Fungal Liver Infection in Immunocompromised Patients: Depiction with Multiphasic Contrast-enhanced Helical CT

PURPOSE: To retrospectively assess multiphasic (nonenhanced, arterial phase, and portal venous phase) computed tomography (CT) of the liver for depiction of hepatic fungal infection in immunocompromised patients.

MATERIALS AND METHODS: The institutional ethics review board approved the study and waived the requirement for informed consent. Sixty multiphasic hepatic CT examinations were performed in 39 immunocompromised patients who fulfilled the criteria for having probable or proved fungal liver infection. The detection and conspicuity of focal liver lesions were assessed on scans obtained during each CT phase. The lesion enhancement pattern was determined, and, accordingly, lesions were stratified into two groups: lesions suggestive of infection (with ring enhancement patterns or high attenuation) and nonspecific hypoattenuating lesions. Statistical analyses were performed by using logistic regression with generalized estimating equations.

RESULTS: A total of 536 liver lesions detected at 36 CT examinations with results positive for fungal infection were assessed. All 36 (100%) examinations yielded positive results during the arterial phase, whereas 25 (69%) of them yielded positive results during the portal venous phase \((P < .001)\). At lesion-by-lesion analysis, the arterial phase scans depicted significantly more lesions (483 of 536 [90%]) than the portal venous phase (329 of 536 [61%]) and nonenhanced (265 of 465 [57%]) scans \((P < .001\) for both comparisons). In addition, on arterial phase scans, 386 of 483 lesions, as compared with 134 of 329 lesions on portal venous phase scans \((P < .001)\), were judged to have an enhancement pattern suggestive of infection. The CT phases did not differ significantly in terms of the conspicuity of detected lesions.

CONCLUSION: In patients suspected of having hepatic fungal infection, arterial phase CT depicts significantly more hepatic lesions than does CT performed during the other phases, and it reveals more lesions with enhancement patterns suggestive of infection. Arterial phase CT should be performed in addition to portal venous phase CT in patients suspected of having hepatic fungal infection.

Invasive fungal infection is a well-known complication of prolonged neutropenia in patients who are undergoing treatment for hematologic malignancies (1–3). The most common fungus to infect the liver and spleen is the *Candida* species; however, this infection is diagnosed antemortem in only about 9% of cases (4,5). A definitive diagnosis is difficult to make because it is based on the findings in biopsy specimen cultures, which are often negative for *Candida* organisms (6). This may be due in part to delays in performing biopsy in these critically ill patients (7). Therefore, ultrasonography (US) and computed tomography (CT) have an important role, secondary to that of antifungal therapy, in the diagnosis of hepatosplenic fungal infection and in the follow-up of affected patients (8).
To our knowledge, the studies on the performance of CT in the detection of fungal microabscesses in the liver that have been published to date pertain to portal venous phase CT of the liver. Thus, the purpose of this study was to retrospectively assess multiphasic (nonenhanced, arterial phase, and portal venous phase) CT of the liver for the depiction of hepatic fungal infection in immunocompromised patients.

**MATERIALS AND METHODS**

**Diagnosis of Fungal Infection**

In this study, the diagnosis of invasive fungal infection of the liver was based on recently published diagnostic criteria established by the European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC-MSG) for clinical research. As suggested by the EORTC-MSG guidelines for research, only the data of patients with proved or probable fungal infection (as defined in the EORTC-MSG guidelines) were included (9).

