

## Management of Thrombotic Thrombocytopenic Purpura in Metastatic Prostate Cancer with only Endocrine Therapy

### Dear Editor,

Thrombotic thrombocytopenic purpura (TTP) is a systemic disorder that presents acutely with multiple organ failure. Although defined classically as a syndrome with a pentad of features, it is accepted now that a diagnosis can be made with the dyad of microangiopathic haemolytic anaemia and thrombocytopenia. It is recognised that patients with malignancy have a higher risk of getting a thrombotic microangiopathy like TTP. We report a 4th case of TTP in prostate cancer and offer a feasible alternative treatment strategy.

### Case Report

A 61-year-old gentleman was admitted to our hospital with a complaint of lethargy associated with haematuria 3 weeks prior to admission. He had low back pain since a fall 3 months prior. On examination, he was profoundly ill, pale and confused. He had multiple bruises over his abdomen and an enlarged craggy prostate was felt per rectum. Investigations showed a low haemoglobin (7.2 g/dL) and platelet count (17,000/uL). The PSA level was 984 ug/L. His coagulation profile was within normal limits. His serum creatinine level was 84 umol/L. His serum lactate dehydrogenase (LDH) level was significantly elevated at 3922 U/L and haptoglobin was <0.10 g/L. His peripheral blood film revealed a microangiopathic haemolytic anaemia (MAHA). A bone marrow aspirate and trephine biopsy was done which revealed a poorly differentiated metastatic carcinoma immunoreactive for prostate-specific antigen (PSA) (Fig.1). A computed tomographic (CT) scan of the pelvis showed an enlarged prostate with bladder infiltration and bone metastases. A bone scan showed widespread bony metastases throughout the skeleton.

With these findings, a diagnosis of metastatic prostate cancer complicated by thrombotic thrombocytopenic purpura (TTP) was made. The option of plasma exchange was considered in the light of previous reports.<sup>1</sup> However, a clinical decision was made to commence anti-androgen therapy (bicalutamide) first. Over 2 weeks, the patient's general condition improved. After 1 week on treatment, his confusion had completely resolved. Two weeks after initiation of therapy, his haemoglobin level was 8.4 g/dL, his platelet count had risen to 64,000 /L and LDH had fallen to 374 U/L. PSA levels also fell to 611 ug/L. Depot LHRH agonist (goserelin) was commenced 2 weeks after initiation of anti-androgen therapy. Continued improvement

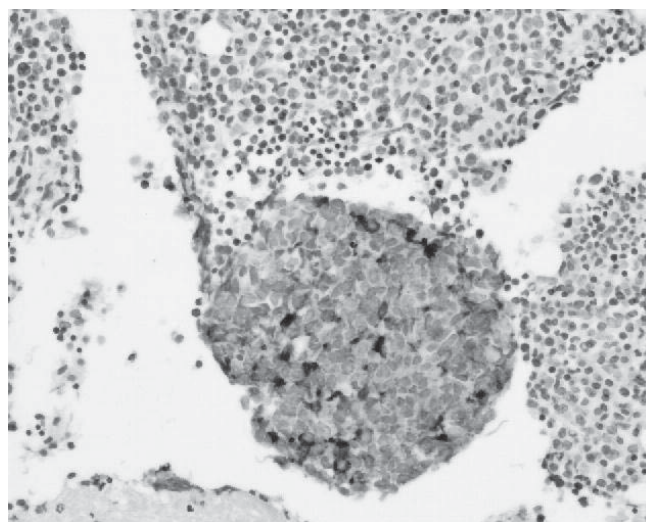


Fig. 1. Positive PSA staining on bone marrow biopsy.

was noted, and he was discharged home well 4 weeks after initiation of anti-androgen therapy. His PSA level nadired after 3 months, at a value of 9 ug/L. Complete resolution of the symptoms, signs and biochemical findings of TTP was also noted.

