



Perirenal Edema as a potential hint towards primary hypertension—Preliminary findings in MRI breast cancer staging

Clemens G. Kaiser^{a,*}, Pascal Baltzer^c, Anna K. Kaiser^b, Julia Knautd^a, Thomas Henzler^a, Werner A. Kaiser^d, Matthias Dietzel^{e,f}

^a Institute of Clinical Radiology and Nuclear Medicine, University Medical Centre Mannheim, Medical Faculty Mannheim-University of Heidelberg, Germany

^b School of Social Science, University of Mannheim, Germany

^c Department of Biomedical imaging and image-guided therapy, Medical University Vienna, Austria

^d Institute of Diagnostic and Interventional Radiology I, Friedrich-Schiller-University Hospital Jena, Germany

^e Institute of Diagnostic Radiology, University of Erlangen-Nuremberg, Erlangen, Germany

^f Department of Neuroradiology, Friedrich-Alexander-University Hospital Erlangen-Nürnberg, Germany

ARTICLE INFO

Article history:

Received 24 May 2016

Received in revised form 25 May 2016

Accepted 26 May 2016

Available online 10 June 2016

ABSTRACT

Purpose: To demonstrate our primary findings, indicating perirenal edema as a first imaging sign towards primary hypertension.

Methods: Out of 3190 consecutive MR-Mammography (MRM) examinations, 777 were performed with an additional body array coil. Incidentally, “perirenal edema” could be linked to a patient history of hypertension. We therefore specifically further observed the correlation.

Results: Of 777 patients 86 (11%) patients showed the perirenal edema sign (PES). Upon inquiry all of these cases (100%) confirmed a past or present history of hypertensive disease (i.e. blood pressure above 140/90 and/or anti-hypertensive treatment).

Conclusion: Our preliminary results strongly indicate a strong correlation between perirenal edema and primary hypertension.

© 2016 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

MR-Mammography (MRM) or dynamic enhanced Breast-MRI (DCE-MRI) has evolved to be increasingly important over the last 20 years. However, the main breast imaging societies are hesitant to support MRM as a screening tool [1]. Guidelines of the American college of radiology (ACR), European Society of Breast Imaging (EUSOBI) as well as European Society of Breast Cancer Specialists (EUSOMA) list among the specific indications for breast MRI mainly patients after operation or radiation of breast cancer, pre-operative staging, cancer of unknown primary (CUP Syndrome) and a genetic disposition (e.g. BRCA1 or 2) [2–5].

In our university hospital a body array coil is placed onto the back of patients in order to cover the upper half of the body from the neck to the upper lumbar region (Fig. 1) in case of a history of previous cancer or the new detection of a malignant lesion in



Fig. 1. Breast and half-body examination in one exam. The body array coil is placed on the back of the patient while being positioned on the breast coil for the examination in a supine position.

* Corresponding author at: University Medical Centre Mannheim, Medical Faculty Mannheim—University of Heidelberg, Theodor-Kutzer-Ufer 1-3, D-68167 Mannheim, Germany.

E-mail address: clemens.kaiser@umm.de (C.G. Kaiser).

order to simultaneously gather staging information. By an incidental finding, some patients would show diffuse perirenal edema around both kidneys in those T2-weighted TSE images, acquired (Fig. 2). Upon inquiry, patients confirmed history of hypertension. These incidental findings initiated a specific observation with the aim to address the question as to how often this new sign is associated with a hypertensive anamnesis and possibly to explain the pathophysiological background of the finding.

2. Material and methods

2.1. Patient collective

Between July 2010 and December 2012 a consecutive total of 1975 MRM examinations were performed with indications for MRM as described above. All patients gave their written consent to this IRB approved study.

376 of these examinations were performed including the additional positioning of a body array coil onto the back of the patient lying in a prone position for their breast exam (Fig. 1). The main indication for this procedure was originally the search for metas-

tases in the upper spine, lung and liver for staging purposes. By chance, perirenal edema were discovered, and defined as high signal fluid spatters and rims surrounding the renal capsule in the perirenal fatty tissue around both kidneys (Fig. 2) in a thickness of 0.3–3.0 cm.

