Pericystic Metabolic Activity in Alveolar Echinococcosis: Assessment and Follow-Up by Positron Emission Tomography

S. Reuter, H. Schirrmeister, W. Kratzer, C. Dreweck, S. N. Reske, and P. Kern

Information on parasite viability in alveolar echinococcosis (AE) cannot be obtained by conventional imaging techniques. We evaluated the glucose metabolism of AE lesions by use of \( ^{18} \text{F} \)fluorodeoxyglucose positron emission tomography (FDG-PET) in 12 inoperable patients. Eight patients showed either perilesional or focal enhancement (“hot spots”), whereas 4 patients had nonenhancing (metabolically inactive) lesions. With PET, necrotic parasitic lesions and areas of enhanced metabolic activity could be clearly discriminated. Most notably, 3 of 8 patients with metabolically active lesions who were reexamined after chemotherapy treatment clearly showed improvement: the initial surrounding hot spots had disappeared in 2 of them, and had significantly decreased in 1. PET may prove valuable in assessing the efficacy of chemotherapy by showing the disappearance of metabolic activity and may also be useful for timely detection of relapses and metastases. Although costly and not readily available, FDG-PET is a promising tool toward improved management of AE and may thus help lower costs of long-term chemotherapy.

Alveolar echinococcosis (AE) is caused by the parasitic cestode Echinococcus multilocularis. Clinical manifestations are due to proliferation of larval masses with primary lesions in the liver. Despite the low prevalence and incidence, AE is a severe disease with a high morbidity and lethal outcome if not treated adequately. Surgical resection of primary lesions allows curative treatment. However, the majority of cases will be diagnosed with unresectable lesions, because early detection of AE is impeded by the lack of distinct clinical symptoms and mainly relies on immunodiagnosis and standard imaging techniques (i.e., ultrasound, computed tomography [CT], and MRI). Many patients who are diagnosed late require life-long pharmacological treatment with benzimidazoles and regular follow-up diagnostics.

Information on parasite metabolic activity cannot be obtained by conventional imaging techniques. Fine-needle biopsy has been advocated for molecular detection of parasite mRNA [1], but this technique is critical, as larval tissue may spread during the procedure and, most important, viable tissue may be missed. In most cases, E. multilocularis will develop parasitic activity characterized by unidirectional growth. One extreme of a parasitic lesion may therefore show metabolic activity while the opposite side consists of necrotic tissue. The ability to differentiate metabolically active from dead parasitic tissue would increase the accuracy of fine-needle puncture and would reduce the number of necessary interventions.

Glucose accumulates in inflammatory areas [2, 3], and it is the primary source of energy for endoparasitic helminths. We evaluated the glucose metabolism of hepatic lesions in patients with AE using \( ^{18} \text{F} \)fluorodeoxyglucose positron emission tomography (FDG-PET), which has proven a valuable method for the evaluation of tissue viability in other hepatic lesions [4–6].

Patients and Methods

Patients. A total of 12 patients with AE (4 women, 8 men) with a mean age of 50 years (range, 24–83 years) were included. Written consent was obtained in each case prior to the PET scan. All patients showed hepatic lesions on ultrasound and CT, and in 5 of them, adjacent structures were affected as well (lung, pericardium, retroperitoneum, kidney, and spine). The diagnosis of AE was confirmed by surgery in 8 patients, by cutting-needle puncture in 1, and clinically (i.e., epidemiology, ultrasound, CT, and serology) in 3. All patients showed immunoreactivity by indirect hemagglutination test (bioMerieux, Nürtingen, Germany) and ELISA (Em2 plus; DPC Biemann, Bad Nauheim, Germany) [7]. Table 1 shows the demographic characteristics of the patients examined. Patients 1, 6, and 12 were examined at time of diagnosis and after several years of chemotherapy.

PET. FDG-PET was done to assess glucose use in the livers of 12 patients who had well-documented E. multilocularis infections with hepatic involvement demonstrated by ultrasound and CT. The patients fasted for at least 12 h before FDG injection. PET studies were done with a CTI-ECAT scanner 931/08/12.
(Siemens, Knoxville, TN). This scanner produces 15 contiguous transverse sections of 6.5 mm thickness. Attenuation correction was done by use of a germanium-68/gallium-68 external ring source before FDG injection. Acquisition time was 15 min per 10.5-cm iterations. Static emission scans starting at the liver dome were obtained 45±60 min after FDG administration (MBq).

