Research paper

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Presentation of extramedullary myeloma manifestations on B-mode (B-US) and contrast-enhanced ultrasound (CEUS)

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Abstract

Aim: In patients with multiple myeloma, extramedullary myeloma manifestations can occur alongside bone marrow infiltration and osseous involvement. The aim of this study was to describe extramedullary myeloma manifestations using B-mode ultrasound and contrast-enhanced ultrasound. **Material and methods:** Between February 2006 and 2021, a total of 21 patients with multiple myeloma and histologically or clinically proven extramedullary myeloma manifestations (n = 24) were included. All patients underwent B-mode ultrasound and contrast-enhanced ultrasound of extramedullary myeloma manifestations. B-mode ultrasound patterns of location, size border characteristics, and echogenicity (hypoechoic/isoechoic or hyperechoic) as well as contrast-enhanced ultrasound enhancement (hyper-, iso-, or hypoenhancement) were analyzed. **Results:** In most cases, extramedullary myeloma manifestations were located in the chest wall (n = 11; 45.8%). In all 24 cases, extramedullary myeloma manifestations were hypoechoic on B-mode ultrasound. N = 16 (66.6%) of extramedullary myeloma manifestations had smooth and n = 8 (33.3%) had irregular borders. The mean lesion size was 5.4 cm. On contrast-enhanced ultrasound, extramedullary myeloma manifestations presented arterial hyper- (n = 20; 83.3%) or isoenhancement (n = 4; 16.7%) followed by parenchymal iso- (n = 1; 4.2%) or hypoenhancement (n = 23; 95.8%). In molecular genetic analysis, every patient with reliable FISH results tested positive for at least one aberration considered "high-risk". **Conclusion:** Extramedullary myeloma manifestations were typically hypoechoic on B-mode ultrasound. On contrast-enhanced ultrasound, they presented characteristic arterial hyperenhancement followed by parenchymal washout. All patients studied for the genetic risk status were found to be "high-risk".

Introduction

Multiple myeloma (MM) is caused by the neoplastic transformation of plasma cells, ultimately leading to end organ damage such as hypercalcemia, renal insufficiency, anemia, lytic bone lesions, and secretion of a monoclonal paraprotein[1]. Plasma cell neoplasms can also present extramedullary – either as solitary plasmocytoma (2–5%)[2] or, more frequently (40%), as extramedullary myeloma manifestations (EMM) in the context of MM[2–9]. EMM are most commonly (65%) observed in the area of the nasopharynx and upper respiratory tract[10]. To obtain histopathological evidence for EMM, a biopsy has to be performed[11].

To date, ultrasound has had no established role in the diagnosis of MM[7,8]. In addition to computed tomography, magnetic resonance imaging and fluorodeoxyglucose positron emission tomography are recommended as diagnostic methods for detecting soft tissue involvement in MM staging[7,8].

In clinical practice, sonography is often the primary imaging modality for tumor detection and characterization. The value of contrast-enhanced ultrasound (CEUS) for tumor characterization varies depending on the organ involved[12,13]. In the evaluation of incidental hepatic tumors, for example, CEUS is already the standard diagnostic procedure[13]. In principle, CEUS can be used to describe tumor

perfusion as an expression of tumor neoangiogenesis[14]. In particular, CEUS is useful for differentiating between viable and necrotic tissue prior to ultrasound-guided biopsy[15].

There are no large case series describing EMM using B-mode ultrasound (B-US) and CEUS. The aim of this study is to present EMM patterns on B-US and CEUS, based on the largest case series known to us to date.

Material and methods

Over a period of 16 years (02/2006–07/2021), a total of 21 patients with multiple myeloma and 24 investigated EMM were included in the retrospective analysis. Among them, there were $n = 5$ female and $n = 16$ male patients. The mean age was 63.3 years (range 46–79). Bone marrow infiltration was present in all patients, confirming these lesions as EMM. Patient characteristics are summarized in Tab. 1. All patients underwent B-US and CEUS of the tumor lesions as part of the routine diagnostic procedure in our hospital prior to ultrasound-guided biopsy or for further differentiation of unknown lesions. B-US data include lesion location, size, border characteristics (smooth, irregular), and echogenicity (hyperechoic, isoechoic, or hypoechoic). CEUS was performed according to the current European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines[16]. For this purpose, the patients received 2.4 ml of the contrast medium SonoVue® (Bracco, Konstanz) administered as a venous bolus injection, followed by 10 ml of sodium chloride.

