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The radiological spectrum of invasive aspergillosis in children: a 10-year review

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Abstract *Background*: Invasive aspergillosis is an uncommon but life-threatening event in the immunocompromised child. Attempts at fungal isolation are often unrewarding and a high index of radiological suspicion is essential in the early diagnosis of infected children. *Objective*: To document the radiological spectrum of disease in invasive aspergillosis in the paediatric population. *Materials and methods*: A retrospective review of the imaging performed in 27 consecutive patients (age 7 months to 18 years) with documented invasive Aspergillosis encountered over a 10-year period at a single institution. *Results*: Radiographic findings of pulmonary disease (20 patients) included segmental and multilobar consolidation, perihilar infiltrates, multiple small nodules, peripheral nodular masses and pleural effusions. No cavitating lesions were seen on CXR. Small cavitating nodules were present on CT in two of eight children. Chest wall disease was particularly associated with underlying chronic granulomatous disease. Disseminated disease manifested as osteomyelitis ($n=5$), cerebral ($n=3$), oesophageal ($n=1$), hepatic ($n=2$), renal ($n=2$) and cutaneous ($n=5$) involvement. Imaging findings are discussed. Twelve patients (44%) subsequently died from Aspergillus-related complications. *Conclusions*: Invasive aspergillosis presents with a wide variety of radiographic findings involving multiple organ systems. Respiratory findings are varied but often non-specific, and a high index of suspicion is necessary in immunocompromised patients. In contrast to adult disease, the incidence of cavitation of pulmonary lesions appears low.

Keywords Children · Lung · Infection · Aspergillosis · Immunodeficiency · Radiography · CT

Introduction

Invasive pulmonary aspergillosis (IPA) is a rare but potentially fatal opportunistic infection in the immunocompromised patient. The majority of cases occur in neutropenic patients [1] undergoing chemotherapy for haematological malignancies, bone marrow and solid organ transplant recipients, and children with primary immunodeficiency syndromes. Aspergillus is a ubiquitous saprophytic mould found in many environmental sites [2], including hospital ventilation systems [3, 4]. Infection is usually via inhalation of spores, although the skin, gastrointestinal tract and nasopharynx can also provide routes of entry. Septate, branching hyphae are observed microscopically and stain with methenamine silver and periodic acid-Schiff stains. Histologically, lung

infection is characterised by angioinvasion with transbronchial spread of organisms into adjacent pulmonary arterioles, resulting in arteriolar thrombosis and consequent haemorrhagic infarction of lung tissue [5]. Contiguous spread of inflammatory masses and haematogenous dissemination of disease may occur.

Despite aggressive treatment, mortality remains high, being over 50% in most series [2, 6, 7] and sometimes exceeding 90% [8], with significant long-term morbidity in survivors. Early treatment can improve survival [9, 10], but definitive diagnosis is difficult and often delayed. Sputum cultures are positive in less than 10% of patients, serological tests are often unreliable and bronchoalveolar lavage may yield false-negative results [5, 6, 10, 11]. Fungal polymerase chain reaction (PCR) assays hold promise for the future [12], but are not yet widely available and their impact on clinical practice remains uncertain. At present, tissue biopsy often remains necessary, but carries risks in thrombocytopenic patients and those with significant respiratory compromise [5]. Even open lung biopsy may be falsely negative early in the course of infection [10].

There have been several recent advances in the treatment of invasive aspergillosis, including the advent of liposomal amphotericin [13] and adjuvant treatments including itraconazole, gamma-interferon and granulocyte colony-stimulating factor-mobilised granulocytes [14, 15]. The use of prophylactic oral triazoles may reduce, but have not eliminated the risk of this disease in susceptible patients [16], and it remains a life-threatening condition.

The spectrum of chest radiographic findings in adult IPA has been well described [6, 17, 18, 19]. More recently, the role of early CT as a non-invasive method of diagnosis has been proposed by Kulman et al. [5, 10, 20] and has entered adult clinical practice. However, there are few paediatric series in the literature [21, 22, 23]. Our aim was to review the imaging performed on a large cohort of children treated at a tertiary referral centre with documented IPA.

