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Immune checkpoint inhibitor related adverse effects and 18F-FDG PET/CT findings

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Running title: Adverse effects of checkpoint treatments and PET scan

Abstract

Immune check-point inhibitor (ICI) treatments activate the T-cells against tumor. Activated T-cells not only attack the tumor but also healthy cells, causing an autoimmune reaction in various tissues. These immune related adverse effects (IRAE) cause ^{18}F-fluorodeoxyglucose (18F-FDG) uptake in various tissues due to inflammation. It is important to recognize and report these findings on 18F-FDG Positron Emission Tomography/Computed Tomography (PET/CT) studies. 18F-FDG PET helps to determine the presence, location and severity of IRAEs. In severe cases, ICI treatments are interrupted or suspended and anti-inflammatory treatments are started. 18F-FDG uptake due IRAEs may mimic metastases or disease progression. Their presence may also help predicting response to treatment and have prognostic implications. In this review article, we will provide basic information about ICI treatments, IRAEs and 18F-FDG PET/CT findings.

Key words: Immune checkpoint inhibitor, 18F-FDG PET/CT, adverse effect, autoimmune

Introduction

Immune check-point inhibitor (ICI) treatments have been increasingly used in oncology in the last 10 years. ICI treatments activate the T-cells against tumor by blocking inhibitory ICI immunoreceptors or their ligands. Activated T-cells not only attack the tumor but also healthy and normal cells, causing an autoimmune reaction in various tissues. These immune related adverse effects (IRAE) cause increased uptake on ^{18}F-fluorodeoxyglucose (18F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT) studies due to inflammation in various tissues. 18F-FDG PET has high sensitivity in detecting inflammation and determining its severity and extent. It is important to recognize and report IRAE related findings on PET images. Based on severity and extent of IRAEs, physicians interrupt or suspend the ICI treatment and start steroid or immunosuppressive treatments. Presence and severity of IRAEs may help to predict response to ICI treatments and may have a prognostic value with a more favorable prognosis (*1-3*). Depending on the location, particularly in lymph nodes, IRAE related uptakes may mimic metastases or disease progression and therefore it is important to be aware of these immune related side effects. In this review article, we will first describe the ICIs, mechanism of autoimmune reactions in patients receiving ICI treatments and then 18F-FDG PET/CT findings.

Immune Checkpoint Inhibitors

Immune checkpoints play an important role in immune regulation. There are various checkpoint molecules (immunoreceptors) on T-cells, some of them are inhibitory (suppressing the T-cells) and some are stimulatory (activating the T cells) (*4,5*). Tumors or antigen presenting cells (e.g. macrophages or dendritic cells) have various ligands on their surfaces which bind to inhibitory or stimulatory checkpoint receptors on T cells resulting in activation or suppression of T cells (*5*). Activated T-cells subsequently kill the microorganisms (viruses, bacteria, fungi, and

parasites) and tumors but then can also attack healthy cells, resulting in autoimmune diseases. Suppression of T-cells prevents autoimmune diseases but results in reduced protection against microorganisms. The tumor microenvironment can also suppress T-cells. In normal conditions, inhibitory immune checkpoint immunoreceptors are activated to prevent T-cells from attacking normal tissues.

In the last 10 years various medications (antibodies) have been developed to block (inhibit) inhibitory checkpoint molecules (immunoreceptors or their ligands) in the treatment of tumors and infection. These medications are called immune checkpoint inhibitors (ICI). Currently approved ICI medications block the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) (ipilimumab), programmed death receptor 1 (PD-1) (pembrolizumab, nivolumab) or its ligand (PD-L1) (atezolizumab, avelumab, durvalumbab, and cemiplimab) (*4,6*). These medications are approved to be used in the treatment of various cancers such as melanoma (ipilimumab, nivolumab, pembrolizumab), non-small cell lung cancer (pembrolizumab, nivolumab), renal cancer (nivolumab, ipilimumab), bladder cancer (atezolizumab) (*4,6*)

Inhibition of CTLA-4 and PD-1/PD-L1 through ICI treatment activates T-cells to kill tumor cells but also causes T-cells to target healthy tissues resulting in immune related adverse effects (IRAE) (autoimmune manifestations). They can also cause a flare of prior autoimmune disease. IRAEs are commonly seen in patients receiving ICI treatments and dependent on dose and type of ICI treatment and various other factors. IRAEs can be clinically evident or silent and can involve any tissues resulting in i.e. encephalitis, hypophysitis, thyroiditis, sarcoid-like reactions, pneumonitis, hepatitis, pancreatitis, adrenalitis, colitis, nephritis, arthritis and skin manifestations. Most fatalities are seen in cases with encephalitis, myocarditis, pneumonitis and hepatitis (*7*). IRAEs can be seen few weeks to months after starting ICI treatment. Clinical, laboratory,

radiological and ^{18}F-fluorodeoxyglucose (18F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT) imaging findings can help to diagnose IRAEs. Optimal management of IRAEs varies according to organ involved and severity or grading of involvement which includes close monitoring, treatment interruption or suspension and corticosteroid administration (prednisone or methylprednisolone) (*8*).

