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Concomitant thyroiditis and orchitis induced by immune checkpoint inhibitors detected on [^{18}F]FDG PET/CT

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Abstract

Background The clinical management of malignant melanoma (MM) has undergone a significant revolution with the implementation of immune checkpoint inhibitors (ICIs). While these therapeutic agents stimulate the host immune system against cancer, they may also lead to immune-related adverse events (IrAEs). Positron emission computed tomography (PET/CT) with 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) has proven successful in detecting IrAEs in cancer patients undergoing ICI. In our case, we report a rare occurrence of ICIs-induced concomitant thyroiditis and orchitis detected on [^{18}F]FDG PET/CT.

Case presentation We present a case involving a 61-year-old man referred to our hospital due to MM. Following surgical excision and sentinel lymph node mapping, he underwent an initial [^{18}F]FDG PET/CT, which yielded negative results. However, a follow-up PET/CT after 9 months revealed metastases in the lungs and lymph nodes. Subsequently, he initiated an ICI-based therapeutic regimen. After 3 months, he reported progressively worsening fatigue and the onset of testicular pain. A testicular ultrasound showed heterogeneous echotexture in both testicles with mildly increased vascularity. A subsequent PET/CT demonstrated complete regression of previously described pathological lesions in the lungs and metastatic lymph nodes. However, diffusely increased tracer uptake was observed in both the thyroid gland and testicles, findings absent in the pre-ICI examination. These were interpreted as IrAEs and promptly treated with corticosteroids, resulting in complete resolution of symptoms.

Conclusions [^{18}F]FDG PET/CT plays a crucial role in staging and monitoring treatment response in cancer patients. When assessing subjects undergoing ICI-based therapies, particular emphasis should be given to detecting unusual IrAEs, as exemplified in our case.

Keywords FDG PET, Immunotherapy, Malignant melanoma, Adverse events, Orchitis, Thyroiditis, Case report

Background

The implementation of immune checkpoint inhibitors (ICIs) has significantly influenced the management of advanced malignant melanoma (MM). However, prompting the host immune system to combat cancer may result in the development of immune-related adverse events (irAEs) [1]. These events are observed in the majority of patients (up to 76%), with off-target effects potentially impacting any organ system or tissue due to an overactive immune response. While many of these events are mild and can be managed, there have been reports of life-threatening events, especially in the case of

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ICI-combination therapy [2], necessitating discontinuation of ICI. In clinical practice, it is crucial to promptly identify and address these toxicities. In this context, we discuss an ICI-induced thyroiditis and orchitis, emphasizing the utility of 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography/CT ([^{18}F]FDG) in this clinical setting.

Case presentation

A 61-year-old Caucasian man was admitted to our hospital for further investigations after a nodular skin lesion was identified on the anterior trunk. Upon clinical examination, he presented with a black nodule measuring approximately 2×3 cm, located below the xiphoid process, exhibiting ulceration and bleeding. He had no significant medical history aside from being under medical therapy for arterial hypertension. He underwent lesion resection, resulting in a nodular, ulcerative melanoma with a Breslow thickness of 3.5 mm and Clark level IV. Sentinel node positivity was detected by scintigraphy in the right inguinal region (N1). One month post-surgery, due to the high-risk nature of the case, the patient underwent PET/CT with [^{18}F]FDG, which was carried out according to the present imaging guidelines [3]. Whole-body PET/CT scan was performed 60 min after the i.v. injection of 3.7 MBq/kg of [^{18}F]FDG with a digital PET/CT scan (GE Discovery Molecular Insights—DMI PET/CT, GE Healthcare, Waukesha, WI). A free-breathing CT scan was performed from the proximal thigh to skull base, and used for attenuation correction purposes as well as for anatomic localization of [^{18}F]FDG uptake. The CT scan was performed using automated dose modulation (range 15–100 mA, 120 kV). Immediately after the CT scan, PET images were acquired covering the identical anatomical region. The PET acquisition time was set to 2 min per bed. All PET images were reconstructed using a Bayesian penalized likelihood reconstruction method (Q.Clear, GE Healthcare, Waukesha, WI). Data sets were reconstructed with a 256×256 pixel matrix. Spatial resolutions were radial 1.62 mm, tangential 2.30 mm and axial 3.09 mm, as assessed by full width at half maximum (FWHM) measurements at 1 cm from center of field of view. The [^{18}F]FDG PET/CT scan provided negative results, and the patient was placed under clinical monitoring.

