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Unveiling the molecular profile of a prostate carcinoma: implications for personalized medicine

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Abstract

Background Prostate cancer is the most common diagnosed tumor and the fifth cancer related death among men in Europe. Although several genetic alterations such as ERG-TMPRSS2 fusion, MYC amplification, PTEN deletion and mutations in p53 and BRCA2 genes play a key role in the pathogenesis of prostate cancer, specific gene alteration signature that could distinguish indolent from aggressive prostate cancer or may aid in patient stratification for prognosis and/or clinical management of patients with prostate cancer is still missing. Therefore, here, by a multi-omics approach we describe a prostate cancer carrying the fusion of TMPRSS2 with ERG gene and deletion of 16q chromosome arm.

Results We have observed deletion of KDM6A gene, which may represent an additional genomic alteration to be considered for patient stratification. The cancer hallmarks gene signatures highlight intriguing molecular aspects that characterize the biology of this tumor by both a high hypoxia and immune infiltration scores. Moreover, our analysis showed a slight increase in the Tumoral Mutational Burden, as well as an over-expression of the immune checkpoints. The omics profiling integrating hypoxia, ROS and the anti-cancer immune response, optimizes therapeutic strategies and advances personalized care for prostate cancer patients.

Conclusion The here data reported can lay the foundation for predicting a poor prognosis for the studied prostate cancer, as well as the possibility of targeted therapies based on the modulation of hypoxia, ROS, and the anti-cancer immune response.

Keywords Prostate cancer, KDM6A, Hypoxia, ROS, Immune response, Personalized medicine

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Background

Prostate cancer (PC) is widely recognized for its elevated occurrence and genomic variability [1] resulting in significant gene alteration [2, 3]. In 2020, the reported number of new cases exceeded 1,414,000 worldwide, with over 375,300 related deaths, underscoring the substantial global impact and burden associated with this neoplasia (https://gco.iarc.fr/tomorrow). Approximately 80% of cases are initially localized, while 20% exhibit metastasis to regional lymph nodes (13%) or distant organs (6–7%) at the time of diagnosis. The presence of metastasis significantly impacts the 5-year survival rate, reaching 100% for localized cases and dropping to 30% for those with metastasis. PC exhibits an extended natural progression, categorized through various parameters including prostate-specific antigen (PSA) levels, histological features, TNM classification, and clinical conditions such as localized PC, advanced PC, and metastatic PC [4–6].

Treatment is currently depending on the stage of the tumor, evaluated both at clinical and histological level. Accordingly, the main therapeutical options include active surveillance, radical prostatectomy, or standalone external-beam radiation therapy [7]. Despite the slow growth of prostate lesions, metastatic formations typically emerge around a decade post-diagnosis, posing a substantial health challenge in patient management [2, 8]. The current clinical and histological prognostic parameters used for PC management are still in evolution. PSA levels used for early screening or recurrence detection, are influenced by several factors such as aging and inflammation [9]. The Gleason score, as well as its new Gleason Group classification, provides a more straightforward representation for clinicians and support in treatment decisions [10]. Nonetheless, several studies demonstrate that PC lesions with the same Gleason group can exhibit different biological behaviors and responses to treatment [11, 12]. In this context, the search of specific molecular profile for PC gains prominence. By integrating molecular markers, genomic profiling, and advanced technologies, researchers and clinicians aim to refine the stratification of PC. A molecular characterization not only holds the promise of improving prognostic accuracy but also opens new perspectives for the development of targeted therapies.

