F-18-Fluorodeoxyglucose Positron Emission Tomography-Guided Sampling of Mediastinal Lymph Nodes in the Diagnosis of Cardiac Sarcoidosis

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Cardiac sarcoïdosis (CS) presents to the cardiology services as an isolated heart condition much more commonly than as one manifestation of a known or clinically evident systemic sarcoïdosis. Its main forms of presentation are atrioventricular conduction block, ventricular tachyarrhythmias, and heart failure, either alone or in various combinations. Distinguishing CS from more common myocardial conditions, ischemic or nonischemic, is critical for the patient care yet frequently a tough challenge. The only absolute diagnosis of CS comes from finding typical granulomatous myocarditis in a sample of myocardium without other explanation. However, because of the patchy distribution of sarcoïd granulomas, endomyocardial biopsy (EMB) more often misses than hits areas diagnostic of CS resulting in a sensitivity no better than 19% to 32%. CS can be diagnosed with less but clinically sufficient certainty also if the histology is proved in an extracardiac tissue sample and clinical manifestations and findings at cardiac gadolinium-enhanced magnetic resonance imaging (Gd-MRI) or F-18-fluorodeoxyglucose positron emission tomography (F-18-FDG PET) are compatible with myocardial involvement. Since the first published cardiac F-18-FDG PET images in CS, with focally increased myocardial glucose uptake signaling inflammatory activity, PET has gained wide use in the initial diagnosis, assessment of disease activity, and monitoring of treatment response in CS. Moreover, whole-body PET can uncover hidden inflammatory foci in extracardiac organs, thus suggesting targets for diagnostic tissue biopsies. We set out to review our nationwide CS registry for details of the use of F-18-FDG PET in the detection of
CS. In the present work, we focus on extracardiac PET findings and show their utility in the diagnosis of CS.

Methods

The registry of Myocardial Inflammatory Diseases in Finland has collected all patients diagnosed in our country with clinically manifest CS since the turn of 1990s. The criteria of CS required for inclusion in the registry have been detailed in our earlier reports. In brief, either myocardial or extracardiac histology of noncaseating granulomatous inflammation has been mandatory in addition to clinical manifestations and findings at cardiac imaging compatible with CS. From this database, we identified 72 patients with CS who had undergone F-18-FDG PET from 2005 to early 2013 as part of their diagnostic assessment after admission. Of them, 4 patients were excluded because of technically inadequate PET studies. The remaining 68 patients constitute the present study population. Their hospital charts were scrutinized in retrospect for demographics, cardiac signs and symptoms, laboratory tests, imaging studies, and diagnostic biopsies, and the data pertinent to the present work were collected for analysis. The study was performed according to the principles of the Declaration of Helsinki. The Ethics Committee for the Department of Medicine, Helsinki University Central Hospital, approved the study protocol, and the Myocardial Inflammatory Diseases in Finland registry study has been approved by the national ethical review board (STM/1219/2009). A proportion of the CS population (25 of the 68 patients) has been reported earlier.

Figure 1 illustrates this diagnostic strategy. Between-group comparisons for continuous variables were assessed with the Student’s t-test. Comparisons of discrete variables between groups were assessed with the chi-square test or Fisher’s exact test. All statistical tests were 2 tailed, and p < 0.05 was regarded as statistically significant.

Results

The CS population comprised 47 women and 21 men with a mean age of 50 ± 9 years. Their main presenting cardiac manifestations were, in order of decreasing frequency, complete atrioventricular block (n = 37, 54%), sustained ventricular tachycardia (n = 18, 26%), congestive heart failure (n = 15, 22%), and new-onset atrial fibrillation (n = 10, 15%). The CS population comprised 47 women and 21 men with a mean age of 50 ± 9 years. Their main presenting cardiac manifestations were, in order of decreasing frequency, complete atrioventricular block (n = 37, 54%), sustained ventricular tachycardia (n = 18, 26%), congestive heart failure (n = 15, 22%), and new-onset atrial fibrillation (n = 10, 15%).
heart failure (n = 7, 10%), ventricular fibrillation (n = 4, 6%), and multiple ventricular premature beats (n = 2, 3%). An impaired LV function at echocardiography on admission (ejection fraction <50%) was found in 33 patients (49%), and Gd-MRI revealed pathologic LV wall late enhancement in 33 of the 43 patients studied (77%). Cardiac PET was abnormal in 62 of 68 patients. It showed both an F-18-FDG “hot spot” and a myocardial perfusion defect in 52 patients and either a perfusion defect or a “hot spot” in 10 patients. Of the 6 patients with normal cardiac F-18-FDG PET, 5 had pathologic late enhancement at Gd-MRI.