Materials and methods

Our cohort included 27 consecutive cases of IPA diagnosed over a 10-year period in the haematology, oncology, immunology and infectious diseases departments of a large tertiary referral hospital. All available imaging was reviewed and correlated with clinical and microbiological data. All 27 patients (21 boys, 6 girls; age range 7 months to 18 years; mean age 5 years) had an underlying disease associated with immunodeficiency or had received immunosuppressive therapy. Twelve children had primary immunodeficiency states (chronic granulomatous disease [CGD; $n=6$] and severe combined immune deficiency syndrome [SCID; $n=6$]); 12 had malignant haematological disorders (leukaemia [$n=7$], non-Hodgkin's lymphoma [$n=2$], myelodysplasia [$n=1$], haemophagocytic lymphohistiocytosis [HLH; $n=1$], aplastic anaemia [$n=1$]); one child had a solid tumour (neuroblastoma); and two children were receiving high-dose corticosteroid therapy for vasculitis. Ten children had recently undergone bone marrow transplantation.

The diagnosis of IPA was established using the Criteria for Diagnosis of Invasive Fungal Infection developed by the European Organisation for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases [24]. Definite infection was established in 16 children by histopathological evidence of invasive fungal infection or by demonstration of septate hyphae cultured from a normally sterile site. Probable infection was defined by positive bronchoalveolar lavage ($n=4$), sputum ($n=6$) and/or serology ($n=1$) in association with clinical features and host factors as defined by the EORTC. Post-mortem evidence was available in two children.

Multiple Aspergillus species were implicated as causative agents including *Aspergillus fumigatus* ($n=8$), *A. flavus* ($n=1$) and *A. nodulans* ($n=1$). In 17 cases the species was not identified.

Results

Disease appeared confined to a single site in 12 children (10 respiratory, 2 cutaneous). In ten children there was histological or microbiological evidence of multisystem disease and in five children there was probable multisystem disease (documented extrapulmonary disease with abnormal chest radiography findings, but without confirmatory respiratory isolation evidence). Extrapulmonary disease included osteomyelitis ($n=5$), cutaneous ($n=4$), cerebral ($n=3$), renal ($n=2$), hepatic ($n=2$), gastrointestinal ($n=1$) and nasopharyngeal ($n=1$) involvement. The initial presentation site was respiratory in 14 (52%) of 27 cases, osteomyelitis ($n=5$), central nervous system ($n=3$), cutaneous ($n=4$) and renal ($n=1$). Twelve patients (44%) subsequently died from Aspergillus-related complications.

Respiratory disease

Chest radiographs were available in 18 of 20 children with documented respiratory disease. Five cases in whom an abnormal CXR was associated with extrapulmonary disease, but no respiratory isolation evidence was available, were not included in the study owing to the difficulty in excluding alternative causes for the radiographic findings. Chest radiographic findings were varied and several patients demonstrated multiple findings (Figs. 1, 2, 3). The major findings were segmental consolidation ($n=7$), multilobar consolidation ($n=4$), perihilar infiltrate ($n=4$), multiple small nodules ($n=4$), larger peripheral nodular mass(es) ($n=2$), and pleural effusions ($n=3$). Ground-glass shadowing progressing to diffuse alveolar shadowing was seen in one child, and in one case the chest radiograph remained normal. In no case was convincing radiographic evidence of cavitation or air crescent formation seen.

In susceptible patients, treatment for fungal infection is often commenced on an empirical basis (in this

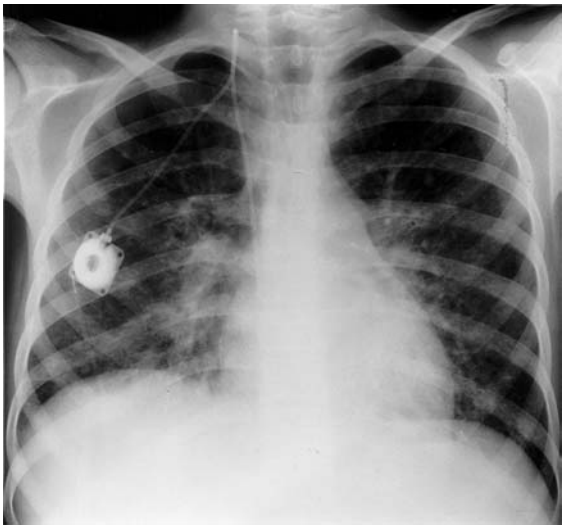

Fig. 1 Multiple small nodules throughout both lungs in association with perihilar shadowing in an 18-year-old boy with CGD

