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Acute myeloid leukemia therapy elicits durable complete response in chemoradio-resistant metastatic paraganglioma

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Abstract

Few effective therapeutic options exist for patients with metastatic paraganglioma. We report on the case of a 16 year-old male who developed acute myeloid leukemia (AML) 30 months following treatment for metastatic paraganglioma. Paraganglioma had been refractory to ¹³¹I-meta-iodobenzylguanidine and temozolomide therapy. However, there was a major reduction in primary tumor allowing its gross total resection, and complete resolution of metastatic disease following AML-directed therapy that included daunorubicin, cytarabine and etoposide. He remains in remission for both AML and paraganglioma 48 months post-AML chemotherapy. Alternative chemotherapeutic agents should be considered for metastatic paraganglioma resistant to conventional therapy.

Keywords

metastatic paraganglioma; acute myeloid leukemia

INTRODUCTION

Pheochromocytomas (PHEO) and paragangliomas (PGL) are rare neoplasms, constituting <7% of pediatric tumors arising from sympathetic nerves with an estimated incidence of < 0.3 cases/million/year. [1] In children, PHEO/PGLs are more frequently hereditary, extra-adrenal and metastatic than in adults.[2] Germline mutations have been identified in up to 60% and 70% of PHEO/PGLs presenting <18 and <10 years of age respectively.[3] Hereditary cases in older patients are associated with the *RET* and *NFI* mutations, whereas younger patients often have germline mutations of *SDH* and related genes and the *VHL* gene.[4] Although patients can survive for years, and in some cases, decades after diagnosis, currently available therapies for malignant PHEO/PGL are not curative[5] and there is a paucity of data on management and outcome in children. A report from the European-American-PHEO/PGL registry identified 177 patients <18 years at diagnosis. Only 16 patients had malignant disease at diagnosis or follow-up, with *SDHB* mutations being most

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common (37.5%). Eight died due to disease progression whereas there were no disease-related deaths in patients with benign disease.[6] A single center experience on 30 pediatric PHEO/PARA patients reported 5 and 10-year disease-specific survival of 78 and 31% respectively.[7] Second malignancies observed were either paraganglial or those expected with gene mutations.[6] We present the first reported case of acute myeloid leukemia (AML) after treatment for metastatic paraganglioma and the unexpected clinical course following treatment for AML.

CASE REPORT

A sixteen-year old male presented with prolonged abdominal pain after sustaining a fall while snowboarding. CT scan revealed a large pelvic mass measuring 5.7×12.9×6.8cm infiltrating the urinary bladder with associated severe right-sided hydronephrosis due to ureteral obstruction (Figure 1). Blood pressure, serum chromogranin, plasma and urine catecholamines were normal. There was no family history of chromaffin cell tumors. Biopsy revealed paraganglioma with characteristic immunohistochemical findings: positive for chromogranin, synaptophysin, focally positive for S100; negative for desmin and myogenin. FDG-PET scan demonstrated hypermetabolic metastatic osseous lesions in the left scapula, sternum and lower coccyx/sacrum which were also meta-iodobenzylguanidine (MIBG) avid (Figure 1) despite the tumor being non-secretory. Germline exome sequencing (Ambry Genetics, CA) showed no mutations or large rearrangements in p53 or mutations in the paraganglioma-related genes *MAX*, *NF1*, *RET*, *SDHA*, *B*, *C* and *D*, *SDHAF2*, *TMEM127* and *VHL*. Somatic exome sequencing (Foundation Medicine, MA) of the primary tumor sampled at diagnosis showed no actionable mutations. The tumor was deemed unresectable and ureteral stenting was attempted to preserve right kidney function but failed, necessitating nephrostomy. In an effort to shrink the tumor and relieve ureteral blockage, he was treated with two non-myeloablative doses of intravenous (IV) ¹³¹I-MIBG (12mCi/kg and 3mCi/kg at 4 and 7 months post-diagnosis respectively) without any response in primary or metastatic sites. He subsequently received oral temozolomide (200 mg/m²/dose daily × 5 days every 21–28 days for 8 cycles) and IV zoledronic acid (4mg/kg/dose monthly × 9 doses) again without tumor response. No further anti-paraganglioma therapy was administered.

Thirty months after diagnosis of PGL and 7 months after completing therapy, he developed persistent asymptomatic thrombocytopenia. Bone marrow (BM) testing showed AML (20% blasts) with M4 morphology, flow cytometry was positive for CD33, CD34, CD45 and CD117. Karyotyping revealed t(8;21) and FISH confirmed translocation of AML-ETO. Molecular studies for FLT3, NPM1, CEBPA and KIT mutations were negative. Cerebrospinal fluid was uninvolved with leukemia. Despite this being a second malignancy, he was considered to have *de novo* AML due to the presence of the classic t(8;21) and was treated with AML-directed therapy consisting of daunorubicin, cytarabine, etoposide, thioguanine and dexamethasone per Children's Cancer Group (CCG) protocol 2891[8] (Supplemental Figure S1). Course was complicated by cellulitis at the nephrostomy site, staphylococcus epidermidis central-line infection and clostridium difficile typhilitis. He entered AML remission after the first induction cycle. Intriguingly after 2 induction cycles and post-induction cytarabine (12 g/m²/week for 2 consecutive weeks) a 50% reduction in volume of the primary paraganglioma and significant reduction in intensity and extent of

osseous metastases was observed on MIBG scan. Extent-of-disease evaluation after completing all AML-directed therapy [9] (Supplemental Figure S1) showed further reduction of soft tissue mass and complete resolution of skeletal metastases on both PET and MIBG scans (Figure 1). He then underwent resection of the pelvic mass followed by reversal of nephrostomy. Immunohistochemical evaluation of the resected tumor showed no expression of the SDHB protein but retention of SDHA. He has since undergone surveillance testing with FDG-PET and MIBG scans and BM testing every 6 months and remains in morphologic, cytogenetic and molecular remission from his AML without any evidence of soft tissue or metastatic PGL.