Tab. 1. Characteristics of $n = 21$ patients with multiple myeloma and $n = 24$ with extramedullary myeloma manifestations

Patients characteristics	Number (%)
Median age (years)	63.3 (range 46–79)
Sex	
Female	5 (23.8%)
Male	16 (76.2%)
Diagnosis of EPM	
Synchronously to new diagnosis of MM	3 (12.5%)
Progression or relapse of MM	21 (87.5%)
Stage at primary diagnosis (Salmon and Durie staging)	
IA	1 (4.8%)
IB	0
IIA	2 (9.5%)
IIB	0
IIIA	12 (57.1%)
IIIB	6 (28.6%)
No data	0
Paraprotein	
IgA	5 (23.8%)
IgM	0
IgG	12 (57.1%)
Light chain myeloma	3 (14.3%)
Non-secretory myeloma	1 (4.8%)
Molecular cytogenetic analysis of fluorescence in situ hybridization (FISH) result	
Low risk	0
Intermediate–low risk	0
Intermediate–high risk	0
High risk	6
No data	15

All examinations were performed using an ACUSON SEQUOIA 512 GI ultrasound machine (Siemens, Germany) and a 4C1 curved-array transducer operating at 4 MHz, conducted by an experienced examiner (C.G.) (German Society for Ultrasound in Medicine (DEGUM) level III). During CEUS, the same transducer was used in a contrast-specific mode (1.5 MHz). On CEUS, a differentiation was made between hyper-, iso- and hypoenhancement of the mass in the arterial, portal venous, and parenchymal phases**.** CEUS enhancement patterns were retrospectively assessed by two independent investigators (C.G. and C.M.). In cases of disagreement, the enhancement was evaluated by a third examiner (C.T.). Depending on the localization, EMM enhancement was compared to the spleen or the surrounding tissue as an in-vivo reference. The homogeneity of the enhancement was evaluated as either homogeneous or inhomogeneous. Tumor lesions with areas of different enhancement were defined as exhibiting complex enhancement. In $n = 16$ lesions, histological confirmation of the diagnosis was based on the extramedullary myeloma manifestation, while in $n = 8$ lesions on other sites of multiple myeloma manifestations.

The medical records of all 21 subjects were reviewed for conclusive molecular cytogenetic analysis using fluorescence in situ hybridization (FISH), allowing molecular risk stratification. Conclusive data were obtained in 6 out of the 21 patients. The low rate of FISH testing in this cohort can be attributed to the high proportion of referrals from office-based physicians, where FISH testing outside clinical trials was not part of the standard of care.

For this study, the definition of chromosomal high-risk status was based on the criteria used in the GMMG-CONCEPT Trial, a study recruiting high-risk patients in intensive quadruplicate treatment regimens[17]. Testing positive for at least one of the following aberrations was considered to represent a cytogenetically high-risk profile: t(4;14), del(17p), t(14;16) or Gain of 1q21.

The study was approved by the local ethics committee (EK_MR_08_04_21_görg). As a descriptive study, only absolute and relative frequencies are reported. Moreover, Cohen's kappa was calculated to assess inter-rater reliability of the CEUS enhancement in the arterial and parenchymal phases.

Results

The investigated EMM were diagnosed synchronously with a new diagnosis of multiple myeloma in $n = 3$ cases, and in $n = 21$, they were diagnosed at the time of disease progression or relapse. In addition to the sonographically examined EMM, all patients had other manifestations of the disease. The location of the sonographic examined EMM was most frequently in the chest wall ($n = 11$; 45.8%), followed by the liver ($n = 4$; 16.7%) and soft tissue ($n = 3$; 12.5%). Other manifestation sites are shown in Fig. 1. On B-US, all 24 cases of EMM were hypoechoic. Of these, $n = 16$ (66.6%) had regular, while $n = 8$ (33.3%) had irregular borders. The mean lesion size was 5.4 cm (range 1–10 cm). On CEUS, EMM presented with arterial hyperenhancement in $n = 20$ (83.3%) and isoenhancement in $n = 4$ of the lesions (16.7%). In the portal venous phase, hyperenhancement was overserved in $n = 3$ lesions (12.5%), isoenhancement in $n = 12$ (50%), and hypoenhancement in $n = 6$ (25%) cases, followed by isoenhancement in $n = 1$ (4.2%) and hypoenhancement in $n = 23$ (95.8%) of EMM in the parenchymal phase (Fig. 2). Due to the ret-

