Clinical Patterns and Outcome in Epithelioid Hemangioendothelioma With or Without Pulmonary Involvement

Insights From an Internet Registry in the Study of a Rare Cancer

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Background: Epithelioid hemangioendothelioma (EHE) is a rare vascular neoplasm of endothelial origin with clinical behavior intermediate between hemangioma and angiosarcoma. The natural history of EHE is highly variable. This study uses an Internet registry to identify clinical patterns with prognostic significance in EHE.

Methods: Cases from the International Hemangioendothelioma, Epithelioid Hemangioendothelioma, and Related Vascular Disorders (HEARD) Support Group were evaluated based on demographics, organ involvement, disease progression, presence or absence of pleural effusion, and treatment. Survival among various cohorts was compared using log-rank analysis of Kaplan-Meier plots.

Results: Two hundred sixty-four patients were identified from April 2004 to November 2009. Fifty-eight cases were excluded because of inadequate information or wrong diagnosis. EHE was more common in female patients (61%). Male gender and age ≥ 55 years were associated with decreased survival. The most commonly affected organs were liver, lung, and bone. No specific organ or combination of organ involvement differentially affected survival, and survival was no different between patients with multiple vs single organ involvement. However, pattern B, defined as lesions without distinct borders (e.g., pulmonary infiltrates, pleural effusion, ascites), hemoptysis, or involvement of more than two bones adversely affected survival in all cohorts.

Conclusion: A novel staging system with prognostic value for EHE is proposed. Pleural effusion or other signs of uncontained tumor growth, hemoptysis, and osseous involvement of more than two bones implied worse survival than did localized and discrete tumors, regardless of number of organs involved. A lay registry can provide useful insights into the clinical behavior of a rare cancer.

Abbreviations: EHE = epithelioid hemangioendothelioma; HEARD = International Hemangioendothelioma, Epithelioid Hemangioendothelioma, and Related Vascular Disorders Support Group
Vascular Disorders (HEARD) Support Group established a Web-based forum for patients with the disease (www.heardsupport.org). We analyzed 206 cases from this database to test the prognostic significance of pleural effusion and to identify other predictive parameters.

MATERIALS AND METHODS

Clinical Database

The University of Illinois Office for the Protection of Research Subjects Institutional Review Board reviewed the project, entitled “Demographic Study of Hemangioendothelioma” (#2007-0772), on October 11, 2007, and determined this study “not to be human research.”

Information collected from the HEARD registry was deidentified by the Web site manager (C. P.) and then forwarded to the study coordinators (K. L., G. W.) devoid of any protected health information as defined by the Health Insurance Portability and Accountability Act of 1996. Cases were reviewed and key data placed into a spreadsheet for analysis. Inclusion required the following: (1) sex, age, and year of diagnosis; (2) tissue-based diagnosis of hemangioendothelioma; (3) basic clinical data (symptoms, organs involved); and (4) at least one follow-up entry, including patient status (alive or dead). Further details can be found in e-Appendix 1.

Statistical Analysis

Survival was analyzed by Kaplan-Meier plots, and differences between groups were assessed using the Mantel-Cox log-rank test. \( P < .05 \) was considered significant. Time for each case was calculated from the date of the initial diagnosis \( (t = 0) \) to an event date (eg, death) or the date of the last follow-up. Plots and statistical calculations were performed using Prism, version 5.0 for Windows (GraphPad; San Diego, California). Statistical analyses are described further in e-Appendix 1.

Definitions

Because pleural effusion is reported to affect survival in EHE, we proposed categorizing EHE as discrete/confined or diffuse/uncontained and hypothesized that this distinction could carry prognostic significance. Preliminary analysis of the registry also indicated that hemoptysis and involvement of three or more bones corresponded with poor outcome. Notably, multiple lesions in one or two bones did not carry the same effect. Therefore, we categorized patients on the basis of their description of disease at the time of diagnosis \( (t = 0) \) as either pattern A or pattern B. Pattern A lesions are discrete or have defined borders. In the chest and abdominal organs, this pattern can include multiple nodules. In the skeleton, pattern A is limited to involvement of two or fewer bones. Pattern B lesions are not confined to distinct nodules. In the chest, this pattern includes pulmonary infiltrates, pleural effusion, extrapulmonary thoracic disease, and the symptom of hemoptysis. In the abdomen, pattern B implies extrapolapic extension (eg, peritoneal studding) or ascites. In the skeleton, it is defined as involvement of three or more bones. Progression indicates transition from pattern A to pattern B.

