

Invasive pulmonary aspergillosis: frequency and meaning of the “hypodense sign” on unenhanced CT

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Abstract. The purpose of this study was to establish the diagnostic value of central hypointensity (“hypodense sign”) in lung consolidations or nodules, in severely immunocompromised or neutropenic patients, suspected of having invasive pulmonary aspergillosis (IPA), and to assess its recognition on unenhanced CT scans. Serial CT scans of the lung were retrospectively reviewed in 43 consecutive immunosuppressed patients with IPA, and assessed for the presence of the hypodense sign using standard mediastinal and lung windowing settings, as well as a special, narrower window setting (width 110–140 HU; level 15–40 HU). The temporal relationship between the occurrence of the first CT-finding suspicious of IPA and the appearance of the hypodense sign, as well as between this and the occurrence of the crescent sign, cavitation or reduction in lesion size, was evaluated. Additionally, CT-scans from 89 immunocompromised patients with viral ($n=45$) or bacterial ($n=44$) pneumonia, investigated in the same time period at our institution were reviewed, with respect to the presence of the “hypodense” sign. Unenhanced CT scans revealed the hypodense sign in 11 neutropenic patients and 2 severely immunocompromised patients, out of a total of 43 patients with IPA evaluated in this study (30.2%). The mean time between the appearance of the first CT-findings of IPA (large nodule or consolidation $\pm$ positive halo sign) and the hypodense sign was 7.8 days, while the time interval between the hypodense sign and the occurrence of crescent sign, cavitation, or decrease of the lesion’s size was 8.3 days. The hypodense sign did not occur in any of the patients with viral or bacterial pneumonia, in the control series. We consider the hypodense sign to be a supplementary tool in the diagnosis of IPA. Its sensitivity was low in our series, but the high specificity makes it valuable in predicting IPA, anticipating the occurrence of cavitation or crescent sign, which are considered specific, but late findings of IPA. The hypodense sign is recognizable also on unenhanced CT, when a narrower lung window setting is used.

Invasive pulmonary aspergillosis (IPA) is a significant cause of morbidity and mortality in immunocompromised patients, especially in those with haematological malignancies and prolonged bone-marrow aplasia [1]. Early recognition of invasive fungal disease is imperative in these patients and the outcome depends strongly on the prompt institution of high-dose antifungal therapy [2, 3]. For this reason, extensive work has been done on the field of diagnostic imaging, especially on CT, yielding precious diagnostic tools, such as the “halo” sign, and the “crescent sign” [4–7]. These two features are not pathognomonic, but highly suggestive for the diagnosis of IPA in an appropriate clinical setting. Whilst the halo sign, consisting of a central nodule or mass of necrosis surrounded by a zone of haemorrhage, is present already in the early phase of disease, thus suggesting IPA, the crescent sign develops days to weeks after the initial presentation of radiographic abnormalities, namely in the resolving phase of the infection, when neutropenia in the peripheral blood is improving [8]. Accordingly, it is only the halo sign that early suggests IPA and therefore helps in initiation of therapy. Other CT-findings, including ill-defined nodules

or large segmental consolidations, are also considered indicative for IPA in immunosuppressed patients [9–11]. However, they have been reported also in association with other pathogens such as bacteria, tuberculosis (TB) and viruses, or even in patients with atelectasis showing therefore only low specificity [12]. Following administration of antifungal therapy, lesions may remain stable until the immune systems recovers, at which time the crescent sign can be seen. During this period of time, lesion characterization remains difficult, delaying adequate therapy.

A retrospective analysis of serial unenhanced CT scans of patients with IPA in our study, revealed another finding in early pulmonary consolidations or nodules that we called the “hypodense” sign. This is known to be caused by vascular obstruction with secondary lung infarction and sequestration in angioinvasive pulmonary aspergillosis, resulting finally in cavitation or lesion resolution. The use of contrast enhanced CT would certainly ease detection of lung infarction and necrosis, but the intravenous application of iodine contrast material in patients, shortly after high-dose therapy or bone marrow transplantation (BMT), is often contraindicated, because of impaired renal function. Moreover, the immunosuppressive therapy, after BMT, also impairs renal function.

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Therefore, most follow-up CT examinations are performed unenhanced.

Thus, the aim of our study was threefold: first of all to assess the frequency of the "hypodense" sign in patients with IPA showing pulmonary consolidations or nodules and its temporal relationship to the other known CT-findings suggestive of aspergillosis ("halo" sign, "crescent" sign); secondly to determine retrospectively the usefulness of the "hypodense" sign in predicting IPA and finally to find out if the "hypodense" sign was also recognizable on unenhanced CT scans.