18F-FDG PET/CT Imaging

18F-FDG PET/CT imaging is used to assess response to ICI treatments in various tumors, particularly melanoma and non-small cell lung cancer. 18F-FDG PET response patterns in ICI treatments show some different (atypical) patterns than those seen with other treatments such as chemotherapy or radiotherapy. This is because ICI treatments induce influx of T-lymphocytes into the tumor which take up 18F-FDG and subsequently further increases metabolic activity of the tumor environment (*9,10*). Immune-related response criteria such as PERCIMT or iRECIST have been established to better assess response to treatments in patients receiving ICI treatments (*11,12*).

18F-FDG PET positive IRAEs, such as sarcoid-like syndrome, thyroiditis, hypophysitis, enterocolitis, pancreatitis, hepatitis, pneumonitis, arthritis, enthesitis, and myositis have been reported in various articles (*13,14*).

18F-FDG PET is very sensitive in detecting early inflammation even before clinical symptoms start and radiological changes develop (*15,16*). Cells involved in inflammation actively uses glucose, which is the main reason for increased 18F-FDG uptake in inflammatory sites. In addition, increased blood flow and capillary permeability also contributes to increased 18F-FDG activity at inflammation sites, which is non-specific and can be seen with any kind of radiotracer. It was reported that a significant number of patients with PET-detectable IRAEs were asymptomatic (*1,17*). Early detection of IRAEs allows early management. Their presence may

help predicting response to treatment and provide prognostic information with a more favorable prognosis (*1-3*). In a study by Sachpekidis et al, in 10% of the patients PET/CT showed sarcoid-like lymphadenopathy as response to treatment and these patients showed disease control (*2*). In another study, 9 patients with IRAE findings on PET had complete response at final evaluation (*1*). Patients with PET-detectable IRAEs had a significantly longer progression free survival than those without IRAEs on PET (*3*).

Colitis is one of the most common manifestations of IRAEs. On non-contrast CT as part of PET/CT, colonic wall thickening and pericolic fat stranding may be seen associated with diffuse or segmental increased 18F-FDG uptake. 18F-FDG PET/CT imaging was reported to be more sensitive than CT in the early detection of colitis as a result of ICI treatment (*6,17,18*). However, 18F-FDG PET has low specificity for colitis due to physiological mucosal, muscular, and luminal activity. In addition, glucophage use can induce high bowel activity and it is recommended to stop it for 48 hr before 18F-FDG PET study. Figure 1 shows sagittal 18F-FDG PET/CT images of a 71 yo patient with history of melanoma. PET/CT image before treatment does not show abnormal findings in sigmoid colon (A). PET/CT scan 4 mos after Nivolumab treatment shows thickening in sigmoid wall with inflamed diverticula and increased uptake without clinical symptoms (B). PET scan 6 mos after discontinuation of Nivolumab (treatment change to Tafinlar/Mekinist due to disease progression) shows only mild thickening in sigmoid wall as late inflammatory residue (fatty infiltration) and only mild uptake.

18F-FDG PET has high sensitivity in detecting rheumatologic manifestations of IRAEs such as arthritis, myositis, tenosynovitis, and polymyalgia rheumatica and determining its extent and severity. Figure 2 shows serial 18F-FDG PET total body images of a 48yr old patient with history of melanoma who received various ICI treatments. PET image after 22 mos of

Nivolumab treatment shows mildly increased uptake in the left knee, bilateral mediastinal and hilar lymph nodes (sarcoid-like) (A). The patient had no clinical symptoms related to these adverse effects seen on PET. PET image after treatment with Pembrolizumab for 3 mos (change in therapy due to persistent metastasis in the 12th rib, not shown in the image A) shows diffusely increased metabolic activity in upper and lower extremity muscles which is indicating myositis when correlating with clinical findings of swollen arms and legs (B). PET image also shows interval slight progression in left knee uptake, mildly increased uptake in the right knee and left ankle, and bowel activity without clinical signs. PET image after 2 mos of Nivolumab treatment shows markedly and diffusely increased uptake in all joints of upper and lower extremities bilaterally (C). Antibody treatment was stopped and prednisolone treatment was started by the clinician upon PET image findings and laboratory and clinical correlation. PET image 12 mos after stopping Nivolumab treatment (steroid treatment stopped six mos prior to PET) shows complete resolution of inflammatory uptake in the joints (D). No evidence of tumor (complete metabolic response) and stable mild sarcoid-like uptake are seen (B, C, D). Figure 3 shows 18F-FDG PET images 1 month (A) and 1 year (B) with Nivolumab treatment in a 40 year-old patient with history of melanoma. In image A, there is increased uptake in bone marrow and mild diffusely increased uptake in the knees. In image B, there is increased uptake in the interspinous bursae of the lumbar spine, which is highly suspicious for polymyalgia rheumatica, and further increase in uptake in the knees.

