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Case Report

Case Report: Severe Veno-Occlusive Priapism in a Thyroid Cancer Patient Treated With Pembrolizumab

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Abstract

The introduction of immune checkpoint inhibitors (ICIs) in clinical practice has marked a turning point in the field of cancer care. ICIs created a viable treatment option for a wide spectrum of different cancer types and have significantly extended the life expectancy of cancer patients. Despite the undoubted advantages brought by these molecules, the enhancement of the immunologic activity against the tumour has a price to pay in terms of multiorgan immune-related adverse effects (irAE). Here we describe the case of a 65-year-old man with anaplastic thyroid carcinoma (ATC) who was started on Pembrolizumab, a humanized monoclonal anti PD-1 antibody, after being ineffectively treated with Lenvatinib, a multiple receptor tyrosine kinase inhibitor. After two months, despite the reduction of the tumour burden, he developed severe priapism due to venous thromboembolism, reverted with high dose prednisone. We dosed the levels of mediators traditionally implicated in the coagulation pathways in our patient, in other thyroid cancer patients treated only with Lenvatinib or unresponsive to Lenvatinib plus Pembrolizumab and in healthy volunteers. We found that the study subject had higher plasmatic concentrations of both pro-inflammatory cytokines and circulating tissue factor (TF). In this light, these results may illustrate that Pembrolizumab is bona fide the trigger of the coagulation disturbance and that pro-inflammatory cytokines can be a biomarker of irAE.

Keywords: Immune related adverse effects; Pembrolizumab; Anaplastic thyroid cancer; Pro-inflammatory cytokines; Priapism

Introduction

ATC represents less than 2% of all thyroid carcinoma subtypes and accounts for the majority of thyroidcancer deaths. It often originates from a process of dedifferentiation from pre-existing thyroid cancer lesions caused by the overlap of oncogenic mutations. ATC is characterized by an aggressive behaviour with rapid enlargement of the tumour mass that can reach several centimetres, frequently leading to local structures infiltration. It is usually a non-functioning tumour though it can be associated with paraneoplastic syndromes due to the production of parathyroid hormone-related peptide (PTHrp) and to several other growth factors and blood cells colony stimulating factors. [1] Despite great advancements in the understanding of ATC biology, prognosis is still among the worst of solid tumours, with a median survival between 3 and 6 months. [2] Current treatment involves traditional approaches such as surgery, radiotherapy and chemotherapy, and new molecular targeted therapies with regard to multiple and

single target tyrosine kinase inhibitors (TKI) and ICIs. Inhibitory immune checkpoints, when activated, induce immune tolerance and provide a security system against autoimmunity. Cancer cells "hijack" these systems in order to gain the ability to escape the restraining control of the immune system and to create an environment favourable to the tumour growth. ICIs are a class of monoclonal antibodies targeting inhibitory immune checkpoints such as CTLA-4 and PD-1/PD-L1 whose inhibition reverses the mechanism of immune escape of the cancer cells. ATC has indeed shown to express PD-L1 in a variable percentage of cases and several studies have proved the efficacy of anti PD-1/PD-L1 molecules, such as Spartalizumab [3] and Pembrolizumab, in the treatment of ATC. Although the effectiveness of immunotherapy is unquestionable, its use in clinical practice has shown to be often burdened by multiple and diversified adverse effects, making ICIs a double-edged weapon. Indeed, the activation boost given to the immune system by ICIs leads to the loss of immune tolerance towards the self and to consequent irAE. The adverse effects caused by immunotherapy can sometimes be life threatening, as in the case of myocarditis or pneumonia, and require early recognition and prompt intervention with treatment discontinuation and immunosuppressive drugs. Here we report the clinical findings in a single patient with ATC treated with Lenvatinib in combination with Pembrolizumab who achieved the stabilization of the tumour burden. After four injections of the anti PD-1 antibody, he sequentially developed coagulative disorders leading at first to ilio-femoral and mesenteric venous thrombosis, with subsequent priapism and haemorrhoid bleeding, and finally to disseminated intravascular coagulation (DIC). Blood sample analysis of the study subject showed higher concentrations of pro-inflammatory cytokines in comparison with patients non-responding to the anti PD-1 antibody or treated only with TKI. These findings suggest that the anti PD-1 activity of Pembrolizumab, though stabilizing the tumour burden, likely triggered the pro-inflammatory cytokine storm that ultimately led to uncommon irAE. Moreover, they indicate a possible use of pro-inflammatory cytokines as a biomarker of immune-related toxicity and of good response to the treatment.