**Patients underwent one CT examination, and 15 underwent more than one. Thirteen patients underwent CT scanning for two separate episodes of neutropenic fever. An average of 1.54 CT examinations per patient (median, 1; range, 1–5) were performed. Overall, the results of 60 liver CT examinations—50 triphasic (nonenhanced, arterial phase, and portal venous phase) and 10 biphasic (arterial and portal venous phases only)—were analyzed.**

**CT Examinations**

CT scans were obtained by using a four-detector row helical CT system (QX/i LightSpeed; GE Medical Systems, Milwaukee, Wis) with the following parameters: 120 kV, 230–330 mA, a table speed of 7.5 mm per rotation, high-contrast mode, and a pitch of 3:1. The scans were reconstructed at collimations of 5 mm with 50% overlap. With use of a power injector (Medrad, Indianola, Pa), nonionic intravenous contrast material (iohexol [Omnipaque 300], 30 mg of iodine per milliliter; Amersham Health, Buckinghamshire, England) was administered at a dose of 2 mL per kilogram of body weight (up to a maximum of 200 mL) at a rate of 3 mL/sec, with a 25-second delay for the arterial phase and a 60-second delay for the portal venous phase. For triphasic scanning, a preliminary nonenhanced CT examination of the liver was performed by using the same imaging parameters.

**Scan Interpretation and Analysis**

First panel analysis: blind reading.—The objective of the first panel analysis was to test the overall performance of each of the three CT phases in the detection of liver lesions. For this purpose, each CT examination was divided into separate phases: nonenhanced, arterial, and portal venous phases. The scans obtained during all phases of the examination were randomized and presented to a panel of two experienced abdominal radiologists with 8 (M.A.H.) and 5 (M.D.M.) years of experience reading abdominal CT images; interpretative decisions were made in consensus. To minimize recall bias, the different phase scans obtained in each patient were read at least 2 weeks apart.

The scans were reviewed in stack mode on a picture archiving and communication system workstation (Merge eFilm, Milwau-kee, Wis). The technical parameters used and patient identifiers were hidden from the reviewers at the time of interpretation. Although the readers knew the purpose of the study, they were blinded to the findings on the other phase scans and to the patients’ clinical and/or laboratory data. The radiologists were allowed to choose the window width and window level for each CT phase, as they saw fit.

On separate standard questionnaires pertaining to each CT phase, the panel was asked to note whether the phase yielded findings positive or negative for focal liver lesions. If focal splenic lesions were present, this was also noted. The total number of focal liver lesions was recorded. For the CT examinations revealing 25 or fewer lesions, the specific number of lesions was given. For patient cases in which more than 25 lesions were depicted, the panel had to determine the appropriate range of the number of lesions: 26–50 lesions or more than 50 lesions. For cases in which more than 13 lesions were identified, the readers performed a complete analysis of the three largest lesions, the three smallest lesions, and at least eight additional lesions (at least one from each liver segment, if present). For each lesion, the following parameters were recorded:

1. Size: Lesion size was determined on the basis of the largest single dimensional measurement on the scan section on which the lesion was largest.
2. Consistency score: A score of 0 meant no lesions were identified; 1, the finding probably was not a lesion; 2, the finding probably was a lesion or an ill-defined lesion; and 3, the finding definitely was a lesion.
3. Lesion enhancement pattern (for arterial and portal venous phases only): A type 1 lesion was hypoattenuating and either subcentimeter in diameter (type 1a) or at least 1 cm in diameter (type 1b). A type 2 lesion had a hypoattenuating center and a hyperattenuating rim, the thickness of which was equal to or less
A positive phase result was defined as one
phases to have yielded positive findings.
The readers judged at least one of the CT
positive for fungal liver infection when
determined whether a given examina-
tion yielded results that were positive or
summarized the responses recorded on
not involved in the scan interpretations,
which was defined as an adjacent wedge-
shaped region of increased enhancement.
A type 4 lesion was any hyperattenuating
shape.

<p>| TABLE 1 |
| Rates of Diagnosis of Hepatic Fungal Infection according to CT Phase |</p>
<table>
<thead>
<tr>
<th>CT Phase</th>
<th>Detection Rate (%)*</th>
<th>95% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>100 (36/36)</td>
<td>90, 100</td>
</tr>
<tr>
<td>Portal venous</td>
<td>69 (25/36)</td>
<td>50, 84</td>
</tr>
<tr>
<td>Nonenhanced</td>
<td>67 (20/30)</td>
<td>47, 82</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are the data used to calculate the percentage: total number of CT phases yielding results positive for fungal infections/total number of CT examinations yielding positive results.