Subsequent regular clinical follow-up showed no signs of relapse. Nine months post-surgery, a [^{18}F]FDG PET/CT revealed increased tracer incorporation indicative of metastases in the right lung and inguinal lymph nodes, characterized by maximum standardized uptake values (SUVmax) of 3.8 and 4.1, respectively (Fig. 1). Since molecular pathology resulted negative for V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) mutation, he commenced treatment with the immune-blocker

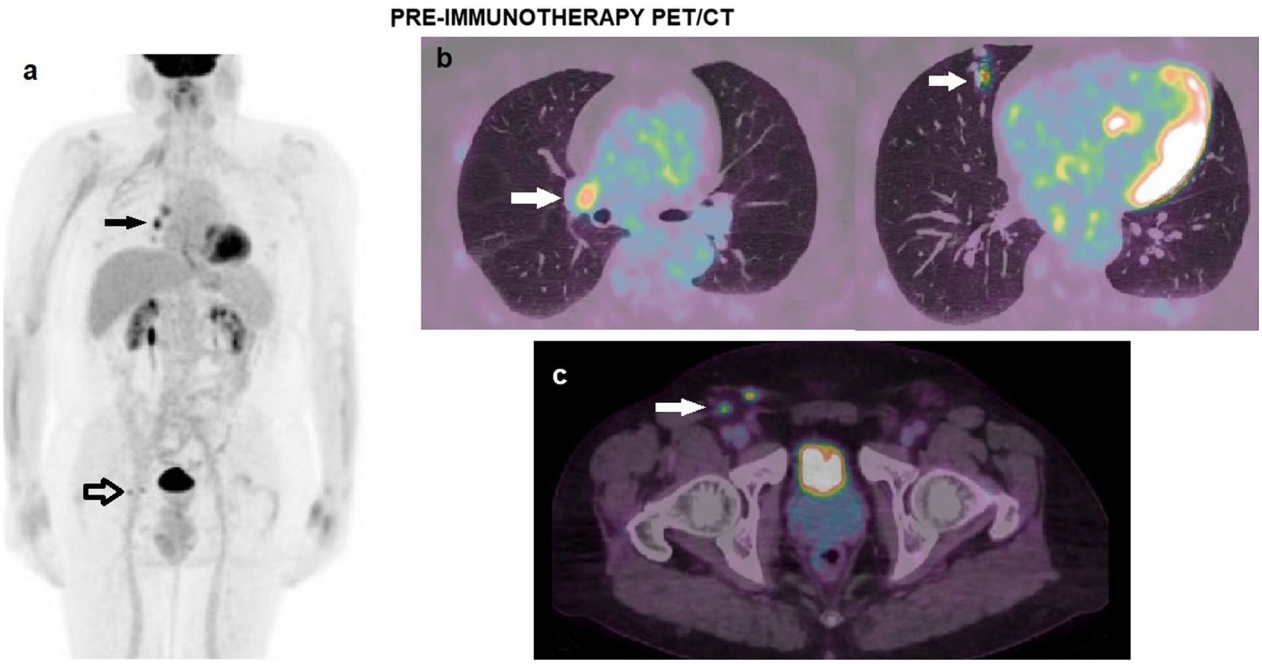

Fig. 1 [^{18}F]FDG PET/CT was conducted prior to immunotherapy. **a** The whole-body PET/CT revealed heightened tracer incorporation in the hilum of the right lung (black arrow) and in the ipsilateral inguinal region (black-bordered arrow). The corresponding fused axial PET/CT images of the thorax **b** pinpointed tracer uptake in the right hilum (white arrow, left side) and in millimetric, rounded lung nodules (white arrow, right side). The fused axial image of the pelvis **c** displayed tracer uptake in the right inguinal lymph nodes (white arrow)

