Contrast-Enhanced Sonography for Differential Diagnosis of Pleurisy and Focal Pleural Lesions of Unknown Cause*

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Background: Ultrasound enables the visualization of pleural-based lesions with a poor correlation to specific pathology. At this time, there are no data about the diagnostic value of contrast-enhanced sonography (CES) in pleural lesions.

Methods: From August 2004 to January 2005, 25 consecutive patients with clinical symptoms of pleurisy and focal pleural lesions of unknown origin seen on B-mode ultrasonography were prospectively studied by CES. The lesions were diagnosed as pleuropneumonia (n = 12), pulmonary embolism/infarction (n = 7), malignant lymphoma (n = 2), pleural metastasis (n = 2), granuloma (n = 1), and unknown cause (n = 1). The diagnosis of the lesions was confirmed by contrast-enhanced CT scanning (n = 20), scintigraphy (n = 3), and follow-up (n = 2). Time to the enhancement of the contrast agent was determined. The CES patterns were evaluated during the arterial phase (ie, 2 to 30 s) and the parenchymal phase (ie, 1 to 5 min). The extent of the enhancement of pleural lesions was classified using normal liver tissue as an in vivo reference (absent, hypoechoic, isoechoic, hyperrechoic, or mixed echogenicity).

Results: In 20 patients, an enhancement of the pleural lesion was seen. All 12 patients with pleuropneumonia had a short time to enhancement (between 1 and 6 s), and a marked enhancement (isoechoic/hyperechoic) during the arterial and parenchymal phase. In the remaining 13 patients with other diagnoses than pleuropneumonia, 5 patients had no enhancement and 8 patients had a delayed time to enhancement (> 6 s). The extent of the enhancement was reduced (hypoechoic/anechoic) in 12 of 13 patients during the arterial and parenchymal phases. Conclusion: In patients with pleurisy and pleural lesions of unknown cause that were found sonographically, CES enables the diagnosis or exclusion of pleuropneumonia.

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Key words: contrast-enhanced sonography; pleurisy; sonography

Abbreviations: CDS = color Doppler sonographic; CES = contrast-enhanced sonography; PE = pulmonary embolism/infarction

The clinical sign of pleurisy is characterized by a breath-dependent localized pleural pain, but the final diagnosis presents a considerable challenge and requires a high index of clinical suspicion from the attending physician. One of the most important differential diagnoses of pleurisy includes pleuropneumonia and pulmonary embolism/infarction (PE).

In the chest, the value of ultrasound has traditionally been limited to the evaluation of pleural-based lesions. In recent years, B-mode sonographic patterns, as well as color Doppler sonographic (CDS) patterns of pleuropneumonia and PE have been described. Based on CDS data, pleuropneumonia is characterized by a pronounced pulmonary arterial vascularity in contrast to an absent or reduced vascularity in patients with PE. A concise exclusion or diagnosis of PE requires additional imaging procedures like ventilation/perfusion scintigraphy, spiral CT scanning, MRI angiography, and pulmonary angiography. Significant progress in the development of ultrasound equipment and the introduction of ultrasound contrast agents have increased diagnostic accuracy especially in liver lesions.

The aim of this article was to present our experi-
ence with contrast-enhanced sonography (CES) and a second-generation contrast agent (SonoVue; Bracco SpA; Milan, Italy)\textsuperscript{12} in the assessment of 25 consecutive patients with pleurisy and sonographically found pleural lesions of unknown cause.

**Materials and Methods**

Between August 2004 and January 2005, 25 consecutive patients with clinical signs of pleurisy and pleural lesions received diagnoses by ultrasound at an internal medicine center and were included in the study. All patients were prospectively investigated by B-mode sonography and CES. Informed consent obtained according to law was obtained for each patient for a CES examination, and approval by the local internal review board was achieved.

The inclusion criteria for the study were as follows: clinical signs of pleurisy; pleural lesion of unknown cause seen on B-mode ultrasonography; and informed consent for CES studies according to the law. The following B-mode sonographic parameters were evaluated: echotexture of lesions using the splenic echotexture as an in vivo reference (ie, echofree, hypoechoic, isoechoic, hyperechoic, or complex); the number of lesions (solitary vs multiple); configuration (ie, round, wedge-shaped, oval-shaped, or polygonal-shaped); and maximal size of the lesions (in case of multiple lesions, the largest lesion was evaluated).

