in the RET protooncogene.

A review of the literature has identified approximately 20 reported cases of PHEO and/or paraganglioma in patients with MEN1 (Table 2). The average reported age is ~46 years old, with the youngest patient identified at the age of 29. Our case represents the oldest MEN1 patient identified with PHEO. Two patients were identified to have bilateral PHEOs and three also died as a result of malignant PHEO. In the majority of cases reported, the size of the PHEO was >2.5 cm, with the exception of one patient who was reported to have a 1 cm PHEO (abstract only) (9). The size of our patient’s PHEO was also initially identified to be ≥2.5 cm. Similar to other familial syndromes, the typical size of PHEO in disease like NF1, MEN2 and VHL can range anywhere from 2.5 cm to 5.6 cm (10, 11, 12). There is no male or female predominance. No clear phenotype—genotype correlation exists for any MEN1 manifestation. Five cases reported hypertension, while our case in addition to two other cases (13, 14) had pathologically confirmed PHEO in the absence of symptoms. Screening with 24-h urinary or plasma metanephrines and catecholamines is warranted in adrenal incidentalomas in patients with MEN1, particularly if the adrenal mass suggests PHEO on imaging (vascular, dense and slow contrast washout on CT) or is growing >1 cm/year.

Radionuclide imaging modalities are critical in the evaluation and management of neuroendocrine tumors. Radiotracers specifically detect and localize neuroendocrine tumors based on tumor receptor availability. In 2016, 68Ga-DOTATATE PET/CT was Food and Drug Administration (FDA) approved for the detection of neuroendocrine tumors. There are no reports on functional imaging studies for PHEO in MEN1. However, data on sporadic PHEO suggests that 18F-FDOPA PET/CT may have minimally better patient-based and lesion-based detection rates than 68Ga-DOTATATE PET/CT (100% vs 90% and 94% vs 81%, respectively) (5). Data from NIH on apparently sporadic PHEOs also demonstrates similar effectiveness between 18F-FDOPA and 68Ga-DOTATATE PET/CT (15). There are at least 20 known...
Table 2  Published cases of pheochromocytoma/paragangliomas in patients with clinical MEN1 or with germline MENT mutations.

| Year | Author | Number of subjects | Germline mutation | Other manifestations of MEN1 | Age of Pheo Dx | Size (cm) | Location (R/L adrenal) | HTN | Catecholamine/ metanephrines elevation | Imaging modality | Follow-up |
|------|--------|--------------------|-------------------|-----------------------------|---------------|----------|----------------------|-----|-------------------------------|----------------|-----------|
| 1976 | Cobin et al. (21) (referenced in Farhi et al. 1976, Manger & Gifford 1977) | 1 unk | HPT, PIT (GH) and pigmentary abnormalities | unk | unk | unk | Y | Both Cat and Epi elevated | unk¹ | death |
| 1977 | Melicow (22) | 1 unk | HPT and PIT (GH) | 66 | unk | R&L | Y | Plasma Cat normal; Met unk | unk | death |
| 1980 | Alberts et al. (29) | 1 unk | HPT, left ACA, and PANC (GAST) | 29 | unk | R | Y | Urine Cat 4.25 ULN; Urine epi ~20 ULN | unk | death |
| 1981 | Anderson et al. (23) | 1 unk | HPT and PIT (GH) | 53 | unk | R | Y | Blood Cat ~13 ULN; Urine Met 99 ULN | Autopsy | death |
| 1981 | Myers et al. (30) | 1 unk | HPT and PIT (GH) | 53 | 2.5 | L | Y | Plasma Cat 4.3 ULN; elevated | CT | persistent HTN, possible right pheo |
| 1996 | Trump et al. (14) | 1 unk | HPT, PANC (GAST), and ACA | unk | unk | unk | unk | unk | unk | unk |
| 1997 (abstract only) | Mozersky et al.* (9) | 1 Positive family history | HPT and PIT (PRL) | 34 | 1 | unk | unk | unk | unk | death |
| 1998 | Carty et al.* (31) | 1 unk | HPT and PIT (PRL) | 32 | unk | unk | unk | unk | unk | death (32 years old) |
| 1999 | Dackiw et al. (32) | 1 c.1215_1216insA | HPT, PAN, PIT, and ACA | unk | >3 | L | unk | unk | CT | |
| 1999 | Sigl et al. (36) | 1 unk | HPT, PAN (INS), and BC | unk | unk | L | unk | unk | OctreoScan | |

(Continued)
| Year | Author | Number of subjects | Germline mutation | Other manifestations of MEN1 | Age of Pheo Dx | Size (cm) | Location (L/R adrenal) | HTN | Catecholamine/ metanephrines elevation | Imaging modality | Follow-up |
|------|--------|-------------------|-------------------|-----------------------------|---------------|-----------|------------------------|-----|-------------------------------|----------------|-----------|
| 2002 | Langer et al. (33) | 1 | reported as frameshift mutation K119X<sup>c</sup> | HPT, PANC (INS), and PIT (PRL) | 48 | 3 | L | unk | Both Cat and Epi elevated | unk<sup>f</sup> | unk<sup>i</sup> |
| 2006 | Jager et al. (34) | 1 | unstated, positive family history | HPT and BC | 35 | unk | unk | unk | unk | unk | unk |
| 2012 | Gatta-Cherifi et al. (2) | 1 | unk | HPT, PANC, PIT (ACTH) and NF1 | unk | unk | R&L | unk | unk | unk | unk<sup>f</sup> |
| 2014 | Jamilloux et al. (35) | 1 | c.824G>A<sup>d</sup> | HPT, PAN and ACA | 50 | unk | Jugulotympanic | Y | unk | CT and OctreoScan | unk |
| 2015 | Dénes et al. (25) | 1 | reported as c.1452delG (p.Thr557Ter)<sup>e</sup> | PIT | unk | unk | unk | unk | unk | unk | unk |
| 2015 | Hasan (38) | 1 | c.783 + 1G>A | PIT | unk | unk | unk | unk | unk | unk | unk |
| 2016 | Okada et al. (37) | 1 | yes, mutation not given | HPT, PANC, and PIT | 65 | 3 | L | Y | Urine NE @ ULN | unk | unk |
| 2016 | El-Maouche et al. (8) | 1 | c.249_252delGTCT | HPT, PANC (INS), PANC, PIT (PRL), and ACA | unk | 4.7 | R | unk | unk | CT | death at the age of 58 due pNET mets |

