Advances in Medical Sciences 64 (2019) 324–330

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original research article

Ultrasound images in hepatic alveolar echinococcosis and clinical stage of the disease

Małgorzata Sulima[a,*], Wacław Nahorski[a,b], Tomasz Gorycki[c], Wojciech Wołyniec[d], Piotr Wąż[e], Iwona Felczak-Korzybska[a], Beata Szostakowska[f], Katarzyna Sikorska[a,g]

[a] Department of Tropical and Parasitic Diseases, University Centre of Maritime and Tropical Medicine (UCMMiT), Medical University of Gdansk, Gdynia, Poland
[b] Department of Tropical and Parasitic Diseases, Institute of Maritime and Tropical Medicine, Faculty of Health Sciences, Medical University of Gdansk, Gdynia, Poland
[c] Department of Radiology, Medical University of Gdansk, Gdansk, Poland
[d] Department of Occupational, Metabolic and Internal Medicine, Institute of Maritime and Tropical Medicine, Faculty of Health Sciences, Medical University of Gdansk, Gdynia, Poland
[e] Department of Nuclear Medicine, Medical University of Gdansk, Gdansk, Poland
[f] Department of Tropical Parasitology, Chair of Tropical Medicine and Parasitology, Institute of Maritime and Tropical Medicine, Faculty of Health Sciences, Medical University of Gdansk, Gdynia, Poland
[g] Department of Tropical Medicine and Epidemiology, Institute of Maritime and Tropical Medicine, Faculty of Health Sciences, Medical University of Gdansk, Gdynia, Poland

ARTICLE INFO

Keywords:
Hepatic alveolar echinococcosis
Ultrasound classification

ABSTRACT

Purpose: Hepatic alveolar echinococcosis (AE) is a parasitic disease caused by the larval stage of the tapeworm *Echinococcus multilocularis*. Ultrasonography is the method of choice in the initial diagnosis of AE. The aim of the study is to present the most frequent sonomorphological patterns of lesions in hepatic AE based on the analysis of ultrasound findings in patients treated for AE at the University Centre of Maritime and Tropical Medicine (UCMMiT; Gdynia, Poland), and to establish whether there is a relationship between the clinical stage of AE and the occurrence of a specific sonomorphological pattern of hepatic lesions.

Patients and methods: We analysed the results of ultrasound examinations of 58 patients hospitalized in the UCMMiT with probable or certain diagnosis of AE. Liver lesions were assessed according to the classification developed by researchers from the University Hospital in Ulm (Germany). Statistical analysis was based on the relationship between the occurrence of a specific sonomorphological pattern of hepatic lesions and the clinical stage of AE.

Results: The most frequently observed patterns of AE lesions in the liver were the hailstorm and the pseudocystic patterns. There was no correlation between the clinical stage of the disease and the ultrasonographic appearance of lesions. There was no statistically significant relationship between the more frequent occurrences of specific ultrasonographic patterns of lesions in the liver and radical or non-radical surgery.

Conclusions: The ultrasonographic appearance of the lesion in liver AE cannot determine the therapeutic management. Treatment plan should be established based on the PMN classification.

1. Introduction

Alveolar echinococcosis (AE) is a parasitic disease caused by the larval stage of the tapeworm *Echinococcus multilocularis* [1]. It is found in the northern hemisphere, in the endemic areas of Western and Central Europe as well as Central and Eastern Asia, especially in China [2,3].

Humans become infected by ingesting tapeworm eggs [3]. The most frequent site of primary parasitic lesions is the liver [4]. Clinically, the parasitic invasion is characterized by a long-lasting asymptomatic phase (average duration of 5–15 years) [3,5]. At onset of symptoms, imaging examination usually reveals the presence of a large tumour-like mass in the liver, suggestive of a proliferative process [6,7]. In some cases, at the time of diagnosis, extrahepatic lesions are also visible, including remote locations, e.g. the lungs (7–20% of cases) or the brain (1–3% of cases) [8,9].

* Corresponding author at: Department of Tropical and Parasitic Diseases, University Centre of Maritime and Tropical Medicine (UCMMiT), Medical University of Gdansk, Powstania Styczniowego 9b, 81-519 Gdynia, Poland.
E-mail address: m.sulima@poczta.fm (M. Sulima).

https://doi.org/10.1016/j.advms.2019.04.002
Received 8 July 2018; Accepted 5 April 2019
Available online 16 April 2019

Early diagnosis and implementation of appropriate treatment is very important. In untreated patients, mortality is high and reaches 90% within 10 years from diagnosis [4,10]. But in recent years major achievement has been reached by careful management of AE cases and life-expectancy of patients is approaching that of the general population [11].