In recent years, molecules implicated in various signaling pathways have been suggested as targets for PC diagnosis, prognosis, and personalized therapies [13–15]. Specifically, germline mutations in DNA damage repair genes [16], pathways associated with cancer-related hypoxia [17], cell death [18], epithelial-to-mesenchymal transition (EMT) [19–21], proliferation, and anti-tumoral immune response have been proposed as main drivers of PC occurrence and progression. Tumor hypoxia, stemming from an irregular and dysfunctional vascular network within the tumor, represents a significant barrier to the effectiveness of immunotherapy [22]. Indeed, hypoxia gives rise to an immunosuppressive tumor microenvironment (TME) [23] by fostering processes such as angiogenesis, metabolic reprogramming [24, 25], remodeling of the extracellular matrix, the EMT, p53 inactivation [26–30], and evasion of the immune response [31–34]. Hence, mitigating cancer-associated hypoxia could potentially serve as an effective strategy to decrease PC proliferation, as well as enhance the effectiveness of various conventional and unconventional treatments, including hormone therapy or immune modulation. In particular, the possibility to modify the anti-tumoral immune response is becoming a therapeutic choice for patients with recurrent PC, as recent evidence has demonstrated the overexpression of immune checkpoint molecules such as PDL-1 and CTLA4 in PC [35–37].

The convergence of morphological and molecular evidence could provide a comprehensive understanding of PC, offering clinicians the tools they need to make more informed decisions regarding prognosis and personalized therapeutic interventions [38, 39]. This synthesis of traditional pathology and cutting-edge molecular biology represents a crucial step forward in advancing our capabilities to detect and cure PC.

To achieve this goal, comprehensive data related to the molecular characterization of specific PC cases are essential. In light of this, in this case report, we present a thorough morphological and multi-omics investigation of a PC sample from a 69-year-old patient. This analysis highlights intriguing molecular aspects that characterize the biology of this tumor such as immune checkpoints up-regulation and very high hypoxia and proliferation molecular signature scores. This paradigmatic case demonstrates the need to individual multi-omic analysis.

Methods

Collection of samples

Tumor tissues collection was performed using standardized protocol [40, 41]. Hematoxylin and Eosin (H&E) stained serial sections were used for pathological quality control (QC). Criteria for selecting tumor samples included a tumor content of at least 30%, necrosis less than or equal to 30%, and the presence of invasive tumor cells. Adjacent normal tissues were also procured. Protein lysate preparation and nucleic acid extraction were carried out using 10 mg of each tissue specimen [42–45]. Throughout the procedure, tissues remained frozen to maintain integrity.

Histological examination utilized serial sections from formalin-fixed and paraffin-embedded (FFPE) blocks [47–49]. Two independent pathologists conducted

histological analysis on hematoxylin and eosin (H&E)-stained slides.

Nucleic acid extraction and quality assessment

As previously described, frozen tissue slices were used for nucleic acid extraction and quality assessment [50].

Library preparation and NGS sequencing

Libraries for whole genome sequencing (WGS) and whole transcriptome sequencing were performed as previously described [50].

NGS data processing

To align NGS data, Grch38 genome assembly was used as reference. As concern the normal samples, the Haplotype Caller from the Genome Analysis Toolkit (GATK) was used for both identification and annotation of short genomic variations. WGS somatic variations were called using a consensus of Mutect2 [51], Strelka [52], Varscan [53] and Somatic Sniper [54]. Structural variations were called using R packages TitanCNA [55], DellyCNV and DellyCall [56], as well as Manta [57]. RNA-Seq differential expression was based on normalized readcount data (TPM: transcripts per million).

Bioinformatical analyses

Mutational signatures were calculated using the R package MutationalPatterns [58–61]. MSI classification was done using R package MSIseq [63]. Metrices to define chromosomal instability were determined using R package CINmetrics [50] and CNHplus [64]. Aneuploidy events were analysed using ASCETS [65]. Aneuploidy event span more than 90% of the chromosome. Visualization of results was done in IGV [66]. TMB was calculated as the number of non-synonymous mutations of protein coding genes divided by exome size in Megabases.

Results and discussion

A 69-year-old patient underwent radical prostatectomy due to the presence of a suspicious nodule in the apical and left posterolateral region. Histological examination allowed the identification of several multifocal cancer lesions, the largest of which measured 2.3 cm. According to the WHO grade, the lesion was classified as an acinar prostate infiltrating carcinoma with a Gleason score of 9 (4+5), grade group 5, very aggressive PC. In the upper left lateral portion of the prostate, the carcinomatous lesion infiltrated the prostatic apex and the surrounding adipose tissue. No metastatic lymph nodes were detected. According to the TNM classification, the tumour was staged as pT2c pN0. The patient did not undergo previous therapy.

