**Necrosis in Human Cystic Echinococcosis: An Underrecognized Tissue Reaction Possibly Related to Host Response**

**Aim:** As Echinococcosis stands out worldwide as an important zoonotic cestode infection caused by various Echinococcus species, histopathological features of the disease are worthy of in-depth study.

**Materials and Methods:** Histopathological changes in adjacent parenchymal tissue in patients with cystic echinococcosis (CE) were evaluated. The study included 91 patients 4-80 years of age (mean age: 36.24 years).

**Results:** The histopathological findings of 83 specimens were as follows: fibrosis: 77.11%; mono-nucleated cells: 71.08%; necrosis: 67.47%; eosinophils: 51.80%; giant cells: 31.33%; neutrophils: 8.43%. Fibrosis, eosinophils, neutrophils, and giant cell infiltration were observed significantly more often than mono-nucleated cell infiltration, germinal membranes, and protoscolex existence (P < 0.01). Necrosis was noted adjacent to the acellular laminated layer in host parenchymal tissue. Liver and kidneys were significantly more prone to necrosis than other localizations (P < 0.01). Necrosis was seen significantly more often in patients with higher IHA titration positivity (P < 0.01).

**Conclusions:** As necrosis has not been previously considered in CE, histopathological examination in necrosis-dominant cyst walls should be evaluated for a differential diagnosis. One possible explanation for necrosis as a histopathological finding in CE could be that it occurs as a natural course of its immunopathogenesis.

**Key Words:** Cystic echinococcosis, histopathology, necrosis

**Introduction**

Worldwide, Echinococcosis stands out as an important zoonotic cestode infection caused by various Echinococcus species. It is also one of the most common parasitic infections (1-3). When a combination of clinical findings, imaging procedures, and serologic tests are used, a reliable diagnosis of Echinococcosis is possible (4). Cystic echinococcosis (CE) is the most frequent echinococcosis infection; the literature abounds...
with publications concerning the epidemiology, radiological and serological diagnosis, therapy, and unusual localizations of this parasitic infection. In operated cases histopathological examination shows the unique features of the parasite and host tissue changes. The presence of the structures related to the parasite in the cyst wall is definitive for histopathological confirmation (5,6). The morphology of the unilocular hydatid cyst is replete with opalescent fluid enclosed by a nucleated inner germinative membrane and an outer acellular laminated layer (ALL), which is about 1 mm thick. This ALL is surrounded by a thin fibrous host tissue and inflammatory cells (7).

Despite huge interest in this disease, to the best of the authors' knowledge, among the histopathological findings of CE necrosis has never previously been a consideration. Necrotic CE specimens could pose a differential diagnostic problem when the parasitic structures are not seen.

In this retrospective histopathological study we evaluated histopathological changes in adjacent parenchymal tissue in patients with CE, and then discuss necrosis, which was noted as a host reaction to the parasite in CE specimens, in terms of its diagnostic value and its relationship with serologic findings.

Materials and Methods

The study group consisted of 91 patients that were diagnosed with CE and had undergone surgery at İnönü University, Turgut Özal Medical Center, Malatya (Eastern Turkey) between January 2002 and December 2005. Demographic and clinical features of the patients, including macroscopic and radiological features of the cysts, clinical history, and serological results, were obtained from the patients' medical records. The surgically resected specimens were re-evaluated histologically using routine hematoxylin-eosin (H&E)-stained sections and the periodic acid-Schiff (PAS) reaction at the medical center's pathology laboratory. The germinal membrane, outer ALL, and the protoscolices of the cysts, as well as the adjacent parenchymal tissue were meticulously evaluated with light microscopy.

Statistical analysis was performed using the following methods: the Levene test, Kolmogorov-Smirnov test, paired and unpaired t-tests, one way-ANOVA, and the Kruskal-Wallis test. P values less than 0.05 were considered statistically significant. All analyses were performed using SPSS for Windows v.6.0 (SPSS Inc., USA).

Results

The study included 91 patients diagnosed with unilocular CE; mean age was 36.24 ± 20.35 years (range: 4-80 years), 37 (41%) were male, and 54 (59%) were female.