Radical resection of the lesion at the initial stage of its development, supported by pharmacological treatment with benzimidazoles is the most effective management. In patients with advanced disease, who are not eligible for complete resection, liver transplantation remains the only therapeutic option and a chance for survival [12–14].

Imaging studies, in addition to serological tests, provide the basis for the diagnostic process as well as monitoring the treatment of patients with alveolar echinococcosis [15]. Histopathological and molecular tests (i.e. polymerase chain reaction - PCR) of the collected material confirm the diagnosis [16,17]. The clinical picture of AE varies, depending on the location of the lesions, the severity of the disease and accompanying complications resulting from the progression of the disease, such as cholestasis, cholangitis, formation of an abscess in the liver, or secondary biliary cirrhosis and portal hypertension. Although in most cases of AE, the lesions are located in the liver, one must always bear in mind the possibility of coexisting distant metastases, which make the diagnosis of AE even more challenging due to its atypical clinical manifestation.

Ultrasound examination is usually the diagnostic modality of choice in patients with abdominal pain, jaundice or febrile conditions, which are often the first symptoms of AE. To date, there has been no generally accepted ultrasound classification of hepatic lesions observed in AE [18].

The aim of our study was to present the most frequently observed ultrasonographic pattern of hepatic lesions in patients treated for AE at the University Centre of Maritime and Tropical Medicine (UCMMiT; Gdynia, Poland) and to establish whether there is a relationship between the stage of AE determining the possibility of radical surgical treatment and the occurrence of a specific pattern of hepatic lesions on ultrasound imaging.

2. Materials and methods

2.1. Retrospective analysis of the patients

The retrospective analysis included the results of laboratory, serological and imaging examinations of 72 patients with probable and certain AE diagnosis (according to Brunetti et al. [16]) hospitalized between 2000 and 2016 at the UCMMiT. Data on the conservative and surgical treatment were also collected. During hospitalization the patients underwent liver function tests, blood immunoglobulin E (IgE) levels, serological tests and imaging examinations in order to establish the diagnosis and monitor the treatment. Serological tests, i.e. ELISA Echinococcus (Bordier Affinity Products SA, Crissier, Switzerland), Em2plus (Bordier Affinity Products SA, Crissier, Switzerland) and Echinococcus Western Blot IgG (LDBIO Diagnostics, Lyon, France), were performed at the Department of Tropical Parasitology of the Medical University of Gdansk according to the manufacturers' instructions. All the patients included in the study had positive results of serological tests. IgE levels performed at the time of diagnosis were varied and there was no correlation between the IgE level and the type of lesion presented in the ultrasound examination.

The stage of hepatic lesions was evaluated using ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). Finally, the study included 58 patients in whom a detailed analysis of ultrasound images was possible and who had one type of lesions. Excluded from the analysis were 13 patients who were followed-up in UCMMiT after previous surgery or liver transplantation, and 1 patient with two different types of lesions occurring at the same time in both hepatic lobes (ossification and pseudocystic patterns).

The study group included 39 patients with certain AE and 19 with probable diagnosis of AE. The diagnosis was considered as certain in patients in whom the disease was confirmed by histopathology or PCR methods. In the group with certain diagnosis, in 7 patients the specimens for histopathological examination were collected without prior suspicion of AE or implementation of antiparasitic treatment. The probable diagnosis was based on the positive results of blood serological tests and characteristic appearance of the lesions on CT.

2.2. AE ultrasound images analysis

Abdominal ultrasound examinations were performed by two clinicians experienced in diagnosis and treatment of AE (IF, MS), initially with the Philips ATL APOGEE 800 W apparatus using the Philips C5-2 Convex Probe and subsequently with the ALOKA α10 Premier device using the Convex UST-9130 Probe. The study analysed the findings of ultrasound examinations performed at diagnosis.

The classification developed by researchers from the University Hospital in Ulm (Germany) was used for the assessment of ultrasound findings [18]. This classification is based on 5 types of lesions:

- Type 1 - a hailstorm pattern appearing as heterogeneously echogenic areas with irregular contours and visible scattered hyperechoic areas, in some cases calcifications can be seen;
- Type 2 - a pseudocystic pattern with an irregular hyperechoic rim that is not vascularized on power Doppler;
- Type 3 - a metastasis-like pattern;
- Type 4 - a haemangioma-like pattern;
- Type 5 - ossification pattern with features of calcifications.

In addition, the location of the lesions in the liver (right/left hepatic lobe), their size and number were analysed in the study.

2.3. Clinical stage of AE analysis

The stage of disease was assessed based on imaging examinations according to PNM classification [19] where P defines the size of parasitic lesions in the liver, N extrahepatic expansion to neighbouring tissues and M presence of distant metastases.