2.2. Image acquisition and interpretation

All MRM exams were performed with a 1.5 Tesla-MR Scanner (Siemens Avanto) using breast protocols as described in other publications [6]. The body array coil along with the application of an additional T2 weighted coronal TSE HASTE sequence in a slice thickness of 5 mm covered the area from the neck to the upper lumbar region, depending on the patients size (Table 1). The T2-weighted HASTE-sequence was performed in a repetition Time (TR) of 1100 ms, an echo Time (TE) of 118 ms, a field-of-View (FOV) of 500 mm in a parallel-imaging technique (PAT, GRAPPA) with a PAT-factor of 2 in 46 coronal slices, resulting in a voxel size of $1.4 \times 1.1 \times 5 \text{ mm}^3$. The total acquisition time of this “half-body”-sequence was 51 s (Table 1). This protocol has been previously described in [18,19]. MRI examinations were evaluated by two

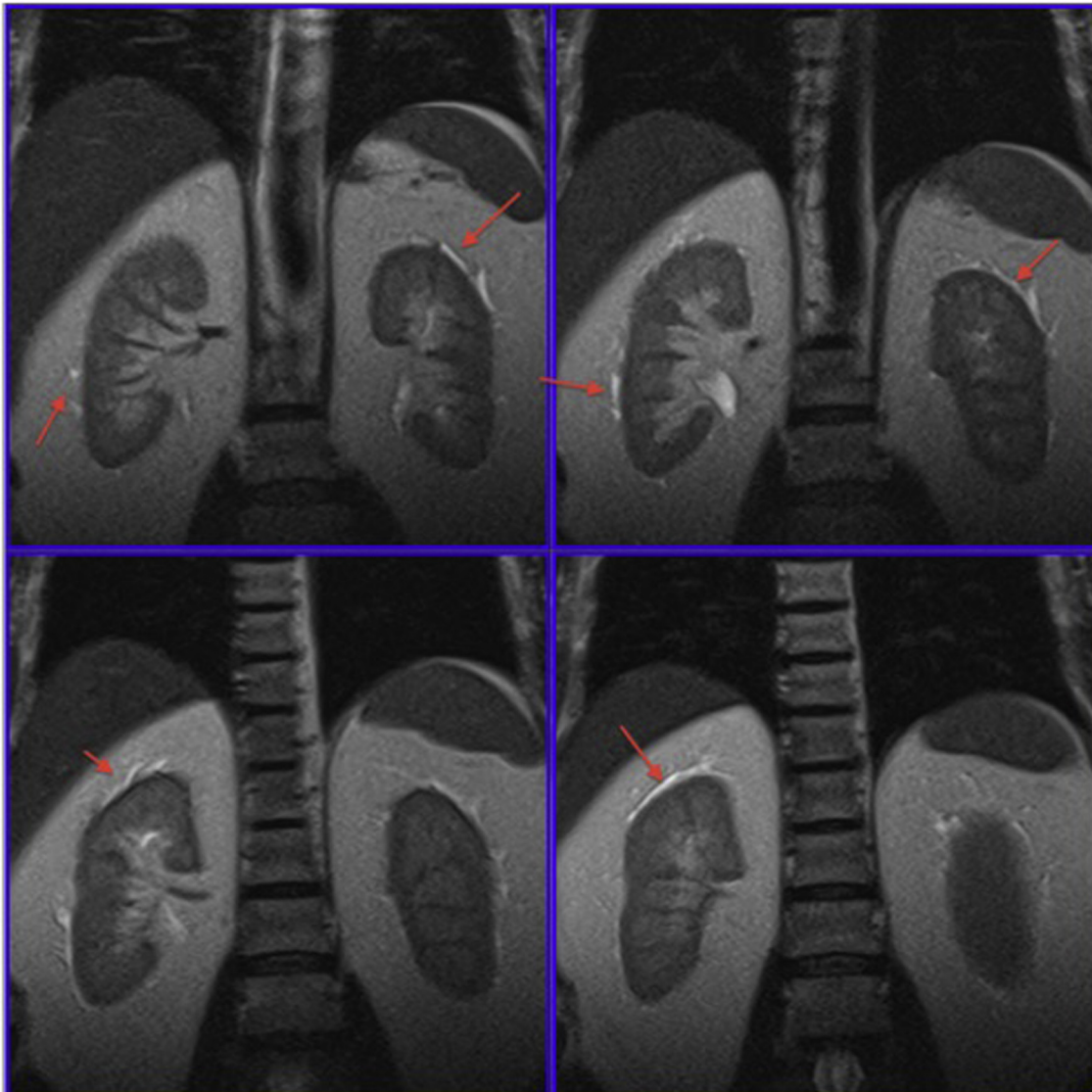


Fig. 2. 63y patient with a history of breast cancer. In the additionally acquired T2-TSE HASTE sequence for staging purposes images display the PES (spotty, T2-TSE hyperintense stains around both kidneys) without any signs of renal parenchyma destruction or renal affection.

Table 1

Examination protocol of the T2 weighted TSE HASTE sequence, which was applied whenever the patient had a history of previous breast cancer, surgery or present breast cancer. The primary intention was the search for osseous metastasis in arms, upper spine, lung and liver. The measurement time of this sequence is 51 s.

Sequence	T2 TSE HASTE
Weighting	T2
Puls sequence	TSE
Orientation	cor
TR (ms)	1100
TE (ms)	118
Flip angle (°)	150
Slice thickness (mm)	5
Gap (mm)	0
Field of view (mm)	500
No. of slices	46
Voxel	1,4 × 1,1 × 5 = 7,7 mm ³

experienced radiologists (one with an experience of >15.000 cases, the other with an experience of >1.000 cases in MRI). For a positive PES, both readers had to agree on its presence. All patients showing this sign were asked about their hypertensive history and other diseases directly after the MR-examination.

3. Results