Case Description

In January 2020, a male in his mid-60s already diagnosed with progressive thyroid carcinoma and in treatment with Lenvatinib 14 mg qd was referred to our hospital following the development of a fast-growing solid neck lesion (Figure 1-A). He was diagnosed with inoperable metastatic papillary thyroid carcinoma with anaplastic component already infiltrating the trachea in August 2019. Due to the disease progression and to high PD-L1 expression on tumour cells, Lenvatinib was increased to 24 mg qd and treatment with intravenous Pembrolizumab 200 mg was added. Pembrolizumab infusions were repeated every three weeks while serial neck computed tomography (CT) scans showed a fast colliquative necrosis and a global reduction of the tumour mass. In March 2020, after the fourth anti PD-1 administration, the patient developed acute urinary retention due to severe veno-occlusive priapism detected on a CT scan (Figure 1-B; 1-C). After placing a percutaneous suprapubic cystostomy, Pembrolizumab was discontinued and prednisone 1 mg/kg, for a total amount of 60 mg qd, was administered. It took three weeks to reach priapism resolution and clinical stabilization, after which daily prednisone was tapered down to 25 mg qd and the suprapubic cystostomy was replaced with a urinary catheter. Unexpectedly, on May 7th 2020 a significant increase in scrotal and penile oedema associated with massive haemorrhoid bleeding occurred. A total body CT scan revealed the presence of a massive bilateral iliofemoral and mesenteric venous thrombosis despite the persistent stability of the tumour burden reduction. Rectal artery embolization and inferior vena cava filter placement were performed, prednisone dose was increased again and treatment with Lenvatinib was discontinued. On May 14th, the patient suddenly developed DIC requiring administration of fresh frozen plasma (FFP) and daily haemodialysis. Despite the restoration of a normal coagulation profile and an acceptable daily diuresis, on June 14th 2020 the patient died from urinary sepsis sustained by a multidrug-resistant Pseudomonas Aeruginosa.

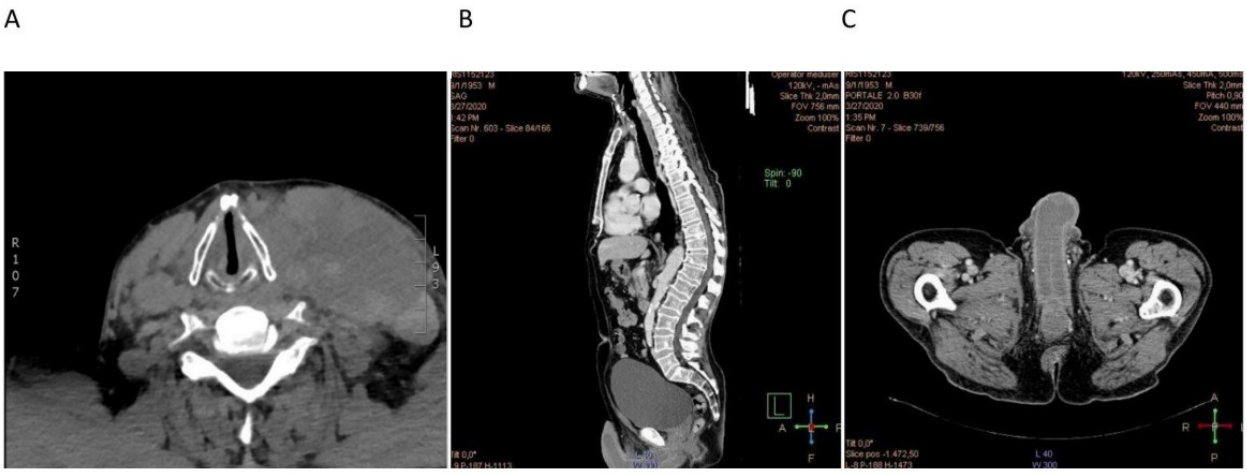

Figure 1: Axial view of February 19th 2020 CT scan showing the left-sided solid neck lesion (A). Sagittal (B) and axial (C) views of March 27th 2020 CT scan showing the occurrence of priapism associated with urinary retention.

