Imaging pulmonary aspergillosis using $^{18}$F-Flourodeoxyglucose biomarker in Positron Emission Tomography Computed Tomography

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Abstract— Early clinical recognition of Aspergillosis infection is difficult yet crucial to prevent fatal complications. Various investigations play important role to confirm the diagnosis. Positron Emission Tomography Computed Tomography using flourdeoxy glucose (FDG) as biomarker has a new role in imaging infection. In this study, we highlight the potential role of this modality in the diagnosis of lung aspergillosis infection. Methodology This retrospective study highlights the semiquantifying value of aspergillosis lung lesions through FDG PET/CT findings of 10 patients. The final gold standard in isolation of aspergillus sp and/or a positive anti-aspergillus serological test. Results We observed the findings from 7 males and 3 female patients between the age of 48-80 (mean 66.8 SD ±9.3). Half of them are elderly patients aged > 65 year old (range 48-80 year-old). 6 patients demonstrated underlying respiratory diseases like chronic obstructive airway diseases, carcinoma of the lung and chronic granulomatous infection like tuberculosis. Eventually, the diagnosis of 8 patients were confirmed through isolation of aspergillus sp while the other 2 final diagnosis were confirmed through positive serological test. From the PET/CT study, the mean semiquantification value of all lung aspergillosis lesions by means of mean maximum Standardized Uptake Value (mean SUV$_{max}$) is 4.25 (n=10; SD±1.904) ranging between 1.64 to 8.30. Conclusion Pulmonary aspergillosis infection demonstrate high metabolic activity with SUVmax > 2.5 during FDG PET/CT study. The imaging characteristic of lung aspergillosis infection in this study is useful to navigate the clinical management.

I. INTRODUCTION

Aspergillosis lung infection can be contained where early prompt treatment remains the critical prognostic factor (1). The common route for infection is through the respiratory system where it can begin initially as lung infiltrates. Aspergillus fumigatus and Aspergillus niger are the two most common species causing lung aspergillosis infection (2). They are often found to be complicating patients with underlying immunocompromised situations or prolonged debilitating disorders (3). Upon successful invasion, over a period of time, aspergillosis lung infiltrate may advance into a fatal form of angioinvasion and/or disseminated form. Thus early and accurate diagnosis is desireable in arresting its progression. Unfortunately, there is no single definitive test in establishing the diagnosis. Combination of clinical informations and results from laboratory studies are common management strategy but time consuming and may be life threatening. Often, routine serological tests for early detection not very useful due to its low sensitivity (4). Positive yield from sputum cultures are as low as 10%. Laboratory studies using biological and body samples require invasive procedures and may be unsuitable for chronically ill patients. Currently, non invasive cross sectional imaging technique computed tomography has been the mainstay imaging tool in the diagnostic work up of aspergillosis infection (5,6,7). Recent effort in fine tuning its performance by innovating an integrated system PETCT, a combined modality has resulted in superior capability in providing useful diagnostic informations from different perspectives in a single seating. This technology advancement improved the clinical management of patients with malignancies resulting in effective treatment deliveries and economy improvement. The initial course of direction for clinical utility of PETCT in oncology is now widened into the field of infections and inflammations (8,9,10). Thus the established morphological appearance of lung aspergillosis infection on CT may further benefit from additional metabolic information provided by FDG tracer uptake. This study tend to highlight the characteristic of aspergillosis lung lesions in integrated Positron Emission Tomography Computed Tomography using FDG as the biomarker.

II. METHODOLOGY

This study was conducted at The Department of Advanced Technology, Ospedale Niguarda, Milan, Italy. Retrospectively, 10 patients with discharge records confirmed diagnosis of pulmonary aspergillosis infection between 2004 till 2009 were evaluated. During hospital admission, prior to
antifungal treatment, all patients were thoroughly investigated in confirming the diagnosis. Isolation of Aspergillus sp organism attempted in all patients from blood, tissue samples and sputum. All patients underwent anti-aspergillus serological tests. Patients also underwent integrated diagnostic imaging study using Positron Emission Tomography Computed Tomography (PET/CT) with fluorodeoxyglucose (FDG) as tracer. A standard protocol prior to PET/CT image acquisition was strictly followed. All patients were instructed to be fasted for at least 6 hours prior to examination. Fasting blood sugar level was ensured to be below 8 mmol/L for non diabetic patients and 10mmol/L for diabetic patients prior to intravenous injection of 8-10mCi of $^{18}$F-FDG. Image acquisition was performed after not less than 45 minutes duration of complete resting. This is to avoid soft tissue and background FDG uptake which can reduce the sensitivity of the study.

