Post-Transplant Lymphoproliferative Diseases in the Elderly after Cardiac Transplantation: The Diagnostic Role of [18f] FDG-PET With Co-Registered CT and the Effect of Sports Activity Rehabilitation Program

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Short title: PET-CT and Sports Activity Rehabilitation Program in Elderly Population after Cardiac Transplantation

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Abstract

The incidence of cancer in organ transplant patients is higher than in the non-transplanted population. The incidence increases with increasing age. The use of Fludeoxyglucose positron emission tomography/CT (PET/CT) is sensitive and specific to detect PTLD LD compared with conventional CT imaging. We analyzed the medical data of 127 patients aged over 60 years, who underwent heart transplantation in the above period, who have been practicing early CT-PET for diagnostic purposes between February 2007 and October 2018.

Of 127 consecutive patients who underwent CT-PET, SUVs up than 4, were found in 84 patients of which 20 were affected by PTLDs, seven patients were affected by chronic non neoplastic inflammatory diseases, the remainder were affected by other neoplasms. The favorable effect of physical activity programs on cardiorespiratory and psychomotor function occur in all patients.

In conclusion, CT-PET at the first doubts about the possibility of the development of neoplasms has allowed a diagnosis and then a treatment more quickly. Education in behavioral norms that improve the patient's quality of life is necessary.

Keywoards: Post-transplant lymphoproliferative disorder, FDG-PET/CT, elder age, physical activity

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1. Introduction

The possibility of acquiring a neoplasm after an organ transplant is certainly greater than in the normal population [1-6], mostly due to the pharmacological immunosuppression to prevent organ rejection [7-8]. Immunosuppressants reduce the attention of the host's immune system to cells that are recognizable as non-self., but, in the meantime, it involves a reduction in the recognition of cells with genetic mutations that are normally induced into apoptosis [9]; a reduced elimination of mutated cells leads to a higher probability to develop neoplasms. In addition, immunocompromised patients have a greater susceptibility to infections like EBV, HPV and HIV that, in turn may favor the onset of neoplasms [10-19]. The cells responsible for the function of recognition of mutated or neoplastic cells are the lymphocytes of subfamily k, member 1 (KLRK1) [20]. These have some KLRK1 ligands such as MICB and MICA which are expressed by kidney, lung, breast, colon, ovary, liver, and prostate neoplasms. The neoplastic cells in turn express receptors for oncogenic growth factors such as EGFR (epidermal growth factor receptor) [21-24]. Dysregulation of these mechanisms most probably favour the onset of neoplasms in immunocompromised patients [25-26]. The higher incidence of neoplasms in post-transplant patients regards lymphoproliferative disorders (PTLDs) includingPlasmacytic hyperplasia PTLD, Florid follicular hyperplasia PTLD, polymorphic PTLD, monomorphic cell types PTLD (B and T/NK cell types), classical Hodgkin's lymphoma (PTLD) [27-29], NHL, uterine and anal neoplasms (related to papilloma virus), liver cancer and HCV- or HBV-related neoplasm [30-33], Kaposi sarcoma, non-melanoma skin cancer [34-36]. PTLDs occurs in up to 10% of adult patients after solid organ transplantation, with an increased incidence in the last 10 years, an increase more evidence in the elderly [37-38]. Transplantation itself is a complex procedure, especially for elderly patients. Psychological support is required in the post-transplantation period together with physiokinesis therapy. Progressive psychophysical rehabilitation must be planned after discharge to improve functional skills [39]. Programs vary from a patient to another and consequently, several parameters should be evaluated: the functional state of the various organs, the

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psychic conditions, the physical-motor skills (strength, flexibility, muscle coordination), the cardiovascular function in stressful conditions, the comorbidities, the associated drug therapy, the social conditions, the habits and feeding capacity [40-41]. All this fundamental in order to organize a network that the patient can constantly follow [42-45]. Programs include aerobic exercise to increase muscle endurance, exercises to strengthen the extensor muscles of the legs and the upper limbs, useful for doing household chores and other activities of the daily life [46-48]. Aerobic training gradually increases for those with faster recovery after transplantation. In these cases, the patients should start with 30 minutes of walking or of stationary cycling with moderate intensity to increase gradually [49,50]. Subsequently, a training program of 5 days a week, consisting of at least 20 minutes of slow running in the open air three times a week and moderate physical activity on the remaining two days. Our patients were evaluated by completing the Long Form International Physical Activity Questionnaire (IPAQ) at the starting point and at follow-up weeks 4, 8 and 12, 18 [51]. Physical activity and session times were measured using the Long Form, the last 7 days, self-administered by the IPAQ. All this improves the patient's quality of life [52].