Laboratory Findings

Peripheral blood samples from the study subject were collected on May 7 th 2020 in concomitance with the occurrence of scrotal and penile oedema worsening and haemorrhoid bleeding. In addition, peripheral blood samples were collected from two untreated healthy volunteers, two thyroid carcinoma patients treated only with Lenvatinib and one thyroid carcinoma patient unresponsive to the treatment with Lenvatinib plus Pembrolizumab. Blood samples (~10 mL) were collected in heparinized tubes, centrifuged at 2000 rpm for 10 minutes and the separated plasma was stored at -80°C until use. The involved subjects signed an informed consent and the Ethics Committee approved this part of the study. The blood samples were screened for 11 cytokines (GM-CSF, IFNγ, IL-1β, IL-12p70, IL-13, IL-18, IL-2, IL-4, IL-5, IL-6, TNFα) and Tissue factor (TF). The indicated cytokines were measured in triplicate in the plasma samples using the ProcartaPlex Human Th1/Th2 Cytokine Panel 11plex (Thermo Fisher Scientific). TF was measured in triplicate in human plasma samples using the Human Tissue Factor ELISA Kit (CD142) (Abcam). We compared the results of TF and cytokines plasma concentrations of the study subject, of healthy controls, and of the other thyroid carcinoma patients (Table 1). Interestingly, the study subject shows the highest levels of most cytokines and TF. In detail, the concentrations of GM-CSF, IFNγ, IL-1β, IL-12p70, IL-2, IL-4, IL-5 were detectable only in our patient and undetectable in all the other subjects. IL-18 and TF were higher in our patient, though measurable also in the other subjects. TNFα concentration was high in our patient and undetectable in the patient who shared the same therapy but with no clinical benefit. IL-13 and IL-6 were undetectable in all the subjects, including the study subject.

Sample	GM-CSF	IFN γ	IL-1 β	IL-12p70	IL-13	IL-18	IL-2	IL-4	IL-5	IL-6	TNF α	TF
	pg/ml	pg/ml	pg/ml	pg/ml	pg/ml	pg/ml	pg/ml	pg/ml	pg/ml	pg/ml	pg/ml	pg/ml
C-♀	OOR<	OOR<	OOR<	OOR<	OOR<	58.3	OOR<	OOR<	OOR<	OOR<	1.90	310,8
C-♂	OOR<	OOR<	OOR<	OOR<	OOR<	51.7	OOR<	OOR<	OOR<	OOR<	0.09	391,3
L-♀	OOR<	OOR<	OOR<	OOR<	OOR<	24.0	OOR<	OOR<	OOR<	OOR<	0.16	112,5
L-♂	OOR<	OOR<	OOR<	OOR<	OOR<	32.4	OOR<	OOR<	OOR<	OOR<	0.67	31,8
L+P-♀	OOR<	OOR<	OOR<	OOR<	OOR<	45.0	OOR<	OOR<	OOR<	OOR<	OOR<	582,7
L+P-♂	**64.4**	**14.1**	**6.0**	**7.86**	**OOR<**	**59.4**	**15.1**	**2.67**	**21.8**	**OOR<**	**6.2**	**682,5**

Table 1: Concentration of TF and of cytokines involved in the inflammatory process in the study subject, in other thyroid cancer patients and in healthy volunteers. C: Untreated healthy volunteers. L: Thyroid carcinoma patient treated with Lenvatinib. L+P: Thyroid carcinoma patient treated plus Pembrolizumab. In bold, data of the study subject. OOR<: out of range below.

