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[Nidha Shapoo](#)*, [Carlos Izaguirre](#), Abdul Rehman, Joseph Mattana, Vladimir Gotlieb

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Case Report

Syndrome of Inappropriate Antidiuretic Hormone Secretion and Thrombotic Microangiopathy as Paraneoplastic Syndromes Complicating BRCA2-Mutated Metastatic Prostate Cancer

Nidha Shapoo *, Carlos Izaguirre, Abdul Rehman, Joseph Mattana and Vladimir Gotlieb

Department of Medicine, New York Medical College/NYC Health + Hospitals/Metropolitan, New York, NY, United States of America.

* Correspondence: nidha.shapoo@gmail.com

Abstract

Background: Metastatic prostate cancer with BRCA2 mutation is associated with aggressive clinical behavior and poor outcomes with standard systemic therapy. While the BRCA2 mutation predicts response to PARP inhibitors and platinum agents, its association with paraneoplastic syndromes is not well described. **Case Presentation:** We report a 72-year-old male who presented with altered sensorium with severe hyponatremia who was diagnosed with syndrome of inappropriate antidiuretic hormone secretion (SIADH) in the context of newly diagnosed metastatic prostate adenocarcinoma. He was treated with free water restriction, hypertonic saline, and triplet systemic therapy (docetaxel, androgen deprivation, and darolutamide) and discharged in stable condition. After one year of disease remission, he developed generalized weakness, hematuria, thrombocytopenia, hemolytic anemia, and renal impairment. Peripheral smear demonstrated schistocytes, consistent with thrombotic microangiopathy (TMA). Bone marrow biopsy confirmed metastatic adenocarcinoma with a BRCA2 frameshift mutation (p. Trp1692MetfsTer3). ADAMTS13 activity was normal, excluding thrombotic thrombocytopenic purpura. He received five cycles of carboplatin/docetaxel chemotherapy along with blood and platelet support, with clinical and hematologic recovery, and was discharged on Olaparib, abiraterone, and leuprolide. Despite initial improvement, he succumbed to the disease within two months. **Discussion:** This case illustrates the aggressive biology of BRCA2-mutated prostate cancer, characterized by rapid progression and limited durability of standard therapies. While SIADH and TMA have been individually reported in prostate cancer, their sequential occurrence in a BRCA2-mutated setting is unique. The case highlights the vigilance for atypical paraneoplastic manifestations, the need for early genomic testing, and the exploration of novel therapeutic strategies in BRCA2-driven disease. **Conclusion:** We present the first reported case of BRCA2-mutated metastatic prostate cancer complicated by the sequential development of SIADH and TMA, underscoring the aggressive clinical trajectory and poor prognosis associated with this molecular subtype.

Keywords: metastatic prostate cancer; BRCA2 mutation; SIADH; hematologic abnormalities; thrombotic microangiopathy; aggressive subtype

Introduction

Metastatic prostate cancer (mPC) is an aggressive disease with a median overall survival ranging approximately between 18 and 36 months [1]. Metastatic castrate resistant prostate (mCRPC) cancer is the most aggressive form, where patients develop resistance to androgen deprivation therapy [2]. The heterogeneity in outcomes for mCRPC is suggested to be due to the underlying molecular genetic features. The most essential genomic mutations are alterations in DNA damage repair genes,

including those involved in DNA homologous recombination repair (HRR), found in up to 30% of mPC. The most common HRR alterations in mCRPC are found in BRCA2, seen in approximately 3-15% of patients [3]. BRCA2-mutated prostate cancers have a more aggressive course with a poor response to chemotherapy and hormonal agents; however, this mutation predicts response to poly ADP-ribose polymerase (PARP) inhibitors [4,5]. While BRCA2-mutated prostate cancer is recognized for its aggressive clinical course, paraneoplastic syndromes and thrombotic microangiopathy (TMA) have not been well described in this subset. Here we report a rare case of BRCA2-mutated metastatic prostate cancer complicated by the sequential development of SIADH and TMA, highlighting an unusual paraneoplastic scenario and a fatal course.

Case Presentation

A 72-year-old man with hypertension presented to the hospital with altered sensorium. He was drowsy with an otherwise unremarkable physical examination, including the absence of any focal neurological deficits. His blood pressure was 130/78 mmHg, heart rate 80/min, temperature 37.5 °C, and SPO2 97% on room air. The results of laboratory investigations are shown in Table 1.

Table 1. Laboratory Investigations.

Components	Result
Hemoglobin	13 g/dL
Total Leukocyte Count	4500/microL
Platelet Count	156000/microL
Serum Sodium	126 mEq/L
Serum Potassium	3.8 mEq/L
Blood Urea Nitrogen	5 mg/dL
Serum Creatinine	0.7 mg/dL
Blood Glucose	154 mg/dL
Serum Osmolality	245 mOsm/kg
Urine Osmolality	468 mOsm/kg
Urine Sodium	75 mEq/L.

