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ORIGINAL PAPER

AE hepatic lesions: correlation between calcifications at CT and FDG-PET/CT metabolic activity

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Abstract

Purpose To correlate the presence of calcifications in alveolar echinococcosis (AE) hepatic lesions to the metabolic activity in 18 fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT).

Methods Our institutional review board approved this study. 61 patients (29 women, 32 men, aged from 15 to 86 years) were included in the study. Images of FDG-PET/CT were interpreted by two independent nuclear medicine physicians. AE hepatic lesions were classified as AE lesions with or without hypermetabolic activity. The presence of calcifications was assessed on unenhanced CT scans by two independent radiologists blinded with regard to the metabolic activity of the AE hepatic lesions. Every single calcification the size of which was < 3 mm and non-measurable calcifications which were forming areas with a powdery appearance were considered as microcalcifications. All other types of calcifications were reported as macrocalcifications. Statistical analysis was performed and p value < 0.05 was considered as statistically significant.

Results Microcalcifications and macrocalcifications were present at CT in 95% (58/61) AE hepatic lesions and 43% (26/61) AE hepatic lesions, respectively. Hypermetabolic activity was present at FDG-PET/CT in 93% (57/61) AE hepatic lesions. 98% (56/57) of the AE hepatic lesions presenting with hypermetabolic activity at FDG-PET/CT showed microcalcifications at CT ($p = 0.01$) when only 40% (23/57) showed macrocalcifications at CT ($p = 0.3$). 100% (23/23) of the AE hepatic lesions with hypermetabolic activity at FDG-PET/CT and macrocalcifications at CT showed also microcalcifications at CT.

Conclusions Hypermetabolic activity of AE hepatic lesions at FDG-PET/CT is strongly correlated to the presence of microcalcifications at CT, independently of the presence of macrocalcifications.

Keywords Alveolar echinococcosis · Calcifications · FDG-PET/CT · CT

Introduction

Alveolar echinococcosis (AE) is a rare parasitic disease caused by a helminthic parasite, *Echinococcus multilocularis*, only present in the northern hemisphere [1, 2]. The larval form (metacestode) develops in the liver and is responsible for a chronic infection which mimics a slow-growing tumor, although it is histopathologically an infectious, thus benign, disease. It can reach adjacent organs and disseminate to distant organs, such as the lungs or the brain. An infiltrating granulomatous and fibrous immune response in the liver is triggered by the metacestode and can lead to destruction of hepatic tissue and obstruction of vessels and bile ducts. If not treated, the disease can be fatal [1]. Early diagnosis is very important as the first line of treatment is radical surgery when the lesion can be totally excised, as recommended by the Expert Consensus of the WHO-Informal Working Group on Echinococcosis (WHO-IWGE) [3]. For inoperable patients, a long-term anti-infective treatment is established with either mebendazole or, more often now, albendazole, two benzimidazole compounds [3]. Even if they have no parasiticidal effect demonstrated in vitro and in

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experimental animals, these parasitostatic drugs may achieve complete inactivation of the lesions after years of treatment in some patients, as Ammann et al. showed no evidence of AE progression within a median of 70 months [4]; this was observed even in patients with advanced and metastatic lesions [5, 6]. Diagnosis of AE is based on imaging (possible case), suspected on the association of characteristic imaging features and specific serum antibodies to *E. multilocularis* antigens in blood tests (probable case), and assessed by histopathologic findings and/or parasite nucleic acids identification in clinical samples (confirmed case) [3].