RESULTS

Demographics

Data from 264 patients were entered in the registry between April 2004 and November 2009. Forty-eight cases were excluded for inadequate detail by inclusion criteria or were lost to follow-up after the initial entry. Ten patients were excluded because of a change in diagnosis. Among the remaining 206 patients, the diagnoses were EHE \( (n = 186, 90\%) \) or hemangioendothelioma of unspecified type \( (n = 20, 10\%) \). The groups were combined because the patients were clinically indistinguishable and had the same overall survival \( (P = .69) \). Geographic distribution included the United States \( (n = 148) \), Australia \( (n = 13) \), United Kingdom \( (n = 10) \), Italy \( (n = 8) \), and others \( (n = 27) \). There were 125 women \( (61\%) \) and 81 men \( (39\%) \). Median age at diagnosis was 38 years (range, 7-81 years). The median duration of follow-up was 1.9 years (range, 0.1-26.3 years). Forty-five \( (21\%) \) deaths of any cause were reported by November 2009. Mean age at death was 47 years (SD, 19 years; range, 15-81 years). Nine \( (13.4\%) \) women (aged 14-40 years) were diagnosed during pregnancy or within 6 months of delivery.

Symptoms

Fifty-seven patients \( (28\%) \) did not report the presence or absence of symptoms. Of the remaining 149 cases, 42 \( (28\%) \) were asymptomatic, and the disease was an incidental finding. Pain was the most common symptom, occurring in 79 of the 107 symptomatic patients \( (74\%) \). The specific location of pain and other symptoms are reported in Table 1.

Organ Involvement

The most commonly affected organs were liver \( (n = 99) \), lung \( (n = 89) \), and bone \( (n = 48) \), although other organs were involved. Single organ involvement occurred in 131 patients \( (64\%) \) (Fig 1). The most common presentations were liver alone \( (21\%) \), liver plus lung \( (18\%) \), lung alone \( (12\%) \), and bone alone \( (14\%) \).
Survival Demographics and Correlation
With Organ Involvement

The overall survival was 90% at 1 year and 73% at 5 years (Fig 2A). Male patients had lower survival than female patients (P = .041) (Fig 2B), and age ≥ 55 years at diagnosis was associated with decreased survival (P = .005) (Fig 2C). No differences in survival were found among the groups having a single affected organ (liver, lung, or bone) or among the most common combinations of organ involvement (liver/lung, liver/bone, lung/bone, liver/bone). Survival was unaffected by single vs multiple organ involvement (P = .54).

Correlation of Survival and Disease Pattern

Patterns A and B refer specifically to liver, lung, and bone disease; therefore, the following analyses are limited to patients with disease in these organs. However, survival among patients with other organ involvement (n = 34) was indistinguishable from those with pattern A (n = 122, P = .85), and combining the groups did not change the results.

Single Affected Organ: Patients with clinical pattern A having a single involved organ had the same survival regardless of the organ (bone vs liver vs lung). Similarly, survival was the same among the equivalent three groups of patients with pattern B. However, survival rates were different between the two clinical patterns for each organ (A vs B for liver, P = .029;

<table>
<thead>
<tr>
<th>Presenting Signs and Symptoms</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>42</td>
<td>28.2</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>107</td>
<td>71.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>28</td>
<td>18.8</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Ascites</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
<td>7.4</td>
</tr>
<tr>
<td>Chest pain</td>
<td>9</td>
<td>6.0</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>8.7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>3.4</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Fracture</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>6</td>
<td>4.0</td>
</tr>
<tr>
<td>Pain, NOS</td>
<td>31</td>
<td>20.8</td>
</tr>
<tr>
<td>Palpable mass</td>
<td>8</td>
<td>5.4</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>6</td>
<td>4.0</td>
</tr>
<tr>
<td>Pneumonia, URTI</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>Vision problems</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Weakness/numbness</td>
<td>3</td>
<td>2.0</td>
</tr>
</tbody>
</table>

The 57 patients who did not comment on the presence or absence of symptoms are excluded from this table, and percentages for each symptom are given as the fraction of the remaining 149 patients. Patients often reported more than one symptom. NOS = not otherwise specified; URTI = upper respiratory tract infection.

