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Case Report

Prostate cancer-associated thrombotic microangiopathy: A case report and review of the literature

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Abstract

Background: Thrombotic microangiopathy (TMA) is a rare and life-threatening complication of prostate carcinoma. Whether plasma exchange has a role in treatment remains a subject of debate. Here we present a case followed by a systematic review of the literature on this subject.

Case report: We describe a 69-year old patient presenting with TMA, which was associated with an underlying metastatic prostate carcinoma. We conducted a search of similar cases in literature.

Results: Our patient was treated and responded well on plasma exchange. Systematic review of the literature showed 17 additional cases of TMA associated with prostate carcinoma of which eleven were treated with plasma exchange with mostly good response.

Conclusion: Based on current data we cannot exclude a potential role for plasma exchange in prostate cancer associated TMA.

More Information

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Introduction

Thrombotic microangiopathy (TMA) is characterized by endothelial dysfunction, leading to platelet thrombi with thrombocytopenia and microangiopathic haemolytic anemia (MAHA) due to mechanical injury of red blood cells in the microcirculation. Given the heterogeneity of underlying conditions associated with TMA, it has been suggested to classify primary or secondary TMA syndromes [1]. The most common form of primary TMA in adults is "A Disintegrin And Metallo- protease with ThromboSpondin-1-like domains" (ADAMTS13) deficiency mediated TMA also called thrombocytopenic purpura-haemolytic uremic syndrome (TTP). Other forms of primary TMA are complement-mediated TMA, metabolism- mediated TMA, coagulation-mediated TMA, Shiga toxin-mediated TMA and drug-mediated TMA.

Since TMA may also be associated with several disorders, including metastasized malignancy, a thorough diagnostic work-up of these patients is indicated. In adults, given its life-threatening potential, treatment with plasma exchange and corticosteroids is usually promptly initiated. This is in contrast to Shiga toxin-mediated TMA where plasma exchange and corticosteroids have no role in the treatment.

Plasma exchange removes eventually autoantibodies while plasma replaces deficient ADAMTS13 and complement factors [2,3].

In the Oklahoma TTP-HUS registry ten (3%) of 351 patients, initially diagnosed as having TTP-HUS and treated with plasma exchange, were subsequently and unexpectedly diagnosed with disseminated malignancy [4]. This syndrome has been reported in various malignancies (e.g. gastric, lung, breast, lymphoma), including that of the prostate. Interestingly, in approximately 90% of the cases malignancy was metastatic at presentation [5].

Different hypotheses exist on the mechanism of cancer associated thrombotic microangiopathy (CA-TMA). Abnormal angiogenesis in the marrow, aggressive growth of tumours, and secondary myelofibrosis may all injure the endothelial cells [6]. The endothelial damage could then cause the release of ultra large VWF multimeres (UL-VWF) thereby leading to MAHA and thrombocytopenia. Others favor mechanical

obstruction by tumour emboli or intraluminal fibrin thrombi [7,8]. Indeed, cancer microparticles may be involved in the initiation of CA-TMA [9]. whilst also activation of the coagulation pathway through tumour cell pro-coagulants like tissue factor and other cancer pro-coagulants, may contribute to the microvascular obstruction [10,11]. A specific mechanism is proposed for mucin generating cancers [12,13]. Carcinoma mucins generate platelet rich microthrombi through adhesion dependent, bidirectional signaling in neutrophils and platelets [14].

Both the indication for plasma exchange therapy, and the role of ADAMTS13 are not considered to play a role in CA-TMA [15]. We present a case of a metastasised prostate cancer associated with TMA recovering after plasma exchange, followed by a systematic review of the current literature on this subject.

Case report

A 69-year old man presented at the emergency department with a 4-day history of nausea, vomiting and malaise. There was no significant medical history nor was he taking any medication, including over the counter medicine, supplements or herbs. Physical examination revealed mild jaundice, no fever or hypertension and no signs of impaired coagulation or neurological dysfunction.

Laboratory results showed mild anemia with a negative direct antiglobulin (DAT) test, thrombocytopenia and renal failure (Table 1). Although coagulation tests showed increased d-dimers, fibrinogen was not decreased and no signs of deep venous thrombosis or fulminant disseminated intravascular coagulation were found. The peripheral blood smear revealed fragmentocytes (Figure 1).