Studies were conducted using PET/CT Biograph equipment with 4 slice multidetector ring. Imaging started with whole body scanogram for planning. Low dose fine axial CT transmission scan was first performed from the eyes to the thigh for attenuation correction and anatomical correlation. This was followed by PET emission study 3 minutes per bed position for 5-7 positions.

The results of FDG PET/CT studies were read by at least by two experience specialists in PETCT. First, the MIP images were analysed looking for focal areas of increase metabolic activity on PET. This will be followed by detail analysis of lesions found in 3-D reconstructed and CT attenuation corrected axial, sagittal and coronal images. Concurrent morphological CT changes on lesions were recorded. A region of interest was manually drawn over any lesions found with focal increase in metabolic activity to record the semiquantification value. The above mentioned observed parameters were tabulated (table 1). The results were compared with gold standard standard diagnosis of aspergillosis infection by isolation of Aspergillus sp including fumigatus, terreus, flavus and or niger singly or in combination. Alternative confirmatory test was achieved through one of the immunological study including antifungal antibody, PCE and/or PRIST studies.

III. RESULTS

All 10 patients who underwent FDG PET/CT study which were conducted within 2 weeks of hospital admission. There were 7 males and 3 female patients between the age of 37-80 (mean 66.8 : SD ± 9.3). 60% of them had underlying respiratory disease while the remaining 40% with no underlying lung pathology.

Finally, the concluding diagnosis in all patients were accomplished through isolation of aspergillus sp organism or positive serological test. Aspergillus fumigatus is the commonest pathogen isolated observed in our study. No organism isolated in 2 patients. The final diagnosis were ascertained through positive serological tests (table 1).

Figure 1 and figure 2 demonstrating two $^{18}$F-FDG PET/CT study with a foci of high metabolic activity in the posterior segment (figure 1) and anterior segment (figure 2) of the left upper lobe. The metabolic activity of the lesions matching the upper colour scale in the left border of the images. White arrows indicating the centre of lesion with raised metabolic activity. 7 months following antymycotic treatment (image b), a repeat $^{18}$F-FDG PETCT revealed partial (figure 1) and complete (figure 2) metabolic response in PET with persistent morphological CT appearance. The final outcome was validated by negative serological test result.

Statistic analysis

From the results of lab and imaging investigations, there are variety of observed parameters (table 1).

We devide our analysis into two categories. In the first category, we use the result of isolation of *aspergillus sp* as the “gold standard” (Table 2). In the second category, we utilize the result of $SUV_{max}$ for active lung aspergillosis lesions where 2.5 was used as cut-off point (Table 3). Activities above the selected point were classified as ‘present of infection’ while activities below the point were classified as ‘non infected lesion’. As a result, there were 9 concordant and 1 discordant findings in relation to the first category for analysis. Aspergillus fumigatus isolated from 60% of cases and Aspergillus terraus in 30%.

The mean maximum Standardized Uptake Value ($SUV_{max}$) from our results of FDG PET/CT study is 4.25 ($n=10$) ranging between 1.64 to 8.30 with a standard deviation of 1.90 (Figure 3). When we analysed the values of $SUV_{max}$ based on Aspergillus sp Isolation, there is no rank-difference in $SUV_{max}$ between those positive and negative cases (Table 2). Similarly, when we analysed classification of $SUV_{max}$ (cut-off value >2.5) with Aspergillus sp isolation, we also fail to find statistical agreement between the two (Table 3). The $SUV_{max}$ values were not normally distributed due to the small sample size.

