SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2016; 33; 423-425

Reticuloendothelial system involvement in untreated sarcoidosis patients as assessed by 18F-FDG PET scanning

Alexandros Kalkanis[1], Marc A. Judson[2], Dimitrios Kalkanis[3], George D. Vavougios[4], Julia Malamitsi[5], Evangelos Georgiou[5]

[1] Department of Pulmonary Medicine, 401 Military and VA Hospital Athens; [2] Albany Medical College, Department of Medicine, Albany, New York, USA; [3] Department of Nuclear Medicine, 251 General Airforce and VA Hospital, Athens, Greece; [4] University of Thessaly, Department of Respiratory Medicine, Larisa, Greece; [5] Medical Physics Laboratory Simulation Centre, Department of Medicine, University of Athens

Dear Editor

Serum sIL-2 receptor (sIL-2R) is considered a marker of T-cell activation (1) because activation of CD4+ T-helper type 1 cells leads to the expression of IL-2 receptors on the cell surface with shedding of soluble IL-2 receptor (sIL-2R) molecules into the microcirculation (2,3). sIL-2R has been suggested as a useful biomarker of sarcoidosis disease activity, as sIR-2R levels have correlated with clinician impressions of disease activity, radiographic stage of disease, serum angiotensin converting enzyme (SACE) levels, gallium-67 scan uptake, and bronchoalveolar lavage CD4+ T-lymphocyte number (4-8). We have recently reported a strong statistical association between sIL-2R levels and F-18-fluorodeoxyglucose (18F-FDG) splenic uptake on positron emission tomography (PET) scans in untreated sarcoidosis patients (9). These results suggest that splenic inflammation may be related to the systemic inflammatory response in sarcoidosis. We conjectured that the spleen may be an important focus for the development and maintenance of the granulomatous inflammation of sarcoidosis. In order to investigate this conjecture further, we analyzed the 18F-FDG uptake in the lumbar vertebral bodies of our cohort as a measure of bone marrow activity. We hypothesized that vertebral body 18F-FDG uptake would correlate with splenic uptake and sIL-2r levels, supporting the concept that a generalized reaction occurs in the reticuloendothelial system in patients with active sarcoidosis.

Patients with an established diagnosis of sarcoidosis according to the 1999 ATS/ERS/WASOG criteria (10) were retrospectively identified from a hospital database. Only patients who had not received anti-sarcoidosis therapy were eligible for this analysis. All enrolled patients underwent a set of biochemical laboratory tests, that included serum interleukin-2 receptor (IL-2R), serum C-reactive protein (CRP), serum angiotensin-I converting enzyme (SACE), and 24-hour urine calcium levels as well as a whole-body combined FDG PET/CT scan, within 48 hours of the blood draw, as a part of an ongoing study in our institute (Sismanogleion General Hospital Athens, IRB21767 04/10/2013). Informed consent was obtained from all the participants.

The FDG scan was performed according to the European Association of Nuclear Medicine (EANM) guidelines (11). A standard whole-body 18F-FDG PET/CT protocol was used in all patients. Patients fasted for at least 6 hours before imaging. The serum glucose concentration, before the injection of 18F-

Received: 3 June 2016
Accepted after revision: 18 August 2016
Correspondence: Alexandros Kalkanis, MD.
Department of Medicine, Division of Pulmonary and Critical Care Medicine,
401 Military and VA Hospital,
Katehaki Av. 115 25 Athens, Greece
E-mail: md.kalkanis@gmail.com

FDG, was less than 150 mg/dl. Image acquisition started 60 minutes after an intravenous injection of approximately 5 MBq/kg of body weight of FDG (up to 480 MBq). All acquisitions were made using an integrated PET/CT scanner (DiscoveryST; GE Medical Systems, Waukesha, Wisconsin, USA). A whole-body image, usually divided into six bed positions, was obtained from the mid femur to the base of the skull. PET emission images were acquired for a 4-minute acquisition period at each bed position. The PET/CT system also included a four-detector row helical CT scanner (140 kV and 80mA). CT images were used for image fusion as well as for the generation of the attenuation correction map. The standard uptake values (SUV) were calculated from the PET count rate by using the following equation: Standard uptake value = tissue concentration (mCi/g) / injected dose (mCi)/ body weight (g). (12)

Data collected from the FDG PET scans regarding the spleen and the bones, including parameters SUVmax and SUVavg, was calculated using the Osirix MD software (Pixmeo, SARL). Spleen SUVmax was measured on PET images as the single hottest pixel within the spleen. Bone involvement was identified in PET scans as any abnormal focus of increased FDG uptake. The region of interest for the bone marrow uptake was the center of each of the lumbar vertebrae (L1-L5) according to the method described by Goudarzi et al (13).

Statistical analysis was performed using the SPSS 21.0 statistical software package (SPSS Inc., IL). Data normality was assessed via the One Sample Kolmogorov-Smirnov (K-S) test; correlations were determined via Pearson›s R and Spearman›s Rho as appropriate. Subsequently, variables that were significantly correlated were fitted in a linear regression model to ascertain whether a linear relationship existed between them. Finally, comparisons were determined via either an independent samples t-test or the Independent samples Mann-Whitney U test for parametric and non-parametric variables, correspondingly.

sIL-2R levels were found to be significantly correlated with log-transformed spleen-maximum standard uptake value (SUV max) (Pearson's R=0.700, P<0.0001). Furthermore, spleen SUV max and log-transformed bone marrow maximum standard uptake value (BM-SUV max) were found to be significantly correlated (Spearman's ρ=0.405, p=0.027); Finally, sIL-2R levels were found to be significantly higher in PET positive bone lesions compared to PET-negative bone lesions [mean and interquartile ranges: 6.28 (5.97) vs 3.96 (0.94), $p=3.031e^{-4}$, Independent samples Mann-Whitney U test]. No significant correlation was found between PET(+) bone involvement and abnormal CRP, SACE, serum or 24-hour urine calcium levels.