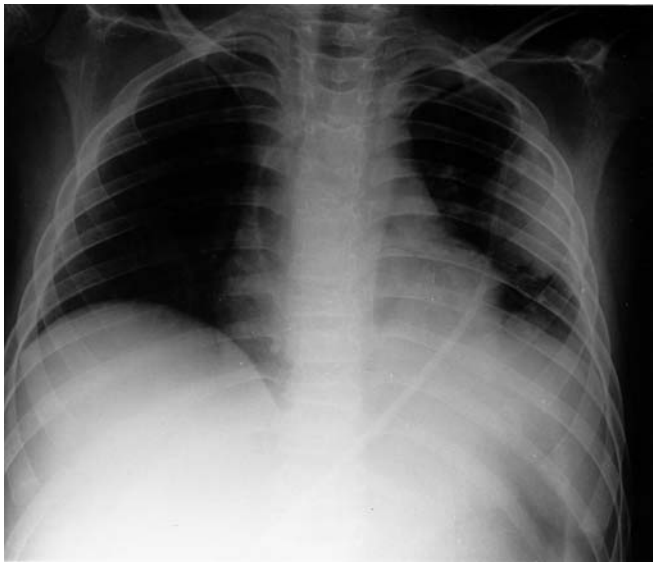

Fig. 2 A large, pleural-based nodular mass in the left mid-zone, left lower lobe consolidation and a small left pleural effusion in an 8-year-old boy after bone marrow transplantation for ALL. See Fig. 5 for CT

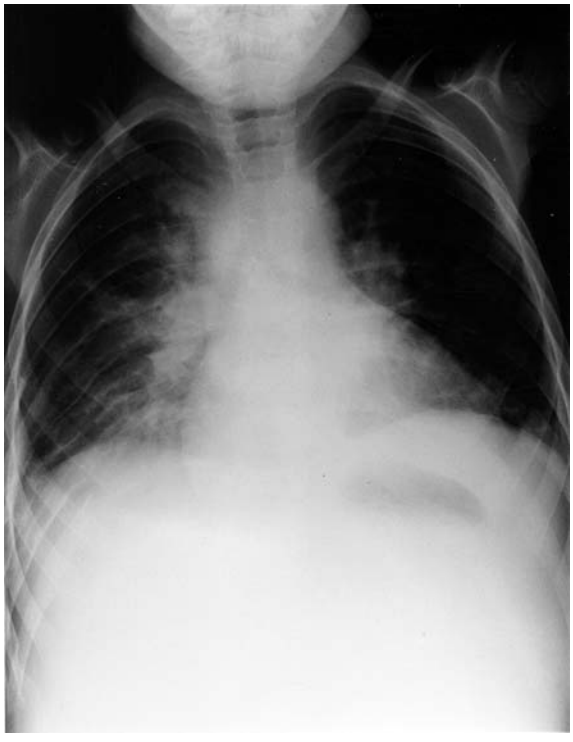

Fig. 3 Perihilar and bibasal infiltrates in a 5-year-old child with osteomyelitis of the thoracic cage. Extensive periostitis and modelling deformity of the lower right ribs is demonstrated

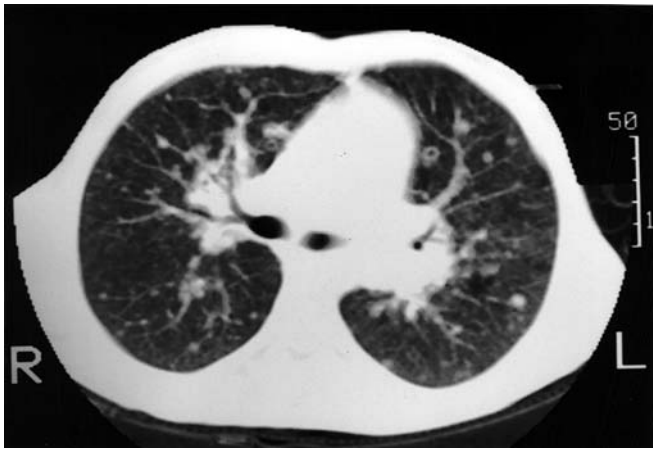

Fig. 4 CT chest view of a 2-year-old boy showing consolidation and multiple small nodules, some subpleurally located and a few demonstrating central cavitation

institution, a fever persisting for greater than 5 days and unresponsive to broad-spectrum antibiotics). In 7 (50%) of 14 children presenting with respiratory disease, the CXR was normal at the time of commencing treatment.

