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Case Report

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Advanced urethral paraganglioma treated with axitinib; outcome and comprehensive molecular analysis

Abstract

Introduction: Paraganglioma is a rare entity that arises from extra-adrenal paraganglia and accounts for less than a quarter of all chromaffin cell-related tumors. There are few cases of urethral paragangliomas reported on the literature. Most of them are hormonally inactive and local excision is curative in localized disease. We present a metastatic urethral paraganglioma in 71 years-old man that underwent a comprehensive search for molecular alterations amenable to pharmacological targeting.

Materials and Methods: The following molecular studies were performed in tumor tissue: HER-2/neu amplification, c-Kit immunohistochemistry, EGFR and BRAF mutations and Foundation MedicineT5a panel (next generation sequencing); in peripheral blood germ line alterations in genes related to familiar paraganglioma were also analyzed.

Results: Though no genetic alteration was found, the patient achieved tumor control with antiangiogenics (first with sunitinib that was later shifted to axitinib because of drug induced hyperbilirubinemia). Here mains asymptomatic 16 months after initiation of therapy.

Conclusion: Paraganglioma should be considered as a tumor constitutively addictive to angiogenesis even in the absence of pathogenic mutations or rearrangements in such pathway.

Keywords: paraganglioma, axitinib, sunitinib

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Abbreviations: 131I-MIBG, 131I-meta iodo benzyl guanidine scintigraphy; MIBG, meta iodo benzyl guanidine; SDHB, succinate de hydrogenase subunit B gene

Case presentation

A 71 year-old-man, with Gilbert's syndrome as the only medical history, presented in February 2013 recurrent episodes of urinary retention and haematuria. Initial diagnosis was benign hyperplasia of the prostate thus 0.4 mg of tamsulosin hydrochloride once a day was prescribed. Symptoms did not improve and four months later a retro pubic adenectomy was performed. Pathological report described a 4.5 cm length malignant tumor of the prostatic urethra with an immuno-phenotype compatible with paraganglioma (positive chromogranin, synaptophysin and S100; negative CK AE1/AE3, EMA, CK 7, CK 20 and CD10); Ki67 index was 5% and the tumor affected surgical margins.

A body CT scan revealed multiple pelvic adenopathies and implants as well as thickening of the urinary bladder wall. A PET-CT with 18F-FDG confirmed such findings (Figure 1A & 1B). Urinary and serous catecholamines were in normal range and 131I-metaiodobenzylguanidine (131I-MIBG) scintigraphy did not show any uptake. Since this is an infrequent condition where little therapeutic options are available, a comprehensive molecular study was initiated aiming to identify alterations amenable to pharmacological targeting. FISH for HER-2/neu gene amplification and ALK translocations, immunohistochemical staining for c-Kit and sequencing of hotspot mutations in the EGFR gene (by the Cobas® EGFR Mutation Test) and BRAF gene (Cobas® 4800 BRAF V600 Mutation Test) were performed showing no alteration.

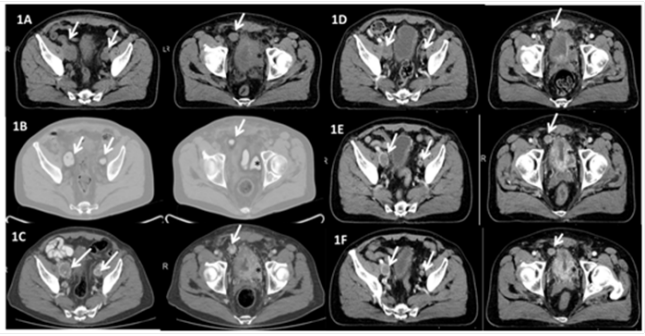

Figure 1 Radiological assessments at diagnosis and along treatment. Left: pelvic adenopathies (white arrows); Right: Tumoral thickening of the urinary bladder wall (black asterisk) and pelvic implant (white arrow)
1A Baseline CT scan (July 2013)
1B Baseline PET CT scan (July 2013)
1C CT scan (September 2013) after two cycles of cisplatin+etoposide. Enlargement of pelvic nodes and bladder mass compared to baseline
1D CT scan (December 2013) after 2 months on sunitinib
1E CT scan (July 2014) after 3 months on axitinib
1F CT scan (October 2014) after 7 months on axitinib.

Additionally tumor samples were subjected to Foundation Medicine T5a test, an assay based on massively parallel DNA sequencing designed to characterize base substitutions, short insertions and deletions (indels), copy number alterations and selected fusions across 287 cancer-related genes. No relevant findings were made (see extra material for a detailed description of the assay, (Table 1)).