2.4. Statistical analysis

Statistical analysis was performed to assess the potential relationship between the presence of specific sonographic pattern of the hepatic lesions and the clinical stage of AE determining the radicality of surgical treatment. The analysis was performed using the functions and procedures of the R project [20]. The χ^2 test and Fisher's exact test for count data were used to determine if there is a significant difference between observed and expected frequencies for the obtained qualitative variables. The logistic regression was used to create a model based on a linear dependence between the dichotomous variable and the independent variables. The results were enriched with the Receiver Operating Characteristic (ROC) curve analysis. In each of the tests mentioned above, the significance level was set at $\alpha = 0.05$.

2.5. Ethical issues

The study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdansk (Poland) on June 25, 2003 as a part of the research project of the State Committee for Scientific Research/the Polish Ministry of Science and Higher Education (KBN/MNiSW). Approval number: NKEBN/457/2003; project numbers: 4PO5D04212 and 3PO5B10625.

Fig. 1. Type 1 - a hailstorm pattern.

3. Results

In a group of 58 patients subjected to ultrasound examination, there were 21 patients (36.2%) in whom hepatic lesions were located in the right lobe and 4 patients (6.9%) with lesions in the left lobe. Most often, in as many as 33 cases (56.9%), both hepatic lobes were affected. In 10 cases, the infiltration extended beyond the liver hilum. The lesions of the largest dimensions were of pseudocystic type and were located in the right lobe. In 7 cases, the presence of extrahepatic lesions was detected (including dissemination to the peritoneum, retroperitoneal space and pelvis, distant foci in the lungs and brain) at diagnosis based on a simultaneous CT imaging.

Analysis of ultrasound findings according to the Ulm classification [18] showed the hailstorm pattern (Fig. 1) in 33 cases (56.9%), pseudocystic pattern (Fig. 2) in 21 cases (36.2%) and haemangioma-like pattern (Fig. 3) in 2 cases (3.4%). The ossification pattern was reported in 2 patients with multifocal lesions (3 and 5 foci) occurring in both hepatic lobes.

The prevalence of specific patterns of ultrasound lesions depending on the clinical stage of the disease in the groups of patients with certain and probable diagnosis of AE is presented in Table 1. The stage of the disease was determined based on the PNM system mentioned above. Patients with stages I and II were considered as eligible for total resection.

Only 4 patients were assigned to the “sonomorphological pattern” 4 and 5. For this reason, the analysis of the data was carried out on a set lacking these sonomorphological patterns.

Information about the number (N) of patients with “sonomorphological pattern” 1 and 2 and the groups defined based on the feature “completely resectable” (yes/ no) is presented in Table 2. The table also lists the percentages calculated against the sum specified for the given rows (NR) and columns (NC).

Pearson's X^2 test with Yates' continuity correction was used to examine the distribution of values in Table 1. The results are: $X^2 = 1.3*10^{-31}$ and p-value = 1. This means that the distribution of values does not depend on the selected features, i.e., the “completely resectable” and the “sonomorphological pattern” advancement.

Table 3 contains information about the number (N) of patients with a given “stage of disease” and “sonomorphological patterns” 1 and 2. Similarly as in Table 2, percentages calculated against the sum specified for the given rows (NR) and columns were also determined (NC).

Since several N values are small (Table 3), the Fisher's Exact Test for Count Data has been used to examine the independence between the features described in the columns and rows. P value = 0.3435 means that the result is not statistically significant. There are no reasons to reject the null hypothesis of this test. This means that the distribution of values does not depend on the selected features, i.e., the “stage of disease” and the “sonomorphological pattern”.

To examine the relations between the variables "sonomorphological pattern" and "completely resectable" more precisely, a mathematical model based on the concept of logistic regression was built. The results (β and p values) are given in Table 4. The values of β obtained from this model are not statistically significant. The variable “sonomorphological pattern” cannot be considered in this model as a variable explaining the variable “completely resectable” (yes/no). The odds ratio is exp (-0.0834) = 0.92. This value (close to 1) means that the odds for the variable “completely resectable”(yes) is almost the same regardless of the selected pattern (1 or 2) of the variable "sonomorphological pattern".

This result was also confirmed by the ROC analysis where the AUC value = 0.510 (Fig. 4).

4. Discussion

Echinococcosis is a dangerous parasitic disease, the diagnosis of which is often very challenging. Based on epidemiological data and clinical presentation, imaging techniques along with serological tests make it possible to diagnose AE in a large proportion of cases. However, the final diagnosis can be established only after histopathological confirmation or demonstrating genetic material by PCR in surgically resected liver tissue [21]. Ultrasonography remains the first-choice modality in both the diagnosis and monitoring of treatment of patients with AE [22]. It is also used as a screening tool in endemic areas, in addition to serological tests [23].

