Follow-up in hepatic alveolar echinococcosis under benzimidazole therapy using computed tomography

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To the Editor: Alveolar echinococcosis (AE), caused by infection with *Echinococcus multilocularis*, is regarded as the most dangerous parasitic zoonosis in the temperate climate zones of the northern hemisphere, particularly across Central Europe and large parts of North-/Central Asia. Left untreated, AE has a very high mortality rate. The liver is the organ most commonly affected showing complex, often infiltrative lesions. When lesions cannot be resected in curative intention, long-term parasitostatic pharmacotherapy with benzimidazoles is indicated to inhibit further extension.[1]

The *E. multilocularis* Ulm classification for computed tomography (EMUC-CT) provides a basis for the systematic description of hepatic AE lesions, thus improving diagnostic investigation and allowing a comprehensive comparison of CT findings.[2] As it has been shown that individual parameters or the duration of pharmacotherapy alone do not allow any conclusions to be drawn about parasitic activity and viability,[3] a differentiated examination of the course of the various morphological forms of the disease seems interesting. To get an impression of the influence of parasitostasis on lesion morphology, this study investigated hepatic AE using the EMUC-CT, based on two CT scans at different time points in patients under continuous benzimidazole therapy. The study was conducted in agreement with the *Declaration of Helsinki* and with the approval of the Ethics Committee of the University Hospital Ulm (AZ: 409/15), the authors certify that they have obtained all appropriate patient consent forms.

From the national German AE database of the University Hospital Ulm, we retrospectively analyzed 72 patients with hepatic AE. These patients had not undergone surgery on the liver for AE lesions and were receiving continuous benzimidazole therapy at the respective standard doses: albendazole 10 to 15 mg/kg body weight per day (two doses) or alternatively mebendazole 40 to 50 mg/kg body weight per day (three doses). On the basis of the World Health Organization case definition criteria,[1] patients were sub-divided into confirmed ($n = 32$) and probable cases ($n = 40$). The patients consisted of 38 women (52.8%) and 34 men (47.2%) with a mean age of 65.8 ± 16.2 years, a mean body mass index of 24.3 ± 3.9 kg/m^2.

CT datasets from the venous phase of contrast-enhanced positron emission tomography-CT scans were used for the assessments of the AE liver lesions. Evaluations in each case were based on the initial imaging and the most recent imaging at the time of assessment. The mean interval between the baseline-CT and the follow-up-CT was 39.8 ± 16.7 months. In each patient, the lesion size was determined from the maximum extent in the transverse plane of the largest space-occupying lesion found in the liver in baseline-CT. The same lesion was evaluated in follow-up-CT. In all 72 cases, the first reader classified the morphology with respect to this largest hepatic lesion according to EMUC-CT and a second reader made an independent evaluation. The inter-rater reliability was 0.8268 (95% confidence interval: 0.7453–0.9084; $P < 0.0001$). In addition, the degree of calcification of the biggest lesion was determined by means of a four-stage

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scale. Furthermore, the total number of AE lesions within the liver was determined. SAS software (Version 9.4, SAS Institute Inc, Cary, NC, USA) was used to perform the statistical analysis. The Shapiro-Wilk test was used to check the normal distribution of the data. Data were analyzed for differences between the groups using the Wilcoxon rank-sum test. Calculation of inter-rater reliability was performed with Cohens-Kappa. A P-value < 0.05 was taken as statistically significant.

In this study according to EMUC-CT, type I "diffuse infiltrating" ($n = 33, 45.8\%$) was the most common primary morphological type, followed in descending order of frequency by type II "primarily circumscribed tumor-like" ($n = 15$, 20.8%), type IIIa/b "primarily cystoid" ($n = 13$, 18.0%), type IV "small cystoid/metastasis-like" ($n = 10$, 14.0%), and type V "mainly calcified" ($n = 1$, 1.4%). Between baseline and follow-up, the primary morphological type changed in only one patient (1.4%), from type IIIa to type V. A change in the EMUC-CT sub-criteria was also monitored for just one patient (loss of "cystoid portion" in type II). The various primary morphologies and sub-criteria thus showed a very high degree of consistency under pharmacotherapy. These observations fit the parasitostatic effect of benzimidazoles, which usually succeed in stopping disease progression.[1,3]

Calcification is pathognomonic of AE. In our study, the EMUC-CT calcification pattern changed in 12 cases (16.7%) between baseline- and follow-up-CTs. It should be noted, that all those cases concerned a morphological change from a more discreet towards a more dominant pattern (eg, from "feathery calcification" to "diffuse calcification"). Besides the EMUC-CT calcification pattern, the overall degree of calcification was rated as "none," "slight," "moderate," or "considerable," in order to assess the course of disease more comprehensively. This showed that the degree of calcification increased distinctly over time—baseline: "none," $n = 5$ (6.9%); "slight," $n = 29$ (40.3%); "moderate," $n = 24$ (33.3%); and "considerable," $n = 14$ (19.4%) *vs.* follow-up: "none," $n = 2$ (2.8%); "slight," $n = 14$ (19.4%); "moderate," $n = 30$ (41.7%); and "considerable," $n = 26$ (36.1%). In accordance with the current results obtained under benzimidazole therapy, previous studies indicate that increasing calcification may be associated with diminishing parasitic activity in AE.[4]

Overall, there was a significant reduction in the mean size of the largest lesion from baseline- to follow-up-CT (86.2 ± 42.4 *vs.* 80.9 ± 41.8 mm; $P < 0.0001$). The relation of size among the EMUC-CT types was in descending order: type IIIb (> type IIIa/b total) > type II > type I > type IIIa > type IV > type V. Regarding the EMUC-CT primary morphology, a significant reduction in size between baseline versus follow-up could be shown for type I (80.6 ± 25.1 *vs.* 75.3 ± 28.5 mm; $P = 0.0092$), type II (110.9 ± 39.4 *vs.* 105.4 ± 39.2 mm; $P = 0.0166$), and type IIIa/b (113.4 ± 53.5 *vs.* 104.2 ± 52.7 mm; $P = 0.0205$). Type IV remarkably did not show significant difference in size in the course of treatment. It was not possible to evaluate type V because of the small number of cases. Type V is completely or almost completely calcified and most likely represents a form of inactive stage or a possible residuum of different types. The potential of general size reduction of AE lesions on benzimidazoles has been shown in earlier studies but without differentiating into EMUC-CT primary morphological types.[5]

As expected, the total number of lesions does not differ much from baseline to follow-up, since the lesions or their residues are known to remain in patients treated with parasitostatic therapy. Independent of the time course, the coefficient of determination ($R^2 = 0.5744$) interestingly indicates a moderate to strong relationship between the mean number of lesions and the mean lesion size of the different primary morphological types: the more lesions there are present in one liver the smaller they are. This issue raises several questions, also concerning a possible influence of the growth behavior among the lesions found in one liver.

Given the stratification of the present study population according to primary morphological types, sub-criteria, and patterns of calcification, we have to consider the sample size as a limitation of the study. Further multi-center studies with large case numbers are required to confirm the results presented here. The subjective assessment of the degree of calcification is another limitation.

In summary, long-term benzimidazole therapy largely preserves the primary morphology of AE lesions with a simultaneous increase in calcification. A significant reduction in the size of AE lesions occurs in types I, II, and III. Reduction in size of such lesions may lead to operability which might have not been given initially.

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Conflicts of interest

None

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