Recall the data for image reconstruction: Images were reconstructed with an iterative reconstruction algorithm [8]. The in-plane resolution (full width at half maximum) were routinely documented in hard copy in a standardized manner.

### Table 1. Characterization of patients with alveolar echinococcosis at time of positron emission tomographic (PET) study.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time since diagnosis (mos)</th>
<th>Age (years), sex</th>
<th>Affected lobe(s) of liver (+ additional structure)</th>
<th>Treatment in relation to PET</th>
<th>Clinical classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;1</td>
<td>24, F</td>
<td>Both</td>
<td>No surgery, prior to chemotherapy</td>
<td>Untreated</td>
</tr>
<tr>
<td>2</td>
<td>&lt;1</td>
<td>56, F</td>
<td>Both</td>
<td>No surgery, prior to chemotherapy</td>
<td>Untreated</td>
</tr>
<tr>
<td>3</td>
<td>&lt;1</td>
<td>50, F</td>
<td>Both (+ spine)</td>
<td>No surgery, prior to chemotherapy</td>
<td>Untreated</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>79, M</td>
<td>Right</td>
<td>No surgery, ABZ for &lt;1 mo</td>
<td>Stable</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>52, F</td>
<td>Both (+ pericardium)</td>
<td>No surgery, ABZ for 2 mo</td>
<td>Stable</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>68, M</td>
<td>Right (+ retroperitoneum, vertebrae)</td>
<td>Palliative surgery, ABZ for 6 mos</td>
<td>Stable</td>
</tr>
<tr>
<td>1b</td>
<td>42</td>
<td>27, F</td>
<td>Both</td>
<td>No surgery, ABZ for 43 mos</td>
<td>Stable</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>39, M</td>
<td>Both (+ kidney)</td>
<td>No surgery, MBZ for 18 mos</td>
<td>Stable</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>25, M</td>
<td>Both (+ lung)</td>
<td>Palliative surgery, ABZ for 14 mos</td>
<td>Progressive</td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td>55, M</td>
<td>Both</td>
<td>Palliative surgery, ABZ for 2 mos</td>
<td>Stable</td>
</tr>
<tr>
<td>10</td>
<td>66</td>
<td>26, M</td>
<td>Right</td>
<td>No surgery, MBZ for 21 mos</td>
<td>Regression</td>
</tr>
<tr>
<td>11</td>
<td>81</td>
<td>73, M</td>
<td>Right (+ retroperitoneum, vertebrae)</td>
<td>Palliative surgery, ABZ for 66 mos</td>
<td>Stable</td>
</tr>
<tr>
<td>12</td>
<td>152</td>
<td>44, M</td>
<td>Both</td>
<td>Palliative surgery, ABZ for 11 mos</td>
<td>Progressive</td>
</tr>
<tr>
<td>12b</td>
<td>212</td>
<td>49, M</td>
<td>Both</td>
<td>Palliative surgery, ABZ for 11 mos</td>
<td>Stable</td>
</tr>
</tbody>
</table>

**Note:** Patients are arranged according to amount of time between diagnosis and PET examination. Note that 3 patients (nos. 1, 6, and 12) were examined twice (second time designated as “b”) during course of disease. ABZ, albendazole; MBZ, mebendazole.

### Results

A total of 12 patients with AE were examined with FDG-PET. A great variability in findings was observed between different patients, ranging from no uptake to complete perilesional enhancement.

Eight patients showed either focally or perilesionally increased FDG uptake, whereas 3 patients had hepatic defects without any FDG accumulation (table 2). Lesions seen on CT could be visualized by FDG-PET as well. The PET images were compared with the corresponding CT images, which permitted accurate anatomic localization of the lesions. Note that some patients had started chemotherapy before PET (table 1).

Figure 1 shows an example of a PET image of a patient with AE that demonstrates focal tracer accumulation (left) and the corresponding CT scan (right), which shows a hypodense lesion with calcifications. Figure 2 shows a representative case of AE with a hepatic defect without peripheral FDG uptake (left), and the corresponding CT scan (right).