Of 777 patients, examined with the body array coil, 86 (11%) patients showed the “perirenal edema sign”. **All of these patients** (100%) confirmed a present of a previous or present hypertensive disease history (i.e. high blood pressure and/or antihypertensive treatment). No patient reported deviant kidney disease in the previous history (e.g. kidney cancer or nephritis or any surgery of the kidneys). A simultaneous urinary tract infection could be excluded. There was no false positive case, resulting in a PPV of 100%.

4. Discussion

To this day, there have been numerous publications about whole body imaging in patients with breast cancer or other oncological entities, mainly with the purpose of improved staging [7].

However, the PES has not yet been reported in medical literature, especially concerning evidence of a histo-pathological correlation with this new diagnostic sign.

This seems somewhat surprising, since the number of whole-body MR-examinations has markedly increased in the last decades. We are assuming, that most authors were primarily looking for metastases.

The astonishing, however, preliminary result of this study was the fact that there was no patient showing this sign without hypertensive correlation (no “false positive” case). It can therefore be assumed, that there is a strong correlation between this sign and hypertension. However, we have so far not evaluated false negative or true negative cases, because only patients clearly showing this sign have been correlated with the gold standard “past or present high blood pressure”.

A possible explanation for this new sign might be the effects of Angiotensin II as an inflammatory mediator [8–10]. Angiotensin II is produced locally in inflamed vessels and induces the synthesis and secretion of interleukin-6, a cytokine that induces the synthesis of angiotensinogen in the liver through a janus kinase (JAK)/signal transducer and activator of transcription (STAT)-3 pathway. Enhanced angiotensinogen production, in turn, supplies more substrate to the activated vascular RAS, where locally produced Angiotensin II synergizes with oxidized lipid to perpetuate atherosclerotic vascular inflammation [11]. Additionally, we know

that blockage of the Angiotensinogen Receptor reduces a row of inflammatory markers (CRP, TNF- α , IL-6) [12].