IRAE related focal areas of uptake or uptake in lymph nodes can mimic metastatic disease or disease progression (*19,20*). Sarcoid-like reactions may mimic lymph node, lung and skin metastases. Sarcoid-like reactions are characterized by the presence of noncaseating granulomas. In sarcoid-like reactions, 18F-FDG PET/CT usually shows bilateral symmetrical hypermetabolic

mediastinal and hilar lymphadenopathy with or without hypermetabolic focal nodular opacities or condolidations in the lungs. Uptake in portocaval lymph nodes and subcutaenous hypermetabolic nodules due to noncaseating granulomas may also be seen in sarcoid-like reactions (*10,21*). Figure 4 shows 18F-FDG PET images of a 60 yo patient with melanoma. PET image for initial staging shows metastatic disease in the lungs, liver, left adrenal and mesenteries and diffuse uptake in the stomach due to gastritis from helicobacter pylori (A). PET scan 6 months after Nivolumab treatment shows complete metabolic resolution of most of the lesions, with some residual tumor in the liver and progression in left adrenal metastasis (B). New symmetrical hypermetabolic lymph nodes in both hila and mediastinum is likely due to sarcoid-like reaction. Nivolumab induced flare in gastric uptake is also seen.

IRAE related thyroiditis might be acute and transient with biochemically and clinically accompanied thyrotoxicosis or progressing to hypothyroidism (*22*). Selected CT images of a 61 year-old patient with melanoma shows reduction in thyroid size 1 year after treatment with Nivolumab as compared to baseline image (Figure 5, A and C). PET image after starting Nivolumab shows diffusely increased uptake in the thyroid gland with a cold defect in lower pole of the right lobe corresponding to a nodule seen on CT (B). TSH was 43mU/l). Figure 6 shows diffusely increased uptake in the thyroid gland in a 65 yo patient with history of melanoma who was treated with Nivolumab for 20 months (whole body). Thyroiditis and hypothyroidism was confirmed with laboratory findings and patient was placed on thyroxine. There is also mild diffusely increased uptake in the liver (SUVmean:3, SUVmax:5.2, liver to blood pool (BP) SUVmean ratio:1.6) and elevated GLDH and gamma-GT, indicating hepatitis. Colonic uptake was due to glucophage use. Due to physiological uptake in the liver, 18F-FDG PET may not show early hepatitis, however in more severe cases it is possible to see diffusely increased hepatic

uptake. ICI treatment related T-cell activation can induce increased uptake spleen (reversal in liver to spleen uptake ratio) which may interfere with detection of hepatitis on PET images (*10*). However, careful visual assessment and obtaining liver to BP SUVmean ratio can help detecting hepatitis in such cases. Normal liver to BP SUVmean ratio ranges from 1.3 to 1.4 in various reports (*23-25*). As the SUVs are affected by body weight and various other factors, liver to BP SUVmean ratio is more accurate than SUVmean alone when assessing metabolic activity of the liver (*25*).

On 18F-FDG PET scan, normal pituitary gland may be visualized with mild uptake. Prominent uptake in the pituitary gland could be from hypophysitis but pituitary adenomas or metastasis should be ruled out by clinical, laboratory and radiological assessment. Figure 7 shows increased uptake in pituitary gland in a 61 year-old patient with history of melanoma who was treated with Nivolumab (pituitary to frontal SUVmax ratio was 1 as compared to 0.3 in a patient with normal uptake in pituitary gland) (A and B). Laboratory values did not show pituitary insufficiency but MRI after 3 months of therapy showed a swollen, inhomogenous enhancing hypophysis with thickened hypophyseal stalk indicative of hypophysitis (D) as compared to before treatment MRI showing typical flat, homogeneous enhancing hypophysis after contrast agent (C) (*26*).

18F-FDG PET/CT has a high sensitivity in determining the severity (grade) and extent of inflammation in certain tissues such as joints and colon, which is important in the management of patients with starting steroid treatment, and interrupting or suspending ICI treatment. However, care should be taken when assessing the inflammation or tumor in patients receiving or recently received high-dose steroid treatment as it may cause a false negative 18F-FDG PET study or underestimation of metabolic activity of inflammation or tumor (*27*,*28*).