Three of 8 patients with increased FDG uptake were reexamined after long-term medical treatment with albendazole (table 3). The patients were given 12.5 mg/kg albendazole on a continuous regimen. After treatment, all AE lesions had retained their size and shape. A complete loss of perilesional or focal enhancement was noted in two patients; 1 is shown in figure 3. In the third patients, FDG uptake persisted but had significantly decreased compared with the image taken before chemotherapy.

During the period of chemotherapy between the 2 PET examinations, all 3 patients were seen regularly in our outpatient department (every 6 months). Their alkaline phosphatase levels markedly decreased over the course of disease (figure 4). Total IgE also decreased over time in 1 patient, whereas it remained
Figure 1. Left, $[^{18}F]$Fluorodeoxyglucose positron emission tomographic (FDG-PET) scan (transaxial section) of a 79-year-old patient (patient 4) recently diagnosed with alveolar echinococcosis. He had received <1 month of albendazole treatment before FDG-PET image was made. Metabolic activity can be detected as focal tracer accumulation in liver (arrow). Right, Corresponding CT scan shows hypodense and partially calcified lesion (arrows).

Figure 2. Left, $[^{18}F]$Fluorodeoxyglucose positron emission tomographic scan of 52-year-old patient (patient 5) with alveolar echinococcosis in transaxial section. Patient had explorative surgery and had received albendazole for 2 months before PET. Image shows large focal defect without perilesional FDG uptake (arrow). Right, Corresponding CT scan shows hepatic defect with calcifications (arrows).

Discussion

In AE, conventional imaging techniques do not convey information about parasite viability. FDG-PET is a painless and noninvasive technique that involves a low radiation dose. It has proven to be a valuable method for the detection of tissue viability, since the accumulation of FDG reflects the enzymatic activity of glucose metabolism [4, 5, 9] and so allows “functional imaging” of various infectious lesions [2, 3]. In the present study, we evaluated the imaging characteristics of FDG-PET in AE. Necrotic parasitic lesions and areas of enhanced metabolic activity could be clearly discriminated because of the growth characteristics of E. multilocularis: The parasitic mass typically enlarges by proliferation in the periphery of the lesion, accumulating necrotic material in the center. The majority of cases were therefore characterized by a central defect with unilateral “hot spots” (focal enhancement) (figure 1, left). In some cases, the lesions resembled those seen in cerebral abscess, lym-
Figure 3. Alveolar echinococcosis (AE) of liver, visualized by $[^{18}F]$fluorodeoxyglucose positron emission tomography (FDG-PET). Top row; Coronal sections; center row; Transaxial sections of same patient. Note nonenhancing (white) hepatic lesion (arrow). Top left and center left, FDG-PET results before treatment. Note perilesional tracer accumulation (black spots), signaling metabolic activity through uptake of $[^{18}F]$FDG. Top right and center right, Results after 42 months of treatment with albendazole. Lesion can still be detected as white nonenhancing defect but shows no signs of surrounding metabolic activity. Bottom row, AE of liver as visualized by CT. Bottom left, Image taken before treatment shows hypodense lesion in liver segment no. 7/8 with minimal calcifications, measuring ~8 cm. Bottom right, Image shows same lesion after 42 months of albendazole. Note differences in lesional calcification.
phoma, or toxoplasmosis [3, 10], with a central defect surrounded by a ringlike enhancing pattern of hypermetabolic tissue (figure 3, top left and center left).

For the first time, we present 3 cases of AE with follow-up examination by FDG-PET and demonstrate the disappearance of perilesional metabolic activity after long-term medical treatment, which signals that therapy was successful. The success of treatment is further substantiated by improvement in the patients’ physical conditions and by the formation of perilesional calcifications (figure 3, bottom right). Other authors had previously suggested that an increase in lesional calcification reflects loss of parasitic activity and successful treatment [11, 12]. Our data support this hypothesis; nevertheless, a causative correlation remains to be established. It is important to emphasize that the detection of calcifications is not by itself sufficient to evaluate parasitic activity and can be misleading, since calcifications may coexist with metabolically active tissue (table 2). On the other hand, calcifications are not a mandatory characteristic for the death of parasites, as suggested by the findings for patient 2, who had neither calcifications on CT nor metabolic activity in PET. The decline in indicative laboratory parameters, namely levels of alkaline phosphatase and total IgE (figures 4 and 5), is another hint that the hepatic condition has improved after treatment. According to observations in many of our patients with AE, total IgE especially appears to be a useful marker for the course of disease [13].