Subjects and methods

43 consecutive patients with IPA (31 male and 12 female) aged 19–73 years (mean 48.3 years), who were diagnosed at our department from June 2000 to June 2004, were retrospectively included in this study and assessed for the presence of the hypodense sign, beginning with the very first findings of pulmonary infection up to the moment where they showed either the crescent sign, cavitation or decrease in size following administration of antifungal drugs. All the patients were either neutropenic, or severely immunocompromised, due to haematological diseases, following high-dose chemotherapy ($n=13$), or BMT ($n=30$). Patients included in this study were diagnosed with following diseases: acute myeloid leukaemia (AML) ($n=14$), acute lymphatic leukaemia (ALL) ($n=6$), non-Hodgkin's lymphoma (NHL) ($n=7$), multiple myeloma (MM) ($n=5$), chronic lymphatic leukaemia (CLL) ($n=2$), chronic myeloid leukaemia (CML) ($n=4$), aplastic anaemia (AA) ($n=1$), systemic AL-amyloidosis ($n=1$), Crohn's disease ($n=1$), myelodysplastic syndrome (MDS) ($n=1$) and 1 patient following renal transplantation. The diagnosis of IPA was established histopathologically using open lung biopsy, video-assisted thoracoscopic surgery, or fine-needle biopsy in 12 patients, by means of bronchoalveolar lavage fluid culture in two patients, or by a positive sandwich ELISA-technique that uses a monoclonal antibody to galactomannan in four patients. 25 patients had a positive polymerase chain reaction (PCR) for *Aspergillus*-DNA in the bronchoalveolar lavage fluid samples, associated with clinical and radiological findings of pulmonary infection.

The CT examinations were obtained with either a single-detector row CT scanner (Somatom Plus 4; Siemens Medical Systems, Erlangen, Germany), or a multi-detector row CT scanner Volume Zoom (Siemens Medical Engineering, Forchheim, Germany). All patients received 3–8 (mean 5.3) unenhanced CT-examinations of the thorax. The mean time interval between the first and the second CT-examination was 5.4 days (range 2–9 days). The next CT-investigation was performed after a mean time of 7.7 days (range 3–19 days), guided by the conventional X-ray and clinical survey.

Scanning parameters for spiral CT of the chest with a single-detector row CT scanner were 120 kVp, 120 mAs, 5 mm collimation and a pitch of 1.5. Axial scans through the thorax were obtained during full inspiration. Additional thin section CT scans were obtained with 1.0 mm collimation and at 10 mm slice interval. On the Volume Zoom scanner a collimation of 4 mm $\times$ 1.0 mm and a slice width of 1.25 mm were chosen. The table speed rotation was 6 mm and the rotation time was 0.75 s, with

a pitch of 1.5. We used an increment of 1.2 mm. The tube voltage was 120 kV and the tube current time product was 90 mAs. Images were reconstructed with a high-spatial-frequency algorithm (high-resolution CT) B70s kernel. All scans were viewed at standard mediastinal windows (level 35 HU; width 450 HU) and lung windows (level –700 HU; width 1500 HU), as well as at a special window (width 110–140 HU; level 15–40 HU).

The CT scans were reviewed separately by two radiologists (MH, CAP) and conclusions were reached by consensus only when discrepancies were identified. Both reviewers of the CT-scans were not aware of the results of the microbiological examinations. The pattern, distribution and extent of pulmonary abnormalities were analysed. The pattern was classified as consolidation in patchy or segmental distribution, nodule, ground-glass opacity (GGO), or reticular. Then, both readers were asked to look for the presence of a central hypodensity ("hypodense" sign) in all nodules or consolidations, using both the standard mediastinal window setting and a special, narrower window setting. In order to establish the sensitivity for both window settings in the diagnosis of the hypodense sign, a separate image analysis was performed by both readers and subsequently statistically evaluated. Central hypointensity of pulmonary segmental consolidations or nodules was diagnosed whenever differences in the density were obvious either by using a standard or a narrower window setting on unenhanced CT-scans. The halo sign was defined as an area of GGO surrounding a nodule, while air crescents surrounding soft-tissue lesions were regarded as the crescent sign.

Additionally, CT-findings from 89 consecutive patients with proven bacterial ($n=45$) or viral ($n=44$) pulmonary infection under immunosuppression were reviewed. The analysis of serial CT examinations in these patients was focused on the presence of the hypodense sign. All patients in the control group were also immunocompromised following high-dose chemotherapy or bone marrow transplantation and were investigated interspersed with cases of IPA during the same time period.