*Reported as 1325insA;<sup>1</sup>reported as 320del2;<sup>2</sup>unable to determine nucleotide but there appears to be an upstream frameshift resulting in a stop codon at K119;<sup>3</sup>reported nucleotide and protein-level notations do not correspond with each other, unable to distinguish correct variant;<sup>4</sup>Manger & Gifford, Langer et al. and Gatta-Cherifi et al. indicate the use of CT/MRI to identify adrenal lesions but do not specifically specify which is used to identify the PHEO in their patient. *<sup>5</sup>, reported as malignant pheo NOS;<sup>1</sup>, paraganglioma; ACA, adrenal cortical adenoma; ACH, adrenal cortical hyperplasia; BC, bronchial carcinoid; Cat, catecholamine; CT, computed tomography; Epi, epinephrine; GAST, gastrinomas; HPT, hyperparathyroidism; HTN, hypertension; Met, metanephrines; MRI, magnetic resonance imaging; PANC, pancreatic neuroendocrine tumor; PIT, pituitary adenoma; ULN, upper limit of normal; unk, unknown/not stated.
susceptibility genes (not including MEN1) (16) driving the pathogenesis of PHEO/paraganglioma in hereditary PHEO, which comprises 35–40% of cases (17). Germline mutations have been associated with improved radiotracer concentrations and is based on molecular clustering. Cluster 1 PHEOs with pseudohypoxic Krebs cycle-related gene, for example, SDHx mutations are best seen on 68Ga-DOTATATE PET/CT, while PHEOs with pseudohypoxia VHL/EPAS1-related signaling mutations are best seen on 18F-FDOPA PET/CT (16). Kinase signaling related PHEO (cluster 2) which includes RET, NF1 and MAX mutations are also best imaged using 18F-FDOPA PET/CT (18, 19). Our patient had elevations in normetanephrine, metanephrines and epinephrine, thus not clearly identifying into one biochemical phenotype. It is not known which imaging modality is best for MEN1-associated PHEO, given the rarity of these tumors in MEN1 patients. In our patient, only 18F-FDOPA PET/CT accurately detected and lateralized the PHEO. It should be noted that 18F-FDOPA PET/CT is not readily available nor routinely used in MEN1. However, this imaging modality may be a helpful tool to distinguish PHEO in an MEN1 patient with bilateral adrenal nodules. The specificity or sensitivity of 68Ga-DOTATATE PET/CT for PHEO in MEN1 in unknown.

A recently described rare syndrome of pituitary adenomas plus PHEO/paraganglioma (3PAs) has been associated with mutations in SDHB (cluster 1) and RET (cluster 2), which are two of the most prevalent germline mutations in patients with PHEO/paraganglioma (20). A report of a 54-year-old male patient with acromegaly and incidentally identified bilateral PHEO had a heterozygous germline variant of uncertain significance in MEN1 (c.1618C>T; p.Pro540Ser) (20). Additional cases with clinical history suggesting MEN1 (prior to the MEN1 gene discovery in 1997) include PHEO combined most commonly with hyperparathyroidism, gastrinoma and/or acromegaly (Table 2) (21, 22, 23, 24).

Loss of heterozygosity (LOH) at the MEN1 locus has been described in two previous PHEO cases in MEN1 patients (25). We also confirmed LOH at the MEN1 locus in the PHEO tumor of our patient, suggesting that MEN1 is implicated in the tumorigenesis of PHEO. Little is known about the role of menin in the pathogenesis of PHEO. Interestingly, 7% of Men1−/− mice develop bilateral pheochromocytomas, which are equally distributed between sexes (26). Further work is needed to identify epigenetic or modifying factors that may explain the rare occurrence of these tumors in MEN1 patients.

In this study, we report a rare case of PHEO in a patient with a germline mutation in MEN1. 18F-FDOPA PET/CT was the most sensitive functional imaging modality when compared to 123I-mIBG and 18F-FDG PET/CT. Rarely, MEN1 patients may develop functional and/or enlarging adrenal nodules >2 cm which require biochemical evaluation, even in the absence of symptomatology. Due to the frequency of bilateral adrenal nodules in MEN1, functional imaging for PHEO may be essential.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent has been obtained from the patient.

Author contribution statement
A A Tepede and J E Blau contributed to the conception, writing and editing of the manuscript. K Pacak, J E Blau, W F Simonds and L S Weinstein participated in the endocrine attendings and were the primary providers in the clinical and research care for the patient and involved in editing and revising the manuscript. N Nilubol performed the laparoscopic retroperitoneal left adrenal adenoma resection and was involved in editing and revising the manuscript. C Millo was the radiologist involved in the interpretation and selection of anatomic and nuclear imaging for publication and was involved in editing and revising the manuscript. J Welch and S K Agarwal performed DNA sequencing on the tumor and were involved in editing and revising the manuscript. C Cochran coordinated the clinical care of the patient. A Jha, D Patel, A Mandl and M Lee were involved in editing and revising the manuscript.

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