**Table 1—Sonographic Findings in Pleural Lesions*\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Clinical Diagnosis</th>
<th>B-mode-US</th>
<th>Time to Enhancement, s</th>
<th>CES</th>
<th>Final Diagnosis</th>
<th>Confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pleurisy, suspected PE</td>
<td>3 × 2 cm, wedge-shaped</td>
<td>2</td>
<td>Isoechoic</td>
<td>Isoechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>2</td>
<td>Pleurisy, fever</td>
<td>3 × 2 cm, wedge-shaped</td>
<td>2</td>
<td>Isoechoic</td>
<td>Isoechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>3</td>
<td>Pleurisy, suspected PE</td>
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<td>3</td>
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<td>Hyperechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>4</td>
<td>Pleurisy</td>
<td>2 × 1 cm, wedge-shaped</td>
<td>4</td>
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<td>Hyperechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>5</td>
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<td>Isoechoic</td>
<td>Isoechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>6</td>
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<td>2 × 2 cm, wedge-shaped</td>
<td>6</td>
<td>Hyperechoic</td>
<td>Hyperechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>7</td>
<td>Pleurisy, suspected PE</td>
<td>2 × 1 cm, wedge-shaped</td>
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<td>Isoechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>8</td>
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<td>2 × 1 cm, wedge-shaped</td>
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<td>Hyperechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>9</td>
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<td>Hyperechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>10</td>
<td>Pleurisy, suspected PE</td>
<td>4 × 3 cm, wedge-shaped</td>
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<td>Hyperechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>11</td>
<td>Pleurisy, fever, dyspnea</td>
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<td>2</td>
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<td>Isoechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>12</td>
<td>Pleurisy, dyspnea (Fig 3)</td>
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<td>2</td>
<td>Isoechoic</td>
<td>Hyperechoic</td>
<td>Pleuropneumonia</td>
</tr>
<tr>
<td>13</td>
<td>Pleurisy (Fig 4)</td>
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<td>Hyperechoic</td>
<td>Mixed</td>
<td>PE</td>
</tr>
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<td>1 × 1 cm, wedge-shaped</td>
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<td>Anechoic</td>
<td>Anechoic</td>
<td>PE</td>
</tr>
<tr>
<td>15</td>
<td>Pleurisy, vein thrombosis</td>
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<td>12</td>
<td>Mixed</td>
<td>Hyperechoic</td>
<td>PE</td>
</tr>
<tr>
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<td>Hyperechoic</td>
<td>PE</td>
</tr>
<tr>
<td>17</td>
<td>Pleurisy</td>
<td>1 × 1 cm, polygonal</td>
<td>1</td>
<td>Anechoic</td>
<td>Anechoic</td>
<td>PE</td>
</tr>
<tr>
<td>18</td>
<td>Pleurisy</td>
<td>0.5 × 0.5 cm, polygonal</td>
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<td>Hyperechoic</td>
<td>Hyperechoic</td>
<td>Pulmonary infarct</td>
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<tr>
<td>19</td>
<td>Pleurisy, homozygotic SCA</td>
<td>0.5 × 0.5 cm, polygonal</td>
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<td>Hyperechoic</td>
<td>Mixed</td>
<td>Granuloma</td>
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<td>Pleurisy, Churg-Strauss syndrome</td>
<td>1 × 1 cm, oval-shaped</td>
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<td>Hyperechoic</td>
<td>Hyperechoic</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>21</td>
<td>Pleurisy, NHL</td>
<td>2 × 1 cm, polygonal</td>
<td>15</td>
<td>Isoechoic</td>
<td>Hyperechoic</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>22</td>
<td>Pleurisy, Hodgkin disease</td>
<td>2 × 1 cm, oval-shaped</td>
<td>12</td>
<td>Isoechoic</td>
<td>Hyperechoic</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>23</td>
<td>Pleurisy, CRC</td>
<td>0.5 × 0.5 cm, rounded</td>
<td>15</td>
<td>Hyperechoic</td>
<td>Anechoic</td>
<td>Unknown cause</td>
</tr>
<tr>
<td>24</td>
<td>Pleurisy, NSCLC</td>
<td>2 × 1 cm, polygonal</td>
<td>15</td>
<td>Hyperechoic</td>
<td>Mixed</td>
<td>Pleurarcarcinosis</td>
</tr>
<tr>
<td>25</td>
<td>Pleurisy, testicular cancer</td>
<td>3 × 2 cm, oval-shaped</td>
<td>15</td>
<td>Anechoic</td>
<td>Anechoic</td>
<td>Lung metastasis</td>
</tr>
</tbody>
</table>