IV. DISCUSSION

The role of integrated functional and morphological imaging modality Positron Emission Tomography and Computed Tomography (PET/CT) using fluorodeoxy glucose (FDG) as biomarker is expanding into infections and inflammation(8,9,10). Experiment conducted by Kubota demonstrated in vivo high accumulation of macrophages and granulation tissues as the reason for increased $^{15}$F-FDG intratumoral distribution (11). Increased local hyperemia and capillary permeability at the initial point of infection lead to aggregation of inflammatory cells like granulocytes, leucocytes and macrophage at the entry point. The resulting increased in local glucose consumption is reflected by raised semiquantitative uptake value (SUV) of all aspergillosis infected foci except in one of our patients. In the evaluation of FDG avid lesions, in addition to qualitative assessment through visual intensity, lesional activity can be semiquantify using standardized uptake value (SUV). The maximum SUV or $SUV_{max}$ is commonly employed in recording the metabolic activity of FDG avid lesions. In our institution, like others , a cut off point of 2.5 is taken to differentiate between benign and malignant condition. However, $SUV_{max}$ should be use with caution as it only indicate the ratio of FDG uptake in the whole body and dependant on multifactorial parameters including
blood sugar, insulin level, body weight and tracer activities. The detail is discussed elsewhere (12,13).

It is well known fact that fluorodeoxyglucose, being an analogue of glucose molecule is a non-specific malignant tracer. Avid FDG activity can be seen in benign and inflammatory conditions. Chronic granulomatous infection recently being proven to demonstrate intense $^{18}$F-FDG uptake with $\text{SUV}_{\text{max}}$ exceeding 2.5 mimicking malignant lesions (14,15,16,17,18,19,20). Our findings further support previous studies aiming at validating the quantification value of $\text{SUVmax} > 2.5$ in active lung aspergillosis infection. We validated our visually intense lesional activity in our patients through positive isolation of aspergillus sp organism from blood products and tissue samples and positive serological studies. The metabolic information from combined PETCT study using FDG as tracer can be an additional feature of importance. An active aspergillus foci which show FDG-avid activity can be an invaluable guidance for interventional tissue sampling procedure avoiding wrong sampling sites for isolation and cellular characterization (21,22,23,24).

In the past, Caillot D and his team (5) observed the usefulness of CT in 36 neutropenic patients with Invasive pulmonary aspergillosis infection and found CT allow earlier diagnosis thus developing a new strategy in clinical management of pulmonary aspergillosis infection. His work was supported by Kami M and his colleague (6) who concluded that chest CT scan to be more beneficial than blood tests and X-ray for early diagnosis of invasive pulmonary aspergillosis infection through their study involving 215 patients 3 years later. The result of our study has potential positive impact in amplifying the present value of CT in the investigation of pulmonary aspergillosis infection. Diagnostic CT can be performed as part of integrated PETCT study to detect invasive ‘halo’ sign which is proven to improved success rate up to 80% where patients can be subjected to emergency pulmonary surgical resection to avoid massive hemoptysis (25,26). With adequate supporting evidence from clinical history and lab investigations, the metabolic information gained during an integrated PETCT study using FDG as metabolic marker, can be utilized in guiding antifungal treatment . Initial $\text{SUV}_{\text{max}}$ can be used in evaluating treatment response (10,27,28). In another study, Horger (29) observed that none of the early HRCT manifestation of lung aspergillosis can predict outcome. By incorporating metabolic information of FDG PET into CT, the clue to outcome prediction can be resolved and warrants future studies involving larger group of patients.

Our study has several limitations. It appears that, from our preliminary findings, $\text{SUV}_{\text{max}}$ fails to discriminate aspergillosis infection from malignancy. This is apparent from analyses of $\text{SUV}_{\text{max}}$ in both rank and classified forms. However, low power of observation is the main limitation of our study in view of inadequate sample size. Thus, larger sample is needed to address this problem. Another issue is that all analyses were carried out in a pre-determined “gold-standard”. The appropriateness of using our definition of ‘gold-standard’ is a clinical decision and is up for debate.

V. CONCLUSION

Active pulmonary aspergillosis infections is FDG avid on $^{18}$F-FDG PET/CT examination. In an appropriate clinical setting, the metabolic information from combined PETCT study using FDG as tracer can be an additional feature of importance to guide interventionist during tissue sampling, navigating clinicians in treatment and in future can be useful information for outcome prediction.

