Increased Incidence and Characteristics of Alveolar Echinococcosis in Patients With Immunosuppression-Associated Conditions

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**Background.** An increased incidence of alveolar echinococcosis (AE) in patients with immunosuppression (IS) has been observed; our aim was to study this association and its characteristics.

**Methods.** Fifty AE cases with IS-associated conditions (ISCs) before or at AE diagnosis were collected from the French AE registry (1982–2012, 509 cases). There were 30 cancers, 9 malignant hematological disorders, 14 chronic inflammatory diseases, 5 transplants, and 1 case of AIDS; 9 patients had ≥2 ISCs. Characteristics of the 42 IS/AE cases and the 187 non-IS/AE cases diagnosed during the period 2002–2012 were statistically compared.

**Results.** There was a significant increase in IS/AE cases over time. Risk factors did not differ between IS/AE and non-IS/AE patients. However, AE was more frequently an incidental finding (78% vs 42%) and was diagnosed at earlier stages (41% vs 23%) in IS/AE than in non-IS/AE patients. Serology was more often negative (14% vs 1%) and treatment efficacy was better (51% regression after 1-year treatment vs 27%) in IS/AE patients. All IS/AE patients but 7 took IS drugs; 7 received biotherapeutic agents. When not concomitant, AE occurred in IS patients within a 48-month median time period. Atypical presentation and abscess-, hemangioma-, and metastasis-like images delayed AE diagnosis in 50% of IS/AE patients, resulting in inappropriate treatment. Liver images obtained for 15 patients 1–5 years before diagnosis showed no AE lesions. Albendazole efficacy was good, but 19 of 48 treated patients experienced side effects.

**Conclusions.** Patients with immunosuppression are at increased risk for occurrence, delayed diagnosis, and progression of AE.

**Keywords.** Echinococcus multilocularis; cancer; biotherapy; liver abscess; liver metastases.
of AE have also been reported in patients receiving immunosuppressive therapy for malignant and inflammatory diseases or after transplant [13–18]. Data on the incidence and clinical presentation of AE in immunosuppressed patients are limited. We accessed the French AE registry, a population-based, case-recording system with the highest number of well-documented cases ever recorded over the last 3 decades [19], to collect AE cases diagnosed in patients with IS-associated conditions (ISCs), labeled here “IS/AE,” and compare them with non-IS/AE patients.

MATERIALS AND METHODS

Patient Selection
The FrancEchino Registry [3], approved by French ethical committees, has recorded all French AE cases since 1982 [19, 20], following the recommendations of the World Health Organization (WHO) Informal Working Group on Echinococcosis (IWGE) [21]. All patients gave us their informed consent.

We collected AE cases from 1 July 1982 to 30 June 2012 in patients who, before or at time of AE diagnosis, presented with chronic (>6 months’ duration) inflammatory/autoimmune diseases (CIDs), AIDS, solid organ or hematopoietic stem cell transplant, solid organ cancer, and malignant hematological disorders. Patients with liver transplant for AE or ISC diagnosed >6 months after AE diagnosis were excluded. Data were compared using χ² and Fisher exact tests.

Comparison of Epidemiological Data
Median age, sex ratio, agricultural activity/occupation, number of at-risk activities (hunting, contact with foxes, consumption of raw berries and vegetables, ownership of a garden/dogs), and residence in at-risk areas [22], recorded from 1982 to 2012, were compared in IS/AE and non-IS/AE patients.

Comparison of Clinical Data
To guarantee data reliability, given that 84% of IS/AE patients (42 patients) were observed during this period, we compared the following parameters recorded prospectively in IS/AE and non-IS/AE patients from 1 July 2002 to 30 June 2012: (1) Echinococcus species serology at diagnosis—positive if at least 1 of the following tests was above the threshold: indirect hemagglutination (IHA) (Fumouze Diagnostics, Levallois-Perret, France), and/or enzyme-linked immunosorbent assay (ELISA) using crude Echinococcus species extracts, Em2plus ELISA (Bordier Affinity Products, Crissier, Switzerland), and/or Western blotting (EmWB) (LD BIO Diagnostics, Lyon, France) [23]. (2) PNM (P: parasite location, N: neighboring structure involvement, M: metastases) staging according to WHO-IWGE [24], and presence/absence of liver calcifications. Liver lesion sizes are not recorded in the database and thus were not compared. Ultrasound (US) and computed tomography (CT) were performed in all patients annually. Magnetic resonance imaging (MRI) was performed on selected patients depending on diagnostic or therapeutic difficulties. (3) Course of AE lesions on conventional imaging, assessed as follows: “recurrence/no recurrence,” after radical resection, “regression” (decreased size and increased percentage of calcification), “progression” (increase in size and/or extension to neighboring organs and/or metastases), “stabilization” (no change in lesions) [24]. (4) Number of IS/AE patients who underwent surgery and, among them, those with complete lesion resection. Because benzimidazole side effects are not systematically recorded in the database, they were not statistically compared.