nivolumab following the standard schedule of a 60-min infusion of 3 mg/kg once every 2 weeks [4]. Initially, the patient exhibited good tolerance to immunotherapy, showing no significant symptoms or signs. However, after three months, he began experiencing fatigue, palpitations, and progressively worsening pain localized to the testicles. Laboratory tests revealed no significant abnormalities, except for a level of thyroid-stimulating hormone (TSH), which was within the high-normal range (i.e., 4.5 uIU/mL, normal range: 0.47–4.68 uIU/mL), alongside normal free thyroxine (T4) values. A testicular ultrasound (US) revealed symmetric testes, measuring 3.8×2.8×3.4 cm (left) and 3.7×2.7×3.5 cm (right), characterized by heterogeneous echotexture in both testicles with mildly increased vascularity and no evidence of focal lesions (no images available). The patient initiated therapy with a nonsteroidal anti-inflammatory drug (ketoprofen, 80 mg/day) but experienced no significant relief from symptoms.

Two weeks after the onset of these symptoms, the patient underwent a scheduled [^{18}F]FDG PET/CT as part of the standard follow-up. The PET/CT results indicated almost complete regression of the previously described pathological findings in the right lung and inguinal lymph nodes, indicating a metabolic response (Fig. 2). Furthermore, there was a diffuse increase in tracer incorporation observed in both the thyroid gland (SUVmax 8.2, SUVmean 5.9) and the testicles (left: SUVmax 5.1 and SUVmean 3.3, right: SUVmax 5.2, SUVmean 3.6) (Fig. 3). Given the diffuse pattern of uptake and the absence of these features in the baseline PET/CT, the [^{18}F]FDG incorporation in both the thyroid and testicles was attributed to immunotherapy-related adverse effects. To address these adverse effects, the patient initiated corticosteroid therapy (i.e., prednisone regimen consisted of 1 mg/kg/day), resulting in the prompt resolution of symptoms associated with thyroiditis and orchitis. Importantly, this intervention was implemented without discontinuing immune checkpoint blockers.

Discussion

Immunotherapy for cancer has revolutionized the landscape of oncology, with its molecular mechanisms rooted in the intricate interplay between the host immune system and specific biomarkers expressed on the surface of cancer cells [5]. A potent weapon in the fight against cancer has emerged in the form of immune checkpoint blockade therapy, albeit with a response rate limited to