References
1. Invasive pulmonary aspergillosis in chronic obstructive pulmonary disease: an emerging fungal pathogen


27. Therapy Monitoring in Aspergillosis Using F-18 FDG Positron Emission Tomography. Christiane Franzius, Martin Biemann, Georg Hulskamp, Michael Frosch, Johannes Roth, Joachim Schiuk, Otmar Schober. Clinical Nuclear Medicine, ?; 26(3):232–275


Table 1. Tabulation of demography data, underlying diseases and results of investigations

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Predisposed disease</th>
<th>Isolation</th>
<th>Aspergillus sp</th>
<th>Immunology test</th>
<th>FDG PET CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood / tissue/sputum</td>
<td>Proven organism</td>
<td>anti AF ab / PCE/PRIST</td>
<td>SUV max</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>77</td>
<td>Lung TB</td>
<td>pos/neg/pos</td>
<td>Fumigatus</td>
<td>pos/pos/neg</td>
<td>6.16</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>48</td>
<td>COPD</td>
<td>neg/pos/neg</td>
<td>Neg</td>
<td>pos/pos/pos</td>
<td>3.27</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>60</td>
<td>nil</td>
<td>neg/neg/neg</td>
<td>Neg</td>
<td>pos/neg/neg</td>
<td>4.81</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>66</td>
<td>Asthma</td>
<td>neg/neg/neg</td>
<td>Fumigatus</td>
<td>pos/neg/neg</td>
<td>3.26</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>67</td>
<td>Diabetes</td>
<td>pos/neg/pos</td>
<td>Fumigatus</td>
<td>pos/neg/neg</td>
<td>1.64</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>64</td>
<td>nil</td>
<td>pos/neg/neg</td>
<td>Terreus/Fumigatus</td>
<td>pos/neg/neg</td>
<td>3.81</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>80</td>
<td>Lung TB</td>
<td>pos/neg/neg</td>
<td>Fumigatus</td>
<td>pos/neg/neg</td>
<td>3.54</td>
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<tr>
<td>8</td>
<td>F</td>
<td>62</td>
<td>nil</td>
<td>pos/neg/neg</td>
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<td>pos/neg/neg</td>
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<tr>
<td>9</td>
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<td>70</td>
<td>Carc lungs</td>
<td>pos/neg/neg</td>
<td>Fumigatus</td>
<td>pos/neg/pos</td>
<td>4.95</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>74</td>
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<td>pos/neg/neg</td>
<td>Fumigatus</td>
<td>pos/neg/pos</td>
<td>8.3</td>
</tr>
</tbody>
</table>

M: male; F: female; TB: Tuberculosis; COPD: chronic obstructive pulmonary disease; pos: positive; neg: negative; na: not available;

Table 1. Tabulation of demography data, underlying diseases and results of investigations

Figure 1. A 52 year-old man diagnosed chronic pulmonary aspergillosis infection (image a) presented with recurrent dyspnea and cough. He showed positive serologic test to aspergillus specific Ig E and IgA antibodies. Anti mycotic treatment started and a repeat 18F-FDG PETCT study was done after 7 months (image b).
Figure 2. A 45 year-old man diagnosed Chronic Pulmonary Aspergillosis confirmed by positive Aspergillus-specific Ig E and Ig G tests. $^{18}$F-FDG PETCT showed focal high metabolic activity in the left upper lobe (white arrows in image a). 7 months following antimycotic treatment (image b), $^{18}$F-FDG PETCT revealed complete metabolic response on PET with persistent bullae formation on CT in response to treatment. The final outcome was validated by negative serological test result.

<table>
<thead>
<tr>
<th>SUV$_{\text{max}}$</th>
<th>Aspergillosis</th>
<th>N</th>
<th>Mean Rank</th>
<th>Sum of Ranks</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>9</td>
<td>5.33</td>
<td>48</td>
<td>0.602*</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>7.00</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*not statistically significant (alpha set at 0.05), Mann-Whitney U test.

Table 2: Bivariate Analysis of SUV$_{\text{max}}$ values vs. Aspergillus sp Isolation

<table>
<thead>
<tr>
<th>SUV Max(&lt;2.5)</th>
<th>Aspergillosis Isolation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0%)</td>
<td>0 (100%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Positive</td>
<td>1 (11%)</td>
<td>8 (89%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>1 (10%)</td>
<td>9 (90%)</td>
<td>10 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

**not statistically significant (p-value=0.725, Kappa = -1.11)

Table 3: Test of agreement between SUV$_{\text{max}}$ (Cut-off value >2.5) and Aspergillosis Isolation

Figure 3. Distribution of SUV$_{\text{max}}$ (n=10).