Data Collected on IS/AE Patients Only
Additional data were collected from patients’ physicians. Blood liver tests, serum C-reactive protein (CRP), blood count, and serology were recorded for IS/AE patients at diagnosis, 3 and 6 months after diagnosis, then every 6 months. When diagnosis was difficult, polymerase chain reaction (PCR) was performed on lesion samples using E. multilocularis–specific DNA probes [25]. Retrospective serology was performed on sera sampled before AE diagnosis whenever available in a biobank. Retrospective imaging was reviewed by a radiologist with expertise in AE.

After 2003, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) combined with CT was performed 1 hour after FDG injection for 26 IS/AE patients to assess AE “metabolic activity.” After July 2007, for 17 patients, it included delayed image acquisition [26]. Yearly evaluation categories of FDG uptake were “increased,” “unchanged,” “decreased,” and “absent.”

Patients received ABZ (10–15 mg/kg/day, continuously), or mebendazole (4.5 g/day) when ABZ side effects occurred. Whenever difficulties in patient management appeared, ABZ sulfoxide plasma levels were measured 4 hours after morning drug intake. Benzimidazole side effects were recorded for all IS/AE patients.

ISC Diagnosis and Follow-up
Data on diagnosis, follow-up, and treatment of the underlying disease(s), including IS drugs administered, were carefully recorded.

RESULTS

Epidemiological Characteristics
Of the 509 AE cases recorded from 1 July 1982 to 30 June 2012, 50 IS/AE cases were observed (first case in 1988). There was a significant increase in AE incidence in IS/AE patients. From
1992 to 2012 the progression rate was higher than in non-IS/AE cases (Figure 1; \( P < .001 \)). There was no overall significant
difference between IS/AE and non-IS/AE patients regarding age (65.5 years vs 60.0 years; \( P = .86 \)), sex (\( P = .90 \)), risk factors (\( P = .90 \)), or geographical area of residence (\( P = .90 \)) (Supplementary Figure 1).

**Comparison of IS/AE and Non-IS/AE Patient Clinical Characteristics From 2002 to 2012**

In the 42 IS/AE patients, compared with the 187 non-IS/AE patients, AE was more frequently an incidental finding (78% vs 42%, \( P < .001 \)), specific serology was more often negative (14% vs 1%, \( P = .001 \)), and PNM localized stages (stages I–II) more frequent (41% vs 23%, \( P < .035 \)). Prevalence of metastases was not significantly different. Liver calcifications were observed in 52% of IS/AE vs 61% of non-IS/AE patients. The difference was not significant (\( P = .36 \)). Thirty-three percent of IS/AE patients underwent operations vs 40% of non-IS/AE patients (\( P = .46 \)). The percentage was the same in both groups for radical resection (85%). Remarkably, regression under benzimidazole therapy after 1 year of follow-up was significantly more often observed in IS/AE patients (51% vs 27%, \( P < .004 \)). All 8 deaths in IS/AE patients were due to ISCs, and none to AE; 3 of
187 non-IS/AE patients (1.6%) died from AE complications. The difference was not significant.

Clinical Characteristics of IS/AE Patients
Associated ISC were mostly cancer, followed by CIDs; 2 ISC were diagnosed in 9 cases (Figure 2). Diagnosis of ISC and AE was concomitant in 16 patients (mainly with cancer). When not concomitant, median time between ISC diagnosis and AE was 48 months (range: 0–288) (Table 1). It was longer for CIDs (88 months [range: 54–288]) than for cancer (30 months [range: 0–204]). Of 49 non-AIDS patients, only 7 had no IS therapy: 5 had cancer surgery only, and 2 had advanced stages of cancer. Median duration of IS therapy was 54 months. Combined chemotherapy was most frequent, followed by corticosteroids and other IS drugs (Supplementary Figure 2). Twenty patients received ≥2 IS drugs; 7 received biotherapeutic agents.

