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REVIEW

Imaging Findings in Aspergillosis: From Head to Toe

Célia Sousa · Romulo Antonio Pasini · Alessandro Pasqualotto · Edson Marchiori · Stephan Altmayer · Klaus Irion · Alexandre Mançano · Bruno Hochhegger

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Abstract Aspergillosis is a mycotic infection induced by airborne fungi that are ubiquitous. Inhalation of *Aspergillus conidia* results in transmission through the respiratory tract. The clinical presentation is dependent on organism and host specifics, with immunodeficiency, allergies, and preexisting pulmonary disease constituting the most important risk factors. In recent decades, the incidence of fungal infections has increased dramatically, due in part to the increased number of transplants and the pervasive use of chemotherapy and immunosuppressive drugs. The spectrum of clinical manifestations can range from an asymptomatic or mild infection to a swiftly progressive, life-threatening illness. Additionally, invasive infections can migrate to extrapulmonary sites, causing infections in distant organs. Recognition and familiarity with the various radiological findings in the appropriate clinical context are essential for patient management and the prompt initiation of life-saving treatment. We discuss the radiological characteristics of chronic and invasive pulmonary aspergillosis, as well as some of the typically unexpected extrapulmonary manifestations of disseminated disease.

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C. Sousa
Radiology Department, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal
e-mail: celia.sousa17@gmail.com

R. A. Pasini · K. Irion · A. Mançano · B. Hochhegger (✉)
Radiology Department, University of Florida, Gainesville, FL, USA
e-mail: brunohochhegger@gmail.com

R. A. Pasini
e-mail: romulopasini@gmail.com

K. Irion
e-mail: klaus.irion@icloud.com

A. Mançano
e-mail: alex.manzano1@gmail.com

A. Pasqualotto
Radiology Department, Universidade Federal de Ciências da Saúde de Porto Alegre, Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil
e-mail: acpasqualotto@hotmail.com

E. Marchiori
Radiology Department, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil
e-mail: edmarchiori@gmail.com

S. Altmayer
Radiology Department, Stanford University, Stanford, CA, USA
e-mail: stephanaltmayer@gmail.com

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Introduction

Aspergillosis is a mycotic infection caused by *Aspergillus* species, mostly *Aspergillus fumigatus*. The exposure to the pathogens is through the respiratory tract by inhalation of the *Aspergillus* conidia; however, clinical and radiologic manifestations of aspergillosis are only apparent in a minority of the patients. The clinical course of the disease and prognosis depends on the primary factors of the organisms, namely virulence and load exposure, as well as primary factors of the host, namely immune status (immunosuppression or immune hyperactivity), the health of the underlying lungs and airways, and genetics [1–6]. The incidence of fungal infection has increased significantly over the last few decades, partly because of the increased number of transplants (hematopoietic stem cells and solid organ transplants) and the widespread use of chemotherapy and immune-suppressive drugs. Aspergillosis is one of the most common mold infections in stem cell transplants and the second most frequent in solid organ transplant patients [7]. Aspergillosis is associated with high morbidity and mortality reaching 40–50% in severely immunosuppressed patients [8–12]. Lungs are the most frequent site of infection, and depending on the host's immune status, pulmonary aspergillosis can manifest as a chronic or more rapidly progressive invasive disease. Chronic pulmonary aspergillosis (CPA) most commonly develops in patients with no or minimal immune compromise with a prior or current structural lung disease. The predominant risk factors include infections (tuberculosis, non-tuberculous mycobacteria infection), chronic obstructive pulmonary disease (COPD), and interstitial lung disease. Table 1 describes the diagnostic criteria and findings in CPA and invasive pulmonary aspergillosis (IPA) [1, 7, 13–17]. Extrapulmonary infection is almost universally depicted in the context of disseminated diseases and may be present in 25–60% of cases. These conditions most frequently result from bloodstream dissemination secondary to vascular invasion at the primary site of infection, spreading to other distant tissues such as abdominal organs, musculoskeletal and central nervous system [18–20]. These infections can be rapidly progressive and life-threatening, particularly in critically immunosuppressed patients. Recognition of the different radiological findings in the appropriate clinical setting is crucial for patient management and initiating prompt life-saving antifungal therapy. We describe the radiological features of invasive and chronic pulmonary aspergillosis and some of the usually unexpected extrapulmonary findings of disseminated disease.

