COVID-19 vaccination mimicking lymph-node progression in a patient with melanoma: a case report

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COVID-19 vaccination has been rapidly implemented among patients with cancer. We present the case of a patient with high-risk resected cutaneous melanoma, who was a candidate for adjuvant treatment, with postsurgery 18-fluorodeoxyglucose (FDG) PET/computed tomography (CT) scan showing positive axillary lymph nodes after COVID-19 vaccination. This report presents a 50-year-old man with a history of stage IIA cutaneous melanoma. During follow-up, the patient experienced subcutaneous and lymph-node disease progression, documented with ^{18}FDG PET/CT scan. The patient underwent laparoscopic left para-aortic lymphadenectomy and excision of subcutaneous lesion. Histologic examination showed presence of melanoma metastases in 2 lymph nodes out of total 17 excised and neoplastic emboli to the subcutaneous tissue. In view of starting adjuvant nivolumab, the patient underwent CT scan restaging, with evidence of suspect centimetric periaortic and paracaval lymph nodes, which were deemed worthy of ^{18}FDG PET investigation. The ^{18}FDG PET/CT was negative for abdominal hypercaptation, but showed left axillary pathologic lymph nodes. The medical history of the patient revealed that he had received intramuscular Moderna COVID-19 mRNA vaccine in the left deltoid, one week before ^{18}FDG PET examination. Since the patient's clinical examination was negative and suspecting postvaccination false-positive adenopathy, bilateral axillary ultrasound was performed, excluding the presence of pathologic lymph nodes. The patient has started adjuvant treatment with nivolumab, which is currently ongoing. This case demonstrates unexpected findings in response to COVID-19 vaccination in a patient with melanoma. In this specific case, the detection of ^{18}FDG PET hypercaptation could significantly change the patient's management. With growing evidence about the pattern and occurrence of adenopathies after mRNA COVID-19 vaccination, recommendations for scheduling and interpretation of ^{18}FDG PET/CT scans among cancer patients will be implemented, in order to reduce equivocal findings and improve outcomes. *Melanoma Res* 31: 490–493

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Introduction

Cancer patients are considered a high-priority category of patients during the novel coronavirus disease 19 (COVID-19) vaccination program [1]. Evidence suggests that patients with cancer are at higher risk for severe COVID-19-related complications and death [2]. Moreover, oncology facilities have faced the challenge of ensuring an adequate continuum of care during the pandemic [3]. Thus, rapid implementation of vaccination programs has revealed paramount to allow delivering safe cancer care in oncology facilities. International guidelines indicate that patients with cancer who are either about to start or are receiving, active anticancer treatments should receive mRNA COVID-19 vaccines (e.g. Pfizer-BioNTech, Moderna) [4].

Several cases of false-positive 18-fluorodeoxyglucose (FDG) PET/computed tomography (CT) scan after COVID-19 vaccination have been reported [5]. This issue gains particular relevance among patients with cancer, and even more in those who are expected to be disease-free after surgery and are candidate for adjuvant therapy. Among patients with melanoma, adjuvant and metastatic settings deeply differ in regards to disease prognosis and therapeutic algorithm. Five-year relative survival for patients with the regional disease is approximately 68%, while it dramatically drops down to less than 30% in patients with metastatic disease [6]. Patients with resected stage III–IV melanoma undergoing radical surgery can receive adjuvant treatment, which has led to significant improvements in survival outcomes [7–9]. While treatment for metastatic disease is chronic, and most patients eventually develop disease progression and die from the disease. Adequate postsurgery disease staging (in order to confirm the absence of residual disease), and timely treatment start (i.e. within 12 weeks from surgery),