<p>| TABLE 2 |
| Rates of Focal Liver Lesion Detection according to CT Phase |</p>
<table>
<thead>
<tr>
<th>CT Phase</th>
<th>Detection Rate (%)*</th>
<th>95% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>90 (483/536)</td>
<td>82, 95</td>
</tr>
<tr>
<td>Portal venous</td>
<td>61 (329/536)</td>
<td>50, 71</td>
</tr>
<tr>
<td>Nonenhanced</td>
<td>57 (265/465)</td>
<td>45, 68</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are the data used to calculate the percentage: total number of lesions detected during the given phase/total number of lesions analyzed.

<p>| TABLE 3 |
| Comparison of Different Lesion Enhancement Patterns on Arterial and Portal Venous Phase CT Scans |</p>
<table>
<thead>
<tr>
<th>Arterial Phase</th>
<th>Not Detected</th>
<th>Nonspecific</th>
<th>Suggestive of Infection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not detected</td>
<td>34 (6)</td>
<td>19 (4)</td>
<td>0 (0)</td>
<td>53</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>12 (2)</td>
<td>79 (15)</td>
<td>6 (1)</td>
<td>97</td>
</tr>
<tr>
<td>Suggestive of infection</td>
<td>161 (30)</td>
<td>97 (18)</td>
<td>128 (24)</td>
<td>386</td>
</tr>
<tr>
<td>Total</td>
<td>207</td>
<td>195</td>
<td>134</td>
<td>536</td>
</tr>
</tbody>
</table>

Note.—Data are numbers of lesions. Numbers in parentheses are percentages (based on the total of 536 lesions). Note the large number of lesions that were not detected or not specific on the portal venous phase scans but were suggestive of infection on the arterial phase scans.

The rates of diagnosis of fungal liver infection at each CT phase were calculated. This diagnosis rate was defined as the number of lesions diagnosed as positive for infection at each phase (ie, on scans obtained during that phase) divided by the total number of lesions evaluated during that phase. The variances and corresponding 95% confidence intervals were estimated by using logistic regression models for each phase with an overdispersion parameter. The confidence interval for the arterial phase was based on exact methods because all liver infections were detected correctly and an asymptotic model could not be fit. The diagnosis rates for the three phases were tested for differences by using exact conditional logistic regression, with each reference-standard liver infection as a stratum. The variation between livers was thus treated as a nuisance parameter. A binary variable indicating whether the fungal infection was correctly diagnosed was the outcome variable, and the CT phase was the independent variable.

The detection rate for each phase was also calculated on a lesion-by-lesion basis. The numerator was the number of lesions seen during a given phase (ie, seen on scans obtained during a given phase), and the denominator was the total number of lesions assessed during all of the phases. For the nonenhanced CT phase, which was not used in all cases,
the denominator was the total number of lesions assessed during all of the phases for those cases in which nonenhanced CT was performed. To address any bias introduced by the second reading performed to match lesions, we repeated the statistical analysis to determine the lesion detection rate without a second reading. Detection rates were compared between phases by using generalized linear regression with a binomial error distribution, a logit link function, and generalized estimating equations to account for the correlation due to multiple lesions per patient. Responses from individual patients were assumed to be statistically independent. Ninety-five percent confidence intervals were calculated by using the variances from the generalized estimating equations modeling. The value of the dependent variable was 0 if a lesion was not detected during a given phase and 1 if a lesion was detected; the independent variable was a categorical variable indicating the phase type. Testing whether the independent variable had a coefficient significantly different from 0 was considered to be a test of whether the detection rates were different.