As to what extent Angiotensin II could be responsible for inflammatory processes strictly outside the renal capsule, however, remains the effort of future studies.

Despite the role of Angiotensin II as the critical part in the Renin-Angiotensinogen-Angiotensin-System (RAAS) we know, that it is produced following hypotension instead of hypertensive changes, we saw in our patients.

According to Johnson et al. and Pautetto et al. [13,14], interestingly the question remains as to whether hypertension is preceded by inflammation or inflammation by hypertension.

On the one hand, hypertension acts as a major determinant of endothelial dysfunction and vascular damage, promoting inflammatory activation of endothelial cells, recruitment of inflammatory cells in the arterial wall and activation of vascular resident elements [14].

On the other hand, vascular and inflammatory tubulointerstitial structural changes occurring in the kidneys have been related to the pathogenesis of essential hypertension [13]. Evidence obtained from animal models of spontaneously developed hypertension showed that an inflammatory infiltration of the kidney by macrophages and lymphocytes.

The renal tubule-interstitial inflammation is observed at a young age in the animals and seems to precede the onset of hypertension [15]. Recent studies in this animal model of hypertension showed that the recruitment of immune cells in the kidney can be prevented by blocking NF- κ B activation. This phenomenon is accompanied by a complete abrogation of hypertension development in spontaneously hypertensive rats (SHR) [16].

Pautetto et al. assume, that even if the factors inducing the inflammatory response in the kidney are not defined, the infiltration of immune cells and the oxidative stress in the renal interstitium can play a pathogenic role in the future development of hypertension. In case this phenomenon has some relevance in humans it could be hypothesized that the low-grade inflammatory status preceding hypertension development could mirror a silent inflammatory damage occurring in the kidney [14].

It is important to notice, that all our “true-positive” patients did not reveal any other morphologic signs of hypertension, as far as detectable on the acquired T2-TSE-HASTE images, such as for example adrenal tumors or vascular changes. Parenchymal renal defects, i.e. purely renal causes, such as nephritis as cause for the PES could also not be found in any of the cases.

Since this study has only offered a glimpse on how many cases of perirenal edema could be correlated to hypertension, further studies need to evaluate how many cases of hypertension can be correlated with the sign.

As a limitation to our study, it has to be critically added, that in our study the patients information about their hypertensive history was only verified in direct interaction with the patients, i.e. no additional measurement of the present blood pressure during or after the MRM examination was performed. Detailed information about the extend of hypertension as well as theoretical relevance for therapeutic consequences in hypertensive treatment are still a matter of the future scientific evaluation.

However, the PES may be the first diagnostic typical or maybe even specific sign of primary hypertension, so far having been considered invisible to MRI-imaging. If these findings can be confirmed in further studies, the PES could be a strong, fast and robust indicator with a high positive predictive value for primary hypertension.

Conflict of interests

There are no conflicts of interest.

Acknowledgment

Published in part (lecture and abstract) during the “6th International Congress on MR-Mammography” in Jena, Germany (27.–29. September 2012) [17].