*aUS = ultrasound; NHL = non-Hodgkin lymphoma; SCA = sickle cell anemia; CRC = colorectal cancer; NSCLC = non small cell lung cancer.*

CES studies were immediately performed after baseline sonography with a contrast-devoted unit (Acuson-Seqouia GI; Siemens Medical Solutions; Erlangen, Germany) that had contrast-specific, continuous-mode software. A low pressure setting was used. A sulfur hexafluoride-based microbubble contrast medium (SonoVue; Bracco SpA) was injected IV in 2 s via a 20-gauge needle. A volume of 4.5 mL was administered, followed by a flush with 5 mL of saline solution. Immediately after the injection of contrast medium, the pleural lesions were observed for evidence of contrast uptake over a period of 5 min. CES studies were analyzed on the basis of a review of sonographic unit-stored clips. CES parameters were determined by two observer (C.G. and T.B) who reached a consensus; a third reviewer (K.G.) decided in cases of disagreement (12 of 50 CES patterns). Two observers (C.G. and K.G.) had > 20 years of ultrasound experience, and one observer (T.B.) had at least 5 years of ultrasound experience. CES studies had been performed for 3 years at our institution by all three observers.

In 10 of 12 patients with a final diagnosis of pleuropneumonia (cases 1 to 12), PE was excluded by contrast-enhanced CT scan. In case 4 and case 10, the diagnosis of pleuropneumonia was...
confirmed by radiograph and clinical follow-up. In the subgroup of patients with a final diagnosis other than pleuropneumonia (cases 13 to 25), diagnoses were confirmed by contrast-enhanced CT scan in nine patients and scintigraphy in three patients (cases 15, 16, and 19). Histologic verification of the lesions was carried out in five patients (cases 20, 21, 22, 24, and 25) [Table 1]. Final diagnoses of the lesions included pleuropneumonia (n = 12), PE (n = 7), malignant lymphoma (n = 2), pleural metastasis (n = 2), granuloma (n = 1), and unknown cause (n = 1 [case 23]).

RESULTS

B-mode echotexture of pleural lesions was hypoechoic in all cases (n = 25). Lesions were solitary in 12 cases and multiple in 13 cases, with a wedge-shaped configuration in 16 cases, a polygonal-shaped configuration in 5 cases, an oval-shaped configuration in 3 cases, and a round configuration in 1 case. The size of lesions was < 1 cm in the largest diameter in 3 cases, between 1 and 3 cm in 20 cases, and between 3 and 4 cm in 2 patients (Table 1).

Vascularity by CES

The beginning of the enhancement of the lesions with visualization of vessels ranged from 1 to 20 s, with a time to enhancement between 1 and 6 s in 12 cases, and between 7 and 20 s in 8 cases. In five cases (cases 14, 17, 18, 23, and 25), no pleural enhancement was observed. Pleural lesions in patients with pleuropneumonia (cases 1 to 12) were characterized by a short time to enhancement (between 1 and 6 s) with a mean (± SD) time of 3.167 ± 1.851 s (group I). Pleural lesions in patients with diagnoses other than pleuropneumonia (cases 13 to 25) were characterized by a delayed time to enhancement (> 6 s) with a mean time of 13 ± 3.78 s (group II) [Fig 1].

Within group I (cases 1 to 12), the extent of enhancement was characterized by a marked tissue enhancement (isoechoic/hyperechoic) during the arterial and parenchymal phase in all patients (Fig 2–3). Four patients had an isoechoic enhancement and seven patients had a hyperechoic enhancement during both phases. In one patient (case 12), an isoechoic/hyperechoic enhancement was observed.