Discussion

PD-1 is a glycoprotein receptor usually expressed by T-lymphocytes. Upon binding its ligands PD-L1 and PD-L2, it downregulates the T-cells activity against the tumour. Thus, cancer cells endowed with PD-L1 on their surface can easily escape the immune system surveillance. In particular, ATC has been shown to express PD-L1 with a prevalence ranging between 65 and 90%. [4] Pembrolizumab, inhibiting the binding between PD-1 and PD-L1, confirmed to be a crucial innovation in the field of cancer care. A retrospective study by Iyer et al. [5] with twelve ATC patients receiving the anti PD-1 as add-on treatment on top of TKIs at the time of disease progression, actually proved Pembrolizumab an effective salvage therapy. Despite the promising results on the use of Pembrolizumab in advanced cancer, the studies indisputably showed the association of anti PD-1 activity with several irAE. Almost every organ is susceptible to be the target of ICI-related AE, with different immunotherapies preferentially targeting different organs. Approximately 10% of patients receiving anti PD-1 antibodies have grade ≥3 irAEs. [6] Occasional any-grade toxicities (in 5-20% of patients) include arthralgia, rash, pruritus, pneumonitis, diarrhoea, and endocrinopathies. [6] An association emerged between increased levels of circulating plasma cytokines and both a higher risk of immune-related toxicities and the treatment response. A study by Lim et al. [7] profiled the cytokines expression in melanoma patients treated with anti PD-1-based immunotherapy, alone or in combination with anti CTLA-4. They found that elevated expression of 11 cytokines (G-CSF, GM-CSF, Fractalkine, FGF-2, IFN2, IL-16, IL-12p70, IL-1a, IL-1B, IL-1RA, IL-2, IL-13) was strongly associated with severe irAEs requiring intervention with high dose immunomodulating agents. In our patient, treatment with Pembrolizumab on top of Lenvatinib during a phase of disease progression produced the immediate stabilization of the tumour mass followed by a process of colliquative necrosis. An in vivo study showed indeed that the PD-1/PD-L1 pathway inhibition increases Lenvatinib anti-tumour activity through a favourable modification of ATC microenvironment. [8] However, the encouraging clinical response was invalidated by an adverse effect on low abdomen, namely a low flow priapism induced by thrombosis of the bilateral iliofemoral and mesenteric veins. In order to prove the causative connection between the side effect and the anti PD-1 treatment, we profiled the expression of TF and 11 cytokines involved in the inflammatory and coagulation pathways. Interestingly, we found that most of the pro-inflammatory cytokines such as GM-SF, IFNγ, IL-1β, IL-12p70, TNFα, IL-2, IL-5 and TF (not IL-6, suppressed in all the subjects, and IL-18, with comparable levels in all the subjects) were more represented in our patient in comparison with two healthy volunteers, two patients with thyroid cancer treated with Lenvatinib and with one patient with ATC unresponsive to Lenvatinib plus Pembrolizumab. On the other hand, anti-inflammatory cytokines showed contradictory behaviour as IL-13 was undetectable in all the subjects, whereas IL-4 was detectable only in the study subject. Another indirect proof that the coagulation disorders and the consequent veno-occlusive priapism were related to the immunotherapy is that high dose prednisone stabilized the side effect. Moreover, prednisone reduction to 25 mg qd was associated with the worsening of the pelvic thromboembolism and possibly with the development of DIC. These data suggest that the irAE

are not a direct consequence of immunotherapy itself, but rather the result of the cytokine storm associated with the good clinical response to the treatment. In conclusion, we describe for the first time a veno-occlusive priapism in a patient treated with Pembrolizumab. In our opinion, the anti PD-1 treatment is bona fide the trigger of the coagulation disturbance. Moreover, these data indicate that evaluating the expression of pro-inflammatory cytokines may help identifying patients who are at major risk of irAE and who would benefit from a close monitoring and a prompt treatment.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

L.M.R. Marcon and A. Mazzieri, as equal contributing first authors, wrote the manuscript. S. Morelli collaborated to the redaction of the paper. S. Moretti performed the analysis. E. Puxeddu, as senior author, was responsible for the final review. All authors approved the submitted version.

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Due to the sudden death of the study subject, we did not receive his direct consent for the paper, on time. For this reason, the authors want to thank patients' family for their consent to present this case and relative's data analysis.

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