The frequencies of the different enhancement patterns on the CT scans obtained during each of the contrast material–enhanced phases also were determined. The enhancement patterns were grouped into patterns suggestive of infection and nonspecific patterns, and the frequency of lesions with patterns suggestive of infection that were seen during each of the contrast-enhanced phases was determined. Because small hypodense lesions—those with the type 1 enhancement pattern—are seen relatively frequently on liver CT scans (13) and confidence to prospectively diagnose them as microabscesses is lower (14), these lesions were termed nonspecific lesions. Lesions with a hyperattenuating rim or associated segmental perfusion abnormalities on contrast-enhanced phase scans are more likely to represent abscesses (15). In addition, a hypervascular enhancement pattern seen on spoiled gradient-echo MR images of liver candidiasis that were obtained immediately after gadolinium enhancement has been described (10). Therefore, for the purposes of this study, lesions with type 2–4 enhancement patterns were considered to be suggestive of infection. The proportions of lesions suggestive of infection that were seen during the arterial and portal venous phases were compared by using logistic regression with generalized estimating equations, as described earlier.

To determine whether lesion conspicuity differed between the different phases,
the proportions of lesions with a conspi-
cuity score of 3 (definitely a lesion) that
were seen during each phase were calcu-
lated. The modeling methods described
for detection rates were used to compare
the different phases.

SAS version 8.2 statistical software (SAS,
Cary, NC) was used for all analyses, except
the exact logistic regression analysis, for
which LogXact 4 (Cytel Software, Cam-
bridge, Mass) was used. \( P < .05 \) was con-
sidered to indicate statistical significance.

RESULTS

Thirty-six of the 60 CT examinations,
performed in 23 of 39 patients, were
found to yield results positive for fungal
liver infection. Thirty of these positive-
result examinations were triphasic, and
six were biphasic. The readers in the first
panel analysis evaluated 316 liver lesions,
and a total of 536 lesions were evaluated
after correlative reading. The sizes of the
lesions seen on arterial phase CT scans
ranged from 0.1 to 12.0 cm (mean, 1.19
cm; median, 1.00 cm); the sizes of the
lesions seen on portal venous phase
scans, from 0.1 to 14.0 cm (mean, 0.91
cm; median, 0.70 cm); and the sizes of
the lesions seen on nonenhanced scans,
from 0.2 to 6.0 cm (mean, 1.09 cm; me-
dian, 1.00 cm). The patients had a mean
of 8.7 lesions each (range, 1–30).

Lesion Detection

Of the 36 positive-result examinations,
11 yielded positive results during the ar-
terial phase but negative results during
the portal venous phase. The rate of di-
agnosis of hepatic fungal infection
achieved by using the arterial phase scans
(100%) was significantly higher than the
diagnosis rates achieved by using the por-
tal venous phase (69%) and nonen-
hanced (67%) scans \( (P < .001 \) for both
comparisons) (Fig 1). The diagnosis rates
for the portal venous and nonenhanced
phases were not significantly different
\( (P = .68) \) (Table 1). Of the 11 examina-
tions that yielded positive results during
only the arterial phase, four revealed

Figure 2. Transverse CT scans obtained in 67-year-old man with acute myeloid leukemia and candidemia. (a) Initially obtained arterial phase scan shows a type 4 (hypertenuating) lesion (arrows) in liver segment V. (b) On portal venous phase scan, no lesion can be appreciated. (c) Follow-up arterial phase scan obtained several weeks later shows the same lesion as in a but with type 2b morphologic features—specifically, a hypotenuating center with a thick hypertenuating rim (arrows). Scan also shows an additional lesion (arrowhead) in liver segment III.

Figure 3. Graph illustrates distribution of different lesion types on both kinds of contrast-enhanced-phase CT scans; proportions are based on a total of 536 lesions. Type 1 lesions were hypotenuating
and either subcentimeter in diameter (type 1a) or at least 1 cm in diameter (type 1b). Type 2 lesions had hypotenuating centers with a hypertenuating rim, the thickness of which was either equal to or
less than the radius of the hypotenuating center (type 2a) or greater
than the radius of the hypotenuating center (type 2b). Type 3
lesions were any lesions with associated transient hepatic enhance-
ment, defined as an adjacent wedge-shaped region of increased en-
hancement. Type 4 lesions were hypertenuating—that is, brighter
than the surrounding liver parenchyma on scans. \( AP = \) arterial phase,
\( ND = \) not detected, \( PVP = \) portal venous phase.
only type 4 lesions. For two examinations, at which a total of eight lesions were depicted, there were follow-up examinations, which revealed changes in the morphologic features or resolution of the lesions.