Multiple Affected Organs: Survival was the same among patients with disease pattern A for all combinations of multiple organ involvement (liver/lung, liver/bone, lung/bone, liver/lung/bone). Insufficient patient numbers prevented comparison of the corresponding groups of patients having pattern B. However, among all patients with multiorgan involvement, pattern A was associated with better survival than pattern B (P < .0001) (Fig 3A).

Multiple vs Single Organs: The combined single organ (liver, lung, and bone) and multiple organ (liver/lung, liver/bone, lung/bone, liver/lung/bone) groups showed no differences in survival within either
organ) having pattern A \((n = 170)\) and comparing them with all patients having single and multorgan disease but with pattern B at diagnosis \((n = 36)\). Again, survival was strongly influenced by the clinical pattern \((P < .0001)\) (Fig 4A).

**Correlation of Survival and Progression**

Patients initially classified as having other organ involvement than liver, lung, or bone can subsequently progress to pattern B, and because their survival is identical to pattern A (discussed previously), they are considered in this analysis as having pattern A at the time of diagnosis. Excluding them from this analysis does not change the results.

**Overall:** More patients presented with disease pattern A \((n = 170)\) at the time of diagnosis than with pattern B \((n = 36)\). Twenty-three patients \((16\%)\) progressed from pattern A to B during the study period. The median time to progression was 2.0 years (mean, 4.8 years; range, 0.3-22.3 years) from the date of diagnosis.

**Survival:** The 1- and 5-year survival figures after progression were 53\% and 24\%, respectively, and the median survival was 1.3 years following disease progression. Patients presenting with pattern B at the time of diagnosis had the worst outcomes (5-year survival, 20\%), and 21 (58\%) patients died during the study period. Subsequent progression carried an intermediate 5-year survival (62\%) compared with those who remained in clinical pattern A (89\%) (Fig 4B).

**Treatment**

Patients were managed conservatively (22\%) or treated with surgery (27\%), chemotherapy (26\%), or radiation (19\%). Details and correlation of treatment with outcome are provided in e-Appendix 1.

**Discussion**

We analyzed the self-reported clinical histories of 206 patients with EHE specifically to ascertain patterns of clinical involvement that affect outcome. Clinical features associated with decreased survival included male sex and a diagnosis in middle age, although metastatic disease per se did not decrease survival compared with single-site involvement. Moreover, we identified clinical features where each was strongly correlated with reduced survival: signs of uncontained spread (eg, pleural effusion or ascites), hemoptysis, and tumor in three or more bones. We designated patients with localized, contained disease as pattern A and those with uncontained disease as pattern B and propose this distinction as a novel staging system for EHE. Notably, patients with pattern B at the
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**Disease Pattern A vs Pattern B**

Deyrup et al. correlated tumor size (>3 cm) and histologic appearance (more than three mitotic figures per high-powered field) with reduced 5-year survival in EHE (59% vs 100%). This correlation contradicts the observation of Makhlouf et al., who found that mitotic count and nuclear atypia did not affect outcome. The HEARD registry did not include histologic data. However, we found that clinical presentation at the time of diagnosis had a strong predictive value. Pattern B disease in the abdomen (e.g., ascites)

time of diagnosis had the worst survival; later progression to pattern B held intermediate outcome, whereas patients with sustained pattern A had the best survival. We identified the potential utility of a patient-based registry in providing a testable medical hypothesis.

Cohort demographics, including mean age, sex disparity (60% women), range of symptoms, scope of organ involvement, survival, and outcome following transplant (including 5-year survival and risk of tumor recurrence) conform with previous reports, supporting the validity of the HEARD registry. EHE was an incidental finding in 42 of the patients (20%), comparable to the number of asymptomatic patients (25%) in the literature review by Mehrabi et al. Interestingly, male patients had poorer overall survival than female patients, supporting the possible contribution of hormone sensitivity to disease progression. Nine of 67 women (13.4%) of childbearing age were pregnant near the time of diagnosis, which is roughly double the expected incidence of pregnancy (6.9%) among this cohort. Age appears to influence outcome. However, actuarial comparison with matched control subjects is necessary to assign excess mortality to EHE in patients aged \( \geq 55 \) years. Concurrent multiorgan involvement is common at the time of diagnosis but did not influence survival in the present cohort.
or extrahepatic, intraabdominal extension) or the chest (e.g., pleural effusion, extrapulmonary thoracic extension, or hemoptysis) were similarly associated with poor survival. This finding is consistent with those of Dail et al., Amin et al., and Kitaichi et al., who reported that pleural invasion was an adverse prognostic indicator.

