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Utility of Scintigraphic Methods in Patients With Fever of Unknown Origin

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Background: We assessed the utility of scintigraphy with indium 111-labeled polyclonal human IgG scintigraphy in patients with fever of unknown origin that fulfilled the criteria of temperature of 38.3°C or more for at least 3 weeks and no diagnosis during 1 week of hospital admission. We compared the utility of this technique with results of scintigraphic techniques reported in the literature.

Methods: Data for all patients seen at our university hospital in whom 111In-labeled scintigraphy was performed were analyzed and checked for the criteria for fever of unknown origin. The literature on the utility of scintigraphic techniques in patients with fever of unknown origin was reviewed.

Results: We studied 24 patients with fever of unknown origin. In 13 patients, focal 111In-labeled accumulation was observed. In nine (38%) of those, the positive 111In-labeled scintigram led to the final diagnosis; in the other four patients (17%), the scintigraphic findings were not helpful. In the 11 patients with negative 111In-IgG scans, extensive diagnostic workup produced no infection as the final diagnosis in nine patients (38%), one had an abscess in a renal cyst that was detected several months later, and in the other the cause of fever was an infected intravenous line. The overall sensitivity and specificity of 111In-labeled scintigraphy were 81% and 69%, respectively. The positive predictive value was 69% and the negative predictive value was 82%.

Conclusions: Our results show that 111In-labeled scintigraphy significantly contributed to the diagnostic process in patients with fever of unknown origin. A positive scan increased the likelihood of finding the cause of the fever, and a negative scan ruled out an inflammatory component with a high degree of certainty. These data compare favorably with data in the literature concerning other radiopharmaceuticals; a larger prospective evaluation of this technique is indicated.


FEVER OF unknown origin (FUO) has been defined by Petersdorf and Beeson1 as a febrile illness of more than 3 weeks' duration, documented temperature higher than 38.3°C on at least three occasions, and uncertain diagnosis after 1 week of diagnostic workup in the hospital. Currently, a variety of diagnostic imaging procedures, including radiography, magnetic resonance imaging, ultrasonography, and scintigraphy, are potentially useful in patients with FUO.

Scintigraphic imaging, including gallium 67,2,3 white blood cells (WBCs) labeled with indium In 111,4-12 and, most recently, technetium Tc99m-labeled BW250/183, an antigranulocyte monoclonal antibody of murine origin,13 has been applied in patients with FUO to detect infectious and other inflammatory foci. A positive scintigram enhances the likelihood of establishing a final diagnosis.6

A relatively new and potentially useful technique for this indication is indium 111-labeled polyclonal human IgG scintigraphy. Recently, the utility of 111In-IgG scintigraphy in the evaluation of various types of focal inflammation and infection has been studied. Reports have been published in the literature on bone and joint infections,14,15 and abdominal,16 pulmonary,17 and vascular18 lesions. This technique is also applicable in granulocytopenic patients.19 Since 111In-IgG is a convenient and safe radiopharmaceutical, comparing favorably with other scin-
PATIENTS AND METHODS

PATIENTS

Records of all patients who underwent 111In-IgG scintigraphy in our hospital were reviewed for FUO. Twenty-four patients (11 women and 13 men; mean age, 51 years; median, 52 years) fulfilled the criteria for FUO. From our studies of FUO carried out during the same period, we found that 45% of the patients with FUO had undergone 111In-IgG scintigraphy.

All patients underwent full biochemical and appropriate further investigations, including extensive negative microbiologic methods, which failed to establish a diagnosis within 1 week of admission. These investigations varied from patient to patient; no protocol was followed. The median follow-up of these patients was 216 days (range, 2 to 1500 days).

The final diagnosis was made by the patients' physicians and checked by one of us (E.M.H.A.K.).

RADIOPHARMACEUTICAL

Human nonspecific polyclonal IgG (Sandoglobulin, Sandoz AG, Nürnberg, Germany) was conjugated to diethylentriamine pentaacetic bicyclic anhydride according to the method described by Hnatowich et al and labeled with indium 111 (indium [111In] chloride, Medgenix Diagnostics, Fleurus, Belgium). Labeling efficiency was always greater than 95%. A dose of 1 to 2 mg of IgG labeled with 75 MBq of 111In was injected intravenously.