On a lesion-by-lesion basis, the lesion detection rate for the arterial phase (90%) was significantly higher than the detection rates for the portal venous (61%) and nonenhanced (57%) phases \((P < .001\) for both comparisons). The detection rates for the portal venous and nonenhanced phases were not significantly different \((P = .23)\) (Table 2). Almost a third of all the lesions (173 [32.3%] of 536) were seen on the arterial phase scans but not on the portal venous phase scans. Nineteen (3.5%) of 536 lesions were seen on the portal venous phase scans but not on the arterial phase scans. Nine (1.9%) of 465 lesions were seen on the nonenhanced scans but not on either the arterial phase or the portal venous phase scans.

We performed a separate statistical analysis of 316 lesions that were analyzed on scans obtained during all three phases at the initial panel reading (without any matching of lesions between phases). As before, the arterial phase was associated with a significantly higher detection rate (84% [267 of 316 lesions]) compared with the portal venous (46% [145 of 316 lesions]) and nonenhanced (38% [102 of 267 lesions]) phases \((P < .001\) for both comparisons), and the portal venous and nonenhanced phases were not significantly different \((P = .08)\). One hundred thirty-eight (43.7%) of 316 lesions were seen on arterial phase scans but not on portal venous phase scans. Sixteen (5.1%) of 316 lesions were seen on portal venous phase scans but not on arterial phase scans. Nine (3.4%) of 267 lesions were seen on nonenhanced scans but not on arterial phase or portal venous phase scans.

Twenty-two of the spleens examined had findings positive for fungal infection. The rates of detecting focal splenic lesions on the arterial phase (20 [91%] of 22 lesions) and portal venous phase (19 [86%] of 22 lesions) scans were not significantly different \((P = .66)\), but the detection rates for both contrast-enhanced phases were significantly higher than the detection rate for the nonenhanced phase (six [30%] of 20 lesions, \(P < .001\) for both comparisons).

### Lesion Type Distribution

The distributions of lesion types seen on arterial phase and portal venous phase CT scans are shown in Figure 3. The arterial phase and portal venous phase scans differed significantly in terms of the number of lesions suggestive of infection (types 2–4) that were detected \((P < .001)\) (Table 3). On the arterial phase scans, 386 (79.9%) of the 483 lesions detected were suggestive of infection. On the portal venous phase scans, 134 (40.7%) of the 329 lesions detected were suggestive of infection (Fig 4). Of the 145 type 1a lesions detected on portal venous phase scans, 66 (45.5%) were suggestive of infection on arterial phase scans. A large difference in the type 4 lesion detection rate also was noted (Fig 5). In a few of the patients for whom follow-up CT scans were available (Fig 2), we documented the regression of type 4 lesions to type 2a or type 2b lesions.

### Lesion Conspicuity

The lesion conspicuity scores for the arterial, portal venous, and nonenhanced phase CT scans were very similar (Fig 6). The proportions of findings considered to be definitely lesions were 83% (401 of 483 lesions) for the arterial phase, 82% (269 of 329 lesions) for the portal venous phase, and 79% (210 of 265 lesions) for the nonenhanced phase \((P > .05\) for all comparisons). The proportions of definite lesions based on whether the lesion had an enhancement pattern suggestive of infection did not differ significantly between the arterial and portal venous phases \((P = .15)\).

### DISCUSSION

During the past few decades, there has been a dramatic increase in the frequency of invasive fungal infections in patients with hematologic malignancies (16,17). These infections are associated with substantial morbidity and mortality in patients with acute leukemia who undergo chemotherapy (18), and the early diagnosis of these infections is important. Multiple factors have been suggested as contributors to the increased incidence of these infections in this patient population. These factors include intensive cytotoxic chemotherapies, the use of prophylactic antibiotics, and bone marrow transplantation (19,20).