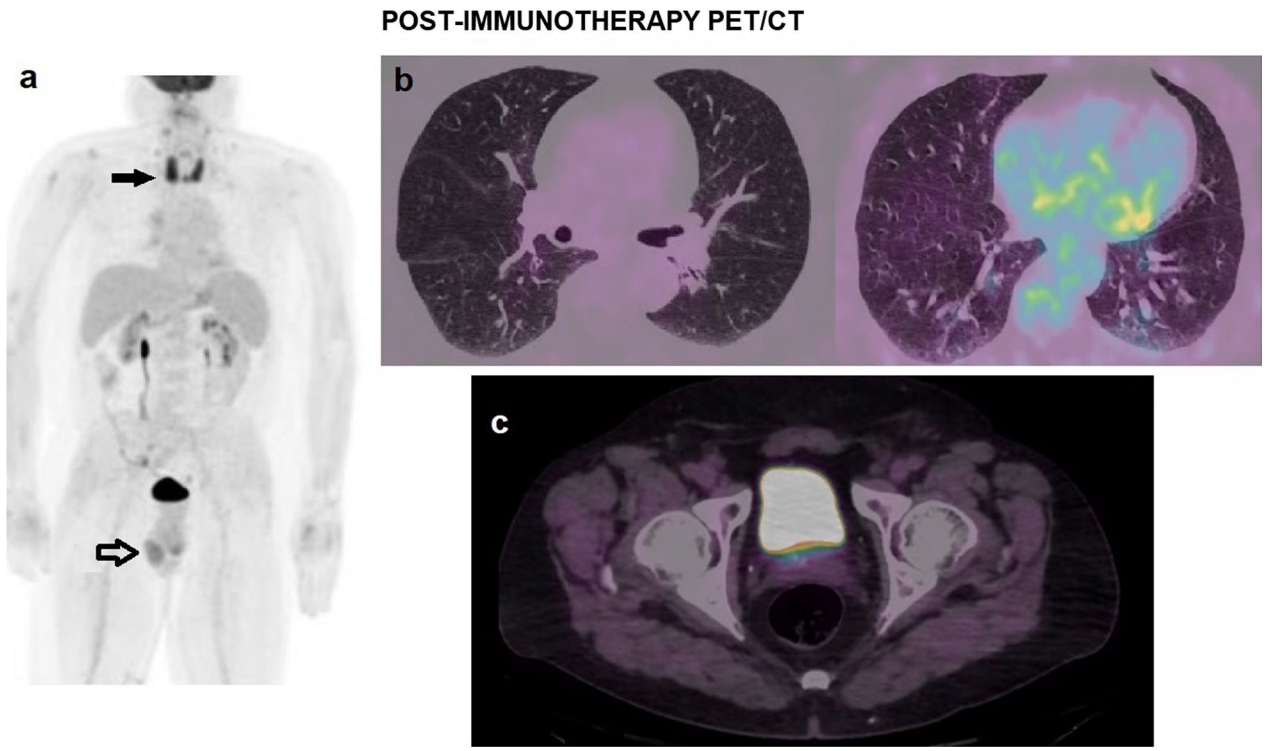

Fig. 2 At 3 months post-immunotherapy, [^{18}F]FDG PET/CT was performed. **a** Whole-body PET/CT revealed a diffuse increase in tracer incorporation in the thyroid (black arrow) and testicles (black-bordered arrow). Fused axial PET/CT images of the thorax **b** showed no meaningful tracer uptake in the right hilum (left side) with nearly complete regression of the lung nodules (right side). The fused axial image of the pelvis **c** did not exhibit pathological uptake in the inguinal region

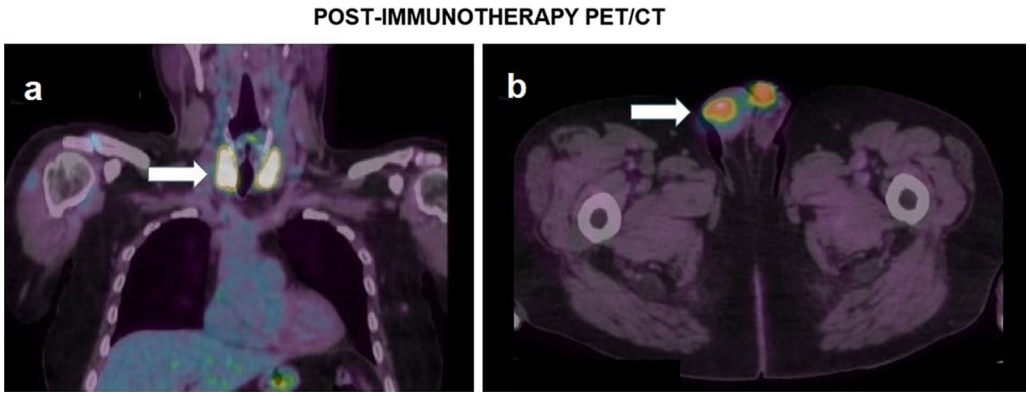

Fig. 3 [^{18}F]FDG PET/CT at 3 months after immunotherapy. **a** A fused coronal PET/CT scan revealed a notable and widespread increase in tracer uptake within the thyroid gland (white arrow). **b** In the fused axial image of the pelvis, heightened bilateral [^{18}F]FDG uptake was observed in the testicles (white arrow)

30–40% of cancer patients. Consequently, it becomes imperative to identify imaging biomarkers capable of distinguishing responders from non-responders. In this context, [^{18}F]FDG PET/CT plays a pivotal role in oncology, serving purposes such as diagnosis, prognostication, and follow-up [6, 7]. However, the distinctive mechanism of action in ICI-based therapy presents challenges in assessing responses, given the potential for atypical patterns like 'pseudo-progression' (temporary increased lesion size followed by regression) or 'hyperprogression' (accelerated tumor growth). To address these challenges, new criteria for interpreting and reporting scans in cancer patients under ICI therapy have been implemented for both CT and PET/CT [8]. Moreover, [^{18}F]FDG PET/CT facilitates the early detection of irAEs, providing an opportunity for intervention before clinical symptoms manifest [9].