References

- [1] C.G. Kaiser, C. Reich, M. Dietzel, et al., DCE-MRI of the breast in a stand-alone setting outside a complementary strategy – results of the TK-study, *Eur. Radiol.* 25 (6) (2015) 1793–1800.
- [2] E.S. Burnside, E.A. Sickles, L.W. Bassett, et al., The ACR BI-RADS® experience: learning from history, *J. Am. Coll. Radiol.* 6 (12) (2009) 851–860.
- [3] S.D. Edwards, J.A. Lipson, D.M. Ikeda, J.M. Lee, Updates and revisions to the BI-RADS magnetic resonance imaging lexicon, *Magn. Reson. Imaging Clin. N. Am.* 21 (3) (2013) 483–493.
- [4] R.M. Mann, C.K. Kuhl, K. Kinkel, C. Boetes, Breast MRI: guidelines from the european society of Breast imaging, *Eur. Radiol.* 18 (7) (2008) 1307–1318.
- [5] F. Sardaneli, C. Boetes, B. Borisch, et al., Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group, *Eur. J. Cancer Oxf. Engl.* 46 (8) (2010) 1296–1316, 1990.
- [6] C. Kuhl, The current status of breast MR imaging Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice, *Radiology* 244 (2) (2007) 356–378.
- [7] G.P. Schmidt, A. Baur-Melnyk, R. Tiling, et al., Comparison of high resolution whole-body MRI using parallel imaging and PET-CT: First experiences with a 32-channel MRI system, *Radiologe* 44 (9) (2004) 889–898.
- [8] E.S. Androulakis, D. Tousoulis, N. Papageorgiou, et al., Essential hypertension: is there a role for inflammatory mechanisms? *Cardiol. Rev.* 17 (5) (2009) 216–221.
- [9] R. Toni, A. Malaguti, S. Castorina, E. Roti, R.M. Lechan, New paradigms in neuroendocrinology: relationships between obesity, systemic inflammation and the neuroendocrine system, *J. Endocrinol. Invest.* 27 (2) (2004) 182–186.
- [10] M.I. Phillips, S. Kagiya, Angiotensin II as a pro-inflammatory mediator, *Curr. Opin. Investig. Drugs Lond. Engl.* 3 (4) (2002) 569–577, 2000.
- [11] A.R. Brasier, A. Recinos 3rd, M.S. Eledrisi, Vascular inflammation and the renin-angiotensin system, *Arterioscler. Thromb. Vasc. Biol.* 22 (8) (2002) 1257–1266.
- [12] B. López, R. Querejeta, N. Varo, et al., Usefulness of serum carboxy-terminal propeptide of procollagen type I in assessment of the cardioreparative ability of antihypertensive treatment in hypertensive patients, *Circulation* 104 (3) (2001) 286–291.
- [13] R.J. Johnson, B. Rodriguez-Iturbe, D.-H. Kang, D.I. Feig, J. Herrera-Acosta, A unifying pathway for essential hypertension, *Am. J. Hypertens.* 18 (3) (2005) 431–440.
- [14] P. Pauletto, M. Rattazzi, Inflammation and hypertension: the search for a link, *Nephrol. Dial. Transplant.* 21 (4) (2006) 850–853.
- [15] B. Rodríguez-Iturbe, Y. Quiroz, A. Ferrebuz, G. Parra, N.D. Vaziri, Evolution of renal interstitial inflammation and NF-kappaB activation in spontaneously hypertensive rats, *Am. J. Nephrol.* 24 (6) (2004) 587–594.
- [16] B. Rodríguez-Iturbe, A. Ferrebuz, V. Vanegas, et al., Early and sustained inhibition of nuclear factor-kappaB prevents hypertension in spontaneously hypertensive rats, *J. Pharmacol. Exp. Ther.* 315 (1) (2005) 51–57.
- [17] C.G. Kaiser, C. Reich, W.A. Kaiser, The 'perirenal edema sign' as a hint towards hypertension—preliminary observations on cofindings in MRI breast cancer staging, *Eur. J. Radiol.* 81 (Suppl. 1) (2012) S74–75.
- [18] M. Dietzel, R. Zoubi, H.P. Burmeister, I.B. Runnebaum, W.A. Kaiser, P.A.T. Baltzer, Combined staging at one stop using MR mammography: evaluation of an extended protocol to screen for distant metastasis in primary breast cancer – initial results and diagnostic accuracy in a prospective study, *Rofo* 184 (2012) 618–623.
- [19] P.A.T. Baltzer, M. Dietzel, H.P. Burmeister, R. Zoubi, M. Gajda, O. Camara, W.A. Kaiser, Application of MR mammography beyond local staging: is there a potential to accurately assess axillary lymph nodes? evaluation of an extended protocol in an initial prospective study, *AJR Am. J. Roentgenol.* 196 (2011) W641–W647.