Chest CT (using contiguous slices) was available in eight cases; five presented with respiratory disease and three with osteomyelitis of the thoracolumbar spine or thoracic cage. Multiple small nodules, some of which were subpleurally located, were seen in four patients (underlying diagnoses were CGD [$n = 2$], HLH, systemic lupus erythematosus). In two of four patients central cavitation of a number of the nodules was observed (Fig. 4). None of the nodules demonstrated the early CT halo sign, a finding probably related to the disease phase of our scans. In two of three patients with segmental or multilobar consolidation on chest radiographs, CT

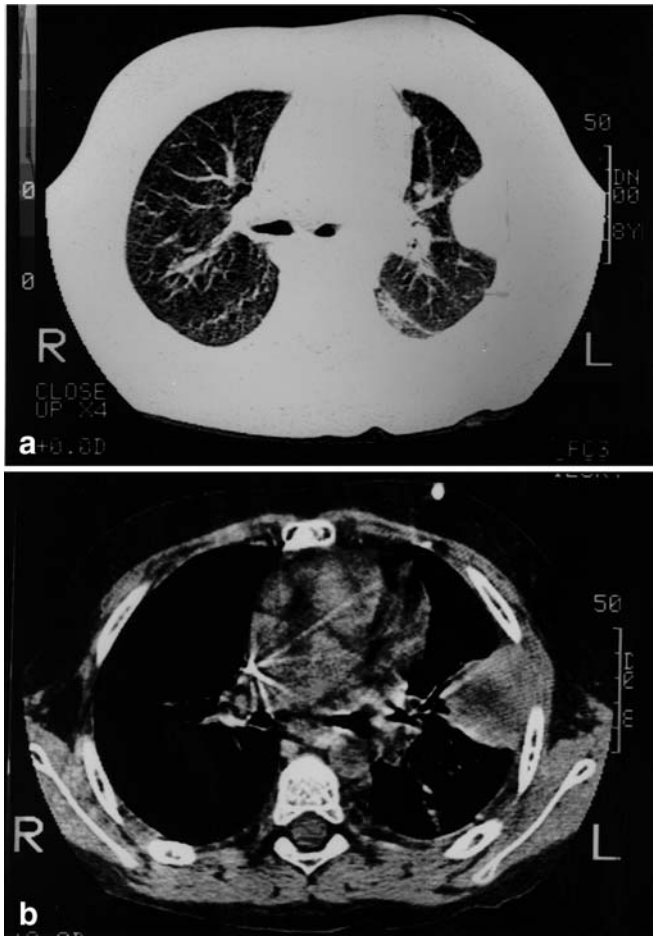

Fig. 5a, b CT of patient shown in Fig. 2. **a** Lung window and **b** soft-tissue window. There is peripheral non-cavitating consolidation in the left upper lobe, in addition to several further small nodules anteriorly. Following severe haemoptysis, surgical exploration revealed an arterial bleeding site and a left upper lobectomy was performed

demonstrated further small nodules not visible radiographically (Fig. 5). In the remaining two children undergoing CT, segmental consolidation and bibasal consolidation adjacent to a paravertebral infective mass were demonstrated (Fig. 6). There was no evidence of cavitation or air crescent formation within any area of consolidation on CT.

Upper respiratory tract disease was associated with pulmonary disease in one case. Extensive bony destruction of the palate and sinuses, demonstrated on chest radiography and CT, required surgical debridement and repair of a palatal fistula.