Genomic and transcriptomic profile of the prostate cancer revealed ERG-TMPRSS2 gene fusion [37] (Fig. 1). This genomic alteration was first described in 2005 [66] and is characterized by a chromosomal rearrangement that leads to the fusion of the promoter region of the transmembrane protease serine 2 (*TMPRSS2*) (locus 21q22.3) with locus 21q22.2 carrying the gene ERG, a member of the transcription factor erythroblastosis virus E26 transforming sequence family (ETS). In agreement with the literature [67], our transcriptomic analysis show that both genes are also highly up regulated in our patient of interest (log2FC: 6.4 and 5.1) (Fig. 1A and B). In addition, we have also found several chromosome rearrangements including large chromosomal deletions (>90% of the chromosome arm) in chromosome arms 16q (cohort: 5.6%) and 18q (cohort: 19.4%), which have been already reported in prostate cancer [68, 69] (Fig. 1C). These alterations are predictors of poor prognosis. Indeed, they are associated with advanced tumor stage, high Gleason score and increased risk of biochemical recurrence [70, 71]. ERG fusion positive PC show a higher frequency of 3p13, 16q23, TP53 and PTEN deletion [72, 73]. In agreement, analyzed PC shows both deletion of 16q and ERG fusion [74].

PC is associated with the accumulation of somatic mutations in the prostate epithelial involving mainly genes that modulate cell growth, cell proliferation, cell death and DNA damage response [75]. However, the mutational burden of prostate cancer is very low [76] and copy number changes and chromosomal rearrangement are the most characteristic genomic alterations displayed in PC [77]. In keeping, we did not find somatic mutations in cancer related genes. Nevertheless, we observed some germline mutations affecting genes involved the regulation of DNA damage response (Table 1). To further support this, the DNA mismatch repair (MMR) signature has a slightly increased frequency (Fig. 2A).

Relevant studies revealed genetic abnormalities affecting DNA repair mechanisms in almost 20–30% of advanced castration-resistant PCs, some of which are inherited and present in the germline [78]. Phase II/III clinical trial findings, along with additional clinical evidence, endorse the exploration of PARP inhibitors and DNA-damaging agents in this specific molecular PC subgroup, building upon successes observed in other cancer types [79–82]. These investigations present a promising avenue for enhancing patient care through tailored therapeutic approaches. The increase in MMR signature suggests the potential for these innovative therapies for patients of our interest.

Compared to a cohort of 40 pancreatic cancer patients, the analysed PC sample also exhibited elevated reference signature 18 (Fig. 2A). According to the Human Genome Variation Society, this signature is linked to C>A a mutation resulting from ROS-induced guanine oxidation, indicating high levels ROS in the tumor environment.