DISCUSSION

Treatment for patients with metastatic PHEO/PGL is typically aimed at palliation rather than cure and options include ^{131}I -MIBG therapy or systemic chemotherapy. There are few data on chemotherapy regimens for metastatic PHEO/PGL, and pediatric reports are only anecdotal. The most commonly studied regimen is a combination of cyclophosphamide, dacarbazine and vincristine (CVD). A single-center retrospective report on 52 patients treated with various regimens suggested a clinical benefit for only those responding to cyclophosphamide-dacarbazine based chemotherapy.[10] A meta-analysis of reports on CVD identified a total of only 50 patients. Complete and partial response rates were 4% and 37% respectively, with a median duration of response of 20–40 months.[11] *SDHB*-mutation-associated PHEO/PGLs are globally hypermethylated[12] and methylation-induced silencing of the MGMT (O(6)-methylguanine-DNA methyltransferase) promoter might render them more susceptible to DNA alkylating agents such as dacarbazine and its orally active analog temozolomide. Indeed, *SDHB*-mutation-associated PHEO/PGLs appear to respond better both to CVD[13] and temozolomide.[14] The lack of response to temozolomide could possibly be explained by the presence of wild-type *SDH* in our patient. Despite reported responses to chemotherapy, patients with germline *SDHB* mutations have been reported to have a poor clinical outcome.[15] It could be speculated that the apparent favorable clinical outcome in our patient could be related to the lack of such a mutation.

It is not clear which drug/drugs led to the PGL response in our patient: response was first evaluated after two cycles of induction chemotherapy at which point he had received cytarabine, daunorubicin, etoposide and thioguanine. There have been anecdotal reports on the activity of some of these agents against PHEO/PGL refractory to CVD. Low dose cytarabine was associated with reduction of bone pain and urinary norepinephrine in a 67-year old male[16] and doxorubicin plus streptozocin with transient remission in a 15-year old with parotid body tumor.[17] Responses to gemcitabine and docetaxel have also been reported. [18] However, complete and durable responses similar to those observed in our patient are rare even in patients with CVD-responsive disease. [11]

Secondary leukemias have rarely been described both after MIBG therapy[19] and after temozolomide.[20] However, the latency period for development of secondary AML is much longer than the 30 months noted in our patient. The presence of t(8;21) is usually associated with *de novo* AML and rarely with secondary AML.[21] We therefore treated our patient with a regimen for standard-risk AML and did not perform allogeneic transplant that is

considered necessary to cure patients with secondary leukemia.[22] It is possible that our patient harbors an as-yet undiscovered germline mutation that predisposed him to develop two unrelated malignancies. Moreover, given the lack of SDHB protein expression, a related genetic aberration that was not detected by routine germline testing could be suspected. In summary, AML-directed chemotherapy resulted in an unexpectedly robust response leading to a complete remission in a patient with malignant PGL previously unresponsive to targeted radiotherapy and alkylator chemotherapy. Even more surprising is the maintenance of complete remission 4 years off therapy. It is possible that anthracyclines and/or cytidine analogs such as cytarabine could have anti-PHEO/PGL activity that is worth further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

AML	Acute myeloid leukemia
PGL	Paraganglioma
PC/PHEO	Pheochromocytoma
MIBG	Meta-iodo benzyl guanidine
FDG PET	Flouro deoxyglucose Positron emission tomography
BM	Bone marrow
FISH	Flourescence in situ hybridization
CCG	Children's Cancer Group
MEN2	Multiple endocrine neoplasia type 2
NF-1	Neurofibromatosis type 1
SDH	Succinate dehydrogenase
SDHB	Succinate dehydrogenase complex iron sulfur subunit B
VHL	Von Hippel Lindau
CVD	Cyclophosphamide, dacarbazine and vincristine
MGMT	(O(6)-methylguanine-DNA methyltransferase
MAX	MYC associated factor X

RET Rearranged during transfection

TMEM 127 Transmembrane protein 127

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Figure 1.

Images A, B and C depict scans at diagnosis. A: CT scan showing large heterogeneous bilobed right pelvic mass, inseparable from the bladder anteriorly and from the right seminal vesicles. B. FDG-PET scan: hypermetabolic pelvic mass (SUV 21). C: MIBG scan showing MIBG-avid skeletal lesions in sternum and left scapula. Images D, E, F and G depict scans after completion of AML chemotherapy. D: CT scan: significantly decreased size of pelvic mass. E: FDG-PET: Significantly reduced metabolic activity in pelvic paraganglioma (SUV 5). F: MIBG scan: Complete resolution of skeletal metastases. G: FDG-PET: complete remission of paraganglioma.