Sensitivity, specificity, prevalence, predictive values of positive and negative findings (PPV, NPV), and accuracy were estimated among all 132 patients with pneumonias of different aetiology, counting first the hypodense sign and then diagnosis IPA as positive for aspergillosis. Exact 95%-confidence intervals (CI) for measures independent of prevalence show how reliable the estimates are. Observer agreement was measured for the recognition of the hypodense sign and the differentiation between the three groups of pathogens by the unweighted kappa coefficient (κ). The strength of this evidence was expressed as the asymptotic standard deviation (SD) of κ .

Results

The hypodense sign was found in 13 out of 43 patients (30.2%) with IPA using a narrow window setting and in only 9 patients using the standard window setting. Interobserver agreement on this was very good ($\kappa=86\%$, SD 9.7%) and became perfect ($\kappa=100\%$), when the special window was used. Among the 13 patients with positive hypodense sign, 8 proved histologically positive for *Aspergillus* species, while 5 were found positive either for galactomannan antigen ($n=2$), or *Aspergillus*-PCR in

the bronchoalveolar lavage ($n=3$). The 13 patients included 3 women and 10 men aged 19–63 years (mean 46.2 years). 11 patients were neutropenic (absolute neutrophil count of <500 cells μl^{-1}) at the time of the initial CT examination. Two patients were severely immunosuppressed following BMT. Nine out of 13 patients were still in neutropenia at the time the hypodense sign was first detected. All patients received empiric therapy with a broad spectrum antibacterial therapy, at the time of clinical signs and symptoms of infection. Antifungal therapy consisted of an amphotericin B compound, or an anti-aspergillus effective azole drug. The first CT investigation was performed in every patient at the time they became clinically ill, and sequentially over the period of time until they showed clinical amelioration or deceased. The results are listed in Table 1. Initial CT-findings in the 13 patients presenting the “hypodense sign” were: consolidation ($n=7$), or large nodule ($n=6$). Five patients had solitary lesions, while nine patients had multiple pulmonary lesions. In all 13 patients lesions were accompanied initially by a halo sign. At follow-up, three patients (3/13) with initially nodular lung opacities developed large consolidations. In the other patients (10/13), lung nodules maintained their initial configuration at follow-up, varying only in size.

The time interval between the first CT findings of pulmonary infection and the appearance of the hypodense sign was 3–23 days (mean 7.8 days), while the time interval between the occurrence of the hypodense sign and the appearance of cavitation, crescent sign, or decrease of the lesion size was 2–19 days (mean 8.3 days). The mean duration of neutropenia was 17 days. Pulmonary parenchymal changes were evaluated first with the lung window setting and thereafter with the standard mediastinal window setting (Figure 1). However, with the usual mediastinal window setting (width 400 HU; level 30 HU) the discrete differences between lung opacity in the peripheral zone of the lesion (30–35 HU) and lower density of necrotic central areas (15–20 HU) were inconsistently perceivable (9/13). Therefore, a narrower soft tissue window (width 110–140 HU; level 15–40 HU) was set, in order to demonstrate the presence of the hypodense sign

(Figure 1a). Following adjustment of the window setting, the hypodense sign could be confirmed in all 13 patients.

On contrast enhanced CT-scans, performed in three patients in order to rule out abdominal infectious foci, delineation of the infarcted lung parenchyma was much easier, as illustrated in Figure 2.

The typical course of the disease, following antifungal therapy is shown in Figure 3. However, not all the lesions are going through all these phases. Especially, the smaller lesions showed a tendency to rapid decrease in size, followed by complete resolution. Thus, the “hypodense” sign was not always followed by the crescent sign or cavitation. The radiological manifestations of IPA in our patient’s group consisted of: nodules in 58% ($n=25$) patients, while consolidations were found only in 18.6% ($n=8$). In the rest of the patients ($n=10$) reticulation or peribronchial opacities were found. Most of the larger nodules or consolidations showed the hypodense sign, at follow-up, while smaller nodules and patchy consolidations did not. Correlation to pathological findings is demonstrated in a 55-year-old female patient with IPA, in Figure 4.