Imaging has an important role in the diagnosis and follow-up of hepatosplenic fungal infection (6,8,10,21). In routine clinical practice, US, CT, and MR imaging may be used. Five patterns of US findings of liver candidiasis (21), which correlate with the stages of the disease, have been described. Data reported in the available literature that correlates these morphologic US patterns with portal venous phase CT findings indicate limited success in correlating US and portal venous phase CT findings. The “wheel within a wheel” and “wagon wheel” patterns represent early disease and usually are not seen at CT, whereas the “bull’s eye” pattern, which may also be seen during the acute stage of disease, is seen only occasionally at CT (21,22). It has been suggested, however, that overall, CT is supe-
rior to US in depicting fungal liver microabscesses (23) and that dynamic contrast-enhanced MR imaging is superior to dynamic contrast-enhanced portal venous phase CT (10). In another study involving patients with leukemia, portal venous phase CT depicted 60% of the lesions depicted by dynamic contrast-enhanced MR imaging (24); these results are in line with the 61% detection rate with portal venous phase CT observed in this study (compared with cumulative data for all three phases).

Results of studies on hypervascular hepatic lesions such as hepatoma, carcinoid metastasis, and melanoma have shown an increase in lesion detection with multiphasic CT, as compared with the lesion detection achieved with portal venous phase CT only (25–27). Inflammatory liver lesions may be associated with transient hepatic parenchymal enhancement during the arterial phase, probably owing to associated hyperemia and portal venous flow stoppage (15). For example, in cholangitis, transient hepatic parenchymal enhancement may be seen in a periporal location (28). Thus, the host response to the inflammatory process influences the imaging features of inflammatory liver lesions.

In addition, it has been well described that fungal lesions in the liver or spleen may not be visible until the patient recovers from the neutropenic stage of disease (11,29,30) and that they may become invisible if neutropenia recurs. These lesions may reappear 1–6 weeks after neutrophils recover; this reappearance indicates that fungal infection is still present and antifungal treatment needs to be continued (29). These facts suggest that the inflammatory response of the host has an important role in defining the characteristic appearance of these lesions on images (29) and may explain the increased diagnostic yield of the arterial phase in this study.

As the results indicate, without the addition of an arterial phase the overall diagnosis of fungal liver infection would have been missed in 11 (31%) of 36 cases, and 173 (32.3%) of 536 lesions would have been missed with use of only the portal venous phase. No difference in the detection of focal splenic lesions between the arterial phase and portal venous phase scans was noted, and both types of phase scans were more sensitive than the nonenhanced scans. Overall lesion conspicuity did not differ between the arterial, portal venous, and nonenhanced phases.

The use of an arterial phase also caused a significant alteration in the characterization of focal liver lesions with enhancement patterns that were potentially indicative of infection. Specifically, 45.5% of the subcentimeter hypoattenuating lesions seen on portal venous phase CT scans were depicted as lesions suggestive of infection on the arterial phase scans.

It is interesting to note that almost a third of all lesions detected on the arterial phase scans were type 4—that is, hyperattenuating without central hypoattenuation. Since only four patients had biopsy results positive for fungal infec-

Figure 5. Transverse CT scans obtained in 62-year-old woman with acute myeloid leukemia, prolonged fever after a neutropenic episode, and altered liver enzymes. Initially obtained portal venous phase CT scan (not shown) showed no focal liver lesions. (a) Arterial phase scan obtained 3 weeks later shows two lesions in the liver dome: a type 2a (hypoattenuating center with thin hyperattenuating rim) lesion (arrowhead) anteriorly and a type 4 (hyperattenuating) lesion (arrow) posteriorly. (b) Neither lesion seen in a can be appreciated on the portal venous phase scan. (c) Follow-up arterial phase scan obtained several weeks later shows that the type 2a lesion seen in a resolved; however, the posterior lesion (arrow) seen in a is still depicted. (d) Follow-up portal venous phase scan obtained several weeks later also does not show any focal lesions.