Within group II (cases 13 to 25), the extent of enhancement was characterized as reduced tissue enhancement (anechoic/hypoechoic) in 12 of 13 cases (Fig 4–5). In the arterial phase, the CES patterns of lesions were anechoic (n = 5), hypoechoic (n = 6), isoechoic (n = 1), and mixed (n = 1). In the parenchymal phase, lesions were anechoic

* In 5 patients of group II
no enhancement was observed by CES

**Figure 1.** The mean (± SD) time to enhancement by CES in 25 patients with pleural lesions.
(n = 5), hypoechoic (n = 5), and mixed (n = 3). The patient in case 20 with a diagnosis of Churg-Strauss-granuloma had a short time to enhancement of 7 s (Fig 5). The patient in case 22 with a diagnosis of Hodgkin disease had an isoechoic enhancement during the arterial phase. Sonographic data were summarized in Table 1.

**DISCUSSION**

Sonographic examination of the pleura has long been recognized as a useful method for diagnosing pleural effusion and has been shown to be a valuable tool in the assessment of pleural-based parenchymal diseases such as pleuropneumonia, PE, and pleuropulmonary malignancies. The poor correlation between B-mode sonographic patterns and the specific pathology of pleural lesions is well-known. So when in doubt, contrast-enhanced CT scanning is the diagnostic "gold standard" for clinical lung pathology and is necessary for a final diagnosis.

The contrast enhancement medium used here

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**Figure 2.** A 72-year-old female patient with pleurisy suspected of having PE and having been diagnosed with pleuropneumonia (case 8). Top, A: with B-mode sonography a 2 × 1-cm wedge-shaped hypoechoic lesion was seen. Bottom, B: CES shows a hyperechoic enhancement in the parenchymal phase (4 min).

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**Figure 3.** A 15-year-old male patient with pleurisy, dyspnea, and a diagnosis of pleuropneumonia (case 12). Top, A: on B-mode sonography a 4 × 1-cm wedge-shaped hypoechoic lesion was seen. Middle, B: CES shows an isoechoic enhancement in the late arterial phase, suggesting pleuropneumonia (41 s). Bottom, C: CES shows a hyperechoic enhancement in the parenchymal phase (4 min) in comparison to the spleen (S).
(SonoVue; Bracco SpA) is a novel ultrasound, second-generation contrast agent. Currently, the use of contrast agents such as this one improve the diagnostic potential of ultrasound examinations in different clinical applications such as in the assessment of carotid and brain arteries, the renal artery, splenic tissue, blunt abdominal trauma, and hepatic lesions. During clinical studies, safety parameters (eg, vital signs, ECG, oxygen saturation, neurologic examination, and clinical laboratory parameters) were monitored, and no clinically meaningful change was noted.

The second-generation agent used (SonoVue; Bracco SpA) can be prepared in a few seconds and can be administrated immediately after baseline sonography is performed. At our institution, the contrast agent is kept in stock at all times so that this technique can be used at any time. In our series, the time for baseline sonography and CES was a maximum of 15 min. The manufacturer’s price for one CES examination (4.8 mL of SonoVue) in Europe is 65 €. In the United States, the administrative process of legitimation for the agent (SonoVue) by the US Food and Drug Administration has not yet been completed.

As shown in our study, all patients with pleuropneumonia have a high specific CES pattern that is characterized by a short time to enhancement and a marked enhancement during the arterial and parenchymal phases. Based on angiographic and CDS...
studies, pleuropneumonia shows a marked vascularity due to a pulmonary arterial supply. This would explain the short time to enhancement and the marked parenchymal enhancement in this subgroup. In the case of pleuropneumonia, there is a characteristic CES pattern, and additional imaging studies with modalities such as CT scanning seem not to be necessary for a final diagnosis.

In contrast, patients with diseases other than pleuropneumonia have a delayed time to enhancement, and a reduced enhancement during the arterial and parenchymal phases. Based on angiographic and CDS studies, PE is characterized by the absence of pulmonary arterial vascularity, whereas malignant diseases predominantly have a bronchial arterial supply. This suggested bronchial arterial supply would explain the delayed time to enhancement and the reduced parenchymal enhancement in this subgroup of patients. As demonstrated in our study, various benign and malignant diseases show this CES pattern. In these patients, additional imaging studies are warranted for final diagnosis.

As a limitation of the study, the small number of studied patients is important to mention. The consistency of the findings is encouraging, but larger studies would be useful to support these findings. Although the real value of the contrast agent (SonoVue; Bracco SpA) is still to be proved, our results show a new potential indication for the use of this second-generation contrast agent.

CONCLUSION

In patients with pleurisy and a pleural lesion of unknown cause, CES enables the physician to diagnose or exclude pleuropneumonia.

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