Cysts were located mostly in the liver (n = 58, 64%) and lungs (n = 21, 23%), either with single or multiple localization. Organs involved in 14 patients (15%) were the peritoneum, omentum, kidneys, thyroid, thorax, abdominal aorta, muscles, and lumbar epidural space. Mean size of the cysts was 7.92 ± 3.52 cm (range: 2-20 cm). In all, 45 of the 49 patients (92%) were IHA positive and the remaining patients (8%) were IHA negative. As all the patients already had CE, the negative test results could also be considered false negatives.

Due to the type of surgical approach, cyst walls and adjacent tissue were absent in 8 specimens, and they were excluded from the study. The histopathological findings of 83 specimens with definitive parasitic structures (germinal membrane, ALL, protoscolices) are shown in Table 1.

Necrosis was observed between the ALL of the parasite and viable host parenchymal tissue (Figure 1 and 2). Neutrophils, eosinophils, mono-nuclear inflammatory cells, and giant histiocytic cells with multiple nuclei were the dominant cellular responses. The outer ALL, which is of high diagnostic value, was present in all specimens. Histopathological findings accompanying necrosis are shown in Table 2. When these findings were statistically analyzed, fibrosis, eosinophils, neutrophils, and giant cell infiltration occurred significantly more often than mono-nucleated cell infiltration, germinal membranes, and protoscolices (P < 0.01).

Table 1. Histological findings of CE in host parenchymal tissue.

<table>
<thead>
<tr>
<th>Histological Findings of CE</th>
<th>Number of Cases</th>
<th>(%)</th>
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<tbody>
<tr>
<td>Fibrosis</td>
<td>64</td>
<td>77.11</td>
</tr>
<tr>
<td>Mono-nucleated cells</td>
<td>59</td>
<td>71.08</td>
</tr>
<tr>
<td>Necrosis</td>
<td>56</td>
<td>67.47</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>43</td>
<td>51.80</td>
</tr>
<tr>
<td>Giant cells</td>
<td>26</td>
<td>31.33</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>7</td>
<td>8.43</td>
</tr>
</tbody>
</table>
Mean diameter of necrosis-positive cysts was 8.07 ± 3.42 cm versus 7.48 ± 3.71 cm for necrosis-negative cysts. The relationship between cyst size and necrosis was not statistically significant (P > 0.05). Mean age of the necrosis-positive patients was 34.16 ± 20.46 years versus 42.89 ± 18.80 years for necrosis-negative patients (P > 0.05). The liver and kidneys were significantly more prone to necrosis than other localizations (P < 0.01). Table 3 shows the localizations of the necrotic cysts. Correlations between IHA and necrosis are in Table 4. Necrosis was seen significantly more often in patients with higher IHA titration positivity (P < 0.01).

Discussion

Histopathological examination of Echinococcosis specimens is important for final diagnosis and is sufficient in most cases (4). Development of a glycan-rich ALL is a characteristic feature of the genus *Echinococcus* (6). In CE the outer ALL is of primary diagnostic value, followed by the other parasitic structures, such as the germinal membrane and protoscoleces (8). The walls are finely laminated and amphophilic, and their characteristic appearance is such that a diagnosis can be made even when only a small fragment is identified in a section. Nonetheless, these small fragments may not be seen in routine H&E-stained sections and positive PAS reactions are quite helpful in this regard (9).

In the present series ALLs were noted in 100% of the patients using the PAS method, whereas germinal membranes were seen in 86%. Inflammatory fibrosis in the neighboring parenchymal tissue has been reported as granulation tissue that includes mononuclear cell infiltration, pressure atrophy, and fibrous tissue (4,8,9). In the present study neutrophils, eosinophils, mononucleated cells, and histiocytic multinucleated giant cells were the dominant cellular responses. Necrosis was observed adjacent to the ALL in host parenchymal tissue. As necrosis in the host tissue is the usual finding in alveolar echinococcosis, but has not been taken into consideration in CE, histopathological findings of...
necrosis-dominant cyst walls should be evaluated meticulously for a differential diagnosis.