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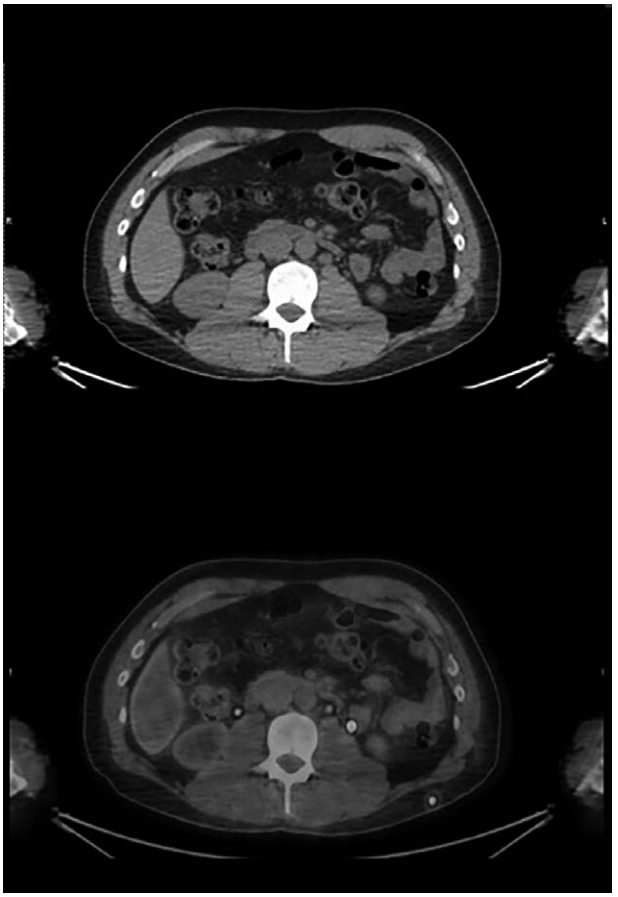
are key points to ensure better results from adjuvant treatment in patients with melanoma [10]. Here, we report the case of a patient with cutaneous melanoma candidate for adjuvant treatment, who had false-positive ^{18}FDG PET/CT axillary lymph nodes after COVID-19 vaccination.

Case report

A 50-year-old man diagnosed with cutaneous melanoma (pT3a) of the lumbar region in 2019, was treated with radical surgery and bilateral axillary lymph-node biopsy, with no evidence of microscopic disease. The patient received no adjuvant treatment (stage IIA disease), and started regular follow-up. During follow-up, the patient was referred to our Institution for a second opinion, upon evidence of left para-aortic lymph node and subcutaneous left lumbar region ^{18}FDG PET hypercaptation. Previous ^{18}FDG PET/CT scans had already evidenced the presence of suspect para-aortic adenopathy; however, this had been kept in follow-up due to aspecific characteristics and borderline standardized uptake values (SUV). The last ^{18}FDG PET performed on January 2021 showed subcutaneous left lumbar region hypercaptation, together with increased dimension (20 mm) and hypercaptation (SUVmax 7.5) of the known abdominal adenopathy (Fig. 1). After excluding the presence of intracranial disease with brain contrast-enhanced (c.e.) CT scan, the patient underwent explorative laparoscopy with left para-aortic lymphadenectomy and excision of the left lumbar subcutaneous lesion. Histologic examination showed the presence of melanoma metastases in 2 lymph nodes out of total 17 excised and neoplastic emboli to the subcutaneous tissue. BRAF mutation analysis was negative. The patient was in good clinical conditions (performance status according to the Eastern Oncology Cooperative Group [ECOG] score: 0), with no relevant past medical history. In view of starting adjuvant immunotherapy with nivolumab, the patient underwent CT scan restaging on April 6th, with evidence of suspect centimetric periaortic and paracaval lymph nodes (Fig. 2a), which were deemed worthy of ^{18}FDG PET investigation. The ^{18}FDG PET/CT performed on April 20th was negative for abdominal hypercaptation (Fig. 2b), but showed left axillary pathologic lymph nodes (Fig. 2d), which had not been evidenced by the previous CT scan (Fig. 2c). The medical history of the patient revealed that he had received intramuscular Moderna COVID-19 mRNA vaccine in the left deltoid, one week before ^{18}FDG PET examination. Considering that the patients' clinical examination was negative, and suspecting postvaccination reactive adenopathy, we performed a bilateral axillary ultrasound, which excluded the presence of pathologic lymph nodes. The patient has started adjuvant treatment with nivolumab, which is currently ongoing.