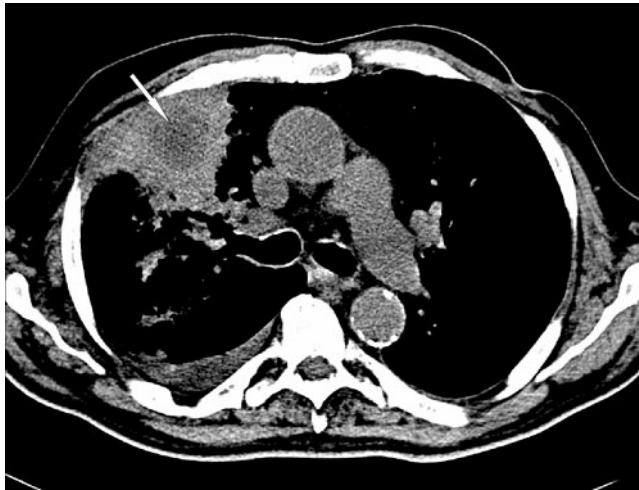
The frequency of the halo sign was 72% ($n=31$). The crescent sign was found only in 44%, while cavitation was demonstrated in 48% ($n=21$) patients. The distribution of cavitation among the two main CT-findings (nodules and consolidations) was 18.6% for consolidation and 30.2% for nodules. Six patients (13.9%) revealed solitary lesions. In 37 patients (86.1%) we found multiple pulmonary lesions.

A review of 44 cases of viral and 45 cases of bacterial pneumonias at our institution, in a similar patient cohort with immunosuppression following high-dose therapy or BMT or both, could not detect any lesion with a similar hypodense sign. This high specificity of 100% (CI 96–100%) was traded in for sensitivity 30% (CI 17–46%), resulting in PPV 100%, NPV 75%, and accuracy 77%. The differentiation of the 33% aspergillosis cases from other pneumonias by consensus resulted in a specificity of 81% (CI 71–88%), sensitivity of 72% (CI 56–85%), PPV of 65%, NPV of 86%, and accuracy of 78%. Observers agreed well when deciding between two groups ($\kappa=77\%$, SD 5.8) and three groups ($\kappa=78\%$, SD 4.7).

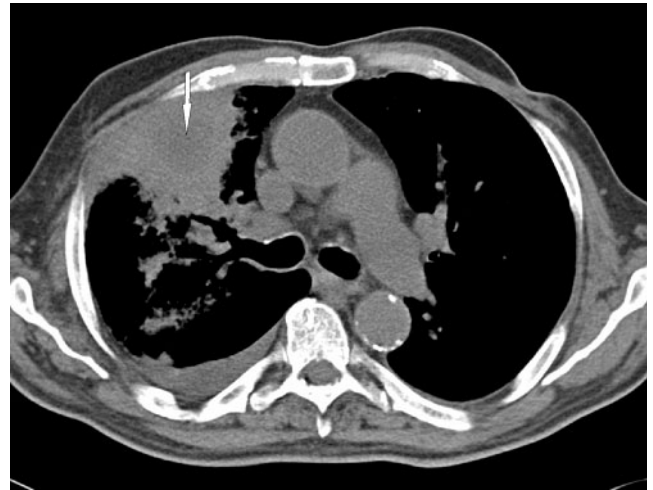
Table 1. Radiological findings in invasive pulmonary aspergillosis patients with positive hypodense sign and their correlation

Patient no./Age (years)/Sex	Underlying disease	No. of lesions	Halo sign	Crescent sign	Cavitation	Days between 1st CT-finding and HS	Days between HS and CS	Validation
1/58/M	NHL	m	+	+	-	3	3	BAL/PCR
2/32/M	ALL	m	+	+	+	7	6	Biopsy
3/63/M	AML	m	+	+	+	9	13	Biopsy
4/58/M	NHL	m	+	+	+	4	3	Biopsy
5/46/M	AML	s	+	+	+	7	19	Biopsy
6/34/M	CML	m	+	+	+	23	14	Biopsy
7/63/M	ALL	m	+	+	+	8	5	BAL/PCR
8/31/M	AML	m	+	+	+	12	7	Biopsy
9/58/M	MM	s	+	+	+	7	2	BAL/PCR
10/60/M	AML	s	+	+	+	3	3	Biopsy
11/19/M	ALL	s	+	+	-	7	5	Biopsy
12/35/M	ALL	m	+	+	+	7	7	Ag +
13/54/M	AML	s	+	+	+	5	4	Ag +