FDG PET/CT scanning is a sensitive tool for detecting active inflammation in vivo and has been increasingly used to assess active inflammation in sarcoidosis (14). In our previous report of prospectively enrolled untreated sarcoidosis patients, we found a strong correlation between serum IL-2R levels and spleen FDG uptake and size.(9) In this analysis, we have extended the relationship of sIL-2R in sarcoidosis to the SUVmax of the vertebral bodies and the bone marrow.

Sarcoidosis is thought to be a systemic disease by virtue of its presence in multiple organs, its association with anergy (15), recurrence in transplanted allografts (16), and development of systemic symptoms including fatigue (17). It is conjectured that the granulomatous inflammation formation in sarcoidosis involves immune trafficking and cross-talk of various inflammatory cells and mediators across various body compartments (18). The spleen may be integral in the process of sarcoidosis granuloma development maintenance. Evidence for the importance of the spleen includes the high specificity of the spleen-derived Kveim reagent for the diagnosis of sarcoidosis (19) and our previous work demonstrating an association between sIL-2R and splenic PET uptake (9). Based our results reported herein, we further postulate that the inflammatory activity of the entire reticuloendothelial system may be increased and involved in the development of sarcoidosis.

References

1. Semenzato G, Pizzolo G, Zambello R. The interleukin-2/interleukin-2 receptor system: structural, immunological, and clinical features. International journal of clinical & laboratory research 1992; 22(3): 133-42.
2. Saltini C, Spurzem JR, Lee JJ, Pinkston P, Crystal RG. Spontaneous release of interleukin 2 by lung T lymphocytes in active pulmonary sarcoidosis is primarily from the Leu3+DR+ T cell subset. The Journal of clinical investigation 1986; 77(6): 1962-70.
3. Muller-Quernheim J. Sarcoidosis: immunopathogenetic concepts and their clinical application. Eur Respir J 1998; 12(3): 716-38.
4. Keicho N, Kitamura K, Takaku F, Yotsumoto H. Serum concentration

of soluble interleukin-2 receptor as a sensitive parameter of disease activity in sarcoidosis. Chest 1990; 98(5): 1125-9.
5. Bargagli E, Bianchi N, Margollicci M, et al. Chitotriosidase and soluble IL-2 receptor: comparison of two markers of sarcoidosis severity. Scandinavian journal of clinical and laboratory investigation 2008; 68(6): 479-83.
6. Grutters JC, Fellrath JM, Mulder L, Janssen R, van den Bosch JM, van Velzen-Blad H. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. Chest 2003; 124(1): 186-95.
7. Lawrence EC, Brousseau KP, Berger MB, Kurman CC, Marcon L, Nelson DL. Elevated concentrations of soluble interleukin-2 receptors in serum samples and bronchoalveolar lavage fluids in active sarcoidosis. The American review of respiratory disease 1988; 137(4): 759-64.
8. Ziegenhagen MW, Rothe ME, Schlaak M, Muller-Quernheim J. Bronchoalveolar and serological parameters reflecting the severity of sarcoidosis. Eur Respir J 2003; 21(3): 407-13.
9. Kalkanis A, Kalkanis D, Drougas D, Vavougios GD, Datseris I, Judson MA, Georgiou E. Correlation of spleen metabolism assessed by 18F-FDG PET with serum interleukin-2 receptor levels and other biomarkers in patients with untreated sarcoidosis. Nucl Med Commun 2016 Mar; 37(3): 273-7.
10. Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. Eur Respir J 1999; 14: 735-7.
11. Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumor PET imaging: version 1.0 Eur J Nucl Med Mol Imaging 2010; 37: 181-200.
12. Strauss LG, Conti PS. The applications of PET in clinical oncology. J Nucl Med 1991; 32: 623-48.
13. Goudarzi B, JaHA, Wahl RL. Measuring the "unmeasurable": assessment of bone marrow response to therapy using FDG-PET in patients with lymphoma. Acad Radiol 2010 Sep; 17(9): 1175-85.
14. Teirstein AS, Machac J, Almeida O, Lu P, Padilla ML, Iannuzzi MC. Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. Chest 2007 Dec; 132(6): 1949-53.
15. Lee NS, Barber L, Kanchwala A, Childs CJ, Kataria YP, Judson MA, et al. Low levels of NF-kappaB/p65 mark anergic CD4+ T cells and correlate with disease severity in sarcoidosis. Clinical and vaccine immunology: CVI 2011; 18: 223-34.
16. Padilla ML, Schilero GJ, Teirstein AS. Sarcoidosis and transplantation. Sarcoidosis Vasc Diffuse Lung Dis 1997; 14: 16-22.
17. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. Eur Respir J 2012; 40: 255-63.
18. Zissel G. Cellular activation in the immune response of sarcoidosis. Semin Respir Crit Care Med. 2014; 35: 307-15.
19. Teirstein AS. Kveim antigen: what does it tell us about causation of sarcoidosis? Semin Respir Infect 1998 Sep; 13(3): 206-11.