The main characteristic pattern of an AE hepatic lesion is the presence of microcysts and calcifications, with no evidence of vascularization inside the lesion. Ultrasound (US) is commonly accepted as the first choice of liver imaging as it is non-invasive, non-irradiant, inexpensive, and available in endemic regions of AE, including for mass screening [7, 8]. Nevertheless, as microcysts and microcalcifications are not always visible by US, computed tomography (CT) and magnetic resonance imaging (MRI) play a major role in AE evaluation. CT is the best imaging tool to affirm the presence and the type of calcifications, as well as the presence or absence of central necrosis of the lesions [7, 9]; it remains more available in most of endemic areas than MRI which is a key exam to disclose the microcysts, pathognomonic of AE, as small nodules with strong hypersignal on T2-weighted images [7] and it is a non-irradiant technique; however, MRI poorly assesses calcifications.

Assessment of the viability of the parasitic lesions is crucial to decide the therapeutic strategy and anti-infective drug withdrawal after years of treatment. A surrogate marker is the 'metabolic activity' of the lesions, best evaluated using fluorodeoxyglucose (FDG)-positron emission tomography (PET) usually combined with computed tomography (PET/CT) which shows an increased uptake of FDG by the periparasitic inflammatory reaction [10, 11]. However, FDG-PET/CT is the most irradiant and expensive technique, rarely available in endemic areas. Azizi et al. [12] demonstrated that the presence of microcysts at MRI was statistically significantly associated with metabolic activity of AE hepatic lesion, as determined by FDG-PET/CT, but MRI is also a quite expensive imaging modality, less available than CT or ultrasound in endemic areas. Until now, US and CT have not been reported to provide any evidence for parasite viability. Calcifications in AE lesions have long been considered as evidence for lesion degeneration as in several parasitic diseases [13]. However, physicians in charge of the care management of AE in reference centers had to recognize that, for the follow-up of patients, calcifications and their extent (at least as judged quantitatively and interpreted as signs of degeneration of the parasitic lesions) were poor markers of lesion progression or regression, and useless for albendazole treatment withdrawal [3]. In 2016, a classification of the different types of calcifications which may be observed in AE lesions has been introduced in a very interesting article by Graeter et al. [14] (EMUC-CT classification), with six calcification patterns including the type B, i.e., "feathery calcifications", quite similar to the microcalcifications as defined in our study, but, to our knowledge, neither this study nor any other study was intend to define a possible pathological or clinical meaning of these different types. Based on the diagnosis and follow-up of a number of patients who had all imaging modalities in our AE Reference Centre (US, CT, MRI and FDG-PET/CT), and of our previous work on the correlation between the presence of microcysts at MRI and increased metabolic activity at FDG-PET/CT, our clinical observations led us to consider a possible association of microcalcifications at CT and hypermetabolic activity at FDG-PET/CT, thus a complete change of paradigm, that took some types of calcifications as evidence for metabolic activity. If confirmed, such findings would be especially of help for those patients who live far from fully equipped radiological settings and would provide an additional tool to the clinicians in charge of the care management of AE, whatever the setting.

The aim of our work was thus to test this hypothesis on a single-center study to set the basis for complementary studies that would involve other reference centers with patients from other endemic areas. We took advantage of the French AE registry (FrancEchino) coordinated by our National Reference Centre [15] to recruit patients with a follow-up in this Centre and study the correlation between presence/absence of 2 types of calcifications, i.e., microcalcifications and macrocalcifications, and increased metabolic activity at FDG-PET/CT.

Methods

Patients

Our institutional review board approved this study. Patient consent was obtained from each patient at his/her inclusion in the AE Registry 'FrancEchino' [15]. All cases included in the study at least fulfilled the definition of 'probable cases', as defined by the Expert Consensus of the WHO-IWGE, i.e., the association of a positive serology for AE, the presence of lesions compatible with AE hepatic lesions on imaging, and compatible epidemiological context, which is the international accepted basis to initiate anti-infective treatment after the decision of a multidisciplinary team consultation [1, 3]. To be included in the study, patients should have undergone an FDG-PET/CT before receiving any anti-infective drug to treat the disease. Exclusion criteria were events that could impair metabolic activity as assessed by FDG-PET/CT, such as immunosuppression, recent surgery (less than 3 months

before FDG-PET/CT acquisition), and artifacts that might interfere with the identification of microcalcifications at CT.