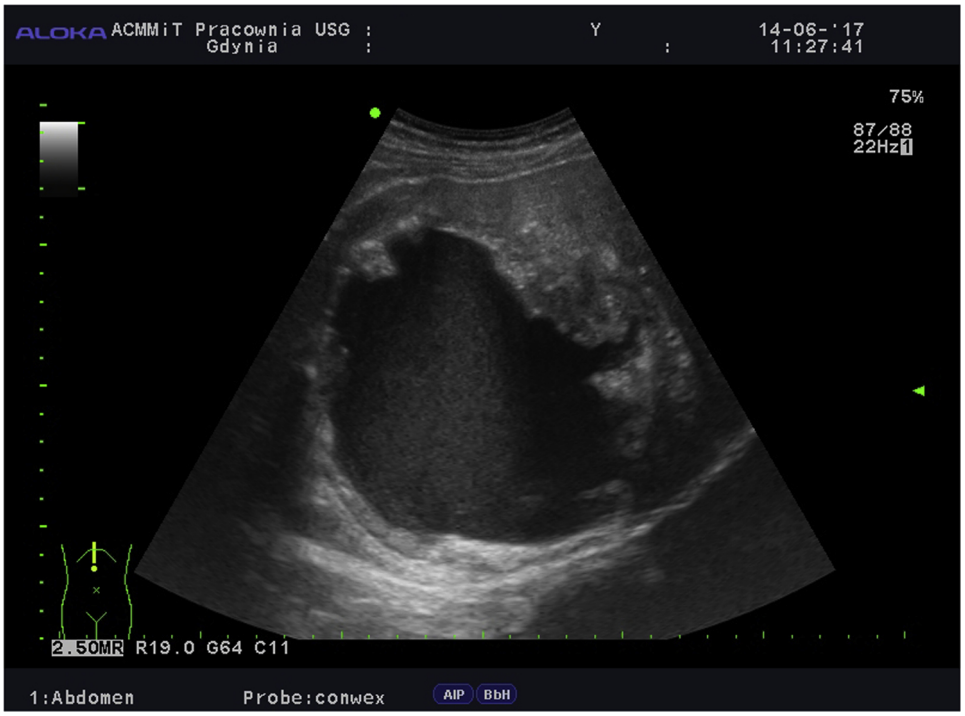

Fig. 2. Type 2 - a pseudocystic pattern.

The paper presents the results of ultrasound examinations of 58 patients with probable and certain diagnosis of AE hospitalized at UCMMiT in Gdynia between 2000 and 2016. This is the largest group in Poland, that has been analysed in terms of liver lesions on ultrasound imaging. In the study, all hepatic AE lesions were qualified as one of the 5 sonomorphological patterns. The most frequently observed pattern in this study (56.9% of cases) was the hailstorm pattern. The second most common pattern was pseudocystic pattern. This type of lesion is characterised by the largest dimensions and often occupies the entire hepatic lobe [18]. The centre of the lesion is anechoic or heterogeneously hypoechogenic. In some cases, centrally located irregular hyperechoic areas are visible. This type of lesion can be observed on the first occasion at the time of diagnosis or during the observation of hailstorm type foci in patients receiving antiparasitic drugs, when it reflects their evolution and central necrosis. Differential diagnosis of pseudocystic lesions includes liver abscesses, cystadenomas and hepatic cystic echinococcosis [18]. For comparison, in the study from Ulm (Germany), hailstorm pattern was observed in 54.1%, pseudocystic in