The incidence of PTLDs seems reflect the type of transplant performed and the intensity of immunosuppression archived, and the EBV status before transplantation. EBV is found in nearly 30% of PTLDs and seems to be involved in their pathogenesis due to its properties to promote B cells proliferation and somehow the neoplastic transformation. The PTLDs are predominantly B-cell proliferative diseases. The onset occurs predominantly in the first year after organ transplantation, but EBV-patients tend to occur in subsequent years.

In this study, particular attention has been given to patients who underwent heart transplantation for an early diagnosis of incidence neoplasms. EBV, HBV, HCV, LDH, all functional hematochemist indexes have been tested at a 4-month interval after transplantation and abdomen and superficial lymph node ultrasound was performed [53-57]. In particular, PET CT was used, at the

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lowest suspicion arisen by hematochemistry or clinical findings, to assess this techmiane can help in the early diagnosis of PTLDs.

2. MATERIALS AND METHODS

This is a retrospective cohort analysis of elderly patients who had received heart transplantation between March 1999 and July 2018 at the AO Dei Colli - V. Monaldi in Naples, Italy.

We analyzed 127 consecutive patients aged over 60 years, who underwent heart transplantation in the above period, who have been practicing CT-PET an early diagnosis of neoplasm between February 2007 and October 2018.

The following parameters were considered: sex, age at the time of transplantation, time of onset of PTLD from the date of transplantation, time of onset at CT-PET, immunosuppressive therapy at the time of onset of cancer. Immunosuppressant drugs used after transplantations were anti-thymocyte globulin (ATG), ciclosporin, everolimus, mycophenolate, prednisone, tacrolimus.

During the first 5 days, ATG was administered, followed by methylprednisolone associated with cyclosporine and mycophenolate or cyclosporine and everolimus or, after 2008, tacrolimus. All procedures were performed in accordance with the Helsinki declaration to the role of the local ethic committee and wish the Italian lows of privacy. All patients singed an informed consent anonymously for the clinical investigation.

3. RESULTS

Of the 127 patients who underwent PET CT, SUVs of 4 ore more, were found in 84 patients of which 20 were affected by PTLDs (Figure. 1,2,3,4) (3 Classical Hodgkin lymphomas (cHL), 14 non-

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Hodgkin lymphoma (NHL), 3 Plasmacytic hypeplasia), 7 patients were affected by chronic non neoplastic inflammatory diseases, and the remainders were affected by other neoplasms.

4. DISCUSSION and CONCLUSION

The incidence of PTLDs has increased in the last decade, because the increased competence and safety of transplantation procedures has meant that these procedures are practiced more often than in the past. In addition, the greater knowledge of PTLDs has improved the diagnostic capacity of physicians. In our study the use of CT-PET at the first diagnostic doubts and this favoured an early diagnosis and an early treatment. The clinical changes we used to give indication for of CT-PET examination were various: increase in LDH serum value, EBV+, lymphocytosis, splenomegaly, lymphadenomegaly, fever without recognized infections, weight loss not due, itching without cause, onset of night sweats, alterations of QPE. Not always CT-PET examination was diagnostic for PTLDs, but other neoplasms have been identified. It has not so far understood whether PET CT to diagnose of PTLDs should be performed only in the 1st years after transplantation or it should be done at any times if a serious suspicion arises that PTLDs has arise.

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Legend to the figure

Figure. 1

A: Coronal Co-registreted Attenuation Corretion CT.

B: Coronal ^{18}F-FDG PET/CT Fusion Imaging.