Immediate treatment with plasma exchanges and prednisone was initiated. ADAMTS13 level obtained prior to plasma exchange -and reported a day post admission- was not decreased (70%). Given the latter, we decided to omit prednisone and continue plasma exchange after one day. Additional investigations revealed an adenocarcinoma (Gleason 4+5 = 9) of the prostate with an elevated serum prostate specific antigen of 296 ug/L (normal < 4 ug/l) with multiple skeletal metastases. After a total of seven sessions of plasma exchanges, the renal function, thrombocytes and lactate dehydrogenase recovered. The patient was prescribed biculatamide 50 mg daily and was discharged from the hospital after seven days. At 2 years follow-up the TMA has not recurred and the patient was doing well with a stable renal function (creatinine 102 umol/L) and PSA of 2.6 ng/ml.

Discussion

Previously reported cases were identified by searching PubMed and Embase databases (search strategy showed in the supplement). We found 17 cases as summarized in table 2. We excluded cases not available in English.

Table 1: Laboratory results.

Variable	On admission	Day 7
Hemoglobin (8,1-11,0 mmol/L)	7.9 mmol/L	5.2 mmol/L
MCV (80-100 fl)	87 fl	94 fl
Platelet count (150-400 x 10^9/L)	36 x 10^9/L	399x10^9/L
White blood cell count (4.0-10.0 x 10^9/L)	15.8 x 10^9/L	10.6 x 10^9/L
Haptoglobin (0.5-3.0 g/L)	0.08 g/L	2.9 g/L
Reticulocyte count (25-100 x 10^9/L)	31 x 10^9/L	UA
Urea (3,0-7,0 mmmol/L)	29.9 mmol/L	11.2 mmol/L
DAT	NEGATIVE	UA
Bilirubin total (< 17 umol/L)	39 umol/L	7 umol/L
LD (150-300 u/L)	1279 u/L	189 u/L
ASAT (0-30 u/L)	52 u/L	16 u/L
ALAT (0-30 u/L)	22 u/L	31 u/L
Potassium (3.5-5.0 mmol/L)	3.8 mmol/L	4.5 mmol/L
Fibrinogen (1.74-4.0 g/L)	3.9 g/L	NA
INR	1.2	1.1
PT (10-13 sec)	13.2 sec	12.6 sec
D-dimer (< 5 mg/L)	6.59 mg/L	6.59 mg/L
APTT (22-33 sec)	28 sec	23 sec
Creatinine	284 umol/L	140 umol/L
eGFR	19 ml/min	44 ml/min

MCV: Mean Corpuscular Volume; DAT: Direct Antiglobulin; INR: International Normalized Ratio; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; LD: Lactate Dehydrogenase; AF: Alkaline Phospathase; AST Aspartate Aminotransferase; ALT: Alanine Aminotransferase (Normal Range); UA: Unavailable

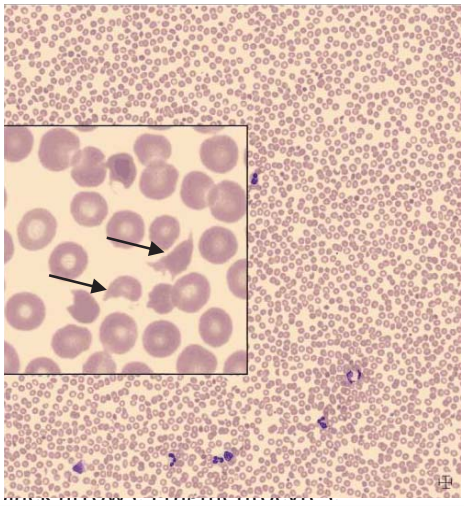

Figure 1: Black arrows: Fragmentocytes.

The main presenting symptoms were vomiting and oliguria secondary to renal failure.