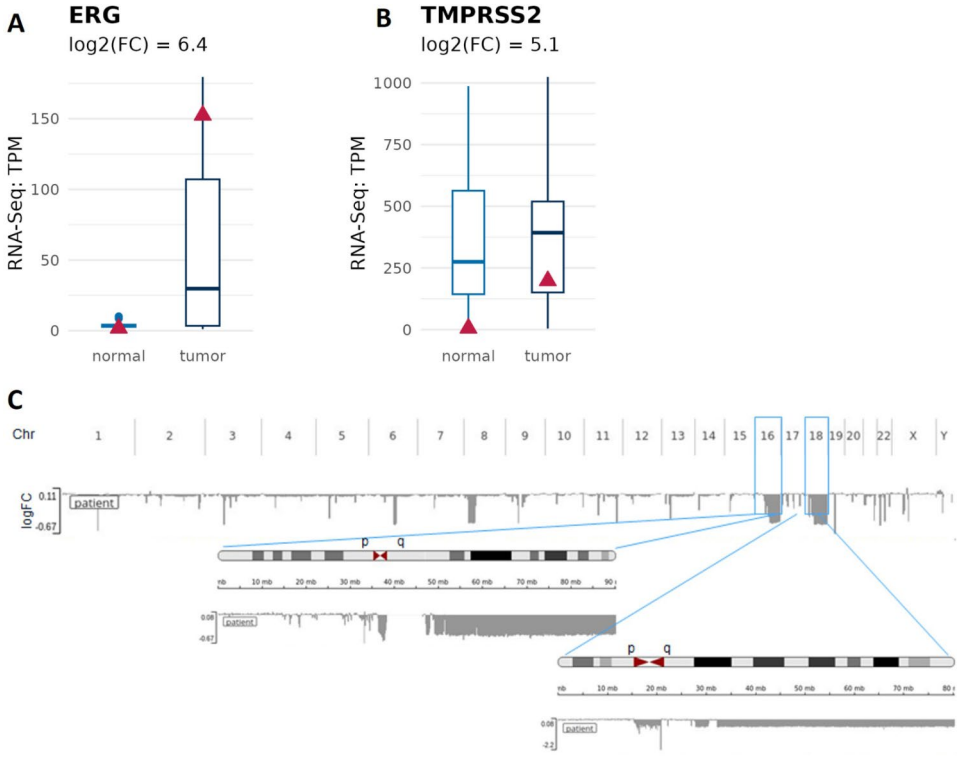

Fig. 1 Tumor isolated from our patient of interest carries ERG-TMPRSS2 gene fusion. **A)** ERG mRNA expression is higher in tumor tissue of our patient of interest when compared to the normal adjacent tissue. **B)** TMPRSS2 mRNA expression is higher in tumor tissue of our patient of interest when compared to the normal adjacent tissue. RNA levels were assessed by RNA sequencing; TPM = transcripts per million. **C**) Image shows aneuploidy of analyzed PC tissue. Boxplots indicate the values of prostate cancer background cohort, and the red triangle refers to our patient of interest

Table 1 Germline variation in genes belonging to DNA damage response pathways in the patient of interest

Symbol	Transcript	Effect	AA change
APEX1	ENST00000216714.7	missense variant	Asp148Glu
BARD1	ENST00000432456.5	splice region variant	
BRCA1	ENST00000357654.7	missense variant	Ser1613Gly
BRCA1	ENST00000357654.7	missense variant	Glu1038Gly, Pro871Leu
CHEK1	ENST00000428830.6	missense variant	Ile471Val
EME1	ENST00000338165.8	missense variant	Glu69Asp
ERCC2	ENST00000391945.8	missense variant	Lys751Gln, Asp312Asn
ERCC4	ENST00000311895.7	splice region variant, intron variant	
ERCC5	ENST00000355739.8	missense variant	Gly1053Arg, Gly1080Arg
ERCC6	ENST00000355832.9	splice region variant, intron variant	
EXO1	ENST00000348581.9	missense variant	Val458Met
FANCA	ENST00000567510.1	frameshift variant	Glu77fs
FANCM	ENST00000267430.9	missense variant	Asn1253Ser, Asn1876Ser
GEN1	ENST00000317402.11	missense variant	Ser92Thr
LIG4	ENST00000356922.5	missense variant	Ala3Val
PMS1	ENST00000409985.5	frameshift variant	Leu164fs
PMS2	ENST00000265849.11	missense variant	Gly857Ala
POLE	ENST00000320574.9	missense variant	Pro1549Ala
POLE	ENST00000320574.9	missense variant	Phe695Ile
POLM	ENST00000492605.5	splice region variant, non coding transcript exon variant	
SEM1	ENST00000606019.5	splice region variant, intron variant	
TOPBP1	ENST00000260810.9	missense variant	Asn1042Ser

