Conclusions:
Octreoscan U.I. is correlated with the degree of dyspnea in patients affected by sarcoidosis and can quantify more accurately the degree of pulmonary involvement, as compared to radiological assessment. Further studies are necessary to evaluate Octreoscan as an early test for predicting disease progression. Octreoscan U.I. could be helpful in monitoring IIP in specific histological subsets (NSIP and DIP) and substitute HRCT in the assessment of UIP for its excellent accuracy.

Key Words:
Sarcoidosis, Idiopathic interstitial pneumonia, Idiopathic pulmonary fibrosis, Dyspnea, Somatostatin receptor scintigraphy, Octreotide scintigraphy, HRCT.

Abbreviation list
ANOVA = Analysis of variance;
ATS = American Thoracic Society;
BAL = Bronchoalveolar Lavage;
DIP = Desquamative Interstitial Pneumonia;
Dlco = Diffusing capacity for Carbon monoxide;
ERS = European Respiratory Society;
HRCT = High-Resolution Computed Tomography;
ILD = Interstitial Lung Disease;
NSIP = Non-Specific Interstitial Pneumonia;
PFTs = Pulmonary Function Tests;
SACE = Serum Angiotensin Converting Enzyme;
SPECT = Single-Photon Emission Computed Tomography;

Abstract. – Study objectives: Clinical, radiological, and serological tests have been proven to be unsatisfactory as markers of activity in sarcoidosis and idiopathic interstitial pneumonia (IIP). We investigated 111In-Octreotide (Octreoscan) scintigraphy as a tool for classifying and assessing disease activity in sarcoidosis and IIP, in comparison of the radiological imaging and dyspnea symptom scores.

Patients: Thirty-three patients (pts) of which 16 with sarcoidosis (mean age 43.6, range 30-58 years) and 17 with histologically diagnosed IIP (mean age 62.2, range 35-79 years), were enrolled in the study. Clinical history was taken as well as, physical examination, chest X-ray and pulmonary function tests were assessed. A high-resolution computed tomography scan (HRCT) was carried out in patients affected by sarcoidosis, who had a normal chest X-ray, and in IIP patients. Both groups were evaluated with the Octreoscan uptake index (U.I.; normal value: ≤ 10).

Results: In patients affected with sarcoidosis, the Octreoscan U.I. was significantly higher than in patients with IIP (16.35 ± 3.1 and 10.06 ± 0.8, respectively; p < 0.01) and was correlated with the radiographic staging (p < 0.01) and with the degree of dyspnea (p < 0.01). In patients with IIP the Octreoscan uptake index was slightly above the normal limit (range 10.3-11.7) in non-specific interstitial pneumonia (NSIP) and desquamative interstitial pneumonia (DIP), whereas in usual interstitial pneumonia (UIP) Octreoscan uptake index was always within normal limit (≤ 10 U.I.). A negative correlation was observed with histological findings (p < 0.01) and with HRCT appearance (p < 0.01).
UIP = Usual Interstitial Pneumonia;
U.I. = Uptake Index;
WA SOG = World Association Sarcoidosis and Other Granulomatosis;
VATS = Video-Assisted Thoracoscopy.

Introduction

Interstitial lung disease (ILD) comprises a large group of heterogeneous disorders including sarcoidosis and idiopathic interstitial pneumonia (IIP). This disease is often underdiagnosed due to the difficulty involved in clinical assessment. Different pathologic patterns have been described for IIP: idiopathic pulmonary fibrosis (IPF), with the histological features of usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), and desquamative interstitial pneumonia (DIP). Chest X-ray, high-resolution computed tomography (HRCT), Gallium 67 (67Ga-citrate) scintigraphy and bronchoalveolar lavage (BAL) are used as diagnostic tools in the assessment of interstitial inflammation, but are not specific in the early stages of the disease. It has been proven that therapy in the advanced stages of the disease has little or no benefit, which is why prompt diagnosis is important. Lung biopsy remains the gold standard for the diagnosis of ILD.

A marker for disease activity that could help monitor and tailor treatment would be helpful. Different authors have compared the assessment of disease activity with chest imaging including HRCT, chest X-ray, and Gallium 67 scans, and monitoring serum angiotensin converting enzyme concentration (SACE). HRCT was found to be more sensitive, specific and accurate in monitoring ILD activity as compared to chest X-ray. It has been proven that therapy in the advanced stages of the disease has little or no benefit, which is why prompt diagnosis is important. Lung biopsy remains the gold standard for the diagnosis of ILD.