Six patients were treated solely with dialysis; three patients received only plasma exchange [16-18]. Furthermore eight patients were treated with dialysis combined with plasma therapy (plasmapheresis or plasma exchange). Fourteen out of the seventeen cases showed full recovery after haemodialysis and/or plasma therapy after which hormone therapy was commenced. TMA recurred in three

cases [19,21]. Two patients died due to disseminated disease [16,17]. one due to cardiac arrest [22].

Interestingly, Kanesvaran, et al. described a patient who was treated solely with anti-androgen therapy (Bicalutamide) [23]. Within two weeks the patient recovered both clinically and biochemically after which he started with LH-RH therapy. He was discharged four weeks after initiation with Biculatamide. Complete resolution of the symptoms, signs and biochemical findings of TMA, was noted. The patient died 8 months after his initial diagnosis with no signs of TMA at time of death.

Perkovic, et al. described a patient treated initially with plasma exchange and prednisone [24]. After 14 days when the diagnosis of prostate cancer became evident, plasma exchange and prednisone were ceased and he was treated with anti-androgen therapy with good response and no recurrence of TMA.

We presented a 69-year old patient with a DAT negative

Table 2: Cases in the literature.

Author	Age	Presenting symptoms	Coagulation assays	Metastasis	Therapy	Outcome	FU
Subramaniam, [18]	57	Lack of energy, petechiae	Normal, (ADAMTS13 normal)	+	PLEX 9 days, day5 leuprorelin, steroids	UA	UA
Ramos, [44]	72	Hematemesis, hematuria, oliguria	Normal (PT, APTT, fibrinogen)	+	8x hemodialysis, 7x plasmapheresis, bicalutamide, goserelin	Discharged after 15 days	After 18 months no recurrence
Basic, [17]	74	UA	UA	+	PLEX	Died from disseminated disease	UA
Caramello, [16]	61*	Confusion, lumbar pain	APTT 66 (26-38), PT 12% (70-130), fibrogen 97 mg/dl (150-450), d-dimer > 800 ng/ml (< 230)	+	FFP, PLEX, iv hydration, loop diuretics after recovery chemotherapy	UA	After 26 months no recurrence
Kanesvaran, [23]	61	Lethargy, haematuria	normal	+	Bicalutamide, after 2 weeks goserelin	After 4 weeks complete resolution of symptoms/ biochemical findings of TTP	After 8 months patient died (no signs of TTP)
Biers, [22]	76 *	Confusion, oliguria, haematuria	normal	+	Dialysis (obstructive acute renal failure, bladder invase prostateca)	Death (cardiac arrest)	UA
Mungall, [45]	• 87 • 83 • 76* • 69*	• vomiting • oliguria, haematuria • vomiting • oliguria, haematuria, bruising, epistaxis	• normal • normal • normal • normal	• haemodialysis, PLEX, where after goserelin (after • haemodialysis wehere after goserlin/cypoterone acetate • haemodialysis • haemodialysis , PLEX	+ + + +	renal function improved in all four cases, time to recovery UA	UA
Perkovic, [24]	67	backpain	normal	PLEX, haemodialysis, prednisolone, vitamin E, after 14 days prostateca was diagnosed, start hormonal therapy, PLEX/ prednisolone was ceased	+	After 6 weeks haematological, PSA normalized	After 18 months no recurrence
Muller, [46]	61*	jaundice, vomiting	Normal	-	4xPLEX, 8 days dialysis	Normalisation creat 2 mo later,	6 years later no recurrence of HUS
Innes, [19]	79	Anorexia, jaundice, malaise, anuria	Normal	+	Haemodialysis 3 weeks	6 mo renal function improved	9 years later 3 recurrences of HUS: dialysis required in the first 2 episodes
Van der Merwe, [20]	• 72 • 62	• Anuria,haematuria, confusion • Loin pain, oliguria	• Normal • Normal	+ +	• Dialysis (peritoneal) for 1 week, aspirin,dipyridamol • Dialysis (peritoneal), PLEX for 8 days, aspirin,dipyridamol	• After 1 mo recovery of renal function • After 14 days recovery of renal function/haematological abnormalities	• After 4 months recurrence of HUS treated with PLEX, where after LHR agonist • TUR prostate
Sennesael, [47]	64	Lumbar pain, haematuria, oliguria	Normal	+	• first epidode: conservative, after 9 days spontaneous improvement of laboratoriumvalues • second episode 8 mo later: haemodialysis (3x)	After 10 days improvement of renal function	After 12 months no recurrence of HUS
Milutinovic, [47]	62	Nausea, vomiting, oliguria, haematuria	Normal	+	8x haemodialysis, plasma, aspirin, persantin	After 3 mo laboratory values recovered/clinic improved	UA