Computed tomography (CT) of the head did not show any abnormality. CT of the abdomen and pelvis with contrast revealed an enlarged prostate, retroperitoneal lymphadenopathy, and multiple osteoblastic bone lesions suggestive of metastatic prostate cancer. The prostate-specific antigen (PSA) was markedly elevated at 521 ng/mL. Urology was consulted, and a prostate biopsy was done, which revealed acinar adenocarcinoma with a Gleason score of 9. The cancer was high-risk, with extra prostatic extension and perineural invasion. Bone scan confirmed widespread metastatic lesions in the axial skeleton. Given his hypotonic hyponatremia in the setting of apparent euvolemia, an inappropriately concentrated urine, normal urine sodium, and absence of other factors that may cause hyponatremia, a diagnosis of SIADH was made.

The patient was treated with fluid restriction, furosemide, and a 3% NaCl solution, resulting in a gradual increase in serum sodium to 135 mEq/L. Triplet therapy consisting of docetaxel, androgen deprivation therapy (bicalutamide followed by Leuprolide), and darolutamide was started, and the patient was discharged in stable condition for outpatient follow-up. He went into remission after six cycles of docetaxel with normalization of PSA to 2.95 ng/mL, and he was continued on leuprolide and darolutamide.

After six months of chemotherapy, the patient presented with generalized weakness and hematuria. The results of laboratory investigations on this admission are shown in Table 2.

Table 2. Laboratory Investigations.

Components	Result
Hemoglobin	8.7 g/dL
Total Leukocyte Count	5920/microL
Platelet Count	25000/microL
Serum Sodium	129 mEq/L
Serum Potassium	4 mEq/L
Blood Urea Nitrogen	20 mg/dL
Serum Creatinine	1.6 mg/dL
Blood Glucose	120 mg/dL
Total Bilirubin	1.8 mg/dl
Direct Bilirubin	0.4 mg/dL
Indirect Bilirubin	1.4 mg/dL
Aspartate transaminase	181U/L
Alanine transaminase	12U/L
Alkaline phosphatase	919U/L
Serum lactate dehydrogenase	1738 IU/L
Reticulocytes	4.91
Serum Haptoglobin	< 20 mg/dL
Serum PSA	1332 ng/mL

The PSA of 1,332 ng/ml was strongly suggestive of disease progression. The peripheral smear revealed schistocytes, nucleated RBCs, and immature granulocytes, suggesting TMA (Figure 1). A bone marrow biopsy confirmed metastatic prostate adenocarcinoma and revealed a BRCA2 mutation (p.(trp1692MetfsTer3) (Figure 2). The patient’s PLASMIC score was 4, and ADAMTS13 activity was normal (81%), ruling out thrombotic thrombocytopenic purpura. The patient was treated with five cycles of docetaxel/carboplatin along with blood product support. Hyponatremia was managed with fluid restriction. The patient showed marked clinical and laboratory improvement with normalization of hematological abnormalities, liver enzymes, renal functions, and hyponatremia. The patient was discharged on a combination of Olaparib, abiraterone, and leuprolide. Two months later, the patient relapsed and died.

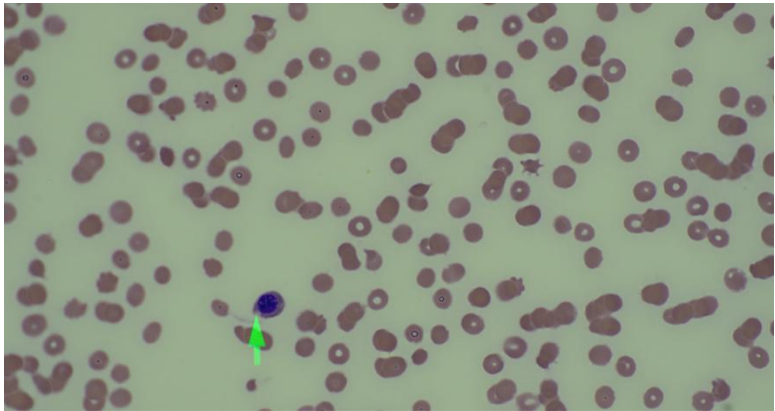


Figure 1. Peripheral smear shows nucleated red blood cells and schistocytes.

