**Objective:** To evaluate whether administration of a D-galactose–based signal enhancer is useful in color Doppler sonography (CDS) for better detection of vascularity patterns, which may help to differentiate malignant from benign lymph nodes in patients with cutaneous melanomas.

**Design:** Comparison of B-mode sonography, native CDS, and signal-enhanced CDS.

**Setting:** Department of Dermatology and Allergology, Ludwig-Maximilians-University, Munich, Germany.

**Patients:** Twenty examinations in 19 patients (median age, 60 years; 10 men) who presented with echo-poor structures suggestive of lymphadenopathy in B-mode sonography during follow-up for cutaneous melanomas.

**Interventions:** Histopathologic and follow-up examinations; documentation by color prints.

**Main Outcome Measures:** Frequency of detection and description of different lymph node vascularity patterns in signal-enhanced CDS.

**Results:** Signal-enhanced CDS revealed additional information about vascularization of lymph node metastases, reactive lymph nodes, hematomas, and seromas, which was helpful for the differential diagnosis in 15 of 20 examinations. For lymph node metastases, signal enhancement facilitated the detection of accessory peripheral vessels in most investigations. Concerning reactive lymph nodes, hilar vessels in part with branching to the lymph node periphery could be identified only after application of the contrast enhancer in most patients. Quantitative variables could not be measured in all cases and did not help to differentiate between malignant and reactive lymph nodes.

**Conclusions:** Administration of a D-galactose–based signal enhancer for CDS in patients with cutaneous melanomas can help to differentiate malignant from reactive lymph nodes. However, these promising results require confirmation in a prospective multicenter study.

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The prognosis of patients with cutaneous melanomas primarily depends on the tumor thickness at the time of diagnosis. Whereas patients with malignant melanomas with a tumor thickness of 0.75 mm or less are cured with high probability by surgical excision of the tumor, the prognosis is worse for patients with thicker melanomas. In these patients, the 10-year survival rate decreases markedly owing to development of metastases. Regional lymph nodes are known to be the first site of disease progression in most patients, and the number of lymph node metastases are reported to be important for subsequent recurrence and prolonged survival. For this reason, early detection of lymph node metastases may be of special value in the follow-up of patients with cutaneous melanoma. B-mode sonography has repeatedly been reported to alter the management of patients with cutaneous melanomas by detection of impalpable metastases in lymphatic drainage areas and regional lymph nodes. Moreover, color Doppler sonography (CDS) has been shown to give additional diagnostic information because of the detection of characteristic vascularization patterns in some, mostly enlarged, malignant and reactive lymph nodes. The current prospective study was performed to evaluate whether application of a D-galactose–based contrast enhancer, routinely used in cardiology, for example, improved the visualization of vascularization pattern in echo-poor structures suggestive of lymphadenopathy detected by B-mode sonography in patients with cutaneous melanomas.
PATIENTS AND METHODS

PATIENTS

A total of 19 patients (10 men and 9 women) seen during follow-up after complete resection of invasive cutaneous malignant melanoma were prospectively included in this study between April 1, 2000, and October 31, 2000, at the Department of Dermatology and Allergology, University of Munich. For all patients, written consent was obtained. Complete follow-up was at least 3 months in all patients. Age range of the patients was 23 to 78 years (mean, 57 years; median, 60 years). Patient characteristics are listed in Table 1. Besides complete history taking and physical examination of the patients, B-scan sonography of lymphatic drainage areas and regional lymph node regions was performed as part of the regular follow-up program or for examination of clinical findings suggestive of lymphadenopathy detected by the patients or the physician. In 20 examinations performed in 19 patients, B-scan sonography revealed uncertain or suggestive results that qualified for further investigation. One patient was investigated twice (in May and August 2000) for different suggestive findings in B-scan sonography.

METHODS

Ultrasound examinations were performed by a single sonographer (M.-H.S.-W.) using a real-time scanner (SSA-340 A; Toshiba Medical Systems, Neuss, Germany) with an 8- to 10-MHz linear transducer. Lymphatic drainage areas and regional lymphatic regions were examined and documented in horizontal and vertical planes in every patient. Ultrasound assessment of detected lymph nodes was first based on morphologic criteria, such as size, shape, and echogenicity of the lymph node center and cortex. Solbiati Indices were calculated as the ratio of maximal and minimal diameters in transversal and longitudinal sonographic sections.1 Mainly following the recommendations of Vassallo et al,3 lymph nodes were considered metastatic if the following criteria were met: Solbiati index less than 2 and/or predominance of low echogenicity of the whole lymph node structure and/or lymph node center with low echogenicity and/or asymmetric regions with low echogenicity in the lymph node margin. In all of the 20 B-scan ultrasound examinations performed, melanoma metastases could not be excluded or verified by clear sonomorphologic clues based on the criteria of Vassallo and colleagues. For this reason, further diagnostic steps were considered necessary.