AE diagnosis was an incidental finding in abdominal imaging in 26 patients, in liver tests in 8, on both in 4, and during laparotomy in 4 (Table 1); incidental diagnosis was more frequent in cancer patients. Four patients presented with unusual acute liver abscess-like symptoms with acute pain and fever (Table 1), 2 presented with pulmonary symptoms, and 1 AIDS patient had prolonged cholestasis. At diagnosis, liver tests were abnormal in 22 patients (cholestasis in 18, cytolysis in 10), C-reactive protein was observed in 14 patients, and <700 cells/µL in 5. All 4 patients with abscess-like presentations were lymphopenic. There was no significant difference in PNM stages between patients with and without lymphopenia.

Hepatic lesions (median size, 53 mm [range: 15–210]) were in the right lobe in 21 patients, left lobe in 7, and in both lobes in 22; 50% of patients had 2–5 lesions. Lesion size was significantly larger (P = .03) in symptomatic patients. Regional invasion was observed in 5 patients and distant AE metastases (in the lung, spleen, sacroiliac bone, retroperitoneal space, and muscles) in 9 (Table 1). When comparing ISC types, no difference was found for PNM stage or size or number of lesions (P = .9). Increased FDG uptake was observed in the liver in all but 1 patient who underwent PET/CT.

Delayed AE Diagnosis in IS/AE Patients
After the first AE symptom/image, diagnosis was delayed in 25 of 50 IS/AE patients, more often in symptomatic (80%) than in asymptomatic patients (43%), due to unusual presentation, metastasis- or lymphoma-like lesions, negative serology and/or pathological exam, or concomitant opportunistic infection (aspergillosis in 2 patients). Median delay was 5 months (2–72), and longer for transplant and CID patients (Table 1). IHA serology was negative in 65% of IS/AE patients at the 1:320 “diagnostic” cutoff, and in 10% at the 1:80 “screening” cutoff [23]. Emt Plus ELISA was negative in 25%, and EmWB showed a
specific *E. multilocularis* pattern in 45% and the “genus” pattern in 45%. The US and CT images suggested cancer metastases in 18 patients, liver abscesses in 4, liver hemangioma in 1, and hematoma in 1 (Figures 3 and 4). Of 12 symptomatic patients, 9 had atypical images. Diagnosis was confirmed by pathognomonic multivesicular images at MRI (Figure 4) in 14 of 24 patients with misleading US and CT images, and by positive PCR on liver biopsies in 8 of 24. In 2 patients, negative liver biopsies delayed AE diagnosis by 2 and 6 years, respectively.

Four patients with digestive cancer were staged TXNXM1 and received chemotherapy and/or radiofrequency, based on radiological images of metastasis and/or FDG uptake in the liver, before AE was eventually diagnosed.
### Table 2. Type of Treatment, Imaging, and Serological Evolution After Treatment Including Albendazole Administration, in 48 Patients (1982–2012) With Alveolar Echinococcosis and Immunosuppression-Associated Conditions

<table>
<thead>
<tr>
<th>Type of ISC, No.</th>
<th>Type of AE Treatment</th>
<th>Imaging</th>
<th>Serology&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18-FDG Uptake at PET/CT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Abdominal Imaging&lt;sup&gt;b&lt;/sup&gt; (US, CT, MRI)</td>
<td>Indirect Hemagglutination (Cutoff ≥80)</td>
</tr>
<tr>
<td></td>
<td>Unchanged</td>
<td>Decreased</td>
<td>Absent</td>
</tr>
<tr>
<td>Malignant hematological disorder, 9</td>
<td>9/9/0/9</td>
<td>2/4</td>
<td>1/4</td>
</tr>
<tr>
<td>Chronic inflammatory disease, 14</td>
<td>9/14/5/14</td>
<td>4/8</td>
<td>1/8</td>
</tr>
<tr>
<td>Transplant, 5</td>
<td>3/5/2/5</td>
<td>1/1</td>
<td>0/1</td>
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<tr>
<td>AIDS, 1</td>
<td>0/1/1/1</td>
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<td>0/1</td>
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<tr>
<td>2 associated ISCs, 9</td>
<td>7/9/2/9</td>
<td>3/6</td>
<td>1/6</td>
</tr>
<tr>
<td>No. of patients/total No.&lt;sup&gt;c&lt;/sup&gt;</td>
<td>32/48/16/48</td>
<td>12/26</td>
<td>5/26</td>
</tr>
<tr>
<td>Type of presentation, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE asymptomatic presentation, 38 (76)</td>
<td>19/36/15/36</td>
<td>9/16</td>
<td>3/16</td>
</tr>
<tr>
<td>Type of AE treatment, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery&lt;sup&gt;a&lt;/sup&gt; + ABZ, 16 (32)</td>
<td>. . .</td>
<td>0/5</td>
<td>1/5</td>
</tr>
<tr>
<td>ABZ without surgery, 32 (64)</td>
<td>. . .</td>
<td>14/21</td>
<td>4/21</td>
</tr>
</tbody>
</table>

Abbreviations: 18-FDG, 18F-fluorodeoxyglucose; ABZ, albendazole; AE, alveolar echinococcosis; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; ISC, immunosuppression-associated conditions; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound.