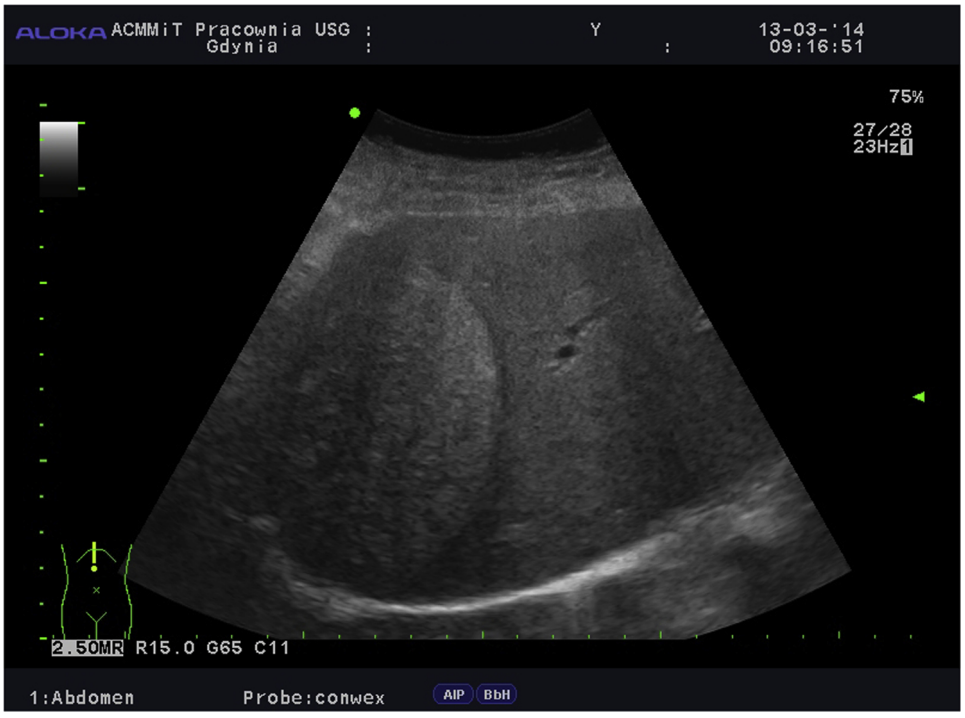

Fig. 3. Type 4 - a haemangioma-like pattern.

Table 1
Patients' characteristics and prevalence of sonomorphological patterns.

	Certain diagnosis	Probable diagnosis	Total
Number of cases	39	19	58
Age at diagnosis (range)	52.3 (6–82)	54 (30–78)	52.9 (6–82)
Females/Males	19/20	11/8	30/28
Stage at diagnosis:			
Stage I	2	2	4
Stage II	14	0	14
Stage IIIa	8	10	18
Stage IIIb	3	1	4
Stage IV	12	6	18
Prevalence of sonomorphological patterns:			
1 – hailstorm pattern	24	9	33
2 – pseudocystic pattern	13	8	21
3 – metastasis-like pattern	0	0	0
4 – haemangioma-like pattern	2	0	2
5 – ossification pattern	0	2	2

Table 2
Number of patients with sonomorphological patterns 1 and 2 in groups defined based on resectability of the lesions.

			completely resectable		
			yes	no	sum
sonomorphological pattern	1	N	10	23	33
		NC	62.5%	60.5%	61.1%
		NR	30.3%	69.7%	100%
	2	N	6	15	21
		NC	37.5%	39.5%	38.9%
		NR	28.6%	71.4%	100%
	sum	N	16	38	54
		NC	100%	100%	100%
		NR	29.6%	70.4%	100%

N - number of elements in subgroups; NR - percentage of the number relative to the sum of counts for the given row; NC - percentage of the number relative to the sum of counts for the given column.

13.5% and ossification pattern in 13% of cases. Haemangioma-like pattern occurred in 8.1% and metastasis-like pattern in 6.5% of cases. According to expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans [16], typical findings observed in 70% of cases are these corresponding to hailstorm and pseudocystic patterns. There are some studies from China [24–26] evaluating the usefulness of serological tests depending on the type of liver lesion of AE in ultrasound examination under field condition. The ultrasound classification used in those studies was based on the size, number of lesions in the liver and presence of central necrotic fluid, without considering the type of lesions. According to the classification used in our study, lesions with necrotic fluid classified as pseudocystic type (pattern 2) were observed in the above-cited studies in 23.6% [24], 32.8% [25] and in 45.1% [26] of cases, respectively.

Our study did not reveal any metastasis-like lesions, which usually pose particular diagnostic challenge. Statistical analysis did not show a

Table 4
Results of logistic regression analysis with completely resectable as the dependent variable.

variable	β	SD	z-value	p(> |z|)
intercept	−0.8229	0.3788	−2.199	0.0279
sonomorphological pattern (2)	−0.0834	0.6139	−0.136	0.8920

independent variable: sonomorphological pattern; SD - standard deviation.