In routine oncologic studies, 18F-FDG PET imaging cannot accurately assess myocardial

inflammation due to various degrees of physiological myocardial uptake. If there is clinical concern for myocarditis, cardiac 18F-FDG PET imaging protocol or cardiac MRI is used to demonstrate myocardial involvement (*29*,*30*).

Pelvicalyceal excreted activity may limit evaluation of kidneys but in renal involvement focal or diffuse renal parenchymal 18F-FDG uptake may be seen in a careful assessment of images (*31*). In addition, delayed PET imaging can help to better assess renal parenchymal involvement.

18F-FDG PET is also limited in assessing the brain due to physiological high uptake in the gray matter. In encephalitis, diffusely decreased and heterogeneous uptake may be seen. In limbic encephalitis increased uptake may be seen in unilateral or bilateral mesial temporal lobes. PET/MR or MR imaging of the brain can further help identify brain involvement, particularly MRI T2 FLAIR sequences are very sensitive in inflammation (*32*,*33*).

Potential skeletal adverse effects related to immune checkpoint inhibitors have been reported as bone fractures and resorptive or destructive bone lesions due to localized inflammation, like a sterile osteitis, leading to osteoclast activation and bone resorption (*34*). These changes can cause increased uptake in the bones on 18F-FDG PET scan but up to now no cases have been reported.

Conclusion

ICI treatment related autoimmune adverse effects are common. It is important to recognize and report IRAE related adverse effects findings on 18F-FDG PET scan.

Disclosure

No potential conflict of interest relevant to this article was reported.

Key Points

Question: What is the importance of recognizing immune checkpoint inhibitor (ICI) treatment related adverse effects findings on 18F-FDG PET scan?

Pertinent Findings: Immune related adverse effects (IRAE) are commonly seen in patients receiving ICI treatments and cause increased uptake in various tissues on 18F-FDG PET studies.

Implications for patient care: Recognizing immune related adverse effects on PET scan is important as their presence and severity alert the physicians to interrupt or suspend the ICI treatment and start anti-inflammatory treatments. Their presence may also help predicting response to treatment. Being aware of IRAE related uptakes on 18F-FDG PET scan also prevents false positive results for metastasis or disease progression.

References

1. Nobashi, T. Baratto, L, Reddy, S.A. Srinivas, S. Toriihara, A. Hatami N et al. Predicting response to immunotherapy by evaluating tumors, lymphoid cell-rich organs, and immune-related adverse events using FDG-PET/CT. Clin. Nucl. Med. 2019; 44:e272–e279.
2. Sachpekidis C. Larribère L. Kopp-Schneider A. Hassel JC, Dimitrakopoulou-Strauss A. Can benign lymphoid tissue changes in 18F-FDG PET/CT predict response to immunotherapy in metastatic melanoma? Cancer Immunol. Immunother. 2019; 68, 297–303.
3. Sachpekidis, C. Kopp-Schneider, A. Hakim-Meibodi, L. Dimitrakopoulou-Strauss, A. Hassel, JC. 18F-FDG PET/CT longitudinal studies in patients with advanced metastatic melanoma for response evaluation of combination treatment with vemurafenib and ipilimumab. Melanoma Res. 2019; 29:178–186.
4. Dyck L, Mills KHG. Immune checkpoints and their inhibition in cancer and infectious diseases. Eur J Immunol. 2017; 47:765-779.
5. He X, Xu C. Immune checkpoint signaling and cancer immunotherapy. Cell Res. 2020; 30:660-669.
6. Vani V, Regge D, Cappello G, Gabelloni M, Neri E. Imaging of adverse events related to checkpoint inhibitor therapy. Diagnostics. 2020; 10:216.
7. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019; 16:563-580.
8. Rudzki JD. Management of adverse events related to checkpoint inhibition therapy. Memo. 2018; 11:132-137.