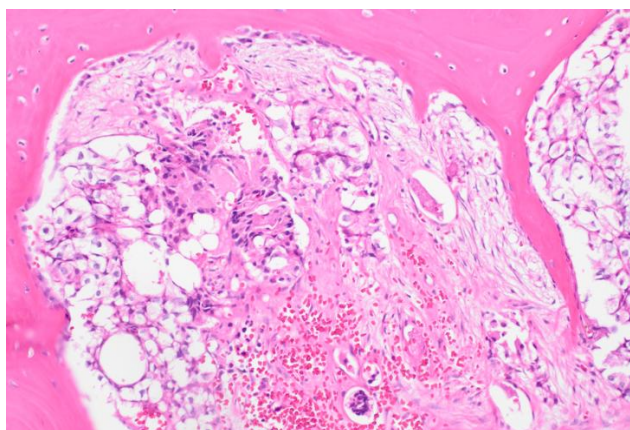


Figure 2. Bone Marrow biopsy showing metastatic prostate carcinoma, H&E, 100x.

Discussion

Paraneoplastic syndromes are rare in prostate cancer. SIADH in prostate cancer has been reported as case reports, with some reports showing an association with poorly differentiated or small cell histology resulting from ectopic secretion of ADH (vasopressin) from tumor cells. SIADH may be the presenting manifestation of cancer or develop during disease progression. Water restriction is the standard initial treatment, though the primary treatment lies in the control of the underlying cancer [6–8]. Abe et al. reported SIADH and humoral hypercalcemia of malignancy in a patient with prostate cancer and pulmonary metastases [8]. The patient was treated with water restriction, hypertonic saline, tolvaptan, and radiation to the prostate due to local symptoms. The serum sodium improved from 114 mEq/L at presentation to 135 mEq/L at discharge [8]. In our patient, SIADH was the initial presentation of cancer and developed at the time of progression. Management with water restriction and treatment of the underlying cancer led to significant improvement in the patient's clinical condition and electrolyte balance.

TMA refers to disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction due to thrombus formation affecting small or larger vessels. The most recognized forms of TMA are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). Cancer-associated TMA has been reported to range from 6 to 15% [9]. The exact mechanism by which solid tumors induce TMA is complex and multifactorial. The clinical spectrum may vary widely from asymptomatic abnormal laboratory tests to acute, severe, potentially life-threatening forms due to massive microvascular occlusion. Patients with TMA often present with fatigue, pallor, jaundice, easy bruising, bleeding complications, and acute kidney injury. The diagnosis typically involves a combination of anemia, thrombocytopenia, a peripheral blood smear showing schistocytes, elevated lactate dehydrogenase, non-conjugated bilirubin, and reticulocyte count, and low haptoglobin suggestive of hemolysis. A normal ADAMTS-13 activity rules out TTP. Cancer-associated TMA is mainly associated with adenocarcinoma histology and with advanced disease. The treatment involves treating the underlying cancer, as plasmapheresis, steroids, or other immunosuppressive agents used in TTP have no beneficial role. Complement inhibitors such as eculizumab have shown promise in treating HUS and chemotherapy-induced TMA [9]. Cancer-associated TMA is a rare condition associated with poor prognosis [10]. TMA associated with prostate cancer is rare and exists as case reports [11,12]. Newton et al. described a patient with prostate cancer who was diagnosed with TMA and found to have recurrent prostate cancer with mediastinal lymphadenopathy. The patient underwent two sessions of hemodialysis, blood and platelet transfusions, and a dose of eculizumab. He was started on hormonal treatment for prostate cancer. The patient improved and was discharged in stable condition [11].

BRCA2-mutated prostate cancer is strongly associated with aggressive disease across the continuum. The patients present more often with high-grade tumors, nodal and distant metastases, and have inferior survival compared to BRCA2-negative tumors. In advanced disease, BRCA2

mutations predict earlier castration resistance and poor response to standard hormone therapy and chemotherapy, with real-world data confirming shorter survival. Pathologically, BRCA2 alterations correlate with intraductal/criform histology and genomic features such as BRCA2/RB1 co-loss, which drive aggressive variant clinical behavior [3,4]. Therapeutically, BRCA2 predicts sensitivity to PARP inhibitors and platinum, explaining our patient’s transient response to platinum-based chemotherapy and Olaparib. Nonetheless, responses are often short-lived in this aggressive subtype [5].

Though our patient improved with supportive care and chemotherapy, hormone therapy, and Olaparib for prostate cancer, the remission was short-lasting, and he succumbed to the disease after 2 months.

Our case adds novelty with the occurrence of SIADH at presentation and cancer-associated TMA at progression. Both have been rarely described in prostate cancer, typically with advanced disease, but not explicitly linked to BRCA2. We hypothesize that tumor burden and marrow infiltration in BRCA2-driven disease created a pro-inflammatory, pro-thrombotic milieu predisposing to these syndromes.

Conclusions

To our knowledge, this is the first reported case of BRCA2-mutated metastatic prostate cancer complicated by SIADH and TMA. BRCA2 status is a key driver of aggressive biology in metastatic prostate cancer, and the unique combination of SIADH and TMA observed here underscores the need for clinicians to consider atypical paraneoplastic and microangiopathic phenomena in advanced disease and the importance of early molecular testing, timely BRCA-directed therapy, and trial-based strategies.

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