Within those 132 patients with AE hepatic lesions with a diagnosis and follow-up in our Centre from December 2008 to April 2018, 67 patients who underwent an FDG-PET/CT before initiation of the anti-infective therapy were selected (31 women, 36 men, aged from 15 to 89 years). Six patients were secondarily excluded: three patients were immunosuppressed; 1 patient underwent hepatic surgery before FDG-PET/CT and 2 patients because CT images were of too poor quality to highlight microcalcifications. FDG-PET/CT from 61 patients (29 women, 32 men, aged from 15 to 86 years) was thus included and analyzed in the study.

Techniques

FDG-PET/CT scanners (Biograph, Siemens, Erlangen, Germany and Discovery 690 VCT, GE Medical Systems, Milwaukee, WI, USA) were performed only on patients with normal blood level of glucose (< 150–200 mg/dL). All patients fasted at least 6 h before performing the exam. First, a whole-body unenhanced CT was performed, then a second acquisition was performed 1 h after an intravenous injection of a 4 MBq/kg dose of FDG by FDG-PET/CT, and one additional acquisition was performed 3 h after the 18 FDG injection, as recommended by Caoduro et al. [16]. The scanning parameters were 130 kV, 90 mAs, pitch of 1.5 and slices of 5 mm thickness. Images of fused FDG-PET/CT were interpreted by two independent nuclear medicine physicians who were not aware of the various types of calcifications and their possible meaning. AE hepatic lesions were classified as AE lesions with hypermetabolic activity if the maximum standardized uptake value (SUVmax) at the site of the AE lesion was higher than the SUVmax on surrounding tissue on one or both of the two FDG-PET/CT acquisitions [12] and as AE lesions without hypermetabolic activity if not. The presence of calcifications was assessed on unenhanced CT scans by two independent radiologists, specialized in abdominal imaging (19 and 6 years' experience) blinded with regard to the metabolic activity of the AE hepatic lesions. Every single calcification the size of which was < 3 mm and non-measurable calcifications which were forming areas with a powdery appearance (Fig. 1) were considered as microcalcifications on unenhanced CT scans. All other types of calcifications were reported as macrocalcifications.

Statistical analysis was performed with Excel® 2016. To determine possible relationship between two variables, a Fisher's exact test was used. P value < 0.05 was considered as statistically significant.

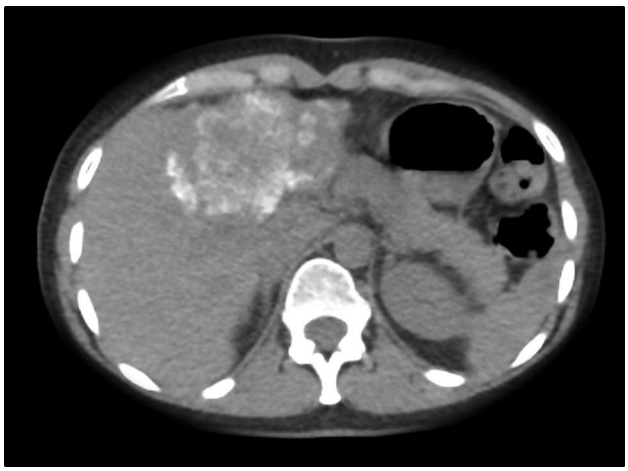

Fig. 1 Unenhanced CT scan shows a large AE hepatic lesion with non-mesureable microcalcifications forming an area with a powdery appearance

Results

Main results are presented in Tables 1, 2 and 3.