rospective nature of the study, there are no CEUS data of the portal venous phase for $n = 3$ cases. The enhancement pattern was predominantly ($n = 20$; 83.2%) homogeneous. Fig. 3 and Fig. 4 present two cases of EMM on ultrasound, complemented by corresponding histopathological findings in one case (Fig. 4). Interobserver reliability measured by Cohen's kappa showed substantial agreement (Cohen's kappa for arterial CEUS enhancement: 0.70 [95% CI: 0.32–1.00]; Cohen's kappa for parenchymal CEUS enhancement: 0.70787 [95% CI: 0.34–1.00]).

With regard to the molecular cytogenetic analysis, every patient with reliable FISH data tested positive for at least one aberration considered "high-risk" (Fig. 5). Specifically,1 patient was identified with del(17p), 2 patients with t(4;14), and 4 patients with gain of 1q21. One patient had t(4;14) and gain of 1q21 (5 copies). Notably, 3 patients additionally harbored a loss of retinoblastoma-1 (rb-1), a del(13q14), which is considered high-risk by some authors[18], but is not yet incorporated in the broader recommendation of risk assessment.

Discussion

The time to diagnosis of multiple myeloma often exceeds six months, as patients may present with nonspecific symptoms such as back pain and fatigue, or may even be asymptomatic in up to 25% of cases[19,20]. Diagnosis is particularly challenging in patients with non-secretory multiple myeloma or isolated extramedullary

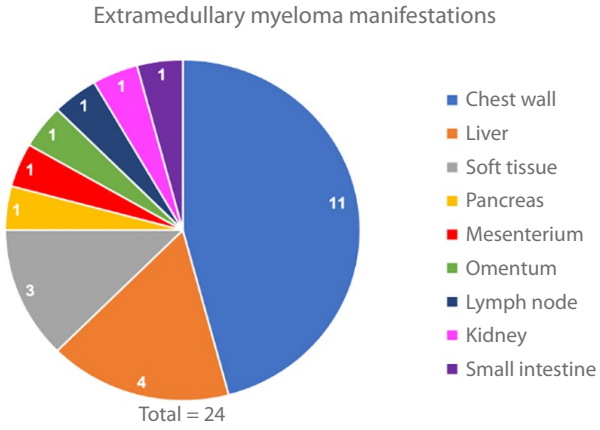

Fig. 1. *Presentation of the different locations of n = 24 extramedullary myeloma manifestations detected by ultrasound*

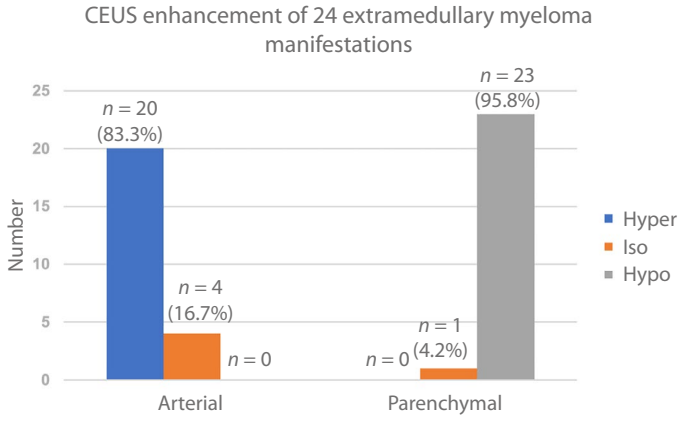

Fig. 2. Presentation of different (hyper-, iso-, hypo) enhancements in the arterial and parenchymal phases of 24 extramedullary myeloma manifestations observed on contrast-enhanced ultrasound