Several areas of intense metabolic activity pertaining to supradiaphragmatic nodes: -Latero-cervical, -Right retroclavicular, - Upper and lower right paratracheal-

Figure. 2

A: Transverse Axis - Co-registreted Attenuation Corretion CT.

B: Transverse Axis - ^{18}F-FDG PET/CT Fusion Imaging.

Pathological metabolic activity pertaining to:

- Apical segment of the Lower Lobe of the Right Lung;
- Nodes: Peribronchial hilar, sub-carinal.

Figure. 3 ^{18}F-FDG PET/CT – 3 Axis Fusion Imaging Reconstruction.

- Pathological activity pertaining:
- Nodes: Barety space, -Mediastinal, -Carenal, subcarinal prevascular, -Pulmonary and Peribronchial hilar on both sides:
- -Posterior basal region of the lower lobe of the left lung.

Figure. 4

- ^{18}F-FDG PET/CT –Fusion Imaging – Coronal Axis Reconstruction
- Pathological metabolic activity pertaining:
- Mediastinal Nodes: -Barety space-Carenal, subcarinal, - Right Peribronchial hilar

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Figure. 1

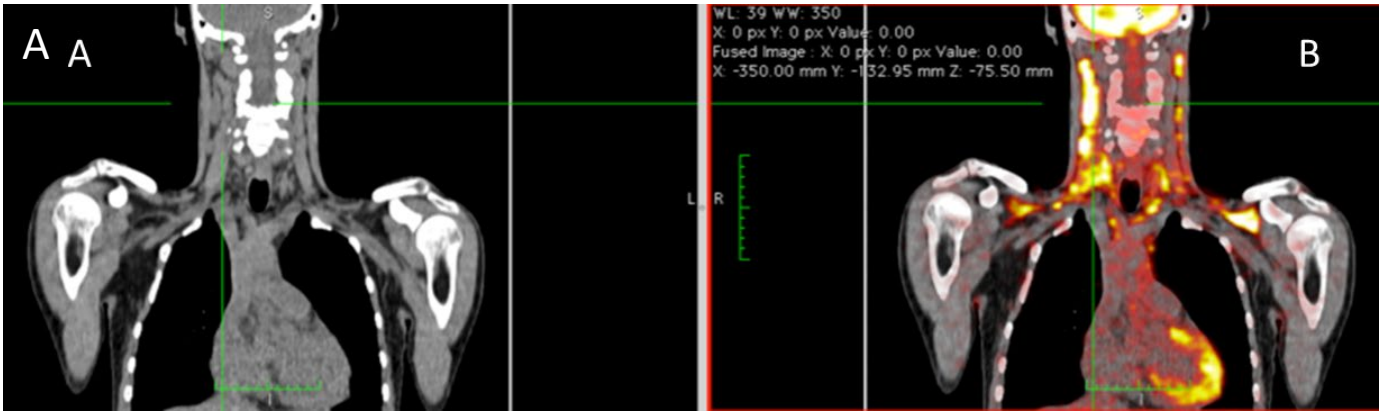

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Figure. 2

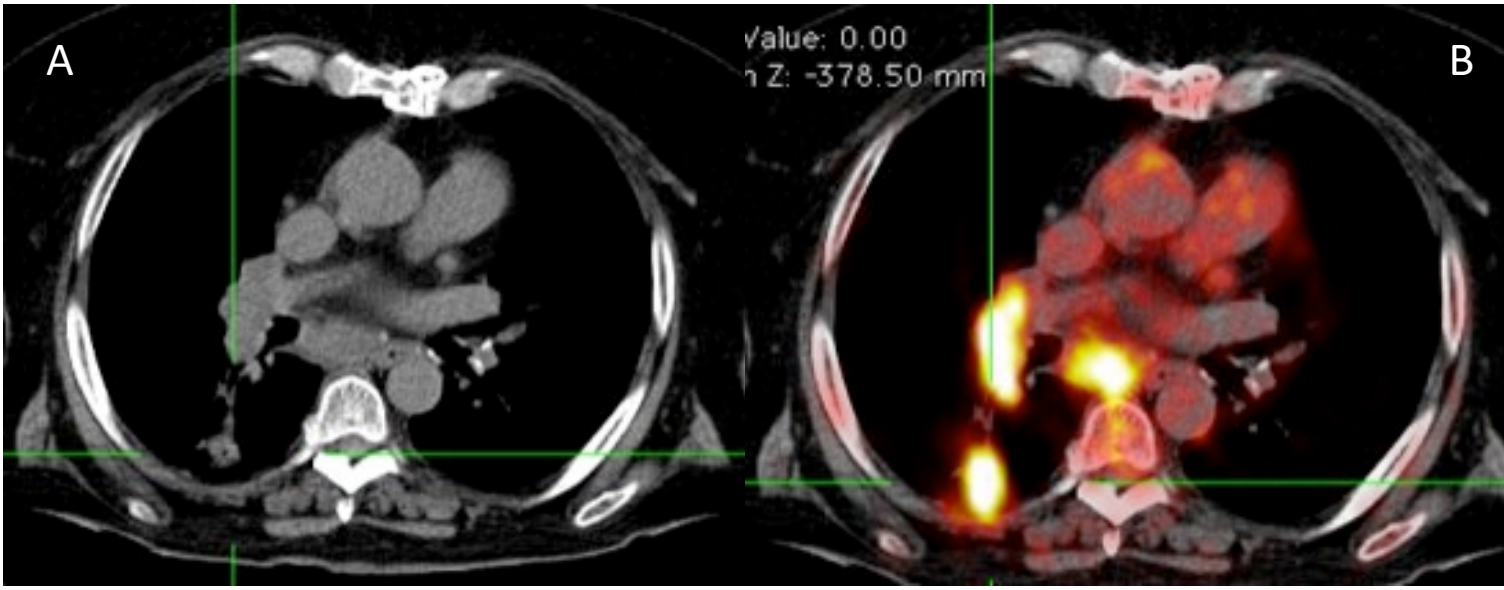

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Figure. 3

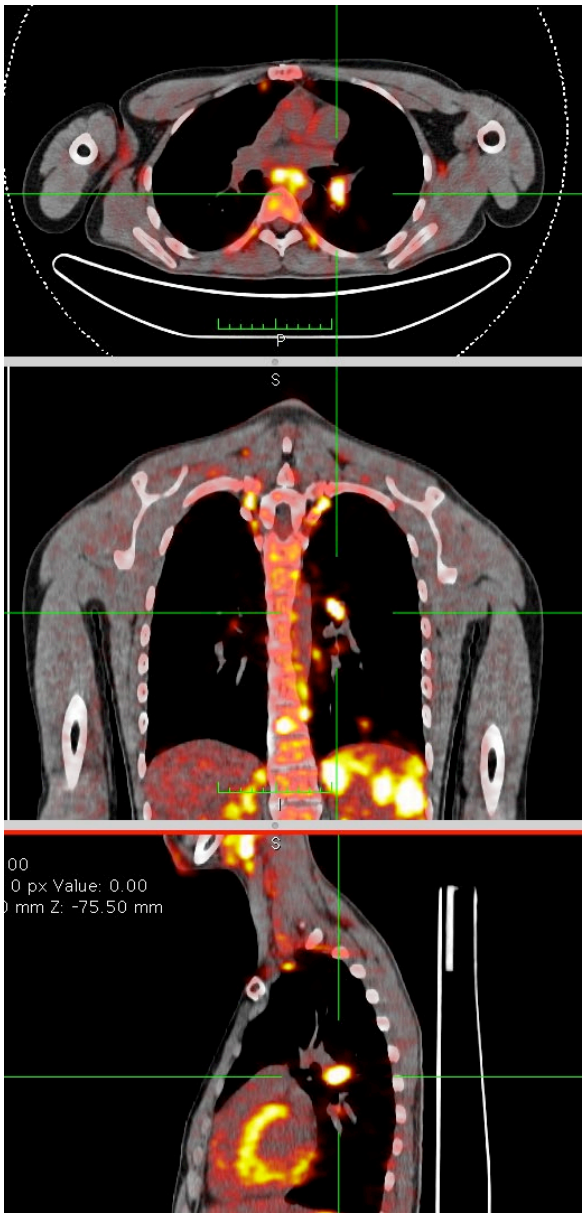

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Figure. 4