In the literature, decreased FDG uptake is considered a useful parameter in assessing the effect of antitumoral treatment [5, 14, 15]. Lack of tracer accumulation on FDG-PET showed a good correlation with the histological findings of necrotic tissue and inactive hepatocellular carcinoma [5]. In analogy to these findings, it is tempting to speculate that loss of perilesional tracer accumulation in our setting correlated with a loss of helminthic activity. The lack of perilesional tracer accumulation indicates the absence of glucose-utilizing parasitic tissue and the absence of a significant inflammatory reaction. We are unable to provide histological evidence of metabolic inactivity of nonenhancing lesions, as we did not obtain tissue specimens from our patients after the PET study (which would have enabled us to spot germinal tissue, a possible indicator of viable metacestode tissue). However, the alterations seen by CT and the overall clinical picture further support the above thesis that parasitic tissue is inactive.

In the present study, it was not possible to demarcate perilesional inflammation from parasitic tissue. Both parasitic and inflammatory tissue are located in the periphery of the lesion, and in analogy to findings in malignant tumors [14], perilesional tracer accumulation most likely signals uptake of FDG by both kinds of tissue. In tumors, both viable tumor cells and inflammatory tissue show metabolic activity and surround a nonenhancing necrotic center. In analogy to these findings, an intense inflammatory reaction is observed around living metacestodes in AE [16]. Since the inflammatory reaction is present in areas of helminthic activity, it indirectly denotes the area of interest. We may therefore deduce that tracer accumulation in FDG-PET indicates either ongoing parasitic activity, inflammation, or a combination of both.

The question arises whether inflammatory reaction may surround nonvital parasitic tissue and may therefore lead to false-positive results by FDG-PET. It has been shown that in tumors, the activity of macrophages correlates with the activity of the tumor itself, and it has been proposed that the inflammatory reaction might be regulated by the tumor [17–19]. In *Taenia taenidea formis* infection [20], however, perilesional inflammation persists immediately after successful treatment of the metacestode. If this holds true for AE as well, false-positive results would indicate a phase of recent parasitic activity.

Our PET images show that most AE lesions are characterized...
by unilateral larval growth. Conventional imaging techniques are unable to detect this focal activity. Fine-needle biopsy has been advocated as a tool to detect viable larval tissue in echnococcosis [1]. However, because of the inhomogeneous distribution of metabolic activity and amorphous material in AE, viable tissue may be missed when using fine-needle puncture. Furthermore, fine-needle puncture involves the danger of spreading the larvae, which is another potential drawback. FDG-PET has the potential to facilitate patient management by visualizing metabolic activity. On one hand, it may reduce the number of necessary fine-needle biopsies by indicating cases the accuracy of fine-needle puncture through visualization of polarized metabolic activity in three dimensions in nonhomogeneously active lesions.

After establishment of the diagnosis of E. multilocularis, FDG-PET may be useful in sparing patients from unnecessary operative procedures in the future. If the assumed correlation between loss of parasite viability and lack of hot spots by FDG-PET proves to be correct, nonenhancing lesions would be considered as dead, which would extend the spectrum of therapeutic options.

We do not possess reliable diagnostic parameters indicating chemotherapeutic success through loss of parasitic activity [21]. Current treatment strategies involve long-term chemotherapy with benzimidazoles, which cannot be interrupted because parasites may resume proliferation after discontinuation [12, 21–23]. However, a parasiticidal effect after long-term treatment with benzimidazoles has been observed [24] as well as spontaneous death of the metacestode at an early stage of infection [25, 26]. Detection of dead parasites could allow long-term medical treatment to be significantly shortened.

In conclusion, FDG-PET is a noninvasive tool for the three-dimensional detection of perilesional metabolic activity in AE. It may thus be useful before fine-needle puncture and may facilitate surgical decisions. The detection of early relapses and metastatic lesions may improve follow-up of patients by allowing timely intervention. Although expensive and not readily available, FDG-PET may prove cost-effective if it permits the duration of chemotherapy to be shortened. Further evaluation of this imaging technique is warranted to optimize therapeutic management, to monitor disease activity, and, as a final goal, to reassess long-term treatment with benzimidazoles on the basis of clearly discriminating imaging findings.

Acknowledgments

We thank Dr. M. Bangerter for critical review and Dr. J. G. Wechsler for stimulating support and development of concepts.

References