Figure 6. Graph illustrates comparison of lesion conspicuity scores for the three CT phases. AP = arterial phase, NC = nonenhanced phase, PVP = portal venous phase.
tion, we do not have histologic correla-
tion for the different morphologic lesion
types encountered. However, biopsy and
autopsy study results have shown that the
nidus of fungal infection in the liver is
walled off by inflammatory cells (22,29).
Therefore, a possible explanation for
the regression of type 4 lesions to type
2 lesions may be that during the early
phase of disease, during neutropenia, the
patient lacks the necessary inflammatory
response to form an identifiable hypoat-
tenuating granuloma. Instead, hyper-
emia secondary to the nidus of infection
is seen. As the patient’s neutrophil count
increases and a granuloma forms, the
typical hypoattenuating lesion is seen,
with or without a hyperattenuating rim
or associated transient parenchymal en-
hancement.

A limitation of this study was the lack
of histologic proof in the majority of pa-
tients. However, as has been shown in
the literature, obtaining histologic proof
in this patient population is difficult (6).
Therefore, our study inclusion criteria
were based on the suggested EORTC-
MSG guidelines for research (9). The true
sensitivities of all imaging modalities in
the diagnosis of fungal liver infection are
difficult to determine. In this study, 16
(41%) of 39 patients who fulfilled the
EORTC-MSG criteria for probable or
proven fungal liver infection had nega-
tive CT scans. It is uncertain how many
of these patients had occult fungal liver
infection.

We excluded all lesions that could be
definitively diagnosed as not related to
infection on the basis of imaging find-
ings or previous or follow-up imaging re-
sults, when available. Thus, we believe
that contamination of the pool of lesions
evaluated in this study by nonrelated les-
ions was minimized. It is conceivable
that some of the type 4 lesions detected
on the arterial phase scans were inciden-
tal hypervascular lesions such as focal
nodular hyperplasia or the uncommon
nodular form of transient hepatic arterial
perfusion disorders (28). However, al-
most 30% of the lesions detected on ar-
terial phase scans in this study were type
4 abnormalities; this proportion far ex-
ceeds the reported prevalence of inciden-
tal hypervascular lesions in noncirrhotic
livers (28,31). Similarly, the frequency of
type 1 lesions far exceeded the incidental
prevalence of multiple hepatic cysts or
biliary hamartomas (32).

Lack of histologic proof also prevented
us from specifically defining the different
CT-depicted morphologic structures en-
countered with pathologic correlates. In-
stead, we used the available literature to
define lesions that potentially repre-
sented microabscesses and thereby deter-
mine the increased specificity achieved
with the arterial phase.

In the patients with liver lesions
there was a large number of lesions per
patient. To minimize bias in such cases,
the readers were asked to select at least
one lesion per segment so that the liver
could be sampled as homogeneously as
possible. With use of this selection
technique, some bias is introduced. For
example, the most conspicuous lesions
are selected, and this practice can cause
an artificial increase in conspicuity
scores for some phases at lesion-by-
lesion analysis. The statistical bias in-
troduced by having multiple lesions in
a given patient, as well as the bias in-
troduced by having a given patient in-
cluded at more than one time point in
the study, was taken into account in the
statistical analyses.

Some patients did not undergo non-
enhanced CT, whereas all patients un-
derwent arterial phase and portal ve-
 nous phase scanning. This factor may
have led to a reduction in the reported
detection rate for the nonenhanced phase.
The decision to perform a biphasic
instead of triphasic CT examination was
arbitrary and based on a transient
change in protocol at our institution;
thus, we expected the associated bias
to be small.

In summary, the significant increase in
sensitivity and lesion conspicuity at ar-
terial phase CT indicates that a multiphasic
technique is needed for the assessment
of focal liver lesions in immunocompro-
mised patients suspected of having hepa-
tosplenic fungal infection. The addition
of an arterial phase may also yield addi-
tional imaging features that could aid
the radiologist in making a more confident
diagnosis of this disease.

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