9. Decazes P, Bohn P. Immunotherapy by immune checkpoint inhibitors and nuclear medicine imaging: current and future applications. Cancers. 2020; 12:371.
10. Prigent K, Aide N. 18F-Fludeoxyglucose PET/Computed Tomography for assessing tumor response to immunotherapy and detecting immune-related side effects: a checklist for the PET reader. PET Clin. 2020; 15:1-10.
11. Aide N, Hicks RJ, Le Tourneau C, Lheureux S, Fanti S, Lopci E. FDG PET/CT for assessing tumour response to immunotherapy: Report on the EANM symposium on immune modulation and recent review of the literature. Eur J Nucl Med Mol Imaging. 2019; 46:238-250.
12. Dimitrakopoulou-Strauss A. Monitoring of patients with metastatic melanoma treated with immune checkpoint inhibitors using PET-CT. Cancer Immunol Immunother. 2019; 68:813-822.
13. Mekki A, Dercle L, Lichtenstein PH, Marabelle A, Michot J, Lambotte, O. et al. Detection of immune-related adverse events by medical imaging in patients treated with anti-programmed cell death 1. Eur. J. Cancer. 2018; 96:91–104.
14. Iravani A. Hicks RJ. Pitfalls and immune-related adverse events. In: Lopci, E., Fanti, S., Eds. Atlas of response to immunotherapy, 1st ed.; Cham, Switzerland: Springer, 2020: 101–115.
15. Signore A, Anzola KL, Auletta S, Varani M, Petitti A, Pacilio, M. et al. Current status of molecular imaging in inflammatory and autoimmune disorders. Current Pharmaceutical Design. 2018; 24:743–753
16. Sollini M, Lauri C, Boni R, Lazzeri E, Erba PA, Signore A. Current status of molecular imaging in infections. Current Pharmaceutical Design. 2018; 24:754–771

17. Lang N, Dick J, Slynko A, Schulz C, Dimitrakopoulou-Strauss A, Sachpekidis C et al. Clinical significance of signs of autoimmune colitis in 18F-fluorodeoxyglucose positron emission tomography-computed tomography of 100 stage-IV melanoma patients. Immunotherapy. 2019; 11: 667–676
18. Bronstein Y, Ng CS, Hwu P, Hwu WJ. Radiologic manifestations of immune-related adverse events in patients with metastatic melanoma undergoing anti-CTLA-4 antibody therapy. Am. J. Roentgenol. 2011; 197:992–1000.
19. Das JP, Halpenny D, Do RK, Ulaner GA. Focal immunotherapy-induced pancreatitis mimicking metastasis on FDG PET/CT. Clin Nucl Med. 2019; 44:836-837.
20. Jespersen H, Bjursten S, Ny L, Levin M. Checkpoint inhibitor-induced sarcoid reaction mimicking bone metastases. Lancet Oncol. 2018; 19:e327.
21. Cheshire SC, Board RE, Lewis AR, Gudur LD, Dobson MJ. Pembrolizumab-induced sarcoid-like reactions during treatment of metastatic melanoma. Radiology. 2018; 289:564-567.
22. Delivanis DA, Gustafson MP, Bornschlegl S, Merten MM, Kottschade L, Withers S, et al. Pembrolizumab-induced thyroiditis: comprehensive clinical review and insights into underlying involved mechanisms. J Clin Endocrinol Metab. 2017;102:2770-2780.
23. Chiaravalloti A, Danieli R, Abbatiello P, Di Pietro B, Travascio L, Cantonetti M et al. Factors affecting intrapatient liver and mediastinal blood pool ^{18}F-FDG standardized uptake value changes during ABVD chemotherapy in Hodgkin's lymphoma. Eur J Nucl Med Mol Imaging. 2014; 41:1123-32.
24. Boktor RR, Walker G, Stacey R, Gledhill S, Pitman AG. Reference range for intrapatient variability in blood-pool and liver SUV for 18F-FDG PET. J Nucl Med. 2013; 54:677-82.

25. Sarikaya I, Albatineh AN, Sarikaya A. Revisiting weight-normalized SUV and lean-body-mass-normalized SUV in PET studies. J Nucl Med Technol. 2020;48:163-167.
26. Caranci F, Leone G, Ponsiglione A, Muto M, Tortora F, Muto M, Cirillo S, et al. Imaging findings in hypophysitis: a review. Radiol Med. 2020 125:319-328.
27. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. J Nucl Med. 2006;47:885-95
28. van der Geest KSM, Treglia G, Glaudemans AWJM, Brouwer E, Jamar F, Slart RHJA et al. Diagnostic value of (18F)FDG-PET/CT in polymyalgia rheumatica: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2020; Epub ahead of print
29. Dweck MR, Abgral R, Trivieri MG, Robson PM, Karakatsanis N, Mani V et al. Hybrid magnetic resonance imaging and positron emission tomography with fluorodeoxyglucose to diagnose active cardiac sarcoidosis. JACC Cardiovasc Imaging. 2018;11:94-107
30. Chen W, Jeudy J. Assessment of myocarditis: cardiac MR, PET/CT, or PET/MR? Curr Cardiol Rep. 2019; 21:76
31. Alessandrino F, Sahu S, Nishino M, Adeni AE, Tirumani SH, Shinagare AB et al. Frequency and imaging features of abdominal immune-related adverse events in metastatic lung cancer patients treated with PD-1 inhibitor. Abdom. Radiol. 2019; 44:1917–1927.
32. Galmiche S, Lheure C, Kramkimel N, Franck N, Boitier F, Dupin N et al. Encephalitis induced by immune checkpoint inhibitors in metastatic melanoma: a monocentric retrospective study. J Eur Acad Dermatol Venereol. 2019; 33:e440-e443.
33. Larkin J, Chmielowski B, Lao CD, Hodi FS, Sharfman W, Weber J et al. Neurologic serious adverse events associated with nivolumab plus ipilimumab or nivolumab alone in

advanced melanoma, including a case series of encephalitis. Oncologist. 2017; 22:709-718.

34. Moseley KF, Naidoo J, Bingham CO, Carducci MA, Forde PM, Gibney GT, et al. Immune-related adverse events with immune checkpoint inhibitors affecting the skeleton: a seminal case series. J Immunother Cancer. 2018; 6:104.

Figure-1 Selected sagittal FDG PET/CT images of the pelvis. Initial scan before treatment shows normal findings in the colon (A), PET/CT scan 4 mos after Nivolumab treatment shows colitis findings in sigmoid colon (arrows) (B), and PET/CT scan 6 months after discontinuation of Nivolumab treatment shows significant reduction in sigmoid activity (details in the text).

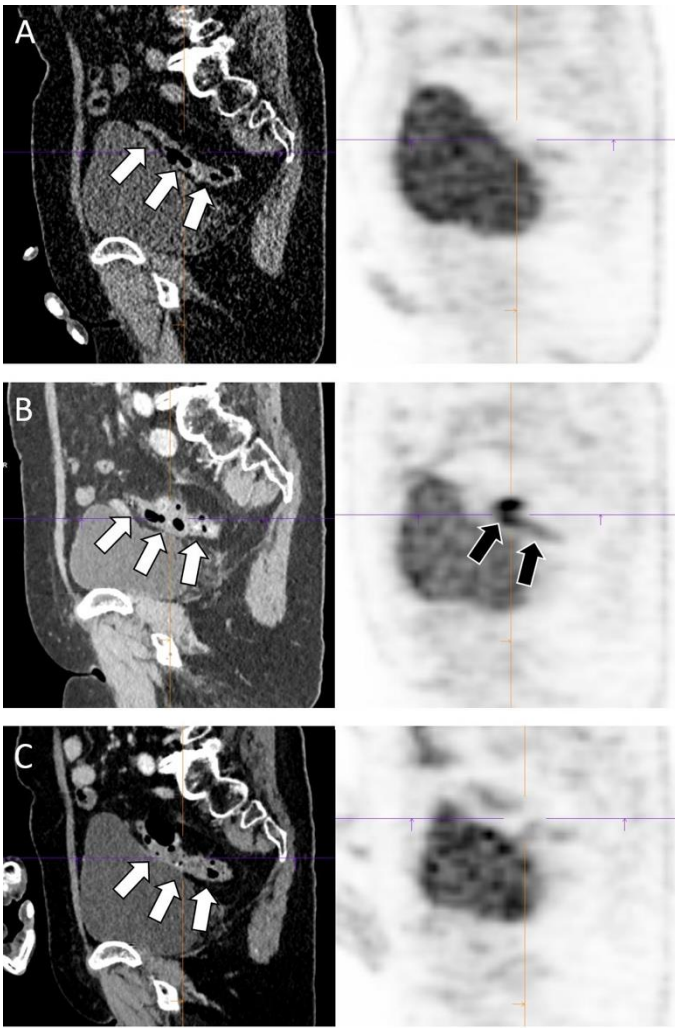


Figure-2 Serial total body FDG PET maximum intensity projection images of a patient with history of melanoma after treatment with Nivolumab (A), Pembrolizumab (B), Nivolumab (C), and after steroid treatment (D). Note the development, progression and regression of arthritis, as well as mild sarcoid-like uptake in the chest and myositis (details in the text).

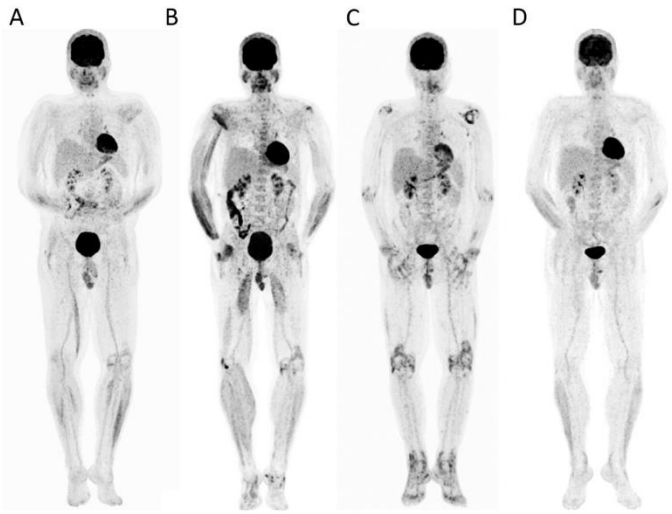


Figure-3 Sagittal total body MIP FDG PET images before (A) and after Nivolumab treatment (B). Increased uptake due bursitis in lumbar spine (arrows) (B) (details in the text).

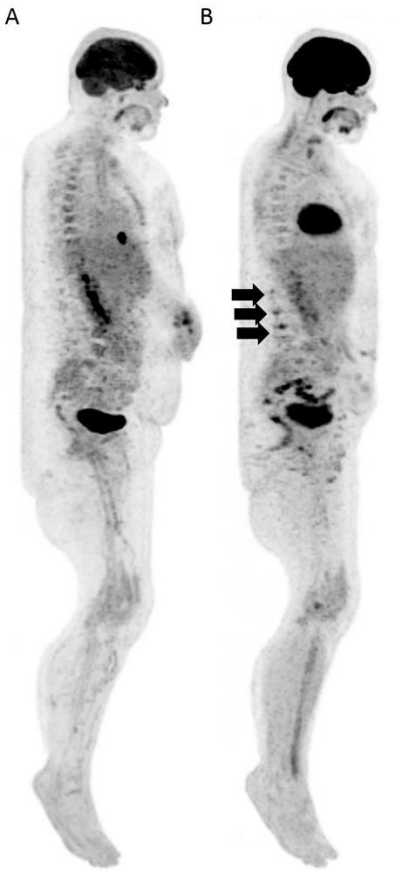


Figure 4 Total body FDG PET MIP images before (A) and after Nivolumab treatment (B). Increased uptake in bilateral hilar and mediastinal lymph nodes due to sarcoid-like reaction and gastritis (arrows) as well as multiple tumoral lesions (B) (details in the text).

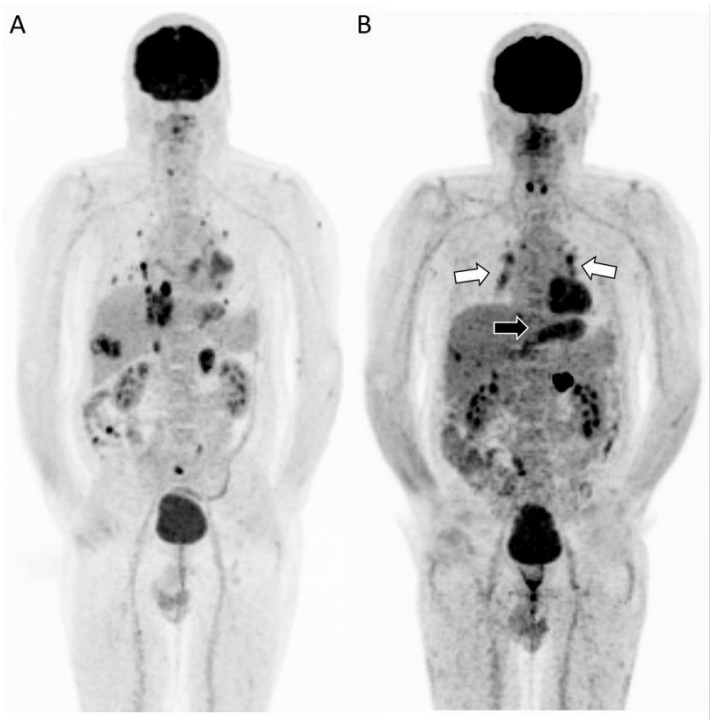


Figure-5 Selected transaxial and coronal CECT (before and after Nivolumab treatment A and C) and PET (B, with start of Nivolumab) images. Diffusely increased uptake in the thyroid and decrease in thyroid size due thyroidits (arrows) (B and C) (details in the text). Note the right lower lobe nodule causing a cold area on PET.