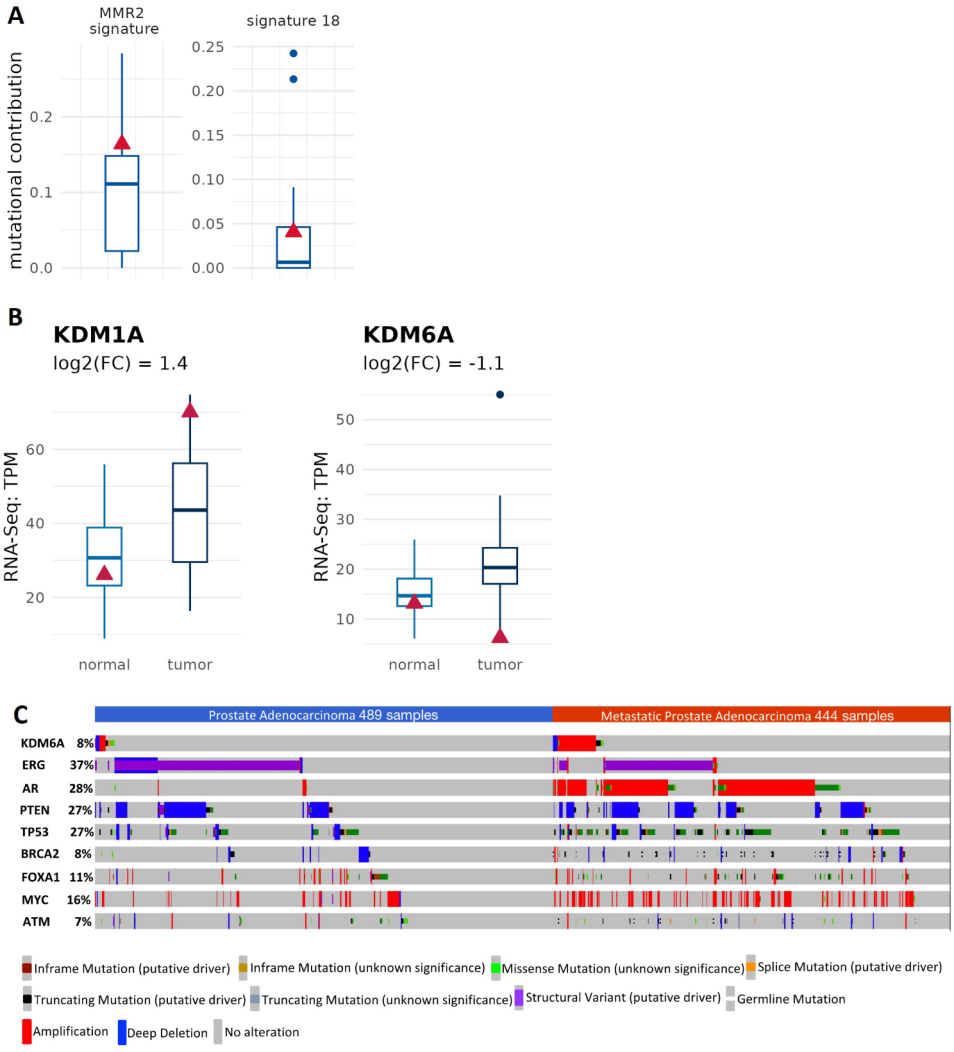

Fig. 2 MMR and ROS related signatures. **(A)** Prostate cancer isolated from the patient of interest display a prevalence in MMR2 signature and slightly elevated contribution to signature 18. **(B)** RNA-Seq analysis showing an increase in the KDM1A expression and a reduction in the KDM6A mRNA levels. **(C)** KDM6A genetic alterations in prostate adenocarcinoma and metastatic adenocarcinoma. An oncoPrint of individual patient tumours which are positive for genetic alterations in KDM6A compared to the most representative genes involved in the pathogenesis of prostate cancer. Patient cohorts (Prostate Adenocarcinoma: TCGA, PanCancer Atlas; Metastatic Prostate Adenocarcinoma: SU2C/PCF Dream Team, PNAS 2019). Boxplots indicate the values of prostate cancer background cohort, and the red triangle refers to our patient of interest

