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 sIL-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-
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. 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 and 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

4. Keicho N, Kitamura K, Takaku F, Yotsuno H. Serum concentration...