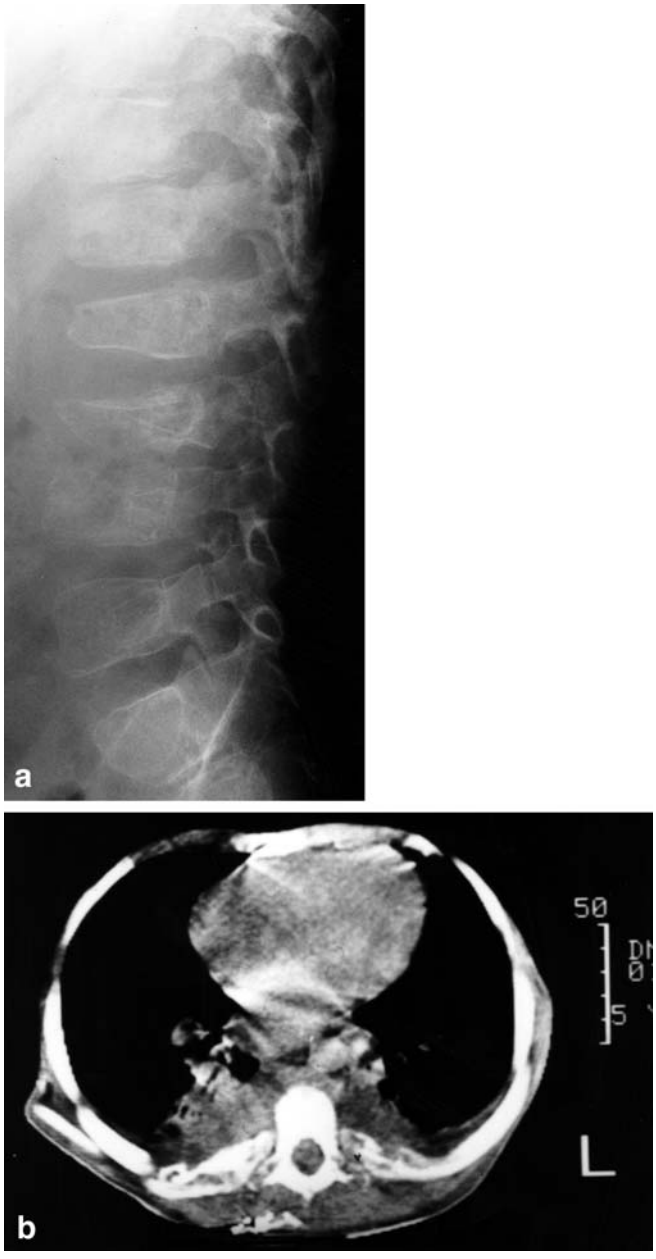

Fig. 6a, b This 5-year-old child with CGD developed vertebral osteomyelitis involving at least 10 vertebral bodies. **a** Lateral lumbar spine radiograph showed diffuse osteopenia with permeative changes and collapse of several vertebral bodies. **b** Contrast-enhanced CT demonstrates a paravertebral soft-tissue mass extending from the mid thorax to below the kidneys. Osteomyelitis of the posterior ribs and consolidation within the right lower lobe are noted adjacent to the mass

Extrapulmonary presentations

Five children presented with osteomyelitis (thoracolumbar spine [$n = 2$], sternum [$n = 1$], rib [$n = 1$], mandible [$n = 1$]). All four cases involving the thoracic cage occurred in children with an underlying diagnosis of CGD. A child with acute myeloid leukaemia (AML) presented with osteomyelitis of the mandible. Clinical features included soft-tissue swelling or palpable abscess

formation, local pain and fever. Radiologically, bone destruction was associated with significant soft-tissue inflammatory masses. Extensive local spread was a characteristic feature. ^{99m}Tc-MDP bone scans showed corresponding areas of increased radioisotope uptake. Two cases of thoracolumbar osteomyelitis were associated with large low-density paravertebral masses on unenhanced and contrast-enhanced CT (Fig. 6). The left kidney was involved by contiguous spread in one child (Fig. 7). In all cases with osteomyelitis, surgical drainage of soft-tissue abscesses or bony resection was necessary in addition to aggressive medical therapy. Those children with underlying CGD survived; the child with AML died.

Children with cerebral involvement ($n=3$) presented with seizures or an altered level of consciousness. CT findings included both poorly defined low-attenuation areas of cerebritis in the deep white matter and the basal ganglia and, in one child, the development of a localised abscess with ring enhancement (Fig. 8). Surgical aspiration of the abscess was performed. However, central nervous system disease was associated with a poor prognosis; all three children died.

Two children developed liver abscesses with multiple hypoechoic lesions demonstrated by US (Fig. 9). Renal disease occurred both as a primary site of infection in an 18-month-old child presenting with macroscopic haematuria and fever, and by contiguous spread from paravertebral disease associated with osteomyelitis (Fig. 7). Oesophageal aspergillosis was documented on tissue biopsy but no gastrointestinal imaging was performed.

Cutaneous invasive Aspergillus infections manifested as erythematous lesions or ulcers on the hands, feet or thigh in four children and were documented by skin biopsy and culture. In two children there was microbiological or radiographic evidence of respiratory involvement and in two cases infection was confined to the skin. In two patients, infection may have been related to previous IV cannula sites. Three children required debridement and excision of necrotic tissue. In one case, extensive cutaneous and subcutaneous disease of the thigh developed and although ^{99m}Tc-MDP bone scan demonstrated abnormal soft-tissue uptake but no bony involvement, this child eventually required an above-the-knee amputation for persistent aggressive disease.

