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## **Case Report and Review of the Literature**

# Prostate Cancer-Associated Trousseau'S Syndrome Versus Asymptomatic Isolated Muscular Calf Vein Thrombosis as the Origin of Acute Submassive Pulmonary Embolism: A Case Report and Review of the Literature

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## ABSTRACT

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in cancer patients. Cancer patients have a four to sevenfold increased risk of VTE compared with non-cancer patients and approximately 20% -30% of all VTE occurs in patients with cancer. Incidence of VTE varies with cancer type and is the highest among patients with metastatic-stage disease. Assessing risk of VTE in the patients with cancer and risk stratification tools as the Khorana score may predict VTE. The highest risk is associated with cancers of the pancreas, stomach, brain, and lung and some hematologic malignancies, whereas lower risks are associated with breast and prostate cancer. The incidence rate ratio (IRR) for prostate cancer is 3.25(2,56 - 4,13) and for pancreas 15.56 (10.50-23.0). We give a case report with a quite perplexing undertaking, where a submassive acute pulmonary embolism (PE) originated from an asymptomatic calf vein thrombosis or intertwined with the Trousseau's syndrome.

**Essential Section:** One of the authors (A.T) was unexpected faced with the diagnosis of poorly differentiated prostate cancer. There were no signs of the disease, the PSA level was normal. As a retired medical oncologist, he had to care for many patients with prostate cancer and had now to cope with this cancer. To make the matter worse he suffered after the radical prostatectomy a submassive asymptomatic pulmonary embolism. Clinically there were no signs if a deep venous thrombosis. The coincidence of both events without clinical signs of a thrombosis could be caused by the Trousseau's syndrome. Prostasomes extracellular vesicles synthesizes by prostate cancer cells and secreted into body fluids are prothrombotic by virtue of the expression of polyphosphate-activated coagulation factor XII.

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### **Case Presentation**

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE) is a major cause of morbidity and mortality in cancer patients. Cancer patients have a four to sevenfold increased risk of VTE compared with non-cancer patients and approximately 20% -30% of all VTE occurs in patients with cancer [1-8]. VTE is also a harbinger of cancer [9-15]. Prognosis of cancers associated with VTE and with an advanced stage of cancer is poor [11,

16, 17]. Symptomatic and incidental VTE are both associated with mortality in patients with prostate cancer [18-20]. The assessing risk of VTE in patient with cancer is of paramount importance and an essential component in diagnosis and therapy of the malignancy as published in the newest guidelines from ASCO and from ASH [21, 22]. The classical Virchow's triad for the pathogenesis of VTE has now been supplemented and expanded by additional risk factors as genetic link between cancer and prognosis [23-25].

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The risk factors for cancer-associated thrombosis are patient-specific factors as ethnicity, comorbidity (obesity, renal and pulmonary disease), female sex, heritable thrombophilia, prior history of VTE, cancer-specific factors as primary tumor site, histologic subtype, stage and grading, time from diagnosis, treatment-specific risk-factors as chemotherapy, hormonal therapy, antiangiogenic therapy, central venous catheters and Ports, supportive therapy with transfusions and Erythropoiesis-stimulating agents [26, 27]. The Khorana score for prediction of VTE and decision-making for thromboprophylaxis in cancer patients and has proven itself very well in the clinic as it is shown in (Figure 1) [28-30].

Khorana Score		
Patient Characteristic   Site of Primary Cancer   > Very High Risk (stomach, pancreas)   > High Risk (lung, lymphoma, gynecologic, bladder, testicular)		Risk Score 2 1
Hgb < 10 g/dL		1
Prechemotherapy leukocyte count ≥ 11 × 10 <sup>9</sup> /L		1
BMI 35 kg/m <sup>2</sup>		1
<u>Total Scor</u> e 0 1-2 3 or hiaher	Risk of Symptomatic VTE Low (0.8-3%) Intermediate (1.8-8.4%) High (7,1-41%)	

Figure 1: Khorana-Score: A predictive model clinical risk score for VTE.

BMI= body mass index [28-30].

Prostate cancer does not belong to the high-risk entities for VTE as gastric and pancreas cancer. The initial incidence rate ratio (IRR) for prostate cancer is 3.25 (2.56 - 4.13) whereas for pancreas cancer the IRR is 15.56 (10.50 - 23.06) [8, 31, 32]. The association between VTE and malignancy was first described in 1865 by Armand Trousseau [33-35]. Since its discovery, the association of cancer and VTE is often termed Trousseau's syndrome. Despite its frequent mention in reviews the term Trousseau's syndrome is not in the MESH headings of Medline or PubMed [7, 33, 34, 36-39]. Literature searching using Boole's operator Prostate cancer and Trousseau's syndrome and Thromboembolic disease did not result in PubMed. So far, the literature on the role of hemostasis in genitourinary malignancies -prostate, bladder and kidney cancer- and VTE is quite scant. A recent review on the role of the coagulation system in genitourinary cancers summarizes the pathophysiology of coagulation activation and the underlying molecular mechanisms and gives no clue for the Trousseau's syndrome [40].

One of the authors (A. Ts.), 73-years-old, turned up in our clinic in January 2020 for clarification of prostate cancer. Except for medicated type of high blood pressure, the patient did not have severe diseases, a prior history of VTE or cancer and there is no family history of prostate nor related cancers. A diagnostic work-up was started with multiparametric MRI (mpMRI) [41-43]. In the peripheral zone right-dorsal a PI-RADS 4-lesion within the organ and a PI-RADS 3-lesion in the transition zone were detected. The MRI-targeted systematic and combined biopsies of the prostate by the transperineal approach were performed in the same month [44, 45]. From the 17 biopsies incl. both

with PI-RADS 3 and PI-RADS-4, 6 showed histopathologically an aciniform adenocarcinoma of the prostate with Gleason-score 5+5=10.