Methods

Sixteen patients with histologically confirmed sarcoidosis (mean age 43.6, range 30-58 years) were compared with 17 patients diagnosed with idiopathic interstitial pneumonia (IIP) complying with the ATS, ERS and ACCP criteria (mean age 62.2 range 35-79 years). All patients underwent an evaluation that included a thorough clinical history, physical examination, chest X-ray and pulmonary function tests (PFTs). Patients’ characteristics are shown in Table 1.

Carbon monoxide diffusion capacity (DL- CO) was measured using the single breath method. Dyspnea was classified and quantified according to Moser’s criteria, giving a score of 0 to 5 as follows: 0 = no dyspnea; 1 = no limitation of normal daily activities but a more severe dyspnea during intense physical efforts than expected with respect to age and physical condition; 2 = no dyspnea during normal daily activities or walking on a plane but dyspnea when going up or down stairs; 3 = dyspnea during normal daily activities; 4 = dyspnea during minimal physical exercise; 5 = resting dyspnea.

All patients with sarcoidosis underwent a chest X-ray and were staged according to the Scadding Criteria (stage 0-IV). Stage 0 = no radiographic abnormalities; stage I bilateral hilar adenopathy without parenchymal abnormalities; stage II, bilateral hilar adenopa-
thy with interstitial parenchymal infiltrates; stage III, interstitial parenchymal infiltrates without hilar adenopathy; and stage IV: residual fibrotic changes. Each chest X-ray was interpreted by two pneumologists.

Patients with a normal chest X-ray but a clinical suspicion of sarcoidosis were evaluated with HRCT. Two patients affected with stage 0 sarcoidosis showed a honeycomb pattern on HRCT.

All patients with IIP underwent a HRCT (General Electrics, Milwaukee, WI) which revealed three patterns: ground glass appearance (4 pts.), a reticular pattern (11 pts.) and a mixed pattern (2 pts.). All HRCT performed were done without intravenous contrast media and proceeding at 1.0 or 1.5 mm-thick sections taken at 1-cm intervals through the entire thorax.

Different tissue samples were obtained from patients affected with sarcoidosis by: (a) CT guided transthoracic percutaneous biopsy (10 pts.), (b) lymph node biopsy – mediastinal or peripheral (7 pts.) and (c) liver biopsy (2 pts.). In our department we did not perform transbronchial lung biopsies. As for patients with IIP, a histological proof was obtained by: CT guided transthoracic biopsy (6 pts.), video-assisted thoracoscopy (VATS) (6 pts.) and open lung biopsy (5 pts.); of these pts 11 had UIP, 5 NSIP and 1 DIP. The histological patterns UIP, NSIP, and DIP as well as those imaged by HRCT were compared with the Octreoscan uptake index (U.I.)

Somatostatin receptor scintigraphy (Octreoscan®-Mallinckrodt Medical, Petten, The Netherlands) whole-body scans obtained at 4 and 24-hours after the administration of 5 mCi of $[^{111}\text{In-DTPA-D-Phe}1]$-Octreotide, were performed on all patients. Thoracic images were obtained with SPECT at the same intervals after injecting the tracer. The whole body acquisition (in 25 minutes) included anterior and posterior views of head, thorax, abdomen, pelvis and legs. Scintigraphic images were acquired with a double-head camera (Prism 2000, Picker). The camera had a medium-energy parallel-hole collimator using a $256 \times 1024$ or a $256 \times 256$ matrix. Acquisition was performed using both $^{111}\text{In}$

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photo peaks (173 and 247 KeV) and a 20% window. The SPECT acquisition was performed with a double Indium photo-peak, 60 projections over 360° rotation and with a 64 × 64 matrix; slices were reconstructed after back projection, using a Butterworth (low pass) filter.

The Octreoscan U.I. defined as the ratio between normalized accumulation of the tracer in the lungs and thigh, was evaluated in correlation with the diagnosis, degrees of dyspnea, and conventional imaging. Octreoscan U.I. is scored employing the similar procedure well established in literature used for Gallium 67 and compared with the data of a normal group analysed to exclude the existence of a possible interstitial lung disease. Normal values of U.I. on 4-h (best statistics) and 24-h were obtained. A corning to these data, the normal value of U.I. at 24-h was fixed at ≤ 10 U.I.

**Statistical Analysis**

All values are presented as mean ± SD. Fisher’s exact test was used to evaluate differences between proportions. Student’s t-test and the One-way ANOVA test were used to compare subgroups. Pearson’s coefficient was used to assess the correlation between Octreoscan uptake and staging and dyspnea in sarcoidosis and in IIP. Statistical analysis and graph generation was performed with the SPSS version 9.0 software. A value of $p < 0.05$ was considered statistically significant.