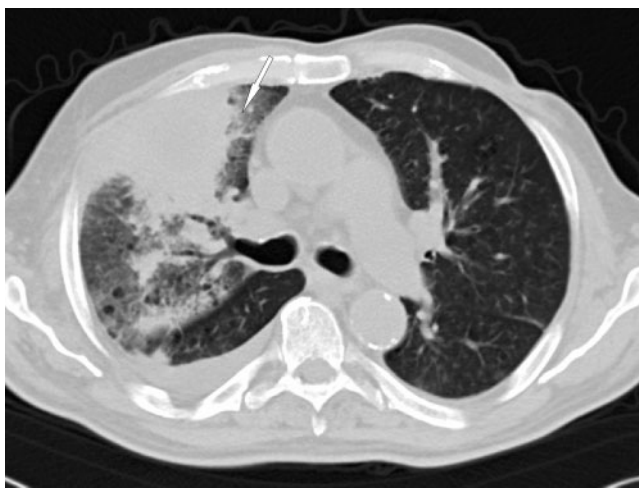
m, multiple; s, solitary; +, positive; -, negative; HS, hypodense sign; CS, crescent sign; BAL, bronchial lavage; NHL, non-Hodgkin’s lymphoma; ALL, acute lymphatic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; MM, multiple myeloma; PCR, polymerase chain reaction.



(a)



(b)

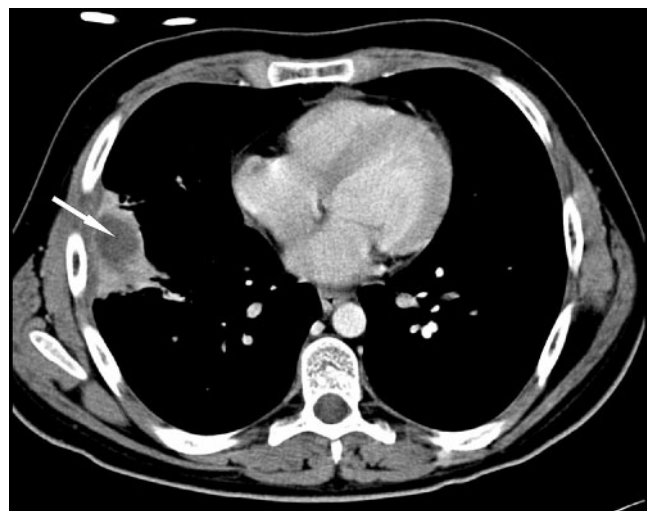


(c)

Figure 1. 63-year-old patient with fever at aplasia following bone marrow transplant for acute leukaemia. Axial unenhanced CT-image (view from below) shows a large area of consolidation in the right upper pulmonary lobe. (a) Using a narrow "soft tissue" window setting, the central hypointensity (white arrow) is easy to delineate (width 120 HU; level 20 HU). (b) Note poor delineation of the infarcted area (white arrow) on the same image viewed by standard "soft tissue" window setting (width 450 HU; level 35 HU). (c) The same lung opacity is viewed by a lung window setting (documented two slices caudally from a,b). This window setting is not suitable for recognition of the central hypointensity, but it demonstrates the halo sign (white arrow).



(a)



(b)

Figure 2. 17-year-old male patient with leukaemia and fever at aplasia after bone marrow transplant. (a) Axial non-enhanced CT-image shows focal subpleural consolidation in the right pulmonary lower lobe, due to lung parenchymal necrosis by invasive pulmonary aspergillosis. On unenhanced CT the central hypodense parenchymal infarction is though easily distinguishable. It is surrounded by inflammatory reaction (black arrow) and a hyperdense ring in between (white arrow), presumably caused by haemorrhage (confirmed by biopsy). (b) One of the follow-up CT examinations was performed after intravenous contrast material administration, in order to exclude other potential infectious complications in the abdomen. Easier delineation of infarcted lung parenchyma is obvious (white arrow). However, unenhanced CT is also of diagnostic quality.