Fig. 1



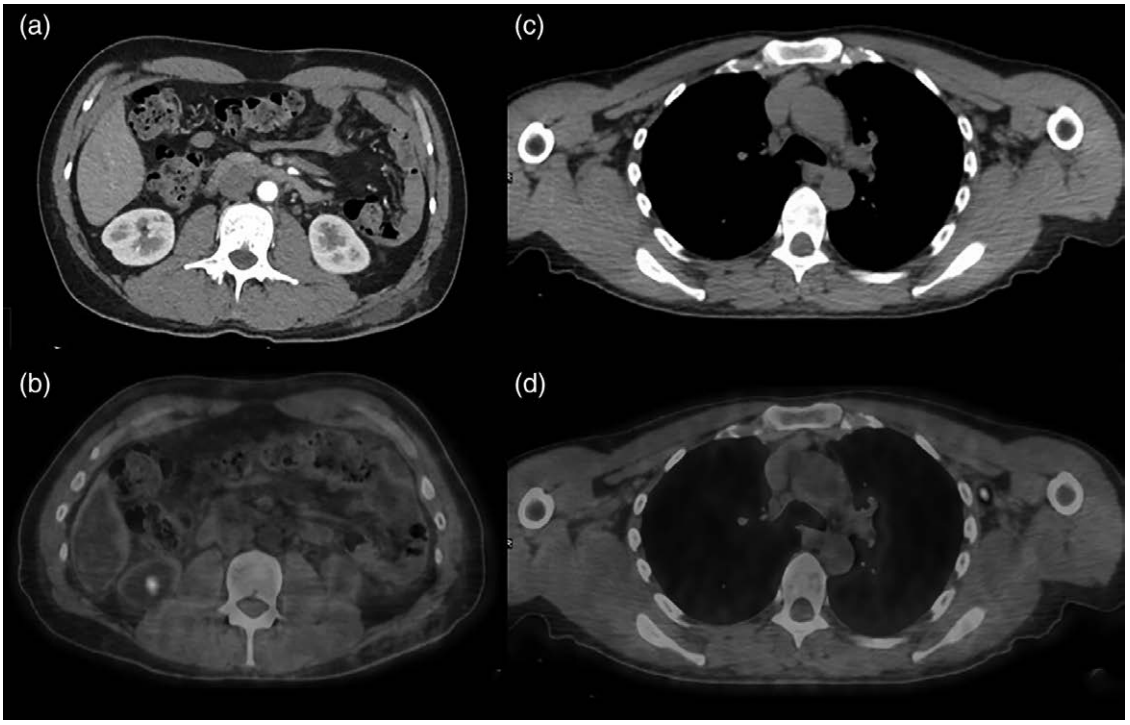
Presurgery ^{18}FDG PET/CT scan showing left para-aortic lymph node and subcutaneous left lumbar region pathologic hypercaptation.

Discussion

Transient FDG uptake can occur in morphologically normal or enlarged lymph nodes (mainly axillary, supraclavicular and laterocervical nodes) after intramuscular ipsilateral deltoid administration of several types of vaccines, including H1N1v and seasonal influenza vaccination [11]. This evidence has recently been confirmed also after COVID-19 vaccination in patients with different types of solid and hematologic malignancies [5,12–19], including patients with cutaneous melanoma [12,15,18,19].