INITIALLY, native color-coded sonography was performed to visualize the vascularization of structures suggestive of lymphadenopathy. Velocity and peripheral impedance of nodal vessels were examined by CDS, if possible. Peak velocities were measured, and resistive indices (RIs) and pulsatility indices (PIs) were determined according to Gosling and Kizil 10 (Figs 3 and 4). The RI, representing the peripheral vascular resistance, and the PI, representing the peripheral vascular obstruction, were gained by an integrated function of the ultrasound device. The RI was defined as the ratio of maximal systolic (S_m) minus end diastolic (D_e) to maximal systolic (S_m) flow velocity:

\[ RI = \frac{S_m - D_e}{S_m} \]

The PI was defined as the ratio of maximal systolic (S_m) minus end diastolic (D_e) to time-averaged maximum (Mav) flow velocity:

\[ PI = \frac{S_m - D_e}{Mav} \]

Afterward, signal-enhanced CDS was performed by administration of an ultrasound signal-enhancing agent (Levovist; Schering, Berlin, Germany), which was applied intravenously as a bolus of 8 mL (concentration, 312.5 mg/mL). The contrast agent suspension was prepared by adding sterile water to the commercially available powder, which consisted of 99.9% D-galactose and 0.1% palmitic acid. Fragmentation in microparticles and binding of small air bubbles was induced by shaking the suspension. Intravenous application of the ultrasound agent increased the scattering of ultrasound waves and led to a signal enhancement up to 25 dB.11 Occurrence of first signal enhancement, duration of signal enhancement, and possible adverse effects were documented. As in native CDS, vascularization pattern and, if possible, RI and PI in CDS were documented. Results of native and signal-enhanced CDS were compared, and the value of quantitative variables, such as RI and PI for receipt of additional differential diagnostic information was assessed.

According to Tschaumiller et al,12 different intranodal vascular patterns contributed to reactive or malignant lymphadenopathy as detected by native CDS. Patterns for reactive lymph nodes included hilar or longitudinal vessels or branching of longitudinal vessels. Patterns for metastases included accessory peripheral vessels, displacement of intranodal vessels, asymmetric avascular areas, or aberrant course of central vessels. In patients with structures highly suggestive of metastases and in uncertain cases, excision and histopathological examination were performed. In patients with benign structures, follow-up examinations by sonography and/or computed tomographic (CT) scanning were used to reconsider the diagnosis raised by signal-enhanced CDS.

RESULTS

Morphologic criteria (size, shape, echogenicity) of the examined structures in B-scan sonography are listed in Table 2. Administration of the D-galactose–based signal enhancer was well tolerated by all 19 patients in 20 examinations. Neither pseudoallergic reactions nor thermal sensations as described by Schlief et al13 could be observed in our patients.

In all patients, the signal enhancer was injected into a peripheral hand or forearm vein as a bolus with an injection time of 5 to 10 seconds. The first detectable effect could be perceived on average about 20 seconds after injection, with a range of 5 to 30 seconds. Duration of signal-enhancing effects was short (between 3 and 8 minutes).

Despite the short examination time, it was possible to document changes in vascularity pattern after injection of the signal enhancer. In 14 (70%) of 20 examinations, signal enhancement led to a better visualization of general vessel topography, showing additional vessels after contrast enhancement or enabling the investigator to...
describe the distribution of vessels in more detail. In 11 examinations, vascularity could be detected only after application of the contrast enhancer. In 3 examinations, vessel distribution could be better described than in native CDS. In 6 examinations, application of signal enhancer did not have any signal-enhancing effects. In 15 examinations, vascularity could be detected only after application of the contrast enhancer. In 3 examinations, avascularity after administration of the signal enhancer did not help to distinguish malignant from benign processes, and further diagnostic steps were initiated. Excision and histopathologic examination revealed subcutaneous soft tissue metastases in 2 patients and a superficially located lymph node metastasis in 1 patient. Table 3 gives the results in more detail.