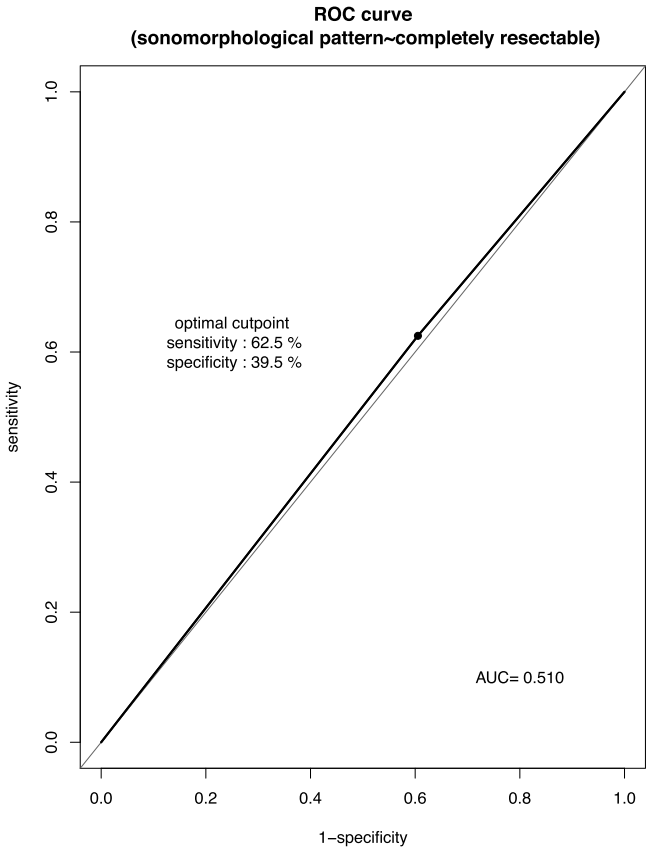

Fig. 4. ROC curve.

Table 3
Number of patients with a given "stage of disease" and "sonomorphological pattern" 1 and 2.

			stage of disease					
			I	II	IIIa	IIIb	IV	sum
sonomorphological pattern	1	N	3	7	10	1	12	33
		NC	100%	53.8%	58.8%	25%	70.6%	61.1%
		NR	9.1%	21.2%	30.3%	3%	36.4%	100%
	2	N	0	6	7	3	5	21
		NC	0%	46.2%	41.2%	75%	29.4%	38.9%
		NR	0%	28.6%	33.3%	14.3%	23.8%	100%
	sum	N	3	13	17	4	17	54
		NC	100%	100%	100%	100%	100%	100%
		NR	5.6%	24.1%	31.5%	7.4%	31.5%	100%

N - number of elements in subgroups; NR - percentage of the number relative to the sum of counts for the given row; NC - percentage of the number relative to the sum of counts for the given column.

relationship between the two most commonly observed patterns of lesions (hailstorm and pseudocystic patterns) and the clinical stage of AE. The pattern of lesions did not determine the radicality of the surgical procedure. On one hand it has been observed that radical surgical treatment was possible in patients with large pseudocystic lesions, but on the other hand smaller lesions were detected, which already at diagnosis were not eligible for radical surgical treatment due to their location (involvement of the liver hilum) or extrahepatic expansion including metastases to distant organs. Therefore, the consensus of experts on echinococcosis recommends simultaneous imaging of the chest and head at the time of diagnosing AE, in order to establish the proper management [16].

Suspicion of AE based on the ultrasound examination allows to properly plan further diagnostics, including avoiding biopsy of hepatic lesions or exploratory laparoscopy. First, serological tests should be performed and imaging diagnostics extended. In the assessment of echinococcal lesions, apart from ultrasound, other imaging methods have been applied, such as CT, MRI, magnetic resonance cholangiopancreatography and positron emission tomography using 18 F-fluorodeoxyglucose (18 F-FDG-PET-CT), which helps in differentiating between active and inactive lesions by assessing metabolic activity around parasitic lesions [27]. In recent years, there have been an increasing number of reports related to the use of contrast-enhanced ultrasound (CEUS) in assessing the extent and activity of echinococcal lesions in the liver. Vascularization patterns of echinococcosis-specific lesions of the liver are better visualized by CEUS and better correlate with 18 F-FDG-PET-CT results in comparison to CT [28]. However, the results obtained are ambiguous and so far CEUS has not been universally accepted as a diagnostic standard in hepatic AE [29]. CT allows for precise assessment of the location and extent of parasitic infiltration in the liver, along with the evaluation of the vascular system and bile ducts at the time of diagnosis [22,30,31], during the qualification for surgery, as well as in the monitoring of patients undergoing resection or receiving conservative treatment. In our study, CT turned out to be more sensitive in the assessment of extrahepatic lesions of AE, especially in adrenal glands, retroperitoneal space and pelvis.

CT is more sensitive and an excellent tool in the assessment of calcifications [6,15,22], better than ultrasound [24] or MRI, which in turn allows for a more accurate assessment of alveolar structures, which are characteristic of AE [7,22,27,32,33] The presence of calcification plays an important role in the assessment of echinococcal lesions. Their number and localization within the parasitic infiltration changes during the natural course of the disease and is also modified by pharmacological treatment. Thus their appearance allows for indirect assessment of the dynamics of the parasitic disease [6,22]. The presence of calcifications does not exclude the metabolic activity of AE lesions on 18 F-FDG-PET-CT [10,27,28]. It only suggests indirectly the duration of the inflammatory process [34].

5. Conclusions

Ultrasonography remains the first-line modality for both the diagnosis and monitoring of treatment in patients with AE. Ultrasound examination of a patient in whom echinococcosis is suspected often significantly shortens the diagnostic process. Ultrasound classification is a primarily diagnostic tool. Performing a blood serum test for echinococcosis allows for avoiding invasive diagnostic procedures, such as a biopsy of lesions or exploratory laparotomy, often performed without prior implementation of antiparasitic treatment, which may cause the spread of infection. Specific ultrasound pattern of lesions does not correlate with the clinical stage of AE or the radicality of surgical treatment.