<sup>a</sup> Two patients with cancer and surgery alone, without ABZ treatment, are not shown in this table (the total number of patients is thus 48).

<sup>b</sup> FDG-PET/CT was performed in 26 of the 50 patients with AE and ISC.

<sup>c</sup> Because of the presence of patients with associated ISCs, the number of cases with each ISC is higher than the total number of patients.

<sup>d</sup> Radiological follow-up was not available in 1 patient with cancer.

<sup>e</sup> Serological follow-up is shown for those patients with positive serology at diagnosis, ie, 36 patients using indirect hemagglutination (follow-up using indirect hemagglutination was not performed in all 5 patients with transplant), and 37 patients using Em<sub>2</sub>ELISA ELISA.
Retrospective Findings in IS/AE Patients

In 7 seropositive patients, on sera sampled 1–5 years before AE diagnosis, IHA and ELISA were negative, with a weak 7-kDa band for 3 sera collected 2 years before diagnosis.

All US, CT, and MRI liver images obtained for 15 patients within the 5 years before AE diagnosis were normal.

Treatment and Follow-up of IS/AE Patients

ABZ was given to all patients but 2 with advanced cancer. Surgery was more frequently performed in patients with cancer (47%) or transplantation (40%) (Table 2). Response to treatment was favorable in 46 of 48 ABZ-treated patients (average follow-up, 44 months [range: 5–245]). FDG-PET images (42% vs 28%) and Em2plus serology (56% vs 25%) tested negative more frequently in these patients (Table 2 and Figure 5). Imaging showed stabilization in 53%, regression in 23%, and no recurrence in 24%. Among nonoperated patients, stabilization or regression was observed in 68% and 32% of cases, respectively. If initially positive, FDG uptake at PET/CT did not change (67%), decreased (17%), or was absent (16%), but it never increased. Em2plus serology became negative in 1 of 3 cases (Table 2). ABZ side effects occurred in 19 of 48 patients: abdominal pain (n = 2), alopecia (n = 5), skin rash (n = 2), pruritus (n = 1), neutropenia (n = 3); alanine/aspartate aminotransferases increased by 2- to 10-fold (n = 14) compared with normal values. Eleven patients with side effects had excessive ABZ sulfoxide levels. ABZ dosage was consequently decreased in 10 patients, replaced by mebendazole in 3 with subsequent switching to ABZ at lower dosages, and interrupted in 1 patient with neutropenia.

DISCUSSION

This report on 50 IS/AE patients from a population-based, nationwide registry of >500 patients argues strongly for the “opportunistic” status of AE. It shows that ISCs affect AE presentation, make diagnosis more problematic, and lead to inappropriate therapeutic interventions. ABZ rapidly stabilized AE, but the high side effect rate made patient care management more difficult.

There was a significant increase in IS/AE case incidence after 2000, and the difference was highly significant during the period 1992–2012. There was no change in our prospective case-retrieval process, and we find it highly unlikely that this increase could be related to earlier detection of AE cases because of changes in diagnosis procedures and follow-up of cancer or CID patients. US and CT exams have been widely available throughout France for the last 4 decades, and thanks to the French health insurance system, they are free of charge for all the above-mentioned patient types. Patient follow-up
recommendations by the scientific/public health bodies have not changed for the last 2 decades. We suggest that the increase was most likely provoked by changes in therapeutic options in Europe. In France, the “First Cancer Plan,” launched in 2003 [27], contained new therapeutic recommendations, including intensified chemotherapy for patients with malignant disorders. This factor, plus the availability of biotherapeutic agents for treatment of both cancer and CIDs, may have reinforced the trend also observed in other European countries [16]. In our study, 86% of IS/AE patients took IS drugs, 38 of 42 in the last decade. The prolonged survival, and follow-up of cancer patients using new imaging procedures, may also have played a role: 2 cases were found by FDG-PET/CT. Our inclusion criteria were conservative. We excluded occurrence of ISCs after AE diagnosis [12,28], and we could have included conditions such as kidney and liver dysfunction, diabetes, or malnutrition. However, the variety of IS levels would have hampered data analysis and posed the risk of overestimation. Immunosuppression covers a broad spectrum, and further studies will enable AE referral centers to better characterize AE courses for each type of condition in the future. Epidemiological characteristics were similar to those observed in non-IS/AE patients. This is not surprising, as E. multilocularis infection is linked to geographical, environmental, and behavioral factors. Also, the median age at diagnosis of ISCs and AE is similar [3,22]. More severe AE was observed in patients with lymphopenia, combined IS drug regimens, and/or biological agents. AE is the first cestode infection ever reported to be associated with tumor necrosis factor (TNF) inhibitors [17,18]. TNF control of E. multilocularis by its hosts has been solidly demonstrated [10]. Clinicians should thus be alerted to AE occurrence, and E. multilocularis should be added to the list of biotherapy-associated opportunistic organisms [29]. Rituximab-induced B-cell depletion may have contributed to the patient’s negative serology, as reported in a renal transplant recipient [16]. Our 5 cases confirm AE occurrence after any allotransplant: not just in liver-transplanted AE patients [30].