IMAGING PROCEDURES

Exclusion criteria for 111In-IgG scintigraphy were agammaglobulinemia, selective IgA deficiency, and a history of severe adverse reactions after intravenous or intramuscular administration of human IgG. Pregnant or lactating women were also excluded from this study.

Scintigraphic images were obtained with a gamma camera (Siemens Orbiter, Siemens Inc, Hoffman Estates, Ill) connected to an image processor (Scintiview, Siemens Inc). All images were collected in digital format in a 256 × 256 matrix. A medium-energy parallel-hole collimator (173-keV peak, 15% symmetric window; 247-keV peak, 13% symmetric window) was used.

The 111In-IgG images were acquired 4, 24, and 48 hours after injection for a preset time of 5, 7.5, and 10 minutes, respectively. At least once, 24 hours after injection, spot views of the total body were obtained. Single-photon emission computed tomographic images were recorded when necessary for more definite localization in three dimensions of areas with increased uptake.

All images were interpreted by three observers, "blinded" to the results of the verification procedures. Disagreements were resolved by consensus opinion. Hyperemic noninflamed lesions may initially show some uptake but no further accumulation of 111In-IgG with time. These scans were interpreted as equivocal and not pathologic. An 111In-IgG scan was interpreted as positive only if consistent, locally increasing accumulation could be noted over time. An 111In-IgG scintigram was considered "true positive" only when this imaging procedure was considered helpful in diagnosis.

The results of the scintigraphic findings were verified by clinical, radiographic, and ultrasonographic methods and preferably by microbiologic methods.

STATISTICS

Differences between groups were analyzed by the Mann-Whitney U test or Student's t test, when necessary.

RESULTS

In 13 (54%) of 24 patients, focal accumulation of activity increasing with time was observed. In nine patients (38%), scintigraphy was diagnostically helpful (Table 1); in eight of these, inflammatory or infectious foci were identified as the cause of the fever (Figure 1 and Figure 2). In four other patients (17%), a positive 111In-IgG scintigram did not lead to the final diagnosis (Table 1).

Table 1 also shows the data for the remaining 11 patients, in whom a negative or equivocal 111In-IgG scintigram was obtained. In six of those patients, extensive workup disclosed no diagnosis; follow-up from the start of fever varied from 224 to 929 days (median, 515 days). In two patients a malignant neoplasm most probably was the cause of fever, and one patient had positive blood cultures with Salmonella enteritidis serotype paratyphi A. The two remaining patients had infections as the cause of the fever despite negative IgG scintigrams; one had an infected renal cyst, diagnosed 3 months after the negative 111In-IgG scan, and the other had an infected central venous catheter.

If we considered results of 111In-IgG scintigraphy as true positive only when this imaging procedure led to the diagnosis, sensitivity was 82%, specificity was 69%, and positive and negative predictive value was 69% and 82%, respectively.

Comparison of the erythrocyte sedimentation rate of patients with positive scans (mean ± SD, 80.8 ± 43.0 mm/h) with that of patients with negative scans (mean ± SD, 70.5 ± 47.5 mm/h) yielded no significant difference (P=.66). Likewise, WBC counts of patients with positive scans (mean ± SD, 9.9 ± 5.7 × 10⁹/L) and patients with negative scans (mean ± SD, 8.0 ± 3.3 × 10⁹/L) did not differ significantly (P=.38).

Comparison of the groups with positive and negative 111In-IgG scans showed that a positive scan significantly increased the likelihood of reaching a diagnosis: in 11 (85%) of 13 patients with a positive scan, a final diagnosis was made, compared with only five (45%) of 11 patients with a negative scan (P=.05).