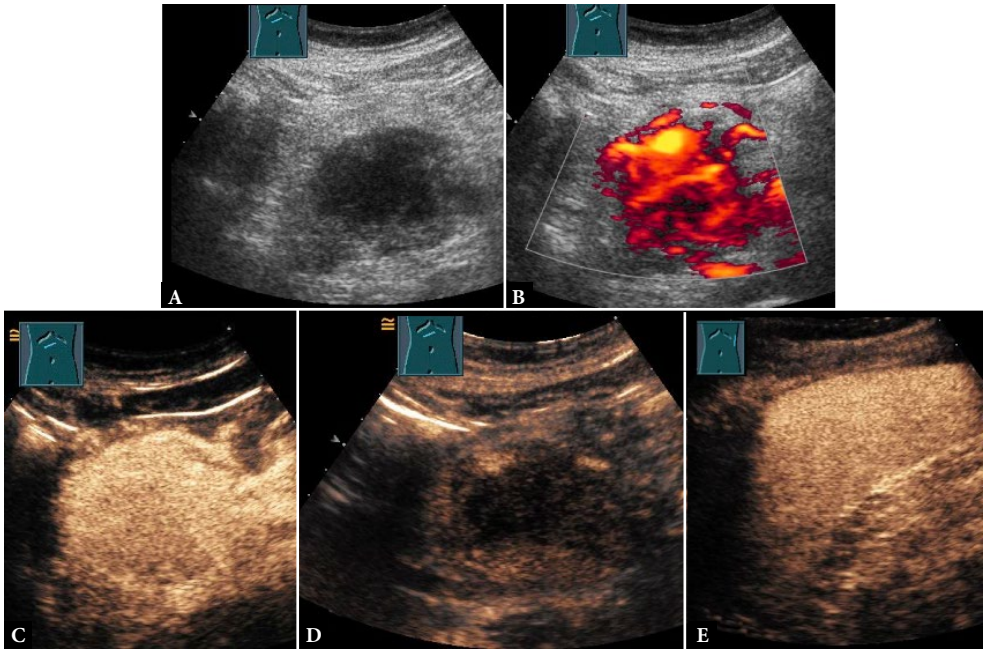

Fig. 3. *Pancreatic plasmacytoma manifestation with a hypoechoic tumor lesion on B-US (***A***) and strong flow signals on color Doppler sonography (***B***). On CEUS, the lesion demonstrates arterial hyperenhancement (***C***) followed by parenchymal hypoenhancement (***D***), compared to the enhancement of the spleen as an in-vivo reference (***E***)*