**Results**

Age was significantly higher in the IIP group (62.2 ± 13.3, range 35-79 years) than among pts affected with sarcoidosis (43.6 ± 8.6, range 30-58 years) ($p < 0.01$). The clinical findings at presentation in patients with sarcoidosis were the incidence of arthralgia ($p = 0.01$), erythema nodosum ($p = 0.04$), fever ($p = 0.02$), and cough ($p < 0.01$) significantly different between sarcoidosis and IIP pts.

In our study all but one patient affected with sarcoid had fever, however, we did not confirm the febrile etiology. Three out of sixteen (3/16) patients in the sarcoidosis group had uveitis. We found no difference in sex, smoking habits, occurrence of fatigue and uveitis between sarcoidosis and IIP patients.

In sarcoidosis the changes in VC and DLco were not significantly correlated with the chest X-ray findings ($p = 0.07$ and $p = 0.09$ respectively). Mean DLco% and VC% were decreased to a similar extent from stage 0 (84.5 ± 6.4% and 84.5 ± 17.7% respectively) to stage III (60.0 ± 10.5% and 60.0 ± 8.5% respectively). However, when observing stages I and II it is evident, that mean DLco% decreased progressively from stage I (74.0 ± 14.4%) to stage II (61.2 ± 12.5%) while VC% remained constant throughout both stages (85.8 ± 12.5% and 80.4 ± 17.2%), diminishing in stage III ($p = 0.04$).

Distribution of patients according to the Scadding staging was as follows: stage 0=2 pts; I = 5 pts; II = 5 pts; III=4 pts. In sarcoidosis the Octreoscan U.I. was 16.35 ± 3.1, in keeping with the presence of granulomatous tissue, and was strongly correlated with the staging ($r = 0.89; p < 0.01$) (Figure 1). In addition, there was a significant positive correlation between the degree of dyspnea (2 pts degree 2, 6 degree 3, 8 degree 4) and Octreoscan U.I. ($r = 0.75; p < 0.01$) (Figure 2).

In-patients with IIP, Octreoscan U.I. was 10.06 ± 0.8, and in 11 cases the value was below the established limit. No correlation was found between the Octreoscan U.I. and the degree of dyspnea (5 pts = degree 3, 6 pts = degree 4, 6 pts = degree 5; $r = -0.39; p = 0.1$). Despite lower overall scores, the Octreoscan U.I. was significantly lower in IIP as compared to patients affected with sarcoidosis ($p < 0.01$). All pts with sarcoidosis had abnormal values compared to IIP (Figure 3).

In NSIP and DIP patients Octreoscan U.I. was slightly above the normal limits (range 10.3-11.7). In all 11 UIP cases with a H R C T reticular pattern, Octreoscan U.I. was always within the normal limits (range 9.3-9.8), showing an accuracy of 100%. Octreoscan U.I. was negatively correlated with histological findings ($r = -0.91; p < 0.01$), and with H R C T appearance ($p < 0.01$).

UIP is the predominant pathologic pattern in IIP, and was associated with a reticular pattern in 11 of 17 cases in our study. In NSIP,
Figure 1. Sarcoidosis - Correlation between the Scadding staging and Octreoscan U.I.

Figure 2. Sarcoidosis - Correlation between Octreoscan U.I. and dyspnea score.
Octreoscan U.I. was correlated significantly with a mixed and ground glass appearance on HRCT.

Discussion

Many studies have tried to assess the accuracy of clinical, radiological, and serological tests in the evaluation of IIP and sarcoidosis showing inconclusive results. In the present study we investigated the value of Octreotide scan as a tool for staging and assessment of disease activity in these lung diseases.

The clinical manifestations of sarcoidosis are protean. The majority of patients present with systemic symptoms such as fatigue, anorexia, fever, chest pain, and cough. In the United States more than half of the patients present with respiratory symptoms. Fever as a presenting symptom may be due to an infective process, which we believe, is a trigger for disease onset. Du Bois et al recently postulated a role for micro organisms in the pathogenesis of sarcoidosis.

In sarcoidosis, disease staging obtained by chest X-ray is still currently used as a prognostic indicator. HRCT for the evaluation of disease activity is indicated in a limited number of patients with a clinical suspicion of disease and a normal chest X-ray. DLco can give a reasonable measure of the extent of disease, but does not discriminate between inflammation and fibrosis. VC is a useful screening test, but cannot distinguish between sarcoidosis and IIP.

\[^{111}\text{In-Octreotide}, \text{ a radiolabelled somatostatin analogue, identifies the proliferation of lymphocytes or the remission in immune-mediated diseases, such as sarcoidosis.}\]

In IIP pts Octreoscan U.I. was significantly lower than in sarcoidosis. In fact, all patients with sarcoidosis showed abnormal values and 11 out of 17 IIP patients were below the cutoff value (10 U.I.). The highest values in the IIP group were in the histological NSIP subset of pts. This may reflect the scarce inflammation present in the early stages of IIP and the total absence in the late phases. It seems probable, however still unproven that a ground glass pattern precedes a reticular or a mixed pattern.