Conflict of interests

The authors declare no conflict of interests

Financial disclosure

The authors have no funding to disclose

The author contribution

Study Design: Małgorzata Sulima, Wacław Nahorski, Wojciech Wołyniec

Data Collection: Małgorzata Sulima, Iwona Felczak-Korzybska, Beata Szostakowska

Statistical Analysis: Piotr Wąż

Data Interpretation: Małgorzata Sulima, Wacław Nahorski, Tomasz Gorycki, Katarzyna Sikorska, Wojciech Wołyniec

Manuscript Preparation: Małgorzata Sulima, Katarzyna Sikorska, Wacław Nahorski, Wojciech Wołyniec, Beata Szostakowska, Tomasz Gorycki

Literature Search: Małgorzata Sulima, Wacław Nahorski

Funds collection: n/a

References

[1] McManus DP, Zhang W, Li J, Bartley PB. Echinococcosis. Lancet 2003;362:1295–304.
[2] Vuitton DA, Zhou H, Bresson-Hadni S, Wang Q, Piarroux M, Raoul F, et al. Epidemiology of alveolar echinococcosis with particular reference to China and Europe. Parasitology 2003;127(S1):87–107.
[3] Conraths FJ, Probst C, Possenti A, Boufana B, Saulle R, La Torre G, et al. Potential risk factors associated with human alveolar echinococcosis: systematic review and meta-analysis. PLoS Negl Trop Dis 2017;11(7):e0005801.
[4] Eckert J, Deplazes P. Biological, epidemiological and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev 2004;17(1):107–35.
[5] Mihmanli M, Idiz UO, Kaya C, Demir U, Bostanci O, Omeroglu S, et al. Current status of diagnosis and treatment of hepatic echinococcosis. World J Hepatol 2016;8(28):1169–81.
[6] Graeter T, Kratzer W, Oeztuerk S, Haenle MM, Mason RA, Hillenbrand A, et al. Proposal of a computed tomography classification for hepatic alveolar echinococcosis. World J Gastroenterol 2016;22(13):3621–31.
[7] Coşkun A, Öztürk M, Karahan OI, Erdogan N, Işin S, Güleç M. Alveolar Echinococcosis of the liver: Correlative Color Doppler US, CT, and MRI Study. Acta radiol 2004;45(5):492–8.
[8] Bresson-Hadni S, Vuitton DA, Bartholomot B, Heyd B, Godart D, Meyer JP. A twenty-year history of alveolar echinococcosis: analysis of series of 117 patients from eastern France. Eur J Gastroenterol Hepatol 2000;12(3):327–36.
[9] Kern P, Bardonnet K, Renner E, Auer H, Pawlowski Z, Ammann RW, et al. European echinococcosis registry: human alveolar echinococcosis, Europe, 1982–2000. Emerg Infect Dis. 2003;9(3):343–9.
[10] Ammann RW, Hoffmann AF, Eckert J. Swiss study of chemotherapy of alveolar echinococcosis-review of a 20-year clinical research project. Schweiz Med Wochenschr 1999;129(8):323–32.
[11] Torgerson PR, Schweiger A, Deplazes P, Pohar M, Reichen J, Ammann RW, et al. Alveolar echinococcosis: from a deadly disease to a well-controlled infection. Relative survival and economic analysis in Switzerland over the last 35 years. J Hepatol 2008;49(1):72–7.
[12] Bresson-Hadni S, Koch S, Miquet JP, Gillet M, Mantion GA, Heyd B, et al. Indications and results of liver transplantation for Echinococcus alveolar infection: an overview. Langenbecks Arch Surg 2003;388:231–8.
[13] Bresson-Hadni S, Blagosklonov O, Knapp J, Grenouillet F, Sako Y, Delabrousse E, et al. Should possible recurrence of disease contraindicate liver transplantation in patients with end-stage alveolar echinococcosis? A 20-year follow-up study. Liver Transpl 2011;17(7):855–65.
[14] Patkowski W, Kotulski M, Remiszewski P, Grąt M, Zieniewicz K, Kobryń K, et al. Alveococcosis of the liver-strategy of surgical treatment with special focus on liver transplantation. Transpl Infect Dis 2016;18(5):661–6.
[15] Liu W, Delabrousse E, Blagosklonov O, Wang J, Zeng H, Jiang Y, et al. Innovation in hepatic alveolar echinococcosis imaging: best use of old tools, and necessary evaluation of new ones. Parasite 2014;21:74.
[16] Brunetti E, Kern P, Vuitton DA. Writing Panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop 2010;114(1):1–16.
[17] Myjak P, Nahorski W, Pietkiewicz H, Nickisch-Rosenegk M, Stolarczy J, Kacprzak E, et al. Molecular confirmation of human alveolar echinococcosis in Poland. Clin Infect Dis 2003;37(8):e121–5.
[18] Kratzer W, Gruener B, Kaltenbach TE, Ansari- Bitzenbergen S, Kern P, Fuchs M, et al. Proposal of an ultrasonographic classification for hepatic alveolar echinococcosis: echinococcosis multilocularis Ulm classification-ultrasound. World J Gastroenterol 2015;21(43):12392–402.
[19] Kern P, Wen H, Sato N, Vuitton DA, Gruener B, Shao Y, et al. WHO classification of alveolar echinococcosis: principles and application. Parasitol Int 2006;55(Suppl):S28–287.