Aspergilloma or fungal ball: it is the most common feature of CPA. Aspergilloma is characterized by a saprotrophic infection of a pre-existing pulmonary or pleural cavity or bronchiectasis by *Aspergillus* infection without tissue invasion. The fungal ball is composed of a mixture of hyphae and extracellular matrix. The predisposing lung diseases include tuberculosis, sarcoidosis, non-tuberculous mycobacteria infection, bronchogenic cysts, pneumatoceles, infarcts, and pulmonary sequestration. Most patients remain asymptomatic, although they may present with mild cough and hemoptysis. Sometimes, hemoptysis may be life-threatening, requiring surgical resection or selective bronchial artery embolization. Chest radiograph reveals a round or oval mass partially filling the pre-existing cavity producing the air crescent. High-resolution computed tomography (CT) is the imaging modality of choice. Most are single but may also be multiple and bilateral. CT shows the thick or thin-walled cavity with a highly attenuated fungal ball inside, changing its location and becoming dependent on a prone position (Fig. 1). The fungal ball is composed of a mixture of air filled with mycelial network and minerals, giving it high attenuation on CT. Bridging strands connecting the fungal ball and the cavity wall suggest aspergilloma [1, 21–23]. Differential diagnoses include cavitating lung carcinoma, lung abscess, metastatic disease, hematoma, and tubercular cavity with Rasmussen aneurysm. The hallmark of aspergilloma is that patients are usually asymptomatic and radiological findings are stable over a long period. The fungal balls may show calcifications, but no enhancement is depicted on postcontrast images [1, 13, 24–27]. In some cases, and mainly when host immunity is compromised, these fungal-filled cavities may start to enlarge and develop new or progressive irregularity and thickening of the wall, surrounding consolidations, new cavitations, new or progressive pleural thickening (CPA). These complex

Table 1 Diagnostic criteria for managing chronic and invasive aspergillosis (6, 13)

Presentation	Term	Immune Status	Findings
Chronic pulmonary aspergillosis (1–3 months)	Aspergilloma	No or minimal immune compromise with prior or current lung disease (tuberculosis, COPD, sarcoidosis)	Cavity (pulmonary or pleural cavity or ectatic bronchus) containing a fungal ball
			No progression over at least 3 months of observation
			Minimal or no related symptoms
			Serologic or microbiological evidence implicating *Aspergillus* spp.
	Aspergillus nodule		One or more pulmonary nodules which may or may not cavitate
			No evidence of tissue invasion
			Differentials: lung carcinoma, metastases, coccidioidomycosis or other pathogens
	ABPA		Hypersensitivity reaction to *Aspergillus* antigens, mostly *A. fumigatus*
			Most patients have asthma, cystic fibrosis or atopy
			Immediate skin reactivity and serum precipitins to *Aspergillus*
			Increased serum IgE and IgG to *A. fumigatus*. Total serum IgE > 1000 IU/mL and peripheral eosinophilia (> 1000 cells/μL)
			Imaging features: upper predominant transient pulmonary infiltrates and centrilobular nodules, central and upper bronchiectasis with mucoid impaction and evidence of high attenuated mucus
	CCPA		One or several lung cavities with thin or thick walls. May contain intraluminal material or fungal balls
			Significant pulmonary and/or systemic symptoms and imaging progression (new cavities, increasing fibrosis and pericavitary infiltrates) over at least 3 months
			Serologic or microbiological evidence implicating *Aspergillus* spp.
	CFPA		Untreated CCPA progresses to CFPA, implicating severe fibrotic destruction of at least two lobes with major loss of lung function
	SAIA	Moderately immunocompromised patients (diabetes mellitus, alcoholism, malnutrition, advanced age, COPD, NTM, CTD, prolonged corticosteroid administration < 10 mg/d)	Invasive form of CPA. Subacute presentation, occurring over 1–3 months
			Similar radiological features to CCPA
			Biopsy specimens show hyphae invading lung tissue and microbiological investigations reflect those in IPA

Table 1 continued

Presentation	Term	Immune Status	Findings
Invasive pulmonary aspergillosis (days to weeks)	Angio-invasive pulmonary aspergillosis	Severely immunocompromised patients (deep and prolonged neutropenia, HSCT and solid-organ transplantation, high-dose corticosteroids, cytotoxic therapy, advanced AIDS, hematological malignancy)	Penetration of hyphae in the vessels wall, causing fungal thrombi, necrosis, and hematogenous dissemination. Most seen in neutropenic patients, with positive galactomannan testing in the sera and BAL
			Imaging findings: micro and macronodules, mass-shaped and infarct-shaped consolidations, cavities, halo signs
	Airway-invasive pulmonary aspergillosis		Fungus invasion of the tracheobronchial tree and endobronchial dissemination of infection. More frequent in non-neutropenic individuals, with positive galactomannan testing in BