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CASE REPORT

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Bilateral cytomegalovirus infection of the adrenal glands revealed by ^{18}F-FDG PET/CT in a patient with T-cell lymphoma

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Abstract

This case report demonstrates the possible subclinical adrenal and pancreatic involvement in immunocompromised patients (in particular those with lymphoma) with a CMV infection and the role of whole-body ^{18}F-FDG PET/CT in detecting these lesions.

KEYWORDS

adrenal mass, cytomegalovirus, fluorodeoxyglucose positron emission tomography computed tomography (^{18}F-FDG PET/CT), Non-Hodgkin lymphoma

1 | INTRODUCTION

Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is useful to characterize adrenal masses but distinction between neoplastic and infectious lesions remains challenging. Causal pathology is particularly difficult to discern in immunocompromised patients with lymphoma who may develop opportunistic infections. We report a bilateral adrenal CMV infection evidenced by ^{18}F-FDG PET/CT in a patient with lymphoma.

Adrenal lesions with gland enlargement have a variety of causes. ^{8}F-FDG PET/CT is a useful tool for the differentiation between benign and malignant adrenal lesions since malignant lesions (in particular adrenocortical carcinoma, metastasis, malignant pheochromocytoma, and lymphoma) are characterized by a high uptake of the tracer while benign lesions (such as benign pheochromocytoma, adenoma, hyperplasia, and hemorrhage) are generally hypometabolic. Specificity of the method suffers from the high uptake of the tracer in infectious adrenal lesions like tuberculosis, histoplasmosis, or fungal infection.[1,2] The clinical context certainly helps in the differentiation between malignant and infectious diseases, but the causal diagnosis remains challenging in patients treated for a malignant condition in which immunocompromission may lead to the unusual clinical presentation of opportunistic infections. Severe viral activation and spread is a major risk in immunocompromised patients, in particular in patients treated for lymphoma.[3] We here report massive cytomegalovirus (CMV) infection of the adrenal glands evidenced by ^{18}F-FDG PET/CT in a patient with a recurrent lymphoma. This report offers the opportunity to discuss the potential role of SEL1L, a protein involved in the processing of misfolded proteins, in the propensity of CMV to invade glandular tissues.[4,5]

2 | PATIENT HISTORY/ EXAMINATION

A 72-year-old man was admitted to the emergency room for unfavorable evolution of a pneumonia treated by antibiotic therapy for about 15 days. Two weeks earlier, he had stopped corticosteroid therapy taken for ten years for a pulmonary and mediastino-hilar lymph node sarcoidosis. In his medical history, we retained a diffuse large B-cell lymphoma (DLBCL) fifteen years earlier, treated by 6 cycles of Rituximab associated with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP). He has been in remission since then. At admission, the patient had completely normal parameters. Clinical examination revealed hypoventilation of the right lung base and bilateral sibilances associated with hepatomegaly. The blood test showed thrombopenia (149,000/mm^3), leucopenia (2610/mm^3) with 5.6% of atypical lymphocytes, an inflammatory syndrome with a CRP value of 38 mg/dl, moderately elevated lipase level (70 UI/L), and signs of hepatic cytolysis and cholestasis. The thoracoabdominal CT scan showed bilateral pulmonary opacities associated with a right lower lung mass and multiple bi-lobar liver lesions (Figure 1). The infectious assessment (bronchopulmonary sputum, blood culture, nasopharyngeal smear, and multiple serological testings) returned negative. Lymphocyte typing revealed a pathological population of T lymphocytes. A whole-body ^{18}F-FDG PET/CT demonstrated hypermetabolic lesions in right pulmonary lower lobar mass with a necrotic center associated with hypermetabolic bi-lobar liver lesions and supra- and subdiaphragmatic lymph nodes (Figure 2A). Trans-bronchial right lower lobar mass and echo-guided liver biopsies showed a peripheral T-cell lymphoma, not otherwise specified. Chemotherapy by CHOP was started.

The whole-body ^{18}F-FDG PET/CT performed after 3 cycles of CHOP showed a partial response of pre-existing lesions in the lower right lung, liver, and lymph nodes. New hypermetabolic lesions were evidenced at the level of bilateral pulmonary opacities, the spleen, and bilaterally in the adrenal glands (Figure 2B).

3 | DIFFERENTIAL DIAGNOSIS

Non-Hodgkin lymphoma (NHL) is the most common type of lymphoma affecting the adrenals, bilaterally in about 50% of cases,[1,2] but extranodal adrenal involvement in NHL remains very rare.[6] Therefore, reactivation of sarcoidosis in the adrenal glands was considered plausible, even if only a few cases of adrenal sarcoidosis have been reported in the literature.[7] This hypothesis was reinforced by the response to chemotherapy of pre-existing lymphomatous lesions in the lower right lung, liver, and lymph nodes. Finally, an infectious origin could also be hypothesized, with tuberculosis being the first candidate since Mycobacterium tuberculosis is the most frequent pathogen invading the adrenal glands.[2]

4 | INVESTIGATIONS

Bronchioloalveolar lavage detected no phenotypic lymphocyte T abnormalities nor signs of a variety of infections (aerobic bacteria, aspergillus, legionella, yeasts, atypical mycobacteria, influenza, respiratory syncytial virus, metapneumovirus, tuberculosis, and pneumocystis), except for the PCR detection of CMV, which was highly positive. CMV PCR in the plasma returned also positive (113 UI/ml). Of notice, CMV serology performed before chemotherapy indicated past CMV infection (IgG>1 U/ml and IgM<0.7 U/ml).

Multiple biopsy fragments of the right adrenal gland obtained by fine-needle puncture under CT control were negative for lymphoma infiltration, but highly suggestive of an acute CMV infection with the presence of virus-induced cell atypia and abundant anti-CMV immunolabelling.

5 | TREATMENT

Since tissue-invasive CMV reactivation in the context of NHL was concluded, the patient was treated with 3

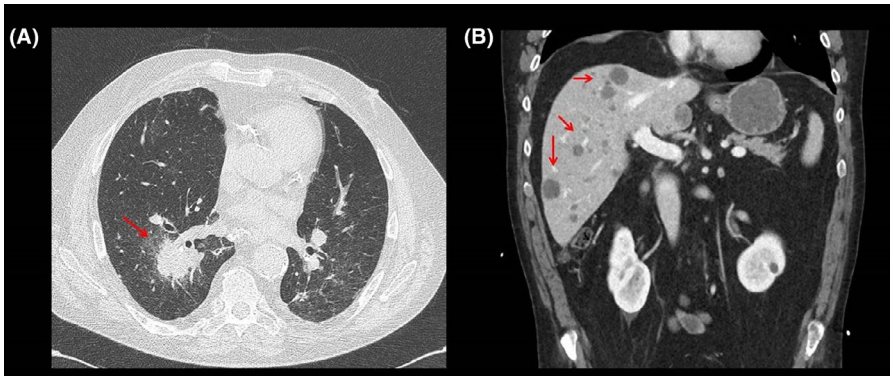

FIGURE 1 thoracoabdominal CT showing bilateral pulmonary opacities associated with a right lower lung mass (A) and multiple bi-lobar liver lesions (B)

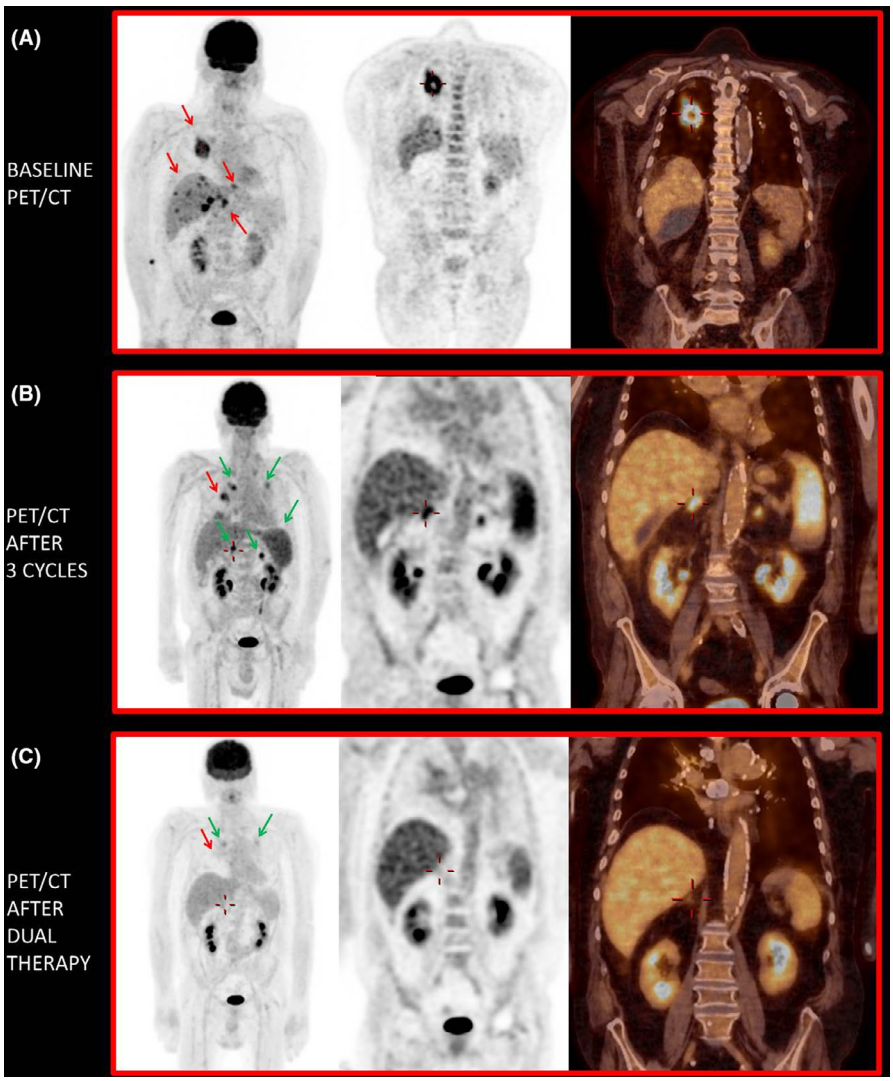

FIGURE 2 (A) Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) demonstrating hypermetabolic lesions in right pulmonary lower lobar mass with a necrotic center (cross) associated with hypermetabolic bi-lobar liver lesions and supra and subdiaphragmatic lymph nodes. (B) ^{18}F-FDG PET/CT performed after 3 cycles of CHOP showing a partial response of pre-existing lesions in the lower right lung, liver, and lymph nodes. New hypermetabolic lesions are evidenced at the level of bilateral pulmonary opacities, the spleen, and bilaterally in the adrenal glands (cross). (C) ^{18}F-FDG PET/CT realized after 6 cycles of chemotherapy and valganciclovir therapy demonstrating a complete response of liver and nodal lesions from lymphomatous origin. Splenic and adrenal lesions (cross) attributed to CMV infection have also disappeared under the dual therapy. The lung lesions of probable mixed origin – lymphoma and CMV – present with a partial response to this therapy. NB: red arrows =lymphoma, green arrows =CMV

additional cycles of chemotherapy combined with valganciclovir (450 mg, 3 times a day) for 4 weeks.

6 | OUTCOME AND FOLLOW-UP

A whole-body ^{18}F-FDG PET/CT realized after 6 cycles of chemotherapy and valganciclovir therapy demonstrated a complete response of liver and nodal lesions from lymphomatous origin. Splenic and adrenal lesions attributed to CMV infection also disappeared under the dual therapy. The lung lesions of probable mixed origin—lymphoma and CMV—presented with a partial response to this therapy (Figure 2C).

The maximum dose of anthracyclines having been reached, the patient was treated with 3 additional cycles of Cyclophosphamide, Vincristine, Etoposide, and Prednisone (COEP).

7 | DISCUSSION

Cytomegalovirus is an opportunistic pathogen that represents a major cause of morbidity and mortality in

immunocompromised patients. CMV reactivation in patients with autologous hematopoietic stem cell transplant has been reported in up to 41% of cases. However, in non-transplant hematologic patients, intense chemoimmunotherapy produces an increased incidence of CMV infection/reactivation. Cytotoxic T cells play a crucial role in the control of CMV disease, which explains why patients with lymphoma (especially NHL) are at high risk to develop a severe form of the disease. Reported risk factors for CMV infection/reactivation (among which several were present in our patient) are high-dose corticoid therapy, advanced lymphomatous disease, poor performance status, and previous treatment with Rituximab, Bortezomib, or Fludarabine.[3,8,9]

As already described in the literature, the tissue-invasive CMV disease can affect any organ or system and the most frequent clinical manifestations are gastrointestinal disease, pneumonia, hepatitis, central nervous system disease, retinitis, nephritis, pancreatitis, and myocarditis.[10] CMV adrenalitis has been mainly described in patients with acquired immune deficiency syndrome (AIDS).[11] Pulakhandam et al.[12] demonstrated that, after reviewing the autopsy of 74 patients with AIDS, 50% had CMV infection among which 84% had adrenalitis; they concluded that the adrenal gland is the most frequently affected organ in AIDS with CMV infection. However, CMV adrenalitis is rare in other patient populations, and only two cases have been reported in patients with lymphoma.[9,13] Stathis et al.[9] described the clinical history of a DLBCL patient treated by R-CHOP chemotherapy leading to complete remission. The patient died of disseminated multi-organ CMV infection involving the lungs and multiple glandular organs, including the pituitary gland, pancreatic islets, and adrenals. In our case, the pancreas was probably also affected given the high lipase level at the admission (normalized after treatment).

The propensity of CMV to affect the pancreas has already been mentioned in patients with solid-organ transplantation with a reported proportion of pancreatitis of 10%.[14,15] The specific involvement of glandular tissue by the CMV, including the adrenals as in our case, may be explained by the pathway of cellular invasion used by the virus. Indeed, SEL1L, a protein related to the endoplasmic reticulum-associated degradation (ERAD) pathway, may play a role in CMV infectivity.[4] Since SEL1L is essentially expressed in protein-expressing cells found in exocrine and endocrine organs, including the pancreas and the adrenal glands, this protein may be the factor explaining the CMV tropism for the adrenals, like in our case and the previously reported ones.[5]

The case here reported should draw our attention to possible subclinical adrenal and pancreatic involvement in immunocompromised patients—in particular those treated for a lymphoma—who presented with a CMV infection. Whole-body ^{18}F-FDG PET/CT may play a role in the detection of such glandular involvement in these patients.

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CONFLICT OF INTEREST

Author's do not have any conflict of interest to declare.

AUTHOR CONTRIBUTIONS

C. Van Bogaert participated in the design of the manuscript, PET-CT images analysis and interpretation, clinical data collection, and drafting of the manuscript. I. Vierasu participated in the design of the manuscript, PET-CT images analysis and interpretation, clinical data collection, and drafting of the manuscript. C. Mathey participated in PET-CT images analysis and interpretation and drafting of the manuscript. A. Theunissen participated in the clinical data collection and drafting of the manuscript. S. Goldman participated in the design of the manuscript, PET-CT images analysis and interpretation, clinical data collection, and drafting of the manuscript.

ETHICAL STATEMENT

The retrospective analysis of data acquired on the PET/CT Vereos has been approved by the Ethics Committee of the institution. Published with the written consent of the patient.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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