In immunocompetent hosts, the specific date of infection is nearly always unknown, but a 10- to 15-year interval is assumed between infection and symptoms [1]. Absence of AE lesions at imaging and negative serology during the 5 years before diagnosis is suggestive of accelerated parasite growth and/or recent infection. However, presence of an “Echinococcus” band at 7 kDa in 3 of our “retrospective” sera suggests, as described in AIDS for a variety of opportunistic diseases [31], a prolonged, latent, lesion-free period between infection and diagnosis. Low PNM stages, “acute” presentation, and atypical images may indicate rapid metacestode growth and/or its early diagnosis in IS/AE patients. We previously described hemangioma-like lesions as “early” AE [11,32]. The already reported [17] unusual abscess-like presentation and images, never described before for AE, could also indicate rapid growth, with limited cellular immune response and fibrosis [16]. Our 4 cases were observed in patients with severe IS. Metastasis-like lesions, also unusual, delayed AE diagnosis and led to erroneous, anticancer treatment. The variety of clinical presentations, atypical images, and negative serology definitely made AE diagnosis difficult in IS patients. IHA serology with a screening cutoff of 1:80 [23] combined with EmWB, which takes all Echinococcus species bands into account, may improve diagnosis efficiency. The current recommendations for diagnostic serology should thus be modified to take this situation into account [21]. In specific cases, when MRIs are not pathognomonic and pathological exams are inconclusive, specific immunostaining [33] and/or PCR performed on lesion biopsies should be used to rapidly ascertain diagnosis and avoid incorrect and potentially damaging treatment.

The similar percentages and high rates of success in IS/AE and non-IS/AE patients who underwent surgery show that the combination of surgery plus ABZ is feasible and efficient. IS therapy should be decreased whenever possible; this was successfully done in 7 cases. All studies on AE patient series have shown that clinical improvement and changes in AE lesions with ABZ alone are usually slow [1,34]. In our series of IS/ AE patients, clinical improvement was fast and impressive, with rapid disappearance of FDG uptake. This could be related to enhanced local ABZ bioavailability due to fast-developing, nonfibrotic AE lesions, but should be assessed by drug measurement and pathology studies. Given the structure of the Franc Echino database, we were unable to statistically compare ABZ side effects in IS and non-IS/AE patients. However, compared with our clinical practice and to the literature [1,21], an unusually high percentage of side effects was observed in our IS/AE patients, including systemic hypersensitivity to ABZ. Severe leukopenia was probably partly due to associated malignant hematological disorders, and/or to the combined side effects of IS drugs. Pharmacological interactions may explain frequent ABZ overdose: ABZ-sulfoxide monitoring would prevent this.

Because the proportion of patients with treatment-induced immunosuppression is increasing, along with E. multilocularis infection risks [4–9], it is likely that the number of IS/AE patients will also increase. There thus may be concern about the burden of AE in the general population, which may be higher than assumed. All physicians in endemic areas should be made aware of this new situation. Our data, which stress early AE detection and good response to ABZ, could easily lead to overoptimism regarding the management and prognosis of IS/AE patients. However, in those patients with side effects, the current situation, with only 2 similar drugs to treat AE, is far from ideal, and the increased number of IS/AE patients may lead to therapeutic cul-de-sacs in the future.
concomitant treatment of AE and the underlying disease(s) may be hazardous because of possible interference and cumulative side effects. For these reasons, proposing surgery whenever complete lesion resection is possible, to avoid long-term use of ABZ, seems a sensible option. Furthermore, intensified research on the treatment of this still deadly, albeit orphan, disease is necessary.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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