[20] R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2018 Available at: https://www.R-project.org/.
[21] Nunnari G, Pinzone MR, Gruttadauria S, Celesia BM, Madeddu G, Malaguarnera G, et al. Hepatic echinococcosis: clinical and therapeutic aspects. World J Gastroenterol 2012;18(13):1448–58.
[22] Bulakçi M, Kartal MG, Yilmaz S, Yilmaz E, Yilmaz R, Şahin D, et al. Multimodality imaging in diagnosis and management of alveolar echinococcosis: an update. Diagn Interv Radiol 2016;22(3):247–56.
[23] Nahorski WL, Knap JP, Pawłowski ZS, Krawczyk M, Polański J, Stefaniak J, et al. Human Alveolar Echinococcosis in Poland: 1990-2011. PLoS Negl Trop Dis 2013;7(1):e1986.
[24] Gao CH, Wang JY, Shi F, Steverding D, Wang X, Yang YT, et al. Field evaluation of an immunochromatographic test for diagnosis of cystic and alveolar echinococcosis. Parasit Vectors 2018;11(1):311.
[25] Tiao-Ying L, Jia-Min Q, Craig PS, Ito A, Yang W, Vuitton D, et al. Review of 311 cases of alveolar echinococcosis and criteria for classification of hepatic ultrasound images. Southeast Asian J Trop Med Public Health 2004;35:213–7.
[26] Li T, Ito A, Chen X, Sako Y, Qiu J, Xiao N, et al. Specific IgG responses to recombinant antigen B and Em18 in cystic and alveolar echinococcosis in China. Clin Vaccine Immunol 2010;17(3):470–5.
[27] Azizi A, Blagosklonov O, Lounis A, Berthet L, Vuitton DA, Bresson-Hadni S, et al. Alveolar echinococcosis: correlation between hepatic MRI findings and FDG-PET/CT metabolic activity. Abdom Imaging 2015;40(1):56–63.
[28] Ehrhardt AR, Reuter S, Buck AK, Haenle MM, Mason RA, Gabelmann A, et al. Assessment of disease activity in alveolar echinococcosis : comparison of contrast-enhanced ultrasound, tree-phase helical CT and [^{18}F]fluorodeoxyglucose positron-emission tomography. Abdom Imaging 2007;32(6):730–6.
[29] Kratzer W, Reuter S, Hirschbuehl K, Ehrhardt AR, Mason RA, Haenle MM, et al. Comparison of contrast-enhanced power Doppler ultrasound (Levovist) and computed tomography in alveolar echinococcosis. Abdom Imaging 2005;30(3):286–90.
[30] Bresson-Hadni S, Vuitton DA, Bartholomot B, Heyd B, Godart D, Meyer JP, et al. A twenty-year history of alveolar echinococcosis: analysis of a series of 117 patients from eastern France. Eur J Gastroenterol Hepatol 2000;12(3):327–36.
[31] Reuter S, Nüssle K, Kolokythas O, Haug U, Rieber A, Kern P, et al. Alveolar liver echinococcosis: a comparative study of three imaging techniques. Infection 2001;29(3):119–25.
[32] Balci NC, Tunaci A, Semelka RC, Tunaci M, Ozden I, Rozanes I, et al. Hepatic alveolar echinococcosis: MRI findings. Magn Reson Imaging 2000;18(5):537–41.
[33] Becce F, Pomoni A, Uldry E, Halkic N, Yan P, Meuli R, et al. Alveolar echinococcosis of the liver: diffusion-weighted MRI findings and potential role in lesion characterisation. Eur J Radiol 2014;83(4):625–31.
[34] Reuter S, Buck A, Manfras B, Kratzer W, Seitz HM, Darge K, et al. Structured treatment interruption in patients with alveolar echinococcosis. Hepatology 2004;39(2):509–17.