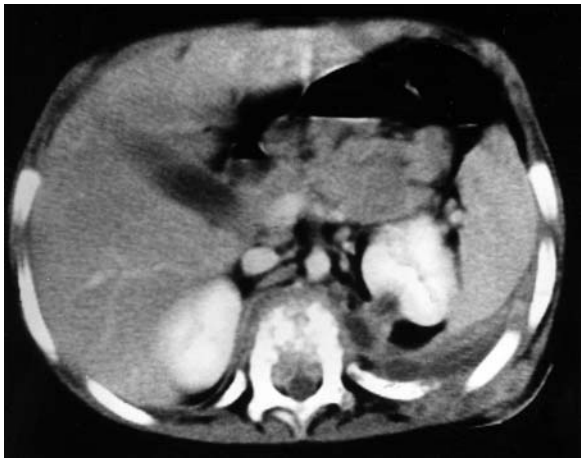

Fig. 7 Contrast-enhanced CT of the abdomen in a 2-year-old child demonstrating lumbar vertebral osteomyelitis with vertebral body destruction, a left paraspinal and chest wall soft-tissue mass containing focal areas of low attenuation and contiguous spread to the left kidney

Discussion

IPA, although an uncommon disease, is of increasing importance in children owing to the expanding role of high-dose chemo/radiotherapy and bone marrow

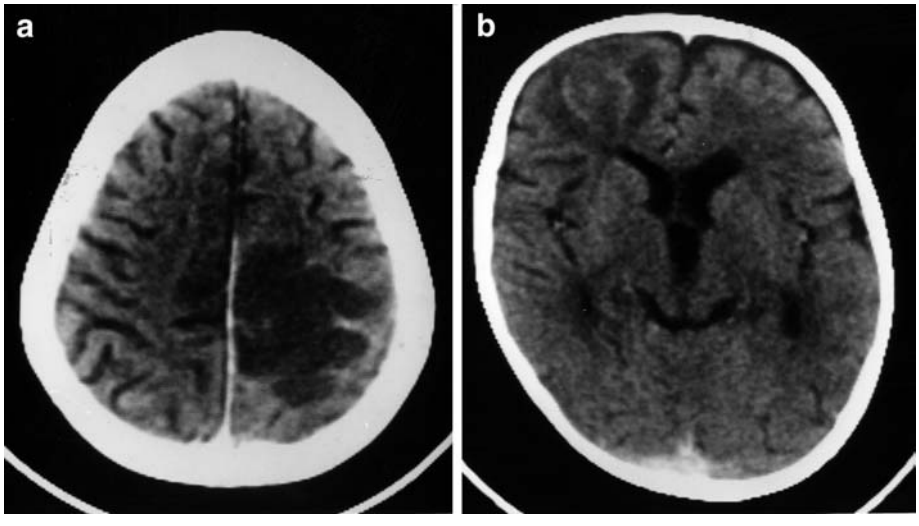

Fig. 8a, b Unenhanced CT of the brain in a 17-month-old boy with SCID showing **a** low-density cerebritis in the left centrum semiovale and **b** a more localised abscess in the deep white matter of the right frontal lobe with a high density rim and surrounding oedema. Aspiration yielded Aspergillus

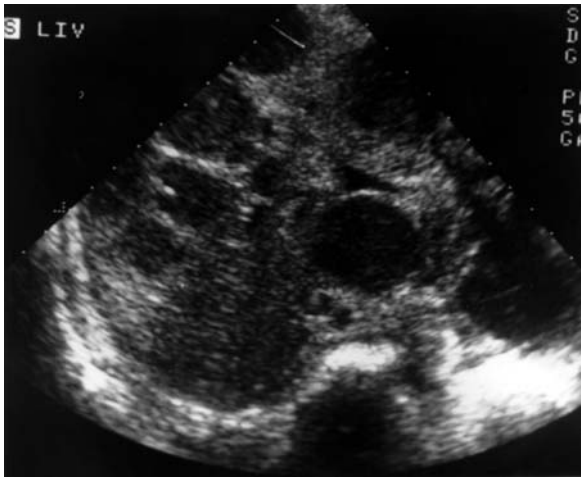

Fig. 9 Ultrasound of the liver with multiple, rounded hypoechoic lesions in a 7-year-old boy with respiratory and hepatic aspergillosis. He had recently commenced chemotherapy for non-Hodgkin's lymphoma

transplantation in haematological malignancies, primary immunodeficiency syndromes and inborn errors of metabolism. The major risk factors predisposing to infection are neutropenia of greater than 3 weeks' duration, corticosteroids and chemotherapy [1, 6]. Definitive microbiological diagnosis is difficult and often delayed [5, 11].