Clinical evidence of lymphadenopathies after COVID-19 Moderna vaccine administration was reported in 1.1% of people in the vaccine group, compared with 0.6% in the placebo group [20]. Among people aged 18–64 years, ipsilateral axillary adenopathy occurred in 11.6% of the recipients after the first dose, and in 16% after the booster dose; the reported frequency was lower among subjects aged ≥65 years, being 6.1% after the first and 8.4% after the booster dose, respectively [20]. Likewise,

Fig. 2



Postsurgery CT and ^{18}FDG PET/CT scan; (a) CT scan showing suspect centimetric periaortic and paracaval lymph nodes; (b) ^{18}FDG PET/CT negative for abdominal hypercaptation; (c) CT scan negative for axillary lymph nodes; (d) ^{18}FDG PET/CT showing left axillary pathologic lymph nodes.

adenopathies were reported more frequently in patients receiving Pfizer-BioNTech vaccination as compared with subjects in the placebo group, and this unsolicited event was reasonably related to the vaccine injection [21]. Lymphadenopathy most commonly occurred in the arm and neck regions for both types of vaccines. The reported onset of lymphadenopathy was 2–4 days after vaccine administration, with a median duration of 1–2 days with Moderna vaccine, and a longer average duration after Pfizer-BioNTech vaccine (approximately 10 days) [20,21].

Recently, a retrospective cohort study investigated the occurrence and pattern of hypermetabolic axillary lymph nodes on ^{18}FDG PET/CT scans from 650 cancer patients receiving Pfizer-BioNTech COVID-19 vaccination [13]. The Authors found that ^{18}FDG PET/CT hypermetabolic axillary lymph nodes were detected in 25.8% of patients after vaccination, with a higher incidence of positive lymph nodes after the booster injection [13]. Another cohort study of 728 cancer patients receiving Pfizer-BioNTech COVID-19 vaccination, showed a higher incidence of hypermetabolic axillary and occasionally also supraclavicular lymph nodes, occurring in 36.4% of patients after the first and in 53.9% after the booster dose [22]. Patients younger than 62 years had higher rates and increased intensity of ^{18}FDG PET/CT hypermetabolic lymphadenopathies. Interestingly, this study evidenced that the incidence of ^{18}FDG PET/CT hypermetabolic lymph nodes was lower during the first 5 days and beyond 13 days after the first dose, while it increased 6–12 days after the first dose and immediately after the booster administration (i.e. 3 weeks after first dose administration). After booster vaccine administration there was a gradual decrease over 3 weeks' time. In this study, 29% of vaccinated patients still presented hypermetabolic lymphadenopathy 3 weeks after the booster administration; however, only 7% had grade 3 or 4 adverse effects [22].

These postvaccination findings pose a significant dilemma in patients with cancer, considering the widespread vaccination programs in this subset of patients: ^{18}FDG PET-positive lymph nodes after vaccination may be confounding, and lead to misinterpretation of tumor staging and disease response during treatment [14]. In this context, adequate patients' questioning on recent vaccination may help to avoid false interpretation of ^{18}FDG PET [13]. Some tumors might be more at risk for diagnostic challenges in the case of ^{18}FDG PET nodal hypercaptation. These include hematologic disease with predominant nodal involvement (e.g. lymphomas, Castleman's disease), or solid tumors which are prone to nodal metastases and have laterality (e.g. breast cancer,

cutaneous melanoma, sarcoma of the upper limbs, lung cancer, head and neck cancer) [14]. Among this latter group, patients should be advised to be vaccinated in the arm contralateral to the tumor expected nodal drainage [14,17].

This case demonstrates unexpected findings in response to Moderna COVID-19 vaccination in a patient with melanoma. In the current context, these findings are likely to be routinely encountered on ^{18}FDG PET imaging, implying careful case-by-case evaluation to allow a correct interpretation of the imaging. In this specific case, the detection of ^{18}FDG PET hypercaptation could significantly change the patient's management. As growing evidence about the pattern and occurrence of adenopathies after mRNA COVID-19 vaccination becomes available, recommendations for scheduling and interpretation of ^{18}FDG PET/CT scans among cancer patients will be implemented in order to reduce equivocal findings and improve outcomes.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interest

There are no conflicts of interest.

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