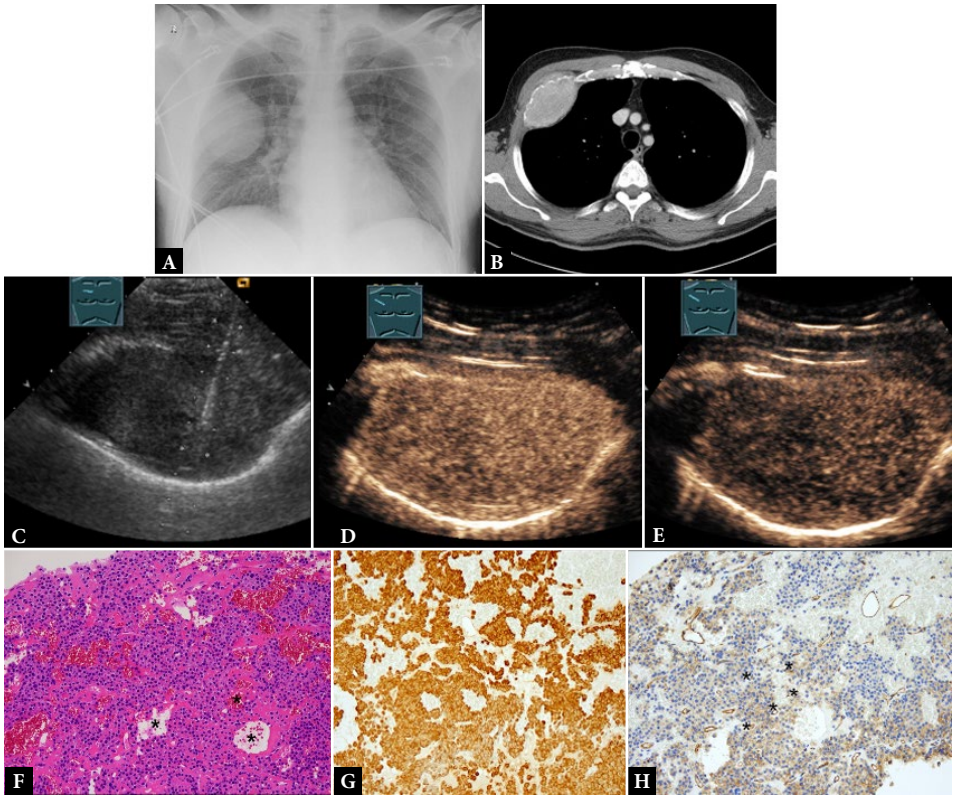

Fig. 4. *Histologically proven thoracic extramedullary myeloma manifestation on X-ray (***A***, courtesy of Prof. A. Mahnken, Radiology, University Hospital Marburg) and CT-scan (***B***; courtesy of Prof. A. Mahnken, Radiology, University Hospital Marburg), with a hypoechoic presentation of EMM on B-US (***C***). On CEUS, the lesion shows arterial isoenhancement (***D***), followed by parenchymal hypoenhancement (***E***). Figure* **F** *shows the core needle biopsy specimen of the lesion, with a dense infiltrate of plasma cells showing kappa light chain restriction (***G***), corresponding to an extramedullary manifestation of multiple myeloma. The plasma cells are arranged adjacent to multiple small vessels (*), partly discernible in hematoxylin and eosin stain (HE staining (×100)). Immunohistochemical staining against CD31 (×100) highlights endothelial cells lining small and medium-sized vessels between the plasma cell infiltrate (***H***). Many tiny, rounded vessels are discernible only with this staining (*)*

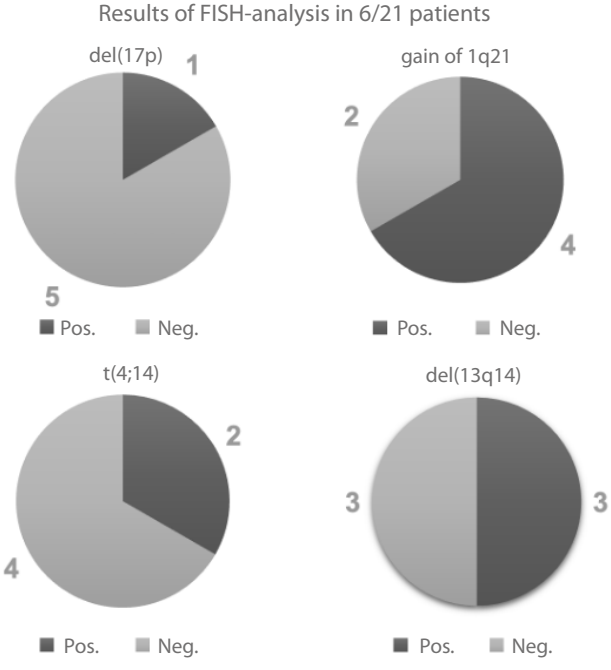

Fig. 5. *Results of FISH analysis in 6 patients with EMM for the evaluation of genetic risk status*

myelomas (3%)[7–9]. A prolonged time to diagnosis (>6 months vs. <3 months) has been associated with an increase in disease-related complications, ultimately impacting disease-free survival from the time of diagnosis (p = 0.003)[19]. Furthermore, extramedullary disease in multiple myeloma is linked to a higher prevalence of high-risk features and a worse prognosis[21]. In one analysis, patients with multiple myeloma without EMM had a five-year overall survival rate of 80%, compared to 63% in those with EMM (p = 0.02)[21]. Another study also found that the absence of EMM was associated with significantly longer progression-free survival (p <0.001)[21]. Therefore, timely diagnosis of EMM is of particular importance.

The present study analyzed the B-US and CEUS patterns of EMM in the largest patient cohort reported to date. EMM demonstrated characteristic imaging features on both B-US and CEUS. All EMM lesions appeared hypoechoic on B-US, which aligns with findings from previous case reports[22].