The period of castrate sensitivity was relatively brief, and after 6 months, the patient's thrombocytopenia recurred, with the PSA level rising from 9 ug/L to 396 ug/L over 4 months. Although palliative chemotherapy was commenced promptly, the disease did not respond to first-line docetaxel/prednisolone or second-line mitoxantrone/prednisolone. The patient eventually passed away 8 months after his initial diagnosis. The patient did not have TTP at the time of death.

Cancer patients are in a hypercoagulable state. They are predisposed to disorders of haemostasis ranging from asymptomatic coagulation profile derangements to life-threatening pulmonary thromboembolisms presenting with shock. TTP is one of the manifestations of this hypercoagulable state. Only a few cases of TTP secondary to metastatic carcinoma have been reported in the literature.<sup>2</sup> Its mechanism of action is said to differ from that of idiopathic TTP. While there have been many hypotheses as to the mechanism of TTP, in some patients the pathogenesis has been attributed to the plasma level of

ADAMTS13 (a disintegrin and metalloprotease domain, with thrombospondin type 1 motif 13), which is a von Willebrand Factor cleaving protease. ADAMTS13 has been shown to be very low in familial and some of the sporadic cases of TTP, and a low level of it is very specific to TTP. Some reports have shown that patients with a very low plasma level of ADAMTS13 respond very well to plasma exchange.<sup>1</sup>

Early recognition of TTP is critical, given the success of treatment, and the poor prognosis of untreated disease, which is associated with progressive end organ damage and a high mortality rate. However the pathogenesis of secondary TTP is still unclear. ADAMTS13 levels have been shown to be normal in patients with cancer hence raising doubts as to the benefit of PE in such instances.<sup>2</sup>

The association between TTP and metastatic prostate cancer has been reported previously.<sup>3-5</sup> In 2 of the 3 reported cases, direct treatment of the TTP was initiated. In the first instance the patient was treated with fresh frozen plasma infusion, antiplatelet agents and dialysis with prompt recovery of symptoms.<sup>4</sup> The most recent report described a patient whose TTP was treated with PE, subsequently experiencing full recovery.<sup>5</sup> A historical report, dating to 1952, was inaccessible.<sup>3</sup> In our report, we selected anti-androgen therapy as the primary modality of treatment, choosing to avoid plasma exchange, with eventual resolution of the TTP.

Plasma exchange is associated with immediate side-effects like chills, fever, low blood pressure from vagus nerve syndrome, excessive bleeding from the use of the anticoagulant and venous puncture hazards including air embolism. Some of the delayed adverse effects include an increased risk of thrombosis due to delayed synthesis of antithrombin 3 and a higher risk of bacterial infections due to humoral immunity deficiency. From this, it is clear that plasma exchange has its inherent adverse effects that must be weighed against its unknown benefits in a patient diagnosed with TTP and malignancy.

We managed our patient's TTP with prompt endocrine therapy targeted at the underlying cancer which led to the resolution of the patient's TTP. This outcome suggests that PE, with its attendant complications, is not necessarily required in patients with TTP secondary to prostate cancer, as previously suggested.<sup>5</sup>

## REFERENCES

1. Sadler JE, Moake JL, Miyata T, George JN. Recent advances in thrombotic thrombocytopenic purpura. *Hematology Am Soc Hematol Educ Program* 2004;407-23.
2. Forman RB, Benkel SA, Novik Y, Tsai HM. Presence of ADAMTS13 activity in a patient with metastatic cancer and thrombotic microangiopathy. *Acta Haematol* 2003;109:150-2.
3. Cibert J, Favre-Gilly J, Traeger J, Durand L. Thrombocytopenic purpuras in the treatment of prostatic cancer with synthetic estrogens. *Sang* 1952;23:541-6.
4. Cherin P, Brivet F, Tertian G, Dreyfus M, Barthelemy P, Dormant J, et al. Recurrent thrombocytopenic thrombotic purpura associated to prostatic cancer. A case. *Presse Med* 1991;20:1073-7.
5. Caramello V, Dovio A, Caraci P, Berruti A, Angeli A. Thrombotic thrombocytopenic purpura in advanced prostate cancer: case report and published work review. *Int J Urol* 2007;14:150-2.

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