Reports of osseous involvement of EHE are rare. The majority of reported cases are multifocal and can present as an incidental finding or with pain or pathologic fractures. Osseous disease occurred in 23% of the patients in the registry, and involvement of more than two bones adversely affected outcome. Concomitant involvement of the skeleton and viscera did not affect survival as long as this occurred within pattern A. Only the appearance of pattern B carried a clear survival disadvantage.

Advantages and Limitations of a Lay Registry

Strengths: To our knowledge, the HEARD registry provides current information on a larger number of EHE patients than any other published source. Notably, the sample size from the three countries comprising an aggregate majority (n = 171) of HEARD patients approaches the estimated prevalence based on approximate frequency of 10^-6 among these populations (United States + Australia + United Kingdom = 380 million), suggesting that the registry comprises a representative sample of all patients with EHE. This notion is supported by the fact that registry demographics and outcome data agree with previous reports. The registry can be interrogated to identify or test clinical hypotheses such as the proposed staging system.

Remarkably, despite the lack of contribution by any medical professional to data collection, the registry yielded demographic and outcome data that conform with previous studies. Moreover, it has provided additional insights into clinical factors that affect outcome. The rarity of EHE precludes large-scale trials, and most publications involve only single cases, small case series, or retrospective literature review. This deficiency prompted Kopodou et al. to call for the establishment of a clinical registry for EHE. Similarly, Mehrabi et al. in the conclusion of a review of 434 patients from 80 articles spanning 21 years, including 51 singlet reports, pointed to the value of a comprehensive, global registry for evaluating treatment and outcomes. An EHE registry of biopsy specimens has proven useful in correlating histopathologic features of EHE with outcome. The present study similarly confirms the value of the HEARD registry, a dynamic, accessible database that can be queried in real time to gain important clinical insights.

Weaknesses: Data entry by medically naive patients carries the problems of questionable reliability and accuracy. Sensitivity presumably is also limited because reports of clinical abnormalities may be skewed to the severe end of the spectrum (e.g., ascites with abdominal distension) where the patient is likely to seek medical care. This might exclude subtle findings and suggests that pattern B is biased toward patients with more extreme disease. There is also inherent bias toward patients who are capable of using the Internet and proficient in English. We did not contact patients, and information collection is limited to one-way retrieval. Important elements of the medical record are lacking, including clinical laboratory results, histology, and radiographic data. The median duration of follow-up of 1.9 years (mean, 3.5 years; range, 0-26 years) limits information about a disease that often follows a protracted course. The reasons for censorship often were unclear because patients rarely provided an explanation for losing contact with the registry. The patients are self-selected and may not be representative of the entire population of those with EHE.

Conclusions

EHE is a vascular neoplasm with a highly variable clinical course. To our knowledge, we report the first study of EHE that uses data from a large patient-directed registry. The analysis identified potentially useful clinical correlates of outcome. Specifically, pleural effusion or other signs of uncontained tumor growth, hemoptysis, or more than two involved bones implied worse survival than did localized and discrete tumors, regardless of the number of organs involved. A lay registry can provide useful clinical insights into the behavior of a rare cancer and a valuable resource for both patients and their physicians. Further study is needed to validate our staging system and identify more accurate prognostic indicators of EHE.

Acknowledgments

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Dr Edelman: contributed to the data analysis and interpretation, statistical expertise, and final approval of the article.

Dr Jenny Yeh: contributed to the collection and assembly of the data and final approval of the article.

Dr Prasad: contributed to the study conception and design and final approval of the article.

Dr Weinberg: contributed to the collection and assembly of the data, data analysis and interpretation, statistical expertise, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article.

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Additional information: The e-Appendix can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/146/5/1312/suppl/D1C.

REFERENCES