Finally germ line DNA was studied through sequencing and multiplex ligation-dependent probe amplification (MLPA) of genes previously related with hereditary paraganglioma (VHL, SDHA, B, C and D, SDHF1 and 2 and MAX). No pathogenic alteration was identified (Table 2). In July 2013 the patient started first line chemotherapy with cisplatin 30mg/m^2 and etoposide 100mg/m^2 days 1 to 3 every 21 days. Toxicity included grade II nausea, grade III constipation, grade III neutropenia and dysgeusia. After two cycles radiological progression was observed and tumor related symptoms worsened (Figure 1C). In October 2013 the patient started sunitinib (37.5 mg daily) with quick improvement of urinary symptoms. He developed conjunctival jaundice (due to grade II hyperbilirubinemia, total bilirubin up to 2.89 mg/dl), grade II hypertension, grade II hand-foot syndrome and grade II hypothyroidism that required hormonal replacement, leading to a dose reduction to 25 mg daily. After two months on therapy, CT scan showed stable disease by RECIST criteria with a decrease in size of some pelvic adenopathies (Figure 1D). No liver metastasis was observed.

Side effects were properly controlled but hyperbilirubinemia, which rose again up to 3.38 mg/dl. Treatment was held and reintroduced at an intermittent schedule (daily sunitinib 25mg, 3 weeks on, one week off). After six months on treatment stable disease was confirmed in CT scan but sunitinib was definitely discontinued because of recurrent hyperbilirubinemia. On April 2014 the patient started axitinib 5mg every 12 hours but a dose reduction to 5 mg daily was again required because of hyperbilirubinemia (serum bilirubin 2.88mg/dl). Currently the patient remains asymptomatic and on treatment, 16 months after initiation of antiangiogenics (Figure 1E & 1F).

Table 1 List of 287 genes studied in the Foundation Medicine T5a assay

ABL1	GID4	CUL4B	FGF23	IRF4	MSH6	PDGFRA	RUNX1	WISP3
AKT1	CARD11	CYP17A1	FGF3	IRS2	MTOR	PDGFRB	RUNX1T1	WT1
AKT2	CASP8	DAXX	FGF4	JAK1	MUTYH	PDK1	SETD2	WTX
AKT3	CBFB	DDR2	FGF6	JAK2	MYC	PIK3C2G	SF3B1	XPO1
ALK	CBL	DIS3	FGF7	JAK3	MYCL1	PIK3C3	SH2B3	XRCC3
ALOX12B	CCND1	DNMT3A	FGFR1	JUN	MYCN	PIK3CA	SMAD2	ZNF217
APC	CCND2	DOT1L	FGFR2	KDM5A	MYD88	PIK3CG	SMAD4	ZNF703
APCDD1	CCND3	EGFR	FGFR3	KDM5C	MYST3	PIK3R1	SMARCA4	
AR	CCNE1	EMSY	FGFR4	KDM6A	NBN	PIK3R2	SMARCB1	
ARAF	CD79A	EP300	FLT1	KDR	NCOR1	PMS2	SMARCD1	
ARFRP1	CD79B	EPHA3	FLT3	KEAP1	NF1	PNRC1	SMO	
ARID1A	CDC73	EPHA5	FLT4	KIT	NF2	PPP2R1A	SOCS1	
ARID2	CDH1	EPHB1	FOXL2	KLHL6	NFE2L2	PRDM1	SOX10	
ASXL1	CDK12	ERBB2	GATA1	KRAS	NFKBIA	PRKAR1A	SOX2	
ATM	CDK4	ERBB3	GATA2	LMO1	NKX2-1	PRKDC	SPEN	
ATR	CDK6	ERBB4	GATA3	LRP1B	NOTCH1	PRSS8	SPOP	
ATRX	CDK8	ERG	GNA11	MAP2K1	NOTCH2	PTCH1	SRC	
AURKA	CDKN1B	ESR1	GNA13	MAP2K2	NOTCH3	PTEN	STAG2	
AURKB	CDKN2A	EZH2	GNAQ	MAP2K4	NOTCH4	PTPN11	STAT4	
AXL	CDKN2B	FAM46C	GNAS	MAP3K1	NPM1	RAD50	STK11	
BACH1	CDKN2C	FANCA	GPR124	MAP3K13	NRAS	RAD51	SUFU	
BAP1	CEBPA	FANCC	GRIN2A	MCL1	NSD1	RAD51B	SYK	
BARD1	CHEK1	FANCD2	GSK3B	MDM2	NTRK1	RAD51C	TBX3	
BCL2	CHEK2	FANCE	HGF	MDM4	NTRK2	RAD51D	TET2	
BCL2L2	CHUK	FANCF	HLA-A	MED12	NTRK3	RAD52	TGFBR2	
BCL6	CIC	FANCG	HRAS	MEF2B	NUP93	RAD54L	TIPARP	
BCOR	CRBN	FANCI	IDH1	MEN1	PAK3	RAF1	TNFAIP3	
BCORL1	CREBBP	FANCL	IDH2	MET	PAK7	RARA	TNFRSF14	
BLM	CRKL	FANCM	IGF1	MITF	PALB2	RB1	TOP1	
BRAF	CRLF2	FAT3	IGF1R	MLH1	PARP1	REL	TP53	
BRCA1	CSF1R	FBXW7	IGF2	MLL	PARP2	RET	TRRAP	
BRCA2	CTCF	FGF10	IKBKE	MLL2	PARP3	RICTOR	TSC1	
BRIP1	CTNNA1	FGF12	IKZF1	MPL	PARP4	RNF43	TSC2	
BTG1	CTNNB1	FGF14	IL7R	MRE11A	PAX5	RPA1	TSHR	
BTK	CUL4A	FGF19	INHBA	MSH2	PBRM1	RPTOR	VHL	
Rearrangements								
ALK	BRAF	ETV4	EWSR1	NTRK1	RARA	TMPRSS2		
BCL2	EGFR	ETV5	MLL	PDGFRA	RET			
BCR	ETV1	ETV6	MYC	RAF1	ROS1			