The mechanisms through which ICI can induce irAEs are still not fully understood, likely involving a complex interplay between auto-reactive T and B cells, antibody-mediated processes, and a diminished T-regulatory phenotype [10]. These intricate phenomena underscore the broad spectrum of potentially affected organs and tissues, the wide array of clinical manifestations, and the variability in the presentation of irAEs on morphological and functional imaging. Notably, clinical trials have frequently reported nodal involvement and thyroid disorders in patients undergoing ICI. ICI-related thyroiditis, exhibiting nonspecific symptoms such as asthenia, weight change, and occasionally cardiac rhythm disorders, contrasts with the rare occurrence of orchitis among possible irAEs [11]. To date, only one case of ICI-related orchitis diagnosed by [^{18}F]FDG PET has been reported, involving a 54-year-old man with stage IV melanoma undergoing sequential nivolumab and ipilimumab therapy [12]. In this case, orchitis correlated with tumor response and spontaneously resolved within weeks, mirroring our findings. It is essential to underscore that a higher incidence of irAEs has been documented in cases involving a combination of different ICIs. However, our patient experienced orchitis and thyroiditis concurrently, despite receiving ICI monotherapy.

It should be emphasized that interpreting [^{18}F]FDG uptake in testicular inflammatory and oncological diseases might pose a challenge for nuclear medicine physicians. It is well-known, in fact, that [^{18}F]FDG exhibits a variable degree of physiological uptake within the testicles due to the varying metabolic activity of their distinct cell populations (namely, Sertoli, Leydig, and germ cells), which are involved in numerous metabolic pathways [13]. Specifically, Leydig cells have been observed to express glucose transporters, as glucose serves as a substrate for steroidogenesis. Consequently, [^{18}F]FDG uptake within the testicles is influenced by age and testosterone levels [14]. Various endeavors have been undertaken to establish a normal range of [^{18}F]FDG uptake, measured by SUV, in healthy testicular tissues. A study involving 203 subjects revealed an overall testicular SUVmean of 2.44 ± 0.45, with an inverse correlation between testicular uptake and age [15]. However, it is essential to underscore that PET-derived parameters are significantly affected by technical variables, including administered activity, timing of acquisition, and the type of PET scanners employed. In light of these considerations, further exploration of this subject may hold significance, particularly with the recent advancements in digital PET technology and long axial field-of-view scanners [16]. Further consideration should be given to the lack of specificity of [^{18}F]FDG uptake. Increased tracer uptake can result from both metastatic localization and inflammation. In routine

clinical practice, nuclear medicine physicians rely on clinical data for image interpretation. In the case we present, the pattern of thyroid uptake, combined with laboratory findings of TSH values within high-normal range, strongly suggested immunotherapy-induced thyroiditis, one of the most common irAEs. Regarding the testicular findings, it is important to note that bilateral testicular metastases from MM, while possible, are extremely rare, and no lesions or masses were detected on ultrasound or PET/CT co-registered images [17]. Importantly, no standardized consensus currently exists regarding the PET assessment of ICI-induced organ inflammation. In our case, we adhered to the commonly applied criteria, relying on the visual identification of a diffuse and homogeneous increase in organ uptake intensity not observed in pre-therapy PET scans [18, 19].

Conclusions

Our case underscores the significance of [^{18}F]FDG PET/CT not only in monitoring the response to immunotherapy but also in detecting uncommon immune-related adverse events, thereby assisting in clinical management. Additional studies and collaboration across multiple centers are essential to establish a standardized definition for immune checkpoint inhibitor (ICI)-induced organ inflammation on [^{18}F]FDG PET/CT.

Abbreviations

irAEs	Immune-related adverse events
MM	Malignant melanoma
ICI	Immune checkpoint inhibitor
[^{18}F]FDG	2-Deoxy-2-[18F]fluoro-D-glucose
PET/CT	Positron emission computed tomography
BRAF	V-Raf Murine Sarcoma Viral Oncogene Homolog B
US	Ultrasound

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Not applicable.

Author contributions

LF, IP, and SM participated in the study design, drafting of the article, analysis, and interpretation of data. LF was the chief investigator and responsible for the data analysis. CP had full access to all of the data in the study and takes responsibility for the integrity of the data. LF and IP were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Further clinical data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Consent to publish was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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