COMMENT

From this study, it can be concluded that 111In-IgG scintigraphy is a promising technique in the workup of patients with FUO, as indicated by an overall sensi-
Knockaert et al[^12] found in patients with FUO that a positive Ga 67 scintigram increased the chances of reaching a final diagnosis; 77% of patients with positive scans in contrast to 34% of those with negative scans were given a final diagnosis. This is in agreement with our findings with the use of ^111^In-IgG; a final diagnosis was made in 10 (77%) of 13 patients with a positive scan and in five (45%) of 11 patients with a negative scan. In previous experience with more than 1000 patients studied with ^111^In-IgG for a variety of indications, ^11^ this technique had a high diagnostic yield, and in comparison with Ga 67 and ^111^In-WBC scintigraphy, it has many advantages. First, unlike gallium citrate Ga 67 and technetium Tc99m hexamethylpropyleneamine oxime–labeled WBCs, ^111^In-IgG is not secreted in the normal bowel, leading to better detection of abdominal infections or inflammation. In addition, the radiation burden of gallium citrate Ga 67 is limited by the absence of granulocyte influx in this type.
### Table 1. Characteristics of Patients According to Results of Indium In 111 IgG Scans* (cont)

<table>
<thead>
<tr>
<th>Patient/ Age, y/ Sex</th>
<th>ESR, mm/h</th>
<th>Clinical Data</th>
<th>Leukocytes, $10^3$/L</th>
<th>Fever Duration, wk</th>
<th>Localization of Uptake</th>
<th>Final Diagnosis</th>
<th>Additional Investigations†</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/25/F 89</td>
<td>Heart murmur; Indonesian travel</td>
<td>6.1</td>
<td>6</td>
<td>Equivocal (pelvis)</td>
<td>Salmonella sepsis, prompt response to antibiotics</td>
<td>X, blood, C</td>
<td></td>
</tr>
<tr>
<td>15/77/M 112</td>
<td>Cough, diarrhea; artificial heart valves</td>
<td>7.4</td>
<td>17</td>
<td>None</td>
<td>Hodgkin's disease and lung cancer</td>
<td>S, B, bronchoscopy</td>
<td></td>
</tr>
<tr>
<td>16/62/M 96</td>
<td>Fatigue; spontaneous recovery after 4 mo</td>
<td>10.0</td>
<td>13</td>
<td>None</td>
<td>No diagnosis</td>
<td>BM, CT, C, US, blood</td>
<td></td>
</tr>
<tr>
<td>17/52/M 40</td>
<td>Fatigue, slight weight loss; pigeon fancier; spontaneous recovery after 10 mo</td>
<td>5.5</td>
<td>12</td>
<td>Equivocal (right lower abdomen)</td>
<td>No diagnosis</td>
<td>X, B, CT, B, US, C</td>
<td></td>
</tr>
<tr>
<td>18/46/M 140</td>
<td>Myalgia of legs; fatigue, anorexia</td>
<td>5.5</td>
<td>30</td>
<td>Equivocal (lungs)</td>
<td>Acute leukemia</td>
<td>CT, US, BM, bone biopsy</td>
<td></td>
</tr>
<tr>
<td>19/63/F 112</td>
<td>Fatigue, lumbar pain, transient diarrhea; spontaneous recovery after 4 mo</td>
<td>11.1</td>
<td>3</td>
<td>None</td>
<td>No diagnosis</td>
<td>US, CT, X, B, blood</td>
<td></td>
</tr>
<tr>
<td>20/53/F 14</td>
<td>Persistent recurrent fever for &gt;4 y</td>
<td>4.6</td>
<td>88</td>
<td>None</td>
<td>No diagnosis</td>
<td>MR, CT, US, B, X, blood, C</td>
<td></td>
</tr>
<tr>
<td>21/35/M 5</td>
<td>Tick bite; recurrent fever with headache; spontaneous recovery after 1 y</td>
<td>4.4</td>
<td>51</td>
<td>None</td>
<td>No diagnosis</td>
<td>CT, X, B, C, blood, US</td>
<td></td>
</tr>
<tr>
<td>22/27/M 4</td>
<td>Fatigue; spontaneous recovery after 10 mo</td>
<td>7.1</td>
<td>18</td>
<td>Equivocal (colon)</td>
<td>No diagnosis</td>
<td>US, colonoscopy, C, blood</td>
<td></td>
</tr>
<tr>
<td>23/54/F 93</td>
<td>Heart murmur, kidney transplant, renal cysts</td>
<td>11.7</td>
<td>5</td>
<td>None</td>
<td>Infected renal cyst, culture negative after use of several antibiotics</td>
<td>S, C</td>
<td></td>
</tr>
<tr>
<td>24/68/F 71</td>
<td>Scleroderma, heart murmur, renal failure</td>
<td>14.5</td>
<td>5</td>
<td>None</td>
<td>Infected central catheter with Staphylococcus epidermidis</td>
<td>CT, X, blood, US, C</td>
<td></td>
</tr>
</tbody>
</table>