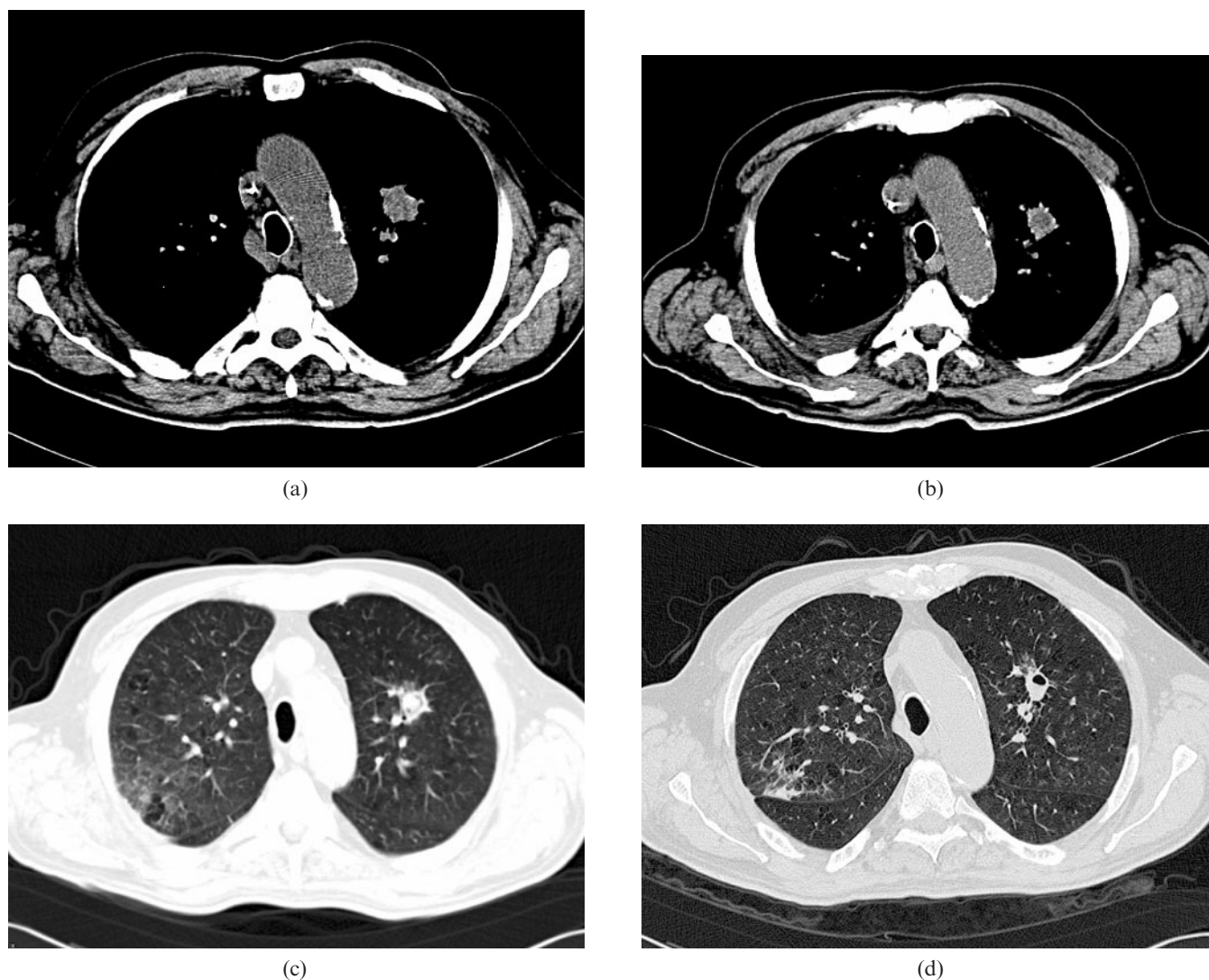


Figure 3. 63-year-old male patient with fever at aplasia following bone marrow transplant for acute myeloid leukaemia. Axial CT scans show follow-up of a nodular invasive pulmonary aspergillosis lesion in the upper lobe of the left lung. (a) A focal nodular lung parenchymal consolidation with homogeneous density is seen in the left upper lung lobe. By appropriate window setting (same window setting as on Figure 1a), (b) central hypodensity can be recognized. (c) Note delineation of the crescent sign, and (d) corresponding cavitation, following successful antifungal therapy.

Discussion

The radiological manifestations of IPA have been studied extensively and are well known. However, there are still no definitive highly specific imaging signs for early recognition of this often fatal infectious complication. Therefore, empiric therapy is usually started as soon as there is clinical suspicion of invasive aspergillosis. The outcome of therapy depends on early diagnosis and recovery of the underlying host defence defect, such as the resolution of neutropenia or immune reconstitution.

The most common manifestation of IPA is haemorrhagic infarction. This is associated with lung sequestra and radiographically with the occurrence of the crescent sign, which is considered highly-suggestive for IPA [13]. Its late appearance in the course of infection (during convalescence) substantially limits its usefulness for early diagnosis of this threatening infectious complication.

There is another extensively discussed feature of early IPA, the so-called halo-sign, which is related to the

presence of haemorrhage surrounding a central necrotic nodule. Some reports suggest that in an appropriate population, the CT appearance of early IPA with a visible halo sign is sufficiently characteristic to justify presumptive diagnosis and treatment. This was also confirmed by our study, where the halo sign was present in 72% of the patients. Unfortunately, the halo sign has also been reported in association with herpes simplex, cytomegalovirus, *Legionella pneumoniae*, TB, and some non-infectious processes, limiting its specificity even in patients at high risk for IPA [14].

