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Case Report

Molecular Evidence of Warburg-Like Metabolic Reprogramming in Prostate Cancer

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Abstract

Fumarate hydratase (FH) is a key enzyme of the Krebs cycle. Germline mutations in the FH gene encoding fumarate hydratase was implicated in autosomal dominant syndromes multiple cutaneous and uterine leiomyomata, hereditary leiomyomatosis and renal cell cancer (HLRCC). We report here a novel FH gene mutationin a patient with metastatic prostate cancer. In addition, somatic mutations in multiple genes known to be involved in aerobic glycolysis were identified in the tumor sample of prostate cancer. Our findings supported a role of metabolic reprogramming may play a role in the prostate cancer tumorigenesis.

INTRODUCTION

Cancer cells have long been known to exhibit alterations*profiles* in their metabolism, a phenomenon known as Warburg effect with elevated aerobic glycolysis [1-3]. In recent years, the discovery of cancer-associated gene mutations in key metabolic enzymes suggests a direct link between cancer and altered metabolism. For example, oncogenes, such as c-Myc and Ras, have been identified to promote the expression of metabolic enzymes and regulators that lead tumor cells to preferential use of glycolysis over mitochondrial oxidative phosphorylation (OXPHOS). On the other hands, the loss of tumor suppressor genes, such as TP53, fumarate hydratase (FH), and succinate dehydrogenase (SDH), can also lead to significant changes in energy metabolism and may contribute to activation of hypoxia-inducible factor (HIF)-1α-dependent pathways and adaptation to tumor hypoxia [4,5].

FH is an enzyme involved in the Krebs cycle that plays a crucial role in the generation of energy and oxygenation of cells [4-6]. Mutations of FH gene have been shown to cause chronic hypoxia that encourages tumor formation. FH mutations have been linked to cause hereditary leiomyomatosis and renal cell cancer (HLRCC) [7,8]. While the literature supporting this relationship is vast, only few reportsof associated FH mutations with other types of malignancies [9-11]. Here, we present the first case of FH mutation in prostate cancer. In addition, we identify somatic mutations in multiple genes known to be involved in glycolysis in the same tumor sample of prostate cancer.

CASE REPORT

A 63-year-old African American man presented to emergency department complaining of urinary retention, blurred vision, and persistent headaches for two months. A magnetic resonance imaging (MRI) of head revealed a mass invading the left ethmoid sinus (Figure 1). The patient underwent left endoscopic partial ethmoidectomy and the histopathological examination suggested metastatic adenocarcinoma, with strongpositive staining to prostatic specific antigen (PSA), and prostatic acid phosphatase (PSAP); and negative for CK7, CK20, S100, P63, Ck20, NSE, synaptophysin, neurofilment, TTF-1, GCDFP-15, CD 117, Estrogen receptor (ER) and Sox10. A total serum prostate specific antigen (PSA) value was 5000 ng/ml. Taken together, the clinicopathologic findings were consistent with a high-grade metastatic prostate carcinoma (Figure 2). A CT scan chest abdomen and pelvis, bone scan showed enlarged prostate with diffuse metastatic lesions to the appendicular and axial skeleton. A transurethral resection of the prostate showed high-grade metastatic prostate carcinoma.

The patient initially treated with radiotherapy for total dose of 5040 cGy over 28 fractions and androgen deprivation with dramatic response. Subsequently he received multiple additional lines therapies. Thirty months after diagnosis of metastatic prostate cancer, the patient is alive with good quality of life.

Next-generation sequencing (NGS) was performed to profile his tumor sample from ethmoidectomy, the results showed CDK12 (K372fs*64, L21*), TP53 mutation (V10I), MYC amplification, and

Table 1: Genomic alterations were identified in multiple genes known to be involved in aerobic glycolysis in the same tumor sample.