*US indicates ultrasound; CT, computed tomography; B, biopsy; C, culture; S, surgery; MR, magnetic resonance imaging; X, x-ray; BM, bone marrow aspiration; PE, pathologic examination; DSA, digital subtraction angiography; and Tc, technetium.

†Investigations performed to verify the diagnosis are shown in boldface. For true-positive scans, all additional investigations were performed for verification.

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**Figure 1.** Patient 2. Abnormal uptake in the left hip and back (arrow) caused by spondyloskisis.

**Figure 2.** Patient 3. Abnormal uptake in the right lower abdomen (arrow) caused by Crohn's disease.
Table 2. Reports on Diagnostic Value of Scintigraphy in Patients With FUO

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Scan</th>
<th>N</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakamura et al,4 1990</td>
<td>Ga 67</td>
<td>49</td>
<td>8 (16)</td>
<td>17 (35)</td>
<td>...</td>
<td>...</td>
<td>85</td>
<td>65</td>
<td>Abstract</td>
</tr>
<tr>
<td>Misaki et al,4 1990</td>
<td>Ga 67</td>
<td>56</td>
<td>23 (41)</td>
<td>10 (17)</td>
<td>19 (35)</td>
<td>4 (7)</td>
<td>100</td>
<td>79</td>
<td>Selected group, abstract</td>
</tr>
<tr>
<td>Hilson and Maisey,4 1979</td>
<td>Ga 67</td>
<td>61</td>
<td>47 (77)</td>
<td>3 (5)</td>
<td>11 (18)</td>
<td>0 (0)</td>
<td>100</td>
<td>79</td>
<td>No criteria for FUO, also postoperative patients</td>
</tr>
<tr>
<td>Teates and Hunter,6 1975</td>
<td>Ga 67</td>
<td>42</td>
<td>9 (21)</td>
<td>5 (11)</td>
<td>25 (61)</td>
<td>3 (7)</td>
<td>75</td>
<td>83</td>
<td>Retrospective, no criteria for FUO</td>
</tr>
<tr>
<td>Suga et al,5 1991</td>
<td>Ga 67</td>
<td>36</td>
<td>17 (47)</td>
<td>0 (0)</td>
<td>15 (42)</td>
<td>4 (11)</td>
<td>80</td>
<td>100</td>
<td>Also postoperative patients, no definition of FUO</td>
</tr>
<tr>
<td>Habibian et al,7 1975</td>
<td>Ga 67</td>
<td>22</td>
<td>12 (54)</td>
<td>5 (22)</td>
<td>3 (15)</td>
<td>2 (9)</td>
<td>86</td>
<td>38</td>
<td>Criteria for FUO of Petersdorf, selected group</td>
</tr>
<tr>
<td>Knockaert et al,8 1989</td>
<td>Ga 67</td>
<td>54</td>
<td>14 (26)</td>
<td>8 (15)</td>
<td>28 (51)</td>
<td>4 (7)</td>
<td>78</td>
<td>78</td>
<td>Criteria for FUO of Petersdorf, selected group, other definition of true positive</td>
</tr>
<tr>
<td>Larson et al,9 1982</td>
<td>Ga 67</td>
<td>40</td>
<td>10 (25)</td>
<td>9 (23)</td>
<td>18 (45)</td>
<td>3 (7)</td>
<td>77</td>
<td>67</td>
<td>Criteria for FUO of Petersdorf, selected group, other definition of true positive</td>
</tr>
<tr>
<td>Knockaert et al,4 1994</td>
<td>Ga 67</td>
<td>145</td>
<td>42 (29)</td>
<td>40 (28)</td>
<td>54 (37)</td>
<td>9 (6)</td>
<td>82</td>
<td>57</td>
<td>Criteria for FUO of Petersdorf, selected group</td>
</tr>
<tr>
<td>Schmidt et al,10 1987</td>
<td>In 111 WBCs</td>