The disease is characterised by angioinvasion, arteriolar thrombosis and haematogenous dissemination. Pathologically, pulmonary findings include necrotising bronchopneumonia, haemorrhagic pulmonary infarction, micro-abscesses, solitary abscesses, lobar pneumonia, and tracheobronchitis [25].

Radiographically, consolidation, which may be segmental, multifocal or diffuse, and nodular infiltrates are described [6, 17, 18, 19, 26]. In adult series, approximately 50% of cases show cavitation [26, 27] with air crescent formation in 40% [27]. Pathologically, the air crescent corresponds to an air-filled space resulting from the resorption of necrotic tissue at the periphery of the lesion [20, 28] and occurs during the resolution phase of the illness, coinciding with recovery from neutropenia. The CT halo sign and its role in the early non-invasive diagnosis of IPA have been described by Kuhlman et al. [5, 10, 20]. A zone of lower attenuation surrounding nodules or a pulmonary mass (the halo sign) corresponds to the ring of haemorrhage which surrounds lesions histologically [28] and antedates the development of cavitation by 1–2 weeks. Although not totally specific [29], its presence is highly predictive of Aspergillus infection in the appropriate clinical setting.

Radiological data from the paediatric population is limited. We have described the radiological findings in a large cohort of paediatric patients encountered over a 10-year period. CXR findings are often non-specific with segmental consolidation, multi-lobar consolidation, perihilar infiltrates and pleural effusions. Multiple small nodules provide a more specific pointer to the diagnosis of fungal disease. Larger, pleural-based nodular masses should also raise suspicion.

No air crescents or other signs of cavitation were seen on chest radiography. In two of eight children in whom CT was available, central cavitation of small nodules was seen, but there were no air crescents or cavitation within areas of consolidation. In previous paediatric series, Allan et al. [21] found cavitating lesions on chest radiography in 6 (22%) of 27 cases of fungal respiratory disease in children less than 21 years of age, and Taccone et al. [22] described cavitation on CT in 6 of 14 children (age range 7–18 years, mean 11 years) with IPA and underlying malignancy; three manifest as air crescents and three demonstrated cavitating small nodules. These figures are lower than in adults although higher than in our experience. The younger mean age of our study group (5 years) may be relevant to our lower incidence of cavitation.

The underlying reason for the low cavitation rate in children is not known. Cavitation occurs late in the disease and coincides with the recovery phase of neutropenia in patients with haematological malignancies or undergoing bone marrow transplantation. However, many paediatric cases occur in children with primary immunodeficiency (CGD or SCID) and persistent qualitative defects in granulocyte function. Thus, differences in host response may account for the low incidence of cavitation. Evidence in support of this is provided by Miller et al. [30] who found no air crescents on chest radiographs in 17 IPA cases in adult AIDS patients and suggest that this was due to the lack of a rapid rise in neutrophil counts, and by Gefter et al. [26] who demonstrated that cavitation was less likely to develop in leukaemic patients if bone marrow recovery failed to occur. However, our study demonstrated an equally low incidence of cavitation in patients with iatrogenic immunosuppression and those with primary immunodeficiency. This, therefore, cannot provide a complete explanation.

Airway-invasive aspergillosis involving infection of the airways with invasion of the basement membrane but without angio-invasion has been described in the histopathological literature [31], but only recently appreciated radiologically [32]. This probably represents 10–34% of cases of IPA [33]. Findings include unilateral or bilateral consolidation and ill-defined nodules on chest radiography and lobar consolidation, peribronchial consolidation and small centrilobular nodules on high-resolution CT [32]. Cavitation is not described. Differentiation of airways-invasive from angio-invasive disease of the lungs requires tissue biopsy. This was available in only one of our ten cases with isolated respiratory disease, and the possibility that some of our cases represent airways-invasive disease must be

considered. However, our study group includes at least ten children with disseminated disease, and hence angioinvasion. The low frequency of cavitation in these cases makes it unlikely that airways IPA provides the explanation. The underlying cause for the low incidence of cavitation seen in children with IPA is, therefore, not fully understood, but must be considered when interpreting chest radiography findings in susceptible patients.

The CT halo sign was not observed in our series. However, this probably reflects the relatively late stage of disease in which our patients were scanned, particularly in the early years of our 10-year cohort when the use of CT was more limited than present-day practice. The value of the halo sign in the early diagnosis of IPA [5, 10, 20, 34] is now well documented, and we recommend early recourse to high-resolution CT in our current practice.