From a differential diagnostic perspective, other malignant primary bone tumors such as osteosarcoma, Ewing's sarcoma, and chondrosarcoma should be considered. However, sonographic imaging data for these entities remain limited to a few case reports[23,24]. In one case series, these tumors also exhibited heterogeneous echogenicity (8/10 cases) and were consistently hypoechoic (10/10 cases) on B-US[25].

On CEUS, EMM were characterized by strong arterial hyperenhancement or isoenhancement in all examined cases, suggesting pronounced tumor neoangiogenesis. To the best of our knowledge, no data are available regarding the CEUS enhancement patterns of osteosarcoma[26]. De Marchi *et al*. identified seven distinct CEUS patterns in other musculoskeletal tumors[27]. The most frequently observed pattern in malignant tumors (50.8%) involved numerous vessels with inhomogeneous enhancement and avascular components[27], which contrasts with the iso- and hyperenhancement seen in EMM. In hepatic manifestations of mesenchymal tumors, marginal hyperenhancement of the lesion with subsequent parenchymal washout has been reported[28,29].

In other tumor entities, such as hepatocellular carcinoma (HCC) or metastases, arterial hyperenhancement on CEUS is often attributed to neovascularization[30,31]. Based on this knowledge, the hyper- or isoenhancement observed in EMM is likely also driven by pronounced neovascularization[32]. Increased vascular density has been observed in the bone marrow microenvironment of multiple myeloma (MM) patients[33]. This neoangiogenesis is induced by aberrant expression of various pro-angiogenic factors by myeloma cells, such as overexpression of hypoxia-inducible transcription factor 1α[33]. The pro-angiogenic activity of myeloma cells is further sustained by vascular endothelial growth factor (VEGF) production[33]. Given that medullary and extramedullary manifestations represent different localizations of the same disease, it is plausible that the extensive vascularization in EMM follows the same pathogenic mechanisms. Accordingly, immunomodulatory drugs known to inhibit angiogenesis, such as thalidomide, have been used for many years in MM therapy and remain integral to combination treatment regimens[34–36]. Supporting this concept, histopathological and immunohistochemical evidence of increased vascularization has been observed in the thoracic region of an EMM patient (Fig. 4 F–G).

Although histologic confirmation is always sought, this study aims to increase awareness within the ultrasound community regarding the characteristic US patterns of EMM. Nevertheless, well-established tumor entities such as metastatic malignant melanoma, renal cell carcinoma, and HCC also typically exhibit arterial-phase hyperenhancement on CEUS and should be considered as important differential diagnoses[37,38].

Furthermore, every patient with reliable FISH results tested positive for at least one high-risk genetic aberration. In the present study, the data support an enrichment of high-risk disease features in MM patients with EMM, consistent with previous reports indicating an association between EMM and high-risk cytogenetic abnormalities, such as del(17p) or t(4;14)[39,40]. There may also be an increased prevalence of RB1 losses (del13q14) in MM patients with EMM.

This study has certain limitations: it is a single-center, retrospective analysis, and molecular tests were not performed in all patients. Additionally, ultrasound is an operator-dependent imaging modality, which inherently introduces interobserver variability.

Conclusion

EMM represents a rare manifestation of multiple myeloma that can occur throughout the body. It is characterized by a hypoechoic appearance on B-US and demonstrates pronounced arterial hyper- or isoenhancement on CEUS. Among the six patients analyzed for genetic risk status, all exhibited high-risk cytogenetic features.

Ethical review board

The study was approved and recommended by the local ethic committee of Philipp University Marburg (Number:EK_MR_08_04_21_görg).

Conflict of interest

Christian Görg received funding from Bracco Imaging. Bracco Imaging supported educational workshops on contrast-enhanced ultrasound at the University Hospital in Marburg.

Author contributions

Original concept of study: CT, CG, CM. Writing of manuscript: CT, CM. Analysis and interpretation of data: CT, CM. Final acceptation of manuscript: CT, CT, CM. Collection, recording and/or compilation of data: CT, CCW, CM. Critical review of manuscript: AB, ESZ, CFD, HF.

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