<td>32</td>
<td>7 (21)</td>
<td>4 (13)</td>
<td>21 (66)</td>
<td>0 (0)</td>
<td>100</td>
<td>84</td>
<td>Criteria for FUO of Petersdorf, selected group</td>
</tr>
<tr>
<td>Syrjäälä et al,11 1987</td>
<td>In 111 WBCs</td>
<td>68</td>
<td>19 (28)</td>
<td>7 (10)</td>
<td>40 (59)</td>
<td>2 (3)</td>
<td>90</td>
<td>85</td>
<td>Other criteria for FUO, selected group</td>
</tr>
<tr>
<td>McDougall et al,12 1979</td>
<td>In 111 WBCs</td>
<td>13</td>
<td>3 (24)</td>
<td>1 (7)</td>
<td>9 (69)</td>
<td>0 (0)</td>
<td>100</td>
<td>90</td>
<td>No criteria for FUO mentioned, selected group</td>
</tr>
<tr>
<td>Davies and Garvie,13 1990</td>
<td>In 111 WBCs</td>
<td>28</td>
<td>3 (11)</td>
<td>5 (18)</td>
<td>18 (64)</td>
<td>2 (7)</td>
<td>71</td>
<td>86</td>
<td>Criteria for FUO of Petersdorf, selected group</td>
</tr>
<tr>
<td>Becker et al,14 1993</td>
<td>Tc anti-NCA</td>
<td>34</td>
<td>8 (24)</td>
<td>1 (3)</td>
<td>13 (38)</td>
<td>12 (35)</td>
<td>40</td>
<td>92</td>
<td>Criteria for FUO of Petersdorf, selected group</td>
</tr>
<tr>
<td>Present study</td>
<td>In 111 IgG</td>
<td>24</td>
<td>9 (38)</td>
<td>4 (17)</td>
<td>9 (38)</td>
<td>2 (8)</td>
<td>82</td>
<td>69</td>
<td>Criteria for FUO of Petersdorf, selected group</td>
</tr>
</tbody>
</table>

FUO indicates fever of unknown origin; TP, true positive; FP, false positive; TN, true negative; FN, false negative; Ga 67, gallium citrate Ga 67; In 111, indium In 111; Tc, technetium; WBCs, white blood cells; and NCA, nonspecific cross-reaching antigen.

of infection.26 In a prospective comparative study in subacute infections, with the use of 111In-WBC and 111In-IgG scintigraphy, Oyen et al11 found a higher diagnostic accuracy of 111In-IgG scintigraphy.

The need to draw blood and to isolate and label leukocytes makes 111In-WBC and 99mTc-WBC scintigraphy more time consuming, complicated, and costly than 111In-IgG scintigraphy. It takes 3 hours to prepare the radiopharmaceutical, and not every department of nuclear medicine has the facilities to label leukocytes. Of major concern are the handling of blood and the possibility of administering the cells to the wrong patient.27 There is a limitation to the use of all scintigraphic techniques, including 111In-IgG: lesions in organs with relatively high physiologic uptake, eg, liver, heart, spleen, and kidneys, can be missed. Because of these advantages and the high diagnostic yield, 111In-IgG scintigraphy may become the first choice in scintigraphic investigations in patients with FUO.

Since this study, like all studies on scintigraphic methods in FUO, is retrospective, the exact role of 111In-IgG scintigraphy in the diagnostic process of patients with FUO is unknown. Prospective studies are necessary to provide such additional information.

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