*: Already known with prostate carcinoma.UA: Unavailable; PLEX: Plasma Exchange; FFP: Fresh Frozen Plasma

fragmentocytic haemolytic anemia, thrombocytopenia and renal dysfunction, posing an indication to start plasma exchange (PE), given the presumed diagnosis of primary TMA. After one day the ADAMTS13 level turned out to be normal, whilst further analysis revealed a metastatic prostate carcinoma.

ADAMTS13, an enzyme that splits ultra large von Willebrand Factor (UL-VWF) protein and discovered in 1998 [25]. has a debatable role in treatment decisions in the clinical CA-TMA syndromes [26-36].

In just one of the described cases beside ours, ADAMTS13 activity was determined and was found within normal limits [18]. We didn't determine ADAMTS 13 antibodies, which could have masked an abnormal ADAMTS13 level, as is suggested to play a role in the pathophysiology [37].

Evaluation and treatment of the largely heterogeneous group of patients presenting with thrombocytopenia and microangiopathic haemolytic anemia is challenging. We believe that diagnosis and thereby treatment decisions in the whole spectrum of TMA, should not depend on ADAMT13 activity. Furthermore we consider it appropriate to initiate plasma exchange therapy when there is a suspicion of TMA. Although it has been argued that for remission of secondary TMA, the underlying disease should be treated, this is not unequivocally substantiated in the context of prostate cancer associated TMA [38,39].

The mechanism by which the prostate carcinoma induced the clinical manifestation of TMA in this case remains unclear. It is well known that prostate carcinoma may display a number of coagulation disorders. The most frequent coagulation disorder is disseminated intravascular coagulation (DIC). Other coagulopathies include TTP, thrombosis and acquired factor VII inhibitor development [40].

Possibly a low-grade DIC might have contributed to the clinical picture in this patient which subsequently responded to plasma exchange. In DIC, plasma exchange is hypothesized to remove different tissue factors, plasminogen activator inhibitor-1, tissue plasminogen activator inhibitor and replenish anti-thrombin III, protein C and S [41]. It is often a difficult balance between thrombosis and bleeding, sometimes even occurring at the same time in DIC. Patients may require pro-coagulants e.g. plasma therapy, vitamin K when bleeding. Platelet transfusions may be given for severe thrombocytopenia. Concurrently, low molecular weight heparin could be initiated, at least in a prophylactic dosage if the phenotype is predominantly thrombotic [42].

There is currently no consensus regarding indication, patient selection, method, timing and duration of plasma exchange for secondary TMA [41]. Treatment decisions are therefore complex. Especially since no intervention is risk free. Potential complications of plasma exchange include those related to insertion of the central line, catheter related infections, citrate toxicity and reactions to plasma [43].

To date there is no evidence available about treating cancer associated TMA with complement inhibitors, monoclonal antibodies or corticosteroids.

Management decisions in the TMA syndromes still prove to be very difficult and remain the responsibility of the clinician. We therefore stress the need for controlled documentation on the effect of various treatments modalities including plasma exchange in CA-TMA. Thereby including the still elusive role of ADAMTS13 and its antibodies, while working towards a standardized measurement assay.

Conclusion

We presented a 69-year old patient with a DAT negative fragmentocytic haemolytic anemia, thrombocytopenia and renal dysfunction, posing an indication to start plasma exchange (PE), given the presumed diagnosis of primary TMA. ADAMTS13 level turned out to be normal, whilst further analysis revealed a metastatic prostate carcinoma. The diagnosis of a full-blown disseminated malignancy was not initially apparent at presentation, but low-grade DIC might have contributed to the clinical picture. The patient fully recovered after seven sessions of plasma exchange. Considering the available data we, in contrast to some, cannot deny a potential role for plasma exchange in prostate cancer associated TMA.

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