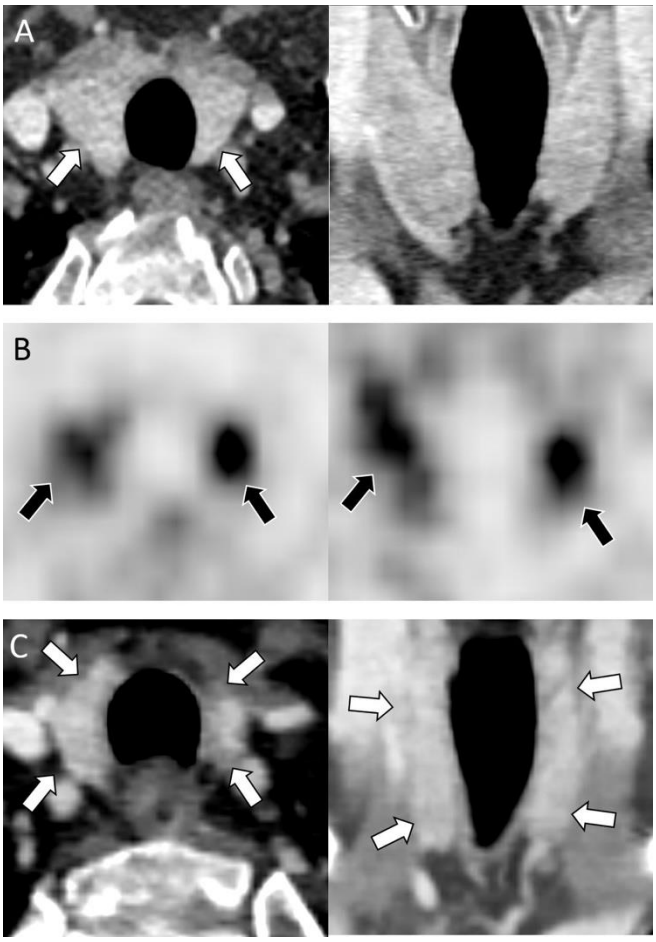


Figure-6 Total body FDG PET image after Nivolumab treatment showing diffuse uptake in the thyroid gland due to thyroiditis and mild diffuse uptake in the liver due to hepatitis as well as diffuse colonic uptake (arrows) (details in the text).

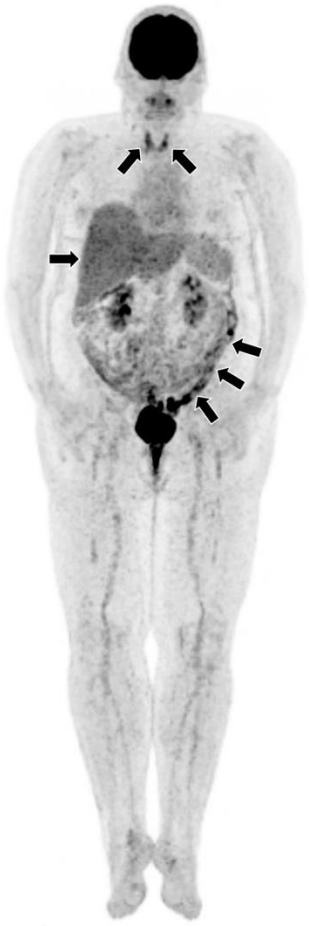
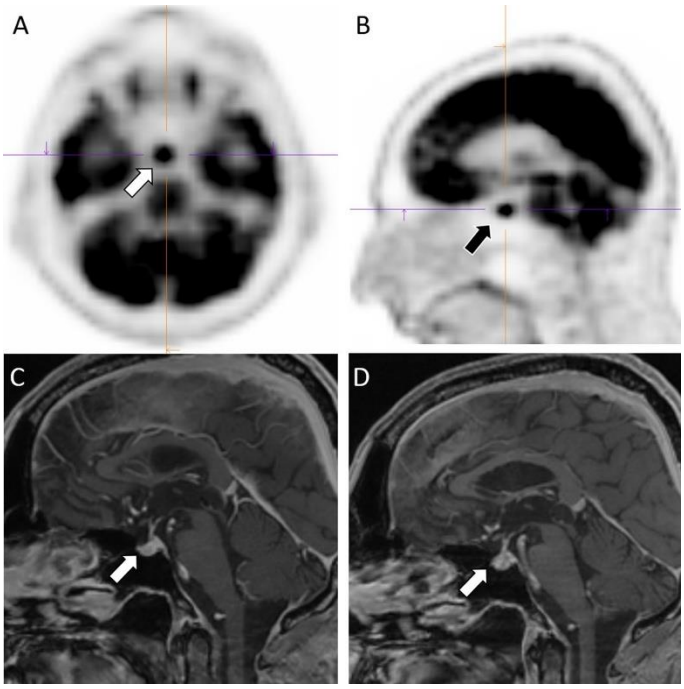


Figure-7 Selected transaxial and sagittal FDG PET (A and B) and sagittal MRI before and after treatment (C and D) show findings consistent with hypophysitis (arrows) (details in the text).



Graphical Abstract