*E. multilocularis* leads to the more aggressive form of echinococcosis, which is one of the most lethal helminthic infections in humans, and exhibits dense necrotic foci that result in microcavitations (6). The ALL of the cyst is incomplete and the inner germinative epithelium proliferates diffusely in an alveolar pattern, spreading like a neoplasm through the tissue (9). It was thought that necrosis was due to thrombosis of the vessels in the host tissue around the cyst and that all necrotic masses located in the liver must include *E. multilocularis* in the differential diagnosis in endemic regions (10); however, the literature has not considered necrosis as a possible histopathological finding in CE. Among the detailed findings of an important histopathological study (11), necrosis was not reported.

In the present study necrosis occurred adjacent to the outer ALL in host parenchymal tissue in 67.47% of the patients. Correlations between necrosis, and patient age and the size of the cysts were not statistically significant (P > 0.05), whereas significantly more of the cysts in the liver and kidneys were necrotic than those in the other organs (P < 0.01). Patient age had no influence on the necrotic response of the adjacent tissue. One could easily interpret from the present series of patients that increased cyst size could lead to more pressure being exerted on the adjacent tissue, resulting in vascular compromise, which could in turn result in more necrosis; however, this was not statistically proven.

Another result of the present study is that in some organs necrosis was seen more frequently and the differences were statistically significant (P < 0.01). Different tissue response in some organs (kidneys and liver) could cause more necrosis, just as hepatic cysts were more likely to elicit an immune response than pulmonary cysts in IHA serologic tests (12). The structure of the lungs might be physically less resistant to the growth of echinococcal cysts, as compared with dense liver and kidney parenchyma (11). Necrosis was seen significantly more often in patients with higher IHA titration positive results. Cystic fluid is known to be highly antigenic and IHA titration usually increases shortly after surgical intervention, when cyst fluid and host tissue are in close contact (13). Higher IHA titration and necrosis could be the common result of cyst fluid and host tissue contact following probable minor trauma and fluid leakage between the ALL and host parenchymal tissue. This should be verified with further studies on the immunopathogenesis of echinococcosis. Actually, for alveolar echinococcosis, parasite-specific humoral and

| Table 3. Localization of necrotic host tissues. Liver and kidneys were more vulnerable to necrosis. |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| (number of cases)                               | Liver (*)                                       | Lungs                                          | Intra-Abdominal                                 | Kidney (*)                                       | Others                                          |
| Necrosis (+)                                    | 35                                              | 10                                             | 7                                               | 4                                               | 1                                               |
| Necrosis (-)                                    | 18                                              | 9                                              | 7                                               | 0                                               | 3                                               |

(*) Statistically significant localization of necrosis.

| Table 4. Necrosis and IHA reactions of the patients. Higher titrated reactions were more common with necrosis. |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| (number of cases)                               | IHA Titration Values                            |-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|                                                | 1/32                                            | 1/64                                            | 1/128                                           | 1/256                                           | 1/512                                           | 1/1024                                           | 1/2048                                           | 1/4000                                           | 1/8000                                           | 1/1600                                           |
| Necrosis (+)                                    | 0                                               | 0                                               | 2                                               | 3                                               | 7                                               | 8                                               | 6                                               | 1                                               | 0                                               | 4                                               |
| Necrosis (-)                                    | 1                                               | 4                                               | 1                                               | 5                                               | 2                                               | 0                                               | 0                                               | 0                                               | 0                                               | 1                                               | 0                                               |
cell-mediated immune responses are crucial to host defense (14). This response has yet to be observed in CE.

The most probable explanation for necrosis as a histopathological finding in CE could be the natural course of its immunopathogenesis. Necrosis in CE is an underscored or omitted finding as a host tissue response. Necrosis, in fact, provides clues to either the pathogenic mechanisms or the virulence of different Echinococcus species. Studies that include large series of CE patients and identify Echinococcus species could help clarify whether or not necrosis is host dependent. These are all promising directions for future echinococcal necrosis research.

References