Table 1 Correlation between the metabolic activity of AE hepatic lesions at FDG-PET/CT and the presence of microcalcifications at CT

	Microcalcifications ($n=58$)	No microcalcification ($n=3$)
Hypermetabolic activity ($n=57$)	56 (98%/96%)[a]	1 (2%/33%)[a]
No hypermetabolic activity ($n=4$)	2 (50%/4%)[a]	2 (50%/67%)[a]

Note that 98% (56/57) of the AE hepatic lesions with hypermetabolic activity at FDG-PET/CT showed microcalcifications at CT ($p=0.01$)

[a]The first % corresponds to the rows and the second % corresponds to the columns

Table 2 Correlation between the metabolic activity of AE hepatic lesions at FDG-PET/CT and the presence of macrocalcifications at CT

	Macrocalcifications ($n=26$)	No macrocalcification ($n=35$)
Hypermetabolic activity ($n=57$)	23 (40%/88%)[a]	34 (60%/97%)[a]
No hypermetabolic activity ($n=4$)	3 (75%/22%)[a]	1 (25%/3%)[a]

Only 40% (23/57) of the AE hepatic lesions with hypermetabolic activity at FDG-PET/CT showed macrocalcifications at CT ($p=0.3$)

[a]The first % corresponds to the rows and the second % corresponds to the columns

Table 3 Correlation between the presence of microcalcifications at CT in AE hepatic lesions and the association of macrocalcifications at CT and no hypermetabolic activity at FDG-PET/CT

	Macrocalcifications + hypermetabolic activity ($n=23$)	Macrocalcifications + No hypermetabolic activity ($n=3$)
Microcalcifications ($n=24$)	23 (96%/100%)[a]	1 (4%/33%)[a]
No microcalcification ($n=2$)	0 (0%/0%)[a]	2 (100%/67%)[a]

Note that 100% (23/23) of the AE lesions hepatic with macrocalcifications at CT and hypermetabolic activity at FDG-PET/CT showed also microcalcifications at CT

[a]The first % corresponds to the rows and the second % corresponds to the columns

Microcalcifications and macrocalcifications were present at CT in 95% (58/61) AE hepatic lesions and 43% (26/61) AE hepatic lesions, respectively.

Hypermetabolic activity was present at FDG-PET/CT in 93% (57/61) AE hepatic lesions.

98% (56/57) of the AE hepatic lesions presenting with hypermetabolic activity at FDG-PET/CT showed microcalcifications at CT ($P=0.01$) (Fig. 2) and only 40% (23/57) showed macrocalcifications at CT ($P=0.3$) (Fig. 3).

100% (23/23) of the AE hepatic lesions with hypermetabolic activity at FDG-PET/CT and macrocalcifications at CT showed also microcalcifications at CT.

Predictive positive value of microcalcifications at CT for the presence of hypermetabolic activity at FDG-PET/CT was 98%.

Discussion

Our study has revealed that in AE hepatic lesions microcalcifications and macrocalcifications should be distinguished because of their opposite meaning.

Actually, considering our results microcalcifications in AE hepatic lesions at CT are statistically associated with hypermetabolic activity at FDG-PET/CT, whereas macrocalcifications are not. Of course, some AE hepatic lesions with macrocalcifications showed hypermetabolic activity at FDG-PET/CT but it was always in case of the associated presence of microcalcifications.

These results about macrocalcifications did not surprised us, even if no previous report exists on this subject, because macrocalcifications are commonly accepted as sequelae of parasitic liver damage [17]. This is not the case for microcalcifications which are known in other diseases (breast cancer for instance) to be associated with progressive lesions.

In our study, the hypermetabolic activity associated with AE hepatic lesions and the presence of microcalcifications were mostly at the periphery of the lesions. However, we know that in cystic echinococcosis (CE) macrophagic reaction takes place in the liver all around the CE hepatic lesion [18]. Moreover, this reaction is associated with the expression of osteopontin. O'Regan et al. 2000 [19] showed that tissue repair can also result in dystrophic calcifications and many granulomatous diseases culminate in calcified granuloma. Although the mechanism remains unknown, osteopontin seems to play a role in the regulation of this calcification process. We can consequently imagine that microcalcifications are the result of macrophagic reaction and osteopontin expression in the liver all around the lesion.