ROS seems indeed associated with poor prognosis, cancer progression, and importantly, resistance to common treatments such as chemotherapy [83, 84]. Therefore, reducing ROS levels could represent a strategy for improving the success of anti-cancer treatments in patients with high reference signature 18. Of note, in our case we have also detected the deletion of the gene coding for lysine demethylases 6 (KDM6A) (Fig. 2B). In PC several epigenetic alterations have been described [85–87], including overexpression of histone lysine demethylases LSD1/KDM1A [88, 89] which is associated with an increased proliferation. To our best knowledge, here for the first time is described a deletion of KDM6A in human PC. To further characterize KDM6A genetic alterations in PC, we took advantage of the online tool cBioPortal for cancer genomics [90–92] for searching genetic alterations across both prostate adenocarcinoma and metastatic prostate adenocarcinoma. As shown in Fig. 2C, the variation frequency of KDM6A is about 8% (cBioPortal), frequency that is comparable with two relevant genes in prostate cancer such as BRCA2 [93] and ATM [94]. The most representative alterations are amplification and deep deletion. Moreover, in few patients several mutations have been identified, including truncating, splice and missense mutations. Among them, truncating mutations of KDM6A have been described mainly in bladder cancer, where are considered likely oncogenic [95]. In particular, those mutations lead to increased cell proliferation and migration. There are also evidences that loss of KDM6A may have a role in resistance to chemotherapy

in acute myeloid leukaemia [96]. Moreover, our bioinformatic analysis highlights a subset of patients in which KDM6A gene is amplified, suggesting a possible oncogenic function. Therefore, further investigation is needed to understand whether KDM6A acts either as tumor suppressor gene or oncogene in PC and whether it can potentially play a role as biomarkers for predicting patient prognosis and/or a possible pharmacological target. Beside the classification of tumor subtype by genomic alterations that may assist in predicting prognosis and to guide treatment decision [97], gene expression signature may be a complementary approach to identify biomarkers for a better management of cancer patients. Our RNA-Seq analysis indicates that tumor isolated from our patient of interest is characterized by a high hypoxia (Fig. 3A) and immune infiltration scores (Fig. 3B), which is associated with worse prognosis [98, 99]. The RNA-Seq analysis conducted on PC unveils a striking increase in the expression of hypoxia-related genes. This suggests a profound hypoxic state within the tumor microenvironment, likely stemming from inadequate oxygen supply due to rapid tumor growth and aberrant vasculature [100–102].

Hypoxia is currently considered a hallmark feature of aggressive cancers, including PC, and is closely associated with poor prognosis [103]. Specifically, hypoxia plays a multifaceted role in shaping the tumor microenvironment and promoting cancer progression. By inducing angiogenesis, metabolic reprogramming, extracellular matrix remodeling, epithelial-mesenchymal transition, p53 inactivation, and immune evasion, hypoxia creates a hostile environment that facilitates tumor growth and metastasis [17, 26, 104]. One notable consequence of hypoxia is the suppression of anti-tumor immune responses within the tumor microenvironment [105, 106]. Therefore, we asked whether immunotherapy may be an option for treating patients that share the same profile of genomic alterations found in our case. To do so, we assessed the specific immunotherapy markers that may hold clinical relevance such as TMB, MSI and immune checkpoint gene expression [107]. As shown in Fig. 4A and B, tumor isolated from our patient of interest show a slight increase in TMB, low MSI and is also chromosome stable. Gene expression profile of PC displays an upregulation of immune checkpoints as CTLA-4, PD-1 and PD-L2 (Fig. 4C). Overall, these biomarkers indicate that in this patient the immunotherapy with checkpoint inhibitors would be recommended.