According to our results, early recognition of central hypodensity ("hypodense" sign) in an immunocompromised patient suspected of IPA is a valuable diagnostic sign with admittedly low sensitivity, but high specificity, facilitating radiological diagnosis. On contrast enhanced CT studies differences in the density between pulmonary necrosis following infarction ("hypodense" sign) and surrounding haemorrhage and inflammation are detected more easily and presumably earlier. However, patients

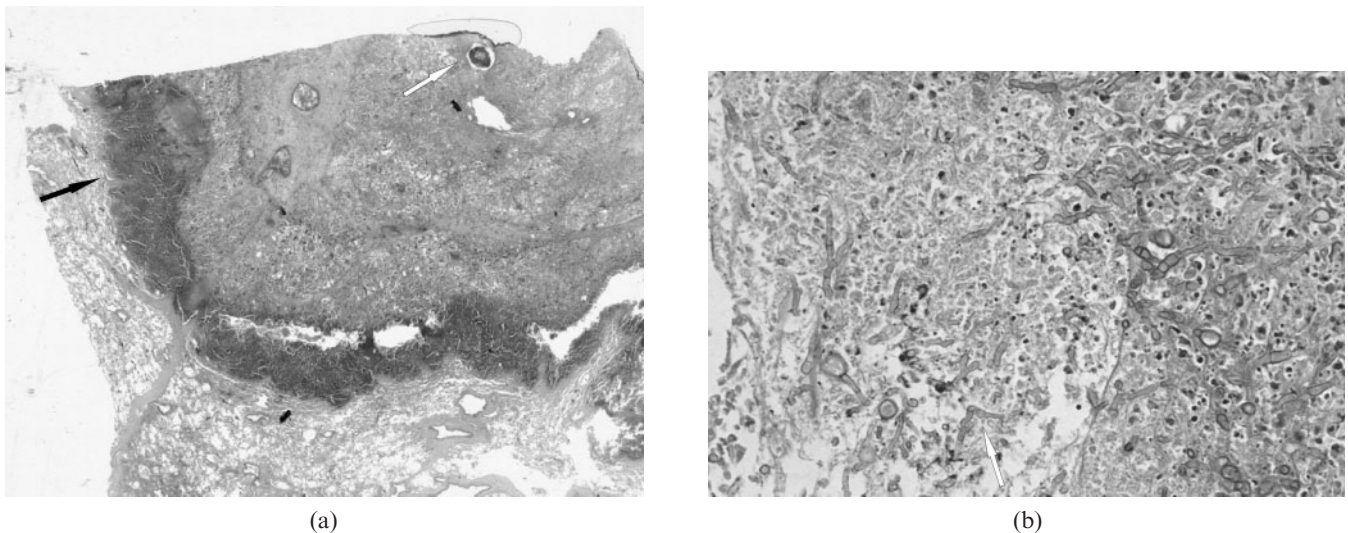


Figure 4. Invasive pulmonary aspergillosis in a 55-year-old female patient with chronic myeloid leukaemia. A magnified view of a slice of the right upper lobe shows vital hyphae of *Aspergillus fumigatus* in a pulmonary lesion with central necrosis. In the periphery of the lesion, beneath the "crescent air", a rim of chronic inflammation is present (black arrow). Note also hyphae in intravascular thrombotic material (white arrow). (a) PAS $\times 5$. (b) Photomicrograph from the area of consolidation shows tissue necrosis. *Aspergillus fumigatus* hyphae could be identified in necrotic tissue (white arrow). PAS $\times 400$.

following high-dose chemotherapy $\pm$ stem cell transplantation often present with impaired renal function, thus CT scans are often performed unenhanced. Although the hypodense sign can be found also in other infectious or non-infectious conditions, for instance in bacterial bronchopneumonia, with abscess formation and cavitation, these complications are usually not encountered in patients with severe neutropenia, because abscess formation is related to the presence of leukocytosis. Therefore, in cases with severe neutropenia, differentiation from abscess due to bacterial infection or other pathogens seems highly reliable. This statement was also supported by our retrospective study of patients with bacterial or viral pneumonias, where no single case with a hypodense sign could be found.