Interestingly, we found in some patients in our series that microcalcifications were changing, but sometimes in a delayed manner, with the disappearance of PET-CT activity. These results have exceeded the objective of our actual work but will be the subject of a future article.

Surgery, when feasible, is the treatment of choice for hepatic AE patients. When this is the case, CT must be performed to provide the number, location and size of the AE hepatic lesions and evaluate vascular and biliary involvement. At CT, the analysis of the presence of calcifications within the AE lesions is easy, provided that an acquisition without contrast is performed. Also, since hypermetabolic activity is never noted in the absence of microcalcifications, an important consequence of our results is that highly irradiating and very expensive FDG-PET/CT could be substituted by the unenhanced CT for the same result. Of course, MRI is even less irradiating than CT but with this imaging tool the problem of calcification analysis remains important. In 2018, Jan Muller et al. [20] had analyzed the performance of MRI using Susceptibility Weighted Imaging (SWI) sequences for the detection of calcifications in AE hepatic lesions. According to this paper, macrocalcifications can be easily be detected but nothing is said about microcalcifications. Indeed, because the minimum size of the calcifications detectable at MRI is not known to date the detection of microcalcifications is still a question.

Like every study, our work has some limitations. First, our study included few AE hepatic lesions with no hypermetabolic activity. Indeed, at the beginning of the disease, without treatment, patients often have active lesions and consequently microcalcifications. Secondly, the evolution of these microcalcifications has not been studied yet. We can imagine that they can be aggregated into macrocalcifications or disappear. Thirdly, we must keep in mind that metabolic activity at FDG-PET/CT does not reflect parasitic activity