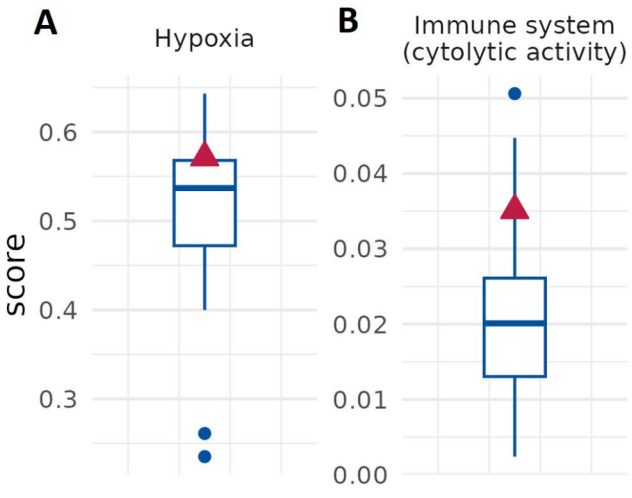

Fig. 3 Cancer gene expression signature. Elevated hypoxia (**a**) and immune system signature (**b**) scores are detected in patient's cancer. Red triangle refers to our patient of interest, boxplots to the prostate cohort

In this context, vascular normalization, a therapeutic approach aimed at restoring the structure and function of tumor blood vessels, has emerged as a promising strategy to counteract the effects of hypoxia in cancer [108]. By improving oxygen delivery and reversing hypoxia-induced signaling pathways, vascular normalization can alleviate the hypoxic conditions within tumors. This, in turn, could elevate the efficacy of cancer immunotherapy by creating a more favorable tumor microenvironment for immune cell infiltration and activation. According to this, we also observed the downregulation of miR-224-5p (Fig. 5A). In fact, this miRNA is involved in the complex network that link hypoxia and anti-cancer immune response [109]. Indeed, the miR-224-5p capability to affect the anti-cancer activity of NK cells on PC is regulated by HIF-1α via NCR1/NKp46 pathway. In light of this, the investigated PC tumor was characterized by the presence of few infiltrated NKs (Fig. 5B).

Overall, strategies that target hypoxia and promote vascular normalization hold great potential for improving cancer treatment outcomes, particularly in the context of immunotherapy. By addressing the immunosuppressive effects of hypoxia and enhancing anti-tumor immune responses, these approaches offer new avenues for enhancing patient survival.

Conclusion

The presented case underscores the crucial importance of molecular profiling in prostate carcinomas, emphasizing the shift towards personalized medicine [25, 105, 110, 111]. By identifying specific genomic aberrations such as the ERG-TMPRSS2 gene fusion, deletion of KDM6A, and elevated immune checkpoint expression, we gain invaluable insights into the underlying mechanisms of tumor development and progression. Furthermore, the detection of the MMR signature and ROS-associated reference signature 18 suggests the potential for targeted therapeutic interventions tailored to the individual patient's molecular profile. These findings emphasize the importance of comprehensive molecular characterization in guiding treatment decisions and improving