The prostate-specific antigen level (PSA) was < 4.0ng per milliliter [46, 47]. For the completion for the primary staging a <sup>68</sup>Ga-PSMA-PET/CT was carried out on 11<sup>th</sup> January 2020 [48-50]. The fused PET/CT showed intense prostate-specific membrane antigen (PSMA) expression confined strictly to the prostate, without PSMA-positive lymph nodes and without metastasis to organs. On 06/03/2020 the daVinci-robot-assisted radical prostatectomy was conducted by one of the co-authors (Prof. J. Roigas) under the usual standard precautions [51-53]. The patient received a prophylactic anticoagulation with LMWH according to the guidelines [21, 22]. The postoperative course was unremarkable. The patient was mobilized and under the supervision of a physiotherapist the patient walked and could also walk stairs. From the third day on he noticed a tinge of blood in his sputum. An otoscopic endoscopic examination revealed no source of bleeding. The patient had no cough, no fever and no swellings of the legs.

From the fourth to the fifth day on he developed slightly increased temperature < 38°C. He had no shortness of breath and no pain. On 13/03/2020 the temperature was measured at 39°C on several occasions during this day. On the same day computed tomography (CT) of thorax and abdomen revealed a multisegmental pulmonary embolism in the middle and in right lower lobe. In the left lower lobe was a pneumonic inflammatory infiltration most likely to be considered as pulmonary infarction [54, 55]. The colour Doppler study disclosed an isolated muscular soleal vein thrombosis of the left lower leg [56, 57]. The deep veins were open. Echocardiography from 17/03/2020 did not reveal right heart failure and showed a ventricular ejection fraction of 60%. Blood and urine culture were negative for pathogenic microbes. In the meantime, the dosis of the LMWH was increased and an i.v- antibiosis with Tazobactam (Tazobac®) 3 x 4.5g was initiated [58-61]. Under this therapy the fever was quickly resolved, and the patient was released on 19/03/2020. The anticoagulation was switched to an oral Factor Xainhibitor - Endoxaban (Lixiana®) 60 mg/die [60-65].

For the critical appraisal whether the acute submassive and asymptomatic pulmonary embolism has its origin in the isolated thrombosis of muscular soleal vein of the left calf, or is a complication of the surgical procedure or last but not least an indication of Trousseau's syndrome due to circulating prostasomes [20, 37, 40, 57, 66-71]. Biomarkers for the prediction of VTE in cancer in the era of " personalized medicine" are plentiful and have to be validated and tested [40, 72-76]. As it was introduced for tumor markers with the tumor marker utility grading system (TMUGS) a similar system for biomarker for prediction of VTE in cancer would be of great help [73, 77, 78]. Very few biomarker tests for VTE prediction have passed these high bars for routine clinical application [76, 79]. The Khorana VTE risk assessment score and the Vienna VTE risk assessment score are scores not specified for prostate cancer [75, 80]. Therefore, there is an urgent need for the development of a VTE risk assessment score for prostate cancer. We hypothesize that prostasomes could function as a source of diagnostic biomarkers for prostate cancer [37, 70, 71, 81-84]. These extracellular vesicles (also termed exosomes) are synthesized in prostate cancer cells and secreted into body fluids [85]. Prostasome are prothrombotic by virtue of the expression of polyphosphate-activated coagulation factor XII, which initiates coagulation through the extrinsic pathway [37, 69]. Tavoosidana et al. demonstrated in box plots plasma levels of prostasomes according to histological Gleason score. The level of prostasomes were significantly elevated in the highest Gleason score [70]. The measurement of prostasomes in peripheral blood may be useful for early diagnosis and assessment of prognosis in organ-confined prostate cancer and for VTE risk assessment. In October 2018, a clinical trial was launched under the title " Prostasomes as Diagnostic Tool for Prostate Cancer Detection" under the Clinical Trials. Gov Identifier: NCT03694483 which is still recruiting and the estimated primary completion date is October 1, 2023. - link. Among others, it was shown that prostasomes are associated with VTE independently from the Gleason score. Just recently an ASCO guideline on " Molecular biomarkers in localized prostate cancer" was released with a special emphasis on commercially available multigene expression classifier[86]. As listed in the patient-specific factors for cancer-associated VTE thrombophilia may be associated with VTE [87-89]. The diagnostic workup includes thrombophilia testing as Factor V Leiden, prothrombin 20210A, Lupus anticoagulants and MTHFR.

The final histopathological result of the patient was: pT2c, pN0, pN0, 0pL0, pV0, R0, Gleason-score 5+4=9. The radical prostatectomy with the histopathological result is no indication for an adjuvant therapy [90]. The clinical outcome for patients with a Gleason score 9-10 prostate adenocarcinoma and in men with organ-confined margin-negative disease had a very low risk of early biochemical recurrence [91-93]. Therefore, after radical prostatectomy with the histopathological results as mentioned above, there is no indication for an adjuvant therapy according to ESMO and NCCN guidelines [90, 94].

The cancer statistics, 2020 and their survival statistics show that prostate cancer belongs to the entities with the highest 5-year survival rates (98%) as melanoma of the skin (92%) and female breast cancer (90%) [95].

### **Competing Interest**

None.

#### **Author Contributions**

A. Ts. performed the literature search, A. G., S. G, and J. R and A. T. conceived, wrote, edited, and approved the manuscript.

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