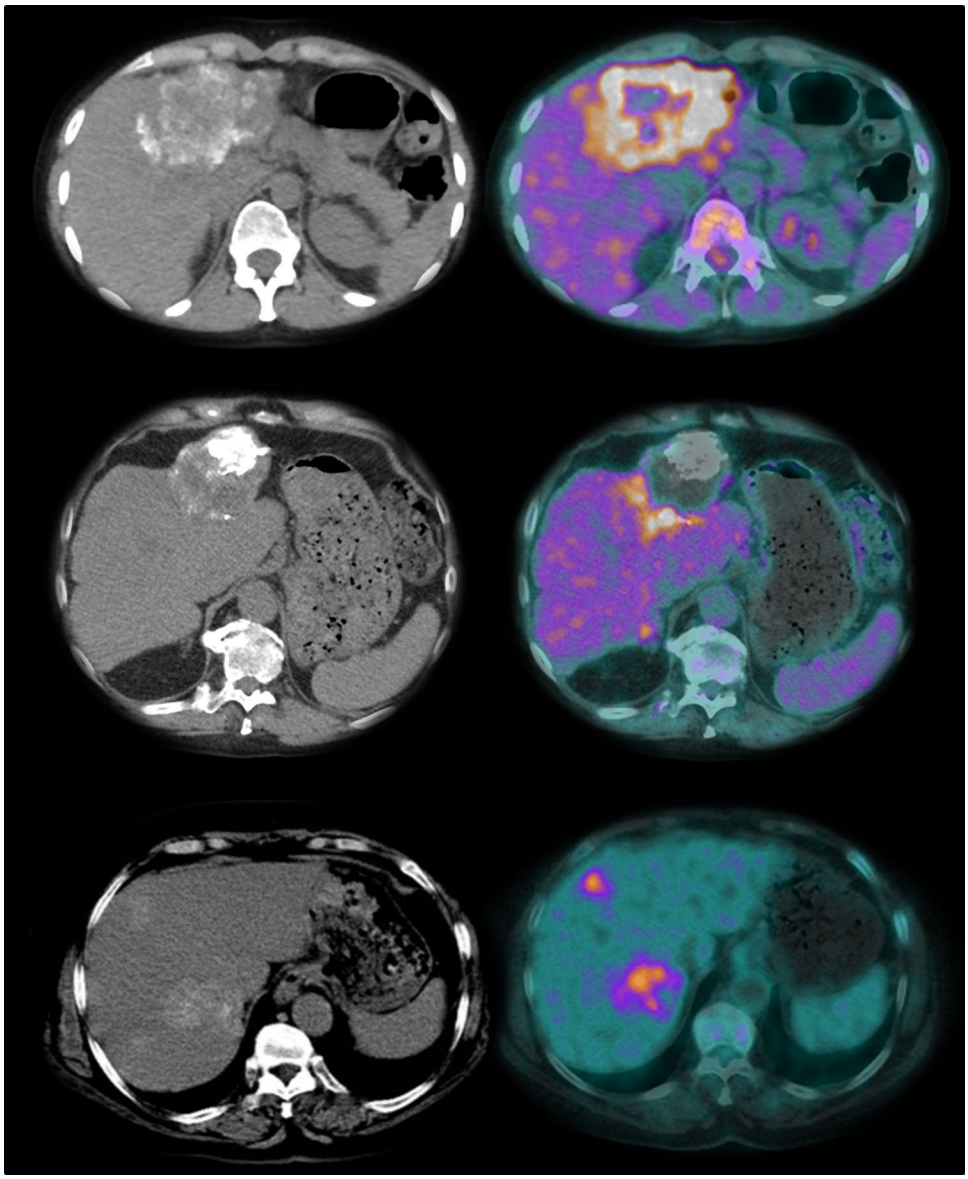

Fig. 2 Comparison of unenhanced CT scans (left) and FDG-PET/CT scans (right) in 3 patients with AE liver lesions. Note the strong association between the presence of microcalcifications at CT and hypermetabolic activity of 3 hepatic lesions at FDG-PET/CT whatever was the presence of macrocalcifications

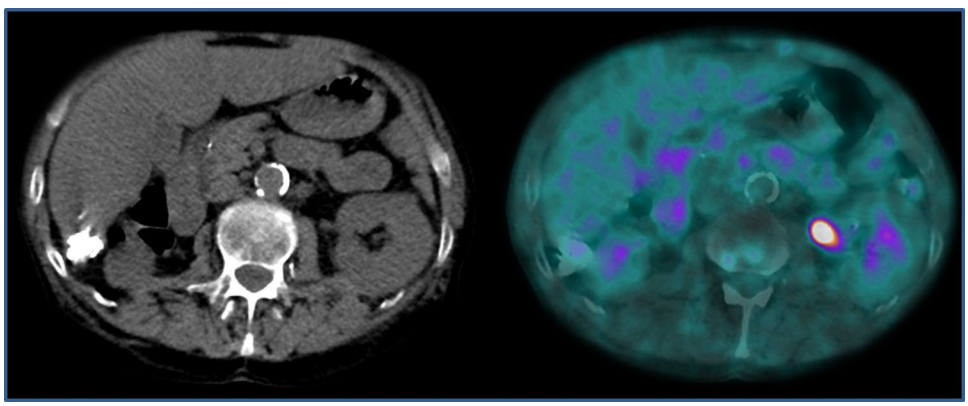

Fig. 3 AE hepatic lesion with typical macrocalcification at CT (left) and no hypermetabolic activity at FDG-PET/CT (right)

but even more probably the inflammatory reaction of the surrounding liver.

In summary, our study showed that a hypermetabolic activity of AE hepatic lesions at FDG-PET/CT is strongly correlated to the presence of microcalcifications at CT, independently of the presence of macrocalcifications. The consequence is that if our results were to be confirmed, highly irradiating and very expensive FDG-PET/CT could be substituted by the unenhanced CT, for the same result.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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