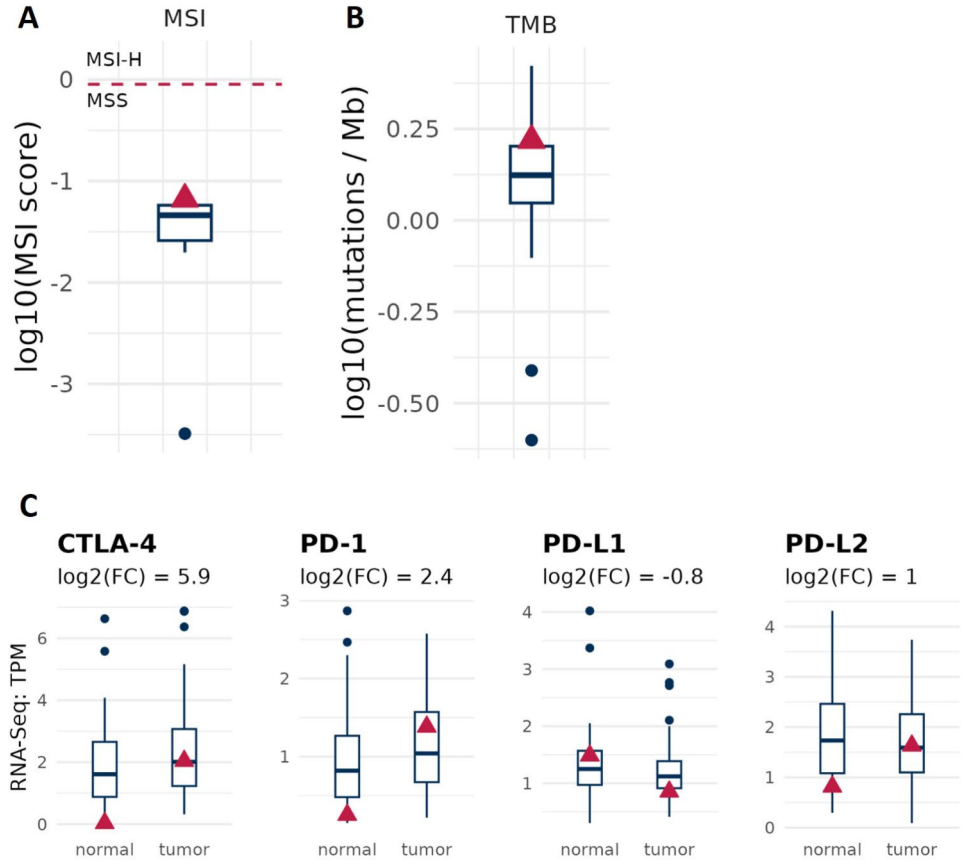

Fig. 4 Immunotherapy markers in our patient. **(A)** Tumor isolated from the patient show elevated tumor mutational burden (TMB). **(B)** microsatellite instability (MSI) compared to the prostate cohort. **(C)** RNA-Seq expression levels of immune checkpoint genes in the patient. CTLA-4, PD-1 and PD-L2 mRNA expression is increased in tumor tissue when compared to the adjacent normal tissue. Boxplots indicate the values of prostate cancer background cohort, and the red triangle refers to our patient of interest

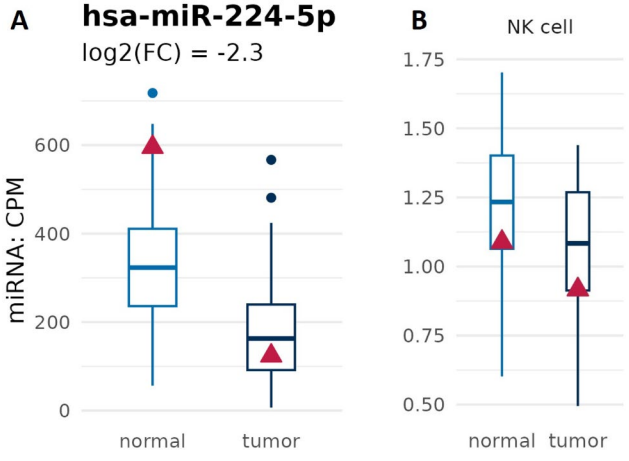

Fig. 5 has-miR-224-5p expression and NK cells tumoral infiltration. **(A)** Graph shows downregulation of has-miR-224-5p in the analyzed PC tissue. **(B)** Few NK cells in the PC. Boxplots indicate the values of prostate cancer background cohort, and the red triangle refers to our patient of interest

patient outcomes [112–114]. Moving forward, integrating molecular profiling into clinical practice holds great promise for optimizing therapeutic strategies and advancing personalized care for PC patients. Specifically, the data reported here lay the foundation for predicting a poor prognosis for the studied PC, as well as the possibility of targeted therapies based on the modulation of hypoxia, ROS, and the anti-cancer immune response.

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Not applicable.

Author contributions
MA, GM, JB, AM and PB conceived the project, MA, GM, JB, MS, YS, GS, EC, GC, JH and FL wrote the manuscript; EG, VR, FS, JB, MC, VI and MS prepared figures. All of the Authors have approved this submitted version.

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Data availability
Data will be made available on reasonable request.

Declarations

Ethical approval
All the procedures carried out in the research with participation of humans were in compliance with the ethical standards of the institutional and/or national ethics committee and with the Helsinki Declaration of 1964 and its subsequent changes or with comparable ethics standards. Informed voluntary consent was obtained from every participant of the study: Approval on 09-2019, number 96 – 19. It is not a clinical trial.

Consent for publication
Not applicable.

Competing interests
GM is editor in Biology Direct.

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