However, because of the small diameter of blood vessels (0.1-0.3 mm) in small lymph nodes, measurement of the RI and PI in CDS was not possible in all examinations. In only 6 (30%) of 20 examinations could quantitative variables be evaluated at all. The RI and PI could be determined in 2 examinations before and after application of the signal enhancer, and in 4 examinations quantitative variables could be determined only after application of the signal enhancer. According to Tschammler et al,13 pathologic arterial Doppler spectra in metastatic lymph node vessels were quantified with an RI of 0.9 or higher or a PI of 1.8 or higher. Before application of the contrast enhancer, measurement of the PI and RI in native CDS did not help to determine metastatic disease, which was found after histopathologic examination after excision of the lesions. After application of the signal enhancer, metastases tended to demonstrate higher PI values (≧1.8), correctly indicating metastases in 3 patients. However, RI values did not exceed the 0.9 threshold, therefore leading to different results for the same lesions. Metastases were assumed if CDS revealed perfusion primarily in peripheral regions of structures suggestive of lymphadenopathy (Figure 1A-C) or in mixed pattern with hyperperfusion of one area and lack of perfusion of another area. For structures highly suggestive of lymphadenopathy after B-scan sonography and/or CDS,
excision and histopathologic examination were initiated. In 6 cases, histologic analysis confirmed the preoperative diagnosis of metastases of malignant melanoma. In 1 patient, a lymph node metastasis of thyroid cancer was found. In 2 patients, excision of suggestive lesions disproved the assumption of melanoma metastases but revealed the diagnosis of a reactive lymph node with marked vessel proliferation in one patient and the diagnosis of a postoperative neuroma in the other.

In 2 patients, administration of signal enhancer led to visualization of homogeneous color pixels in mainly echo-poor structures by application of slight pressure with the transducer. Therefore, hematomas containing liquid areas after prior lymph node dissection were assumed in 2 patients (Figure 2A and B). This was confirmed by histopathologic examination in one patient and by sonographic control examinations with increase of echogenicity during several weeks in the other.

In 2 patients, echolucent, roundish structures without any signal enhancement after injection of signal enhancer led to the presumptive diagnosis of postoperative seromas that resulted from lymph node dissection. Sonographic-oriented fine-needle aspiration revealed clear liquid in one patient who tested cytologically negative for any malignant cells, confirming the diagnosis of a seroma. Sonographic and CT follow-up examinations revealed identical findings consistent with postoperative seroma throughout 6 weeks in the other patient.

A misdiagnosis of an atypical lipoma was established in 1 patient after B-scan sonography revealed an indistinct, in part echo-rich, mainly echo-poor structure (Figure 3).

The diagnosis of reactive lymph nodes was established after B-scan ultrasound and signal-enhanced CDS for visualization of hilus vessels (sometimes with branching to the lymph node margin) (Figure 4A-C) in 5 patients. In 1 patient, a small reactive lymph node was assumed without any signal enhancement only because of B-scan ultrasound criteria. All of these patients had at least 1 follow-up sonographic and/or CT scan examination 4 to 8 weeks later. Since no signs of lymph node enlargement or increase of echo-poor areas could be found during follow-up examinations, the first diagnosis of reactive lymph nodes was confirmed in all 6 patients. A synopsis of the results of contrast-enhanced CDS, postoperative histologic analysis, cytologic analysis, and follow-up examinations is given in Table 4.
Administration of ultrasound contrast enhancers has been shown to be helpful in echocardiography for diagnosis of left heart failure and for the examination of vessels such as the transcranial arteries, renal arteries, or portal veins. In all of these indications, the amplitude of ultrasound signals is increased after application of a signal enhancer. In the case of the D-galactose–based contrast enhancer Levovist, shaking of the contrast suspension leads to fragmentation in microparticles and binding on small air bubbles. This induces an increase of scattering and, therefore, a signal enhancement, which can be used for diagnosis of intravascular blood flow even in very small vessels (0.1-0.3 mm in diameter).

Recently, intravenous application of Levovist was reported to improve visualization of vessel topography in lymph nodes of patients with squamous cell carcinomas of the head and neck and in lymph nodes of patients with malignant Hodgkin and non-Hodgkin lymphomas. The authors found signal-enhanced CDS superior to native CDS in the differentiation of malignant from reactive lymph nodes of the neck.

To our knowledge, the current prospective study reports for the first time the results of lymph node ultrasound examinations using the D-galactose–based contrast enhancer in patients who present with structures suggestive of lymphadenopathy in B-scan ultrasound during follow-up for cutaneous melanoma. In 15 of 20 examinations, correct additional information improving diagnostic certainty could be obtained because of signal enhancement or lack of signal enhancement after application of signal enhancer. Two hematomas and 2 seromas could be diagnosed correctly. Five of 7 reactive lymph nodes showed hilus vessels, in part with branching to the lymph node periphery, and 1 small reactive lymph node remained avascular. Both flow patterns are described for reactive lymph nodes. Five of the 8 histologically proven metastases revealed a peripheral flow pattern or a mixed pattern with avascular areas and areas with a chaotic intranodal flow. These vascular patterns are in accordance with those described by Tschammler et al, who investigated reactive and malignant lymph nodes in patients with varying tumors using color Doppler flow imaging but no signal enhancer. However, in our study, 1 histologically proven lymph node metastasis and 2 soft tissue metastases did not reveal any vascularity after application of the contrast enhancer. A similar effect was reported by Moehrle et al, who investigated melanoma patients using native CDS. They found the absence of vessels or a reduced perfusion to support the diagnosis of melanoma metastases. Moehrle and colleagues speculated that avascular regions may represent necrotic areas within metastatic lymph nodes. In our patients, all avascular metastases (1 lymph node metastasis, 2 soft tissue metastases) were located rather superficially within the subcutaneous tissue. A possible explanation for the avascularity of superficially located metastases may be the short-lasting contrast-enhancing effect, which may end before those metastases can be visualized.