Consistent with previous studies, osteomyelitis of the thoracic cage was particularly associated with underlying CGD [35, 36], in which local extension of disease from lung parenchymal infection can occur in up to one-third of cases [35] (Fig. 10). Osteopenia and local bony destruction associated with large, contiguous, soft-tissue inflammatory masses are characteristic, and abscess formation often requires surgical intervention. Extradural extension may occur in vertebral osteomyelitis and is best demonstrated with MRI [36]. Osteomyelitis may also occur secondary to haematogenous spread, resulting in single or multifocal lesions distant to the primary focus of disease.

Cerebral aspergillosis is associated with a particularly poor prognosis. Several patterns of disease are recognised [37]. Multiple areas of low density on CT or high signal on T2-weighted MRI involving the cortex or subcortical white matter and sometimes associated with areas of haemorrhage represent infarcts. At post-mortem examination, intra-arteriolar fungal thrombi are found. Multiple ring-enhancing lesions consistent with abscesses may develop, predominantly sited at the grey-white matter junction. Yamada et al. [38] have recently described low signal on T2-weighted MR images between the abscess wall and the central necrosis, with concentrated iron, an essential element for fungal growth, identified in this transition zone on histology. Dural enhancement is also described and may be associated with enhancing paranasal sinus disease or dural enhancement of the optic nerve sheath. Finally, epidural and subdural abscesses may be found [39].

Disseminated infection occurs in 10–30% of patients with IPA [6, 33] and may involve the gastrointestinal tract, skeletal system, brain and spinal cord, kidneys, liver, skin, sinuses, thyroid, spleen, heart, aorta, testes and adrenals [2, 6, 25, 40, 41, 42, 43]. Clinical and radiological suspicion of multisystem disease should be high, and early imaging is helpful in the investigation of potential disease sites.

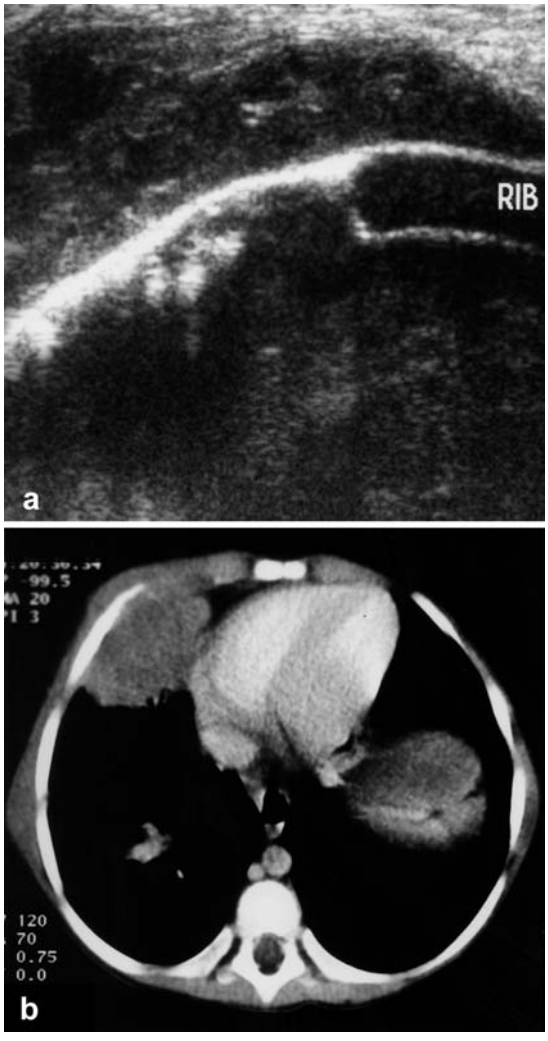

Fig. 10a, b A 7-year-old boy with CGD presented with a palpable, anterior chest-wall mass. **a** Ultrasound demonstrates a hypoechoic soft-tissue mass adjacent to the costochondral junctions of several ribs. **b** Contrast-enhanced CT shows right middle lobe consolidation extending to involve the anterior chest wall, abutting the pericardium and crossing the oblique fissure into the right lower lobe (not shown)

In conclusion, IPA is an aggressive, rapidly disseminating and destructive disease with a high mortality, reaching 44% in our series. Approximately 50% of children present with respiratory disease. However, chest radiographic findings are varied and often non-specific, and a high index of suspicion is necessary in susceptible patients. CT can be useful in demonstrating the multiplicity of lesions, chest wall involvement and the presence of cavitation. However, the incidence of cavitation in the paediatric population appears to be significantly less than in their adult counterparts, and its absence must not preclude radiological consideration of this potentially life-threatening condition.

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