Genomic	Alterations	Function	Clinical Significance	Regulate glycolysis
c-MYC	amplification	Transcription factor	oncogene	+
FH	V435M	Fumarate hydratase	tumor suppressor	+
TP53	V10I	Tumor suppressor	tumor suppressor	+
PDK1	A353T	Pyruvate Dehydrogenase Kinase 1	key enzymes in the pathway of glucose metabolism	+
MTOR	H1739Q	mammalian target of rapamycin	glycolytic shift	+
TSC1	A808V	Tuberous sclerosis	tumor suppressor	+
FAT1	N383K	Protocadherin FAT1	tumor suppressor	+
ABL2	G6A	Tyrosine-protein kinase ABL2	upregulates aerobic glycolysis	+
PREX2	amplification	Phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 2	guanine nucleotide exchanger	+
NOTCH1	R1350H	Notch homolog 1	glycolytic shift	+
MAP3K1	S816A	Mitogen-activated protein kinase kinasekinase 1	serine/threonine kinase	+
MDM4	D154G	murine double minute 2 gene	Negative p53 regulator	+
ESR1	H6Y	Estrogen receptor alpha	steroid hormones receptor	+

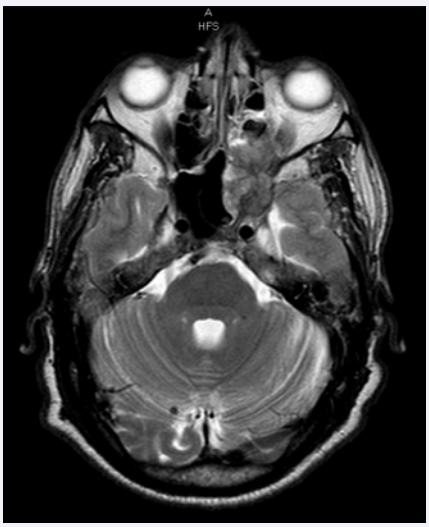

Figure 1 Magnetic resonance imaging (MRI) revealed a 4.5 × 4.5 × 3-cm mass invading the left ethmoid sinus.

mostly interesting, a FH (fumarate hydratase) mutation (V435M) was identified. The V435M single base substitution results in a missense mutation, likely resulting in a conformational change in the C-terminal domain, impacting the ability of the enzyme to move from open to closed conformation, with subsequent change in fumarate binding. In addition, one or more alterations of sixteen genes which known to be involved in regulation glycolysis in caner were also detected in this patient's tumor, including c-Myc, Ras, p53, phosphoinositide 3-kinase (PI3K), pyruvate dehydrogenase kinase-1(PDK1) and mammalian target of rapamycin complex 1 *(MTOR).*

DISCUSSION

Reprogramming of the cellular energy metabolism constitutes a hallmark of cancer and may serve as a basis for novel therapeutic intervention [3]. However, alterations in genes encoding enzymes involved in glucose metabolism in prostate cancer are largely unknown. The identification of molecular alterations in multiple oncogenes and tumor suppressor genes in our patient are very intriguing. These include the Krebs cycle genes FH and PKD, as well as several the well characterized oncogenes, such as PI3K, AKT, C-MyC, and RAS, that known to promote glycolysis; while tumor suppressors p53 negatively regulates the expression of the glycolytic protein phosphoglycerate mutase-2 (PGM2) and