In addition to qualitative variables such as nodal morphological structure and distribution of vascularity, quantitative variables such as velocity and corresponding RI and PI have been investigated to obtain more objective criteria. In the past, different groups tried to establish quantitative thresholds for defining vascularity of malignant respectively benign lymph nodes. Choi et al defined a PI more than 1.5 and an RI more than 1.0 to be characteristic for malignancy, whereas Steinkamp et al postulated 1.6 and 0.8 as thresholds for PI and RI, respectively. The most often used classification is the one of Tschammler et al, who found lymph nodes with a
PI of 1.8 or more and an RI of 0.9 or more to be suggestive of malignancy. In our patients, quantitative variables were disappointing. In only 2 of 20 examinations, the RI and PI could be determined before application of the signal enhancer. In both examinations, the RI and PI did not reveal pathologic values and therefore did not help support the diagnosis of metastases, which were suspected on morphologic criteria and subsequently confirmed by histopathologic analysis. In 6 of 20 examinations, measurement of quantitative variables after application of the contrast enhancer was possible, yet in only 3 of 8 metastases did PIs exceed the 1.8 threshold, correctly indicating malignancy. The RIs did not exceed the 0.9 threshold in these examinations. Our results are in accordance with those of other investigators who recently were unable to confirm former data on PI and RI thresholds differentiating malignant from metastases of other tumors.12,23,24 Moehrle et al6 speculated that melanoma metastases, investigated by native CDS, may have lower indices than metastases of other tumors. However, in our study, indices could be increased after application of the signal enhancer in 3 of 8 metastases, indicating that melanoma metastases do not generally have lower vascularization indices than metastases of other tumors. Although some of the metastases tended to demonstrate higher PIs exceeding 1.8 in our patients, qualitative variables do not allow a reliable differential diagnosis, since measurements were possible in only 6 of 20 examinations. Recording of Doppler spectra and calculation of RI or PI seem to be time-consuming and of little diagnostic value in this context.

In conclusion, administration of the D-galactose–based contrast enhancer gave additional information on sonomorphologic aspects of vascularity for differentiation of reactive lymph nodes, lymph node metastases, hematomas, and seromas. Yet, for soft tissue metastases or superficially located small lymph node metastases, D-galactose–based CDS was not clearly superior to native CDS. Improved accuracy of diagnosis was mainly because of qualitative assessment of vascularity. Quantitative variables such as PI and RI were not of high di-

Table 4. Synopsis of Results of Signal-Enhanced Color Doppler Sonography, Histologic Analysis, Cytologic Analysis, and Follow-up Examinations

<table>
<thead>
<tr>
<th>Diagnoses by Signal-Enhanced Color Doppler Sonography</th>
<th>Histopathologic Examination</th>
<th>Cytomorphologic Examination</th>
<th>Follow-up Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases (n = 9)</td>
<td>6 Melanoma metastases, 1 metastasis of thyroid cancer, 1 neuroma, 1 reactive lymph node</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Reactive lymph nodes (n = 6)</td>
<td>...</td>
<td>...</td>
<td>6 Reactive lymph nodes</td>
</tr>
<tr>
<td>Hematomas (n = 2)</td>
<td>1 Hematoma</td>
<td>...</td>
<td>1 Hematoma</td>
</tr>
<tr>
<td>Seromas (n = 2)</td>
<td>...</td>
<td>1 Seroma</td>
<td>1 Seroma</td>
</tr>
<tr>
<td>Lipomas (n = 1)</td>
<td>1 Melanoma metastasis</td>
<td>...</td>
<td>...</td>
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</tbody>
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*Ellipses indicate not applicable.
agnostic value. However, further prospective studies in larger patient groups might be helpful to evaluate the possible beneficial effect of ultrasound signal enhancers for differentiating malignant from reactive lymph nodes in patients with cutaneous melanomas in more detail.

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