We have demonstrated a highly significant positive correlation between Octreoscan U.I. dyspnea symptom scores, radiological imag-
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...ing and clinical activity. Octreoscan has been shown to be a sensitive and specific tool in quantifying the extent of granulomas involvement, such as in pulmonary sarcoidosis, but can also detect disease progression in other organs when total body SPECT is applied. In contrast, Gallium 67 correlates scarcely with HRCT, BAL and serum ACE. It is predominantly taken up in the lung by macrophages and falls with clinical and radiographic improvement, giving false negative results in about 30% of patients affected with sarcoidosis and false positive results in up to 70% of UIP patients. Octreoscan is of extreme usefulness in the latter where it has an accuracy of 100%. It is of particular value also when evaluating patients with Gallium 67 false negative scans, facilitating biopsy of peripheral and mediastinal Octreoscan positive lymph nodes, avoiding unnecessary pulmonary biopsies.

Moreover, Octreoscan offers better imaging in sarcoidosis patients on steroid therapy, as compared to Gallium 67 scan. The Octreoscan advantage is further emphasized when considering that imaging requires a tracer dose of 5 mCi, a considerably lower dose than that required for Gallium 67 scans (5 mCi-10 mCi). The former involves emission of γ radiation while the latter emits γ as well as β radiations that bind avidly to living tissues. Furthermore, Gallium 67 has a half-life of 78 hours and is not excreted by first-order kinetics, which results in the retention of a considerable amount of radiations in comparison to lung scanning with micro albumin aggregates and chest X-ray. The radiation dose exposure to the ovaries is over six times the dose when performing a plain abdominal X-ray.

In our study we found a negative correlation between Octreoscan U.I., UIP and a reticular appearance on HRCT, due to the high degree of fibrosis involved. In contrast, no correlation was demonstrated with the degree of dyspnea in pts affected with IIP. HRCT is increasingly used for the evaluation of disease extent in IIP. However, the degree of parenchymal infiltration could be too slight in the early stages of IPF in order to be detected by HRCT. A normal HRCT, although rare, cannot be used to exclude UIP. Moreover, over half the patients with proved UIP had an uncertain diagnosis on the basis of HRCT and clinical evaluation. Thus, only experienced clinicians can make a confident diagnosis of UIP in many patients without the need for biopsy. The presence of a predominant ground glass appearance on HRCT is associated with a longer survival rate in correlation with a cellular biopsy (active alveolitis) and low dyspnea symptom scores. In contrast, the predominance of mixed or reticular patterns is a predictor of a poor survival, correlated with fibrosis and a higher severity of the dyspnea score.

In common concert with the literature our data highlighted that unlike patients who have UIP, an accurate diagnosis and management of patients affected with sarcoidosis is obtained by a combination of clinical, radiographic and scintigraphic tools. We suggest that performing an Octreoscan once a year could help monitoring the progression of certain ILDs with accuracy. We showed that this tool provides valuable information in IIP patients while its usefulness in sarcoidosis needs yet to be further studied.

Although applying Octreoscan is costly, it avoids the need to perform both Gallium 67 and HRCT scans, which together approximate Octreoscan costs. Furthermore, the latter avoids unnecessary exposure to radiations involved in spiral-CT and Gallium 67 scans (β particles). Further advantage of Octreoscan in clinical staging is currently under investigation. The limitation of our study is in the fact that confirmation of diagnosis was obtained by CT guided transthoracic biopsies (a method that is not mentioned by the ATS/ERS/WASOG guidelines) in 10 out of 16 patients affected with sarcoidosis. Multi-organs biopsies were performed in 3/16 patients in this group and in 6/17 patients affected with IIP. However, we think that the high diagnostic sensitivity (88%) and accuracy (92%) shown in our series justify applying the technique. Our results meet with those obtained in similar series sited in the literature and with 72% of TBLB.

In summary, Octreoscan U.I. is strongly correlated with the degree of dyspnea in sarcoidosis and can effectively quantify the pulmonary involvement compared to radiological assessment.
Further studies are warranted to evaluate Octreoscan as an early test in the prediction of disease progression. To date, HRCT remains the procedure of choice when assessing the extension of UIP. Octreoscan U.I. could be helpful in monitoring the NSIP and DIP histological subsets of IIP, probably because these histological patterns are characteristic for a preponderant inflammatory infiltrate (particularly lymphocytes) and less fibrosis. Octreoscan could substitute HRCT in the assessment of UIP with excellent accuracy.

References
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