This study also shows that slight differences in tissue density between necrosis and lung consolidation are detectable on unenhanced CT scans if narrower soft tissue window settings are used, and that they occur prior to the crescent sign, thus, improving earlier diagnosis of IPA. Hence, the hypodense sign proved to be a precursor of the crescent sign, anticipating it by a range of 2–19 days (mean 8.3 days). In spite of the fact that both early CT-findings, the halo sign and the hypodense sign are ultimately not pathognomonic, their association strengthens the presumptive diagnosis of IPA. Similar changes are supposed to occur also in patients with small nodular pulmonary lesions, but recognition of these changes proves difficult, even after image magnification. This is perhaps due to the very thin associated peripheral areas of non-infarcted lung consolidation. The consequent application of intravenous contrast material or the supplementary use of MRI in patients with pulmonary nodules or consolidations could be an alternative to our study.

One of the limitations of this study is the limited number of patients and the lack of histological validation in all patients. This might explain the relatively low frequency of the hypodense sign in our patients' cohort, due perhaps to the coexistent cases of airway IPA, which does differ from the angioinvasive form. Another limitation of our study is

the lack of comparison with other pulmonary fungal infections (e.g. candidiasis, mucormycosis), which are supposed to behave similarly due to their angiotropic attributes. However, this differentiation would have no significant impact on therapy.

To our knowledge, there have been no other published data at this time, on this issue, although hypointense areas in lung consolidations in patients with IPA were mentioned sporadically by other authors [15].

In summary, we are proposing routine image analysis of unenhanced CT scans, in patients suspected of IPA, using a narrower soft tissue window setting, in order to detect central hypodensity due to lung infarction, which seems to have a high predictive value in this patient population, preceding the crescent sign.

References

- Geftter WB. The spectrum of pulmonary aspergillosis. *J Thorac Imag* 1992;7:56–74.
- Kuhlman JE, Fishman EK, Burch PA, Karp JE, Zerhouni EA, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: the contribution of CT to early diagnosis and aggressive management. *Chest* 1987;92:95–9.
- Glimp RA, Bayer AS. Pulmonary aspergilloma: diagnostic and therapeutic considerations. *Arch Intern Med* 1983;143:303–8.
- Hruban RH, Meziane MA, Zerhouni EA, Wheeler PS, Dumler JS, Hutchins GM. Radiologic-pathologic correlation of the CT halo sign in invasive pulmonary aspergillosis. *J Comput Assist Tomogr* 1987;11:534–6.
- Kuhlman JE, Fishman EK, Burch PA, Karp JE, Zerhouni EA, Siegelman SS. CT of invasive pulmonary aspergillosis. *AJR Am J Roentgenol* 1988;150:1015–20.
- Brown MJ, Miller RR, Müller NL. Acute lung disease in the immunocompromised host: CT and pathologic findings. *Radiology* 1994;190:247–54.
- Mori M, Galvin JR, Barloon TJ, Gingrich RD, Stanford W. Fungal pulmonary infections after bone marrow transplantation: evaluation with radiography and CT. *Radiology* 1991;178:721–6.

8. Min JK, Kyung SL, Jhigook K, Kyung-Jae J, Hong GL, Tae SK. Crescent sign in invasive pulmonary aspergillosis: frequency and related CT and clinical factors. *J Comput Assist Tomogr* 2001;25:305–10.
9. Hyung JW, Kyung SL, Jung-Eun C, Jung HH, Tae SK, Hong GL, et al. Invasive pulmonary aspergillosis: prediction at thin-section CT in patients with neutropenia- a prospective study. *Radiology* 1998;208:777–82.
10. Bray A, Pirroni T, Sallustio G, et al. Clinicoradiological patterns of invasive pulmonary aspergillosis. *Radiology* 1997;205:673.
11. Blum U, Windfuhr M, Buitrago-Tellez C, et al. Invasive pulmonary aspergillosis: MRI, CT and plain radiographic findings and their contribution for early diagnosis. *Chest* 1994;106:1156–61.
12. Gaeta M, Volta S, Strosio S, et al. CT “halo sign” in pulmonary tuberculoma. *J Comput Assist Tomogr* 1992;16:827–8.
13. Curtis AMB, Smith GJW, Ravin CE. Air crescent sign of invasive aspergillosis. *Radiology* 1979;133:17–21.
14. Primack S, Hartman TE, Kyung SL, Müller NL. Pulmonary nodules and the CT halo sign. *Radiology* 1994;190:513–5.
15. Kang E-Y, Kim DH, Woo OH, Choi J-A, Oh Y-W, Kim CH. Pulmonary aspergillosis in immunocompetent hosts without underlying lesions of the lung: radiologic and pathologic findings. *AJR Am J Roentgenol* 2001;178:1395–9.