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Table 2 Description of direct sequencing and Multiplex Ligation-dependent Probe

Gene	Molecular study	Technic
SDHA	sequencing	PCR and direct sequencing was performed of the coding region and flanking intronic region (8bp) of the genes: SDHA (reference sequence NM_004168.2*; chromosome 5) SDHB (reference sequence NM_003000.2; chromosome 1) SDHC (reference sequence NM_003001.3; chromosome 1) SDHD (reference sequence NM_003002.2; chromosome 11) VHL (reference sequence NM_000551.3; chromosome 3)
SDHB	sequencing	
SDHC	sequencing	Capture target regions using oligonucleotide probes (Next era rapid, Ilumina) and subsequent realization of next generation sequencing (Miseq, Ilumina) was completed. The alignment and identification of bases were performed using the Burrows / Wheeler Aligher, BWA Miseq reporter), followed by analysis with Next Gene (Soft Genetics) program. When necessary, the Sanger sequencing was performed in the regions in which bases were insufficient cover aged. average coverage lower than 100X or minimum coverage lower than 20X *
SDHC	sequencing	
VHL	sequencing	
		MLPA analysis (MRC Holland) of the chromosomal region comprising the genes:
SDHA	deletions / duplications	SDHA (cr5) Reference sequence NM_004168.2 (SDHA)
SDHB		SDHB (cr1) Reference sequence NM_003000.2 (SDHB)
SDHC		SDHC (cr1) Reference sequence NM_003001,3 (SDHC)
SDHD		SDHD (cr11) Reference sequence NM_003002,2 (SDHD)
SDHAF1		SDHAF1 (cr19) Reference sequence NM_001042631.2 (SDHAF1)
SDHAF2		SDHAF2 (cr11) Reference sequence NM_017841.2 (SDHAF2)
VHL		VHL (cr3) Reference sequence NM_000551.3. (VHL)
MAX		MAX (cr 14) Reference sequence NM_002382,4 (MAX)

Amplification performed on germ line DNA.

Discussion

Paraganglioma is an infrequent tumor that arises from extra-adrenal paraganglia and accounts for less than a quarter of cases of all chromaffin cell-related tumors. There are few cases of urethral paragangliomas reported on the literature. Most of these tumors are hormonally inactive. Although haematuria may be the presenting symptom, it is important to exclude additional more common and possibly more sinister lesions such as transitional cell carcinoma. Local excision appears to be curative in most of reported cases.[1,2]

Surgery and metaiodobenzylguanidine (MBIG) are cornerstones of treatment for advanced disease.[3,4] Unfortunately our case was deemed as unresectable due to multiple pelvic implants and no MIBG uptake was observed at diagnosis. Chemotherapy was initially administered but demonstrated to be useless and toxic. A comprehensive search for molecular alterations amenable to pharmacological targeting failed to guide treatment choice thus; antangiogenic therapy was initiated based on recently communicated data with sunitinib.[5-9] Though tumor control and clinical improvement were achieved, recurrent hyperbilirubinemia, likely related to Gilbert's syndrome led to a switch to axitinib. Recently a link between this syndrome and hyperbilirubinemia along sunitinib or pazopanib treatment has been shown. This is the first report to communicate clinical benefit of a malignant paraganglioma treated with axitinib.

Around 50% of metastatic paraganglioma is caused by hereditary germ line mutations of the mitochondrial enzymatic complex II succinate dehydrogenase subunit B gene (SDHB) which finally produces a downstream activation of angiogenesis. Additionally vascular endothelial growth factors and their receptors 1 and 2 are known to be over expressed in metastatic pheocromocitomas and paragangliomas regardless of SDHB mutations.[10]

Other genes involved in hereditary paragangliomas (VHL, SDHA, C and D and their cofactors SDHAF and MAX) are known to cause a similar stimulation of angiogenesis. These findings have led to the design of two clinical trials assessing the utility of both sunitinib and axitinib in pheochromocitoma and paraganglioma (NCT00843037 and NCT01967576, respectively).[11] Interestingly our case, despite a comprehensive molecular analysis, did not present alterations in neither the mentioned genes nor additional 287 cancer related genes included in the Foundation Medicine T5a test.[12] These studies cover all the recommended genes regarding screening of familiar paraganglioma.[13] However we did not study epigenetic alterations that have been described as major contributors to some related pathologies as renal carcinoma, nor mutations in any additional genes. Thus, activators of angiogenesis could be present in the tumor but undetected by our techniques.

Conclusion

Paraganglioma should be considered as a tumor constitutively addictive to angiogenesis even in the absence of pathogenic mutations or rearrangements.

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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