Cardiac and whole-body PET combined showed pathologically increased F-18-FDG uptake (Figure 2) in MLN in totally 43 of the 68 CS patients (63%). Most of the PET-positive lymph nodes were located in the right upper and lower paratracheal regions, subcarinally and in the subaortic and para-aortic areas. Their number ranged from 2 to 14 per patient (mean 4), and their size averaged 1.2 ± 0.3 cm. Table 1 gives a complete list of sites of pathologic extracardiac F-18-FDG uptake in the 57 patients who underwent whole-body PET imaging. The data show that although 18 of 57 patients (32%) had F-18-FDG accumulation outside mediastinum, all except 1 of them also had parallel MLN involvement. None of the 6 patients with normal cardiac PET had abnormal extracardiac F-18-FDG activity, indicating that these 6 studies (9% of all) were completely false negative.

Table 1
Details of extracardiac localization of F-18-FDG uptake at whole-body PET in 57 patients with CS

<table>
<thead>
<tr>
<th>Foci of abnormal extracardiac F-18-FDG uptake</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinal lymph nodes (only)</td>
<td>21</td>
</tr>
<tr>
<td>Mediastinal lymph nodes, lungs</td>
<td>6</td>
</tr>
<tr>
<td>Mediastinal and extrathoracic lymph nodes</td>
<td>6</td>
</tr>
<tr>
<td>Mediastinal and extrathoracic lymph nodes, lungs</td>
<td>2</td>
</tr>
<tr>
<td>Mediastinal and extrathoracic lymph nodes, spleen</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal and extrathoracic lymph nodes, spleen and liver</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal lymph nodes, lungs, liver and thyroid gland</td>
<td>1</td>
</tr>
<tr>
<td>Liver (only)</td>
<td>1</td>
</tr>
<tr>
<td>No extracardiac uptake</td>
<td>18</td>
</tr>
</tbody>
</table>

CS = cardiac sarcoidosis; F-18-FDG = F-18-fluorodeoxyglucose; PET = positron emission tomography.

Figure 2. Examples of cardiac (A) and whole-body (B) F-18-FDG PET studies showing “hot” MLN together with foci of activity in the heart and outside the thoracic cavity.

Figure 3. The path to the histologic proof of sarcoidosis. In 60 patients with unknown histology at presentation, 101 tissue samples were taken and studied histologically in 3 successive biopsy rounds. Totally 24 MLNB and 71 EMBs were done. Granulomatous inflammation was ultimately confirmed in 24 of 24 MLNBs and in 30 of 71 EMBs. “*” Indicates “other” biopsy sites that included 2 transbronchial lung biopsies, 2 inguinal lymph node biopsies, and 1 post-transplantation study of the native heart;+/n = number of patients with positive biopsies per number of patients biopsied. MLNB = mediastinal lymph node biopsies.
The consensus report preferred extracardiac tissue as a perfect target for extracardiac biopsies to confirm the histology of sarcoidosis after nonrevealing EMB. Because 2/3 of our patients in need of histologic diagnosis had “hot” mediastinum at PET, starting with mediastinoscopy instead of EMB had certainly simplified and shortened the diagnostic path to a considerable extent (see Figure 3). In this light, our results clearly support the new consensus statement favoring extracardiac biopsies over EMB. In contrast, EMB is still needed to confirm the diagnosis of isolated CS and it also enables other than histologic studies, like myocardial gene expression profiling, that may help detect CS.

Abnormal extracardiac uptake of F-18-FDG at PET was observed much more commonly in the mediastinum than in all other extracardiac sites together (63% vs 26%). Teirstein et al. also found in their whole-body PET studies that MLN constitute by far the most common site of hidden extracardiac disease in sarcoidosis. Lymphatic drainage from the left side of the heart is collected in the right upper para-tracheal nodes that could explain why granulomatous inflammation in CS frequently involves the mediastinal nodes but spares the hilar nodes. Although MLN provide a yielding biopsy target in suspected CS, other causes of noncaseating granulomatous lymphadenitis must always be excluded, and as Thachil et al. have shown, particularly, cautious interpretation is needed in areas endemic for tuberculosis.

**Disclosures**

The authors have no conflicts of interest to disclose.