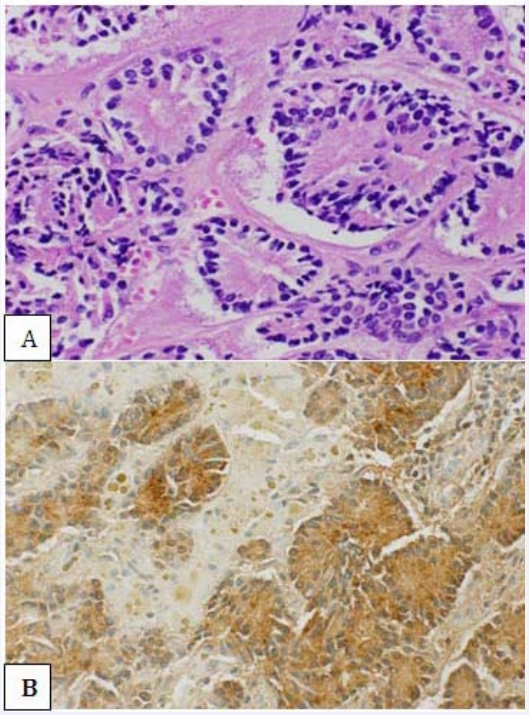

Figure 2 Tumor sample from endoscopic partial ethmoidectomy: a) Hematoxylin-eosin (H-E) staining showing groups of glandular cells with different grades of atypia. b) The tumor cells show positive staining for prostate specific antigen (PSA).

promotes the expression of Tumor Protein 53-Induced Glycolysis and Apoptosis Regulator (TIGAR), which depletes the glycolytic activator 2,6-fructose biphosphate, and inhibit glycolysis [4,5,12] (Table 1).

FH is an enzyme of the tricarboxylic acid (TCA) cycle, involved in fundamental cellular energy production. Whilst homozygous FH mutations cause fumaric aciduria, a condition associated with infantile encephalopathy and brain malformations [12], heterozygous FH mutations followed by the loss of heterozygosity of the second allele cause Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) [8,9]. FH-deficient RCC is associated with a metabolic shift termed the "Warburg effect",characterized by the activation of aerobic glycolysis and oncogenic pathways [24]. FH is also mutated in paraganglioma, pheochromocytoma [13] and [14], and downregulated in sporadic clear cell carcinomas [15] and deleted in neuroblastoma [16,17].The FH gene has been classified as a tumor suppressor gene [18,19].

Our patients reported a negative family history for renal cancer and cutaneous leiomyomatosis. At last follow-up, none of the patient's immediate family members had been tested for germline FH mutations, limiting further analysis of familial cancer predisposition.

In a recent review of a large database of approximately 90,000 cases evaluated for genomic alterations [20], only 4 other patients were found to have the specific alteration identified in this prostate patient. Of the 1339 patients with prostate cancer, 3.6% prostate undifferentiated carcinomas, 3.0% prostate acinar adenocarcinomas, and 1.4% prostate neuroendocrine carcinomas had FH alterations.

The application of next-generation sequencing (NGS) has substantially increased our understanding of prostate cancer biology [21,22]. Detection of germline and somatic mutations in prostate cancer patients not only expands the current repertoire of driver mutations and downstream effectors in tumorigenesis, but also sheds light on how oncometabolites may exert their oncogenic roles. Another potential benefit of identifying metabolic-enzyme gene mutations that are pathogenic in prostate cancer is that such cancers may be susceptible to pharmacologic manipulations that are more effective and less toxic than existing therapies [21-23].There are currently no FDA approved therapies for this patient's tumor type nor of any other tumor type with the same mutation. In our case, alterations in the C-terminal binding domain of FH might be pathologically significant and inform drug development. Several therapeutic approaches for targeting the metabolic basis of FH-deficient kidney cancer are under development or are being evaluated in clinical trials [24-26]. A Phase 2 trial of bevacizumab and erlotinib reported overall response rate in 60% of patient with HLRCC [27]. The findings from this case and previous report [20], suggest that deregulation metabolic pathway activation may contribute to prostate cancer pathogenesis.

CONCLUSION

We described here a novel mutation in the FH gene in a 63-year-old African American man with advanced prostate cancer. To our knowledge, this is the first reporton prostate cancer with somatic FH mutation. In addition, we identify somatic mutations in multiple genes known to be involved in aerobic glycolysis ("Warburg-like" profiles) in the same tumor sample of prostate cancer.Our observations suggest that deregulation metabolic pathway activation may contribute to prostatecancer carcinogenesis; novel therapy should be developed for this subgroup patients.Finding more cases of prostate cancer with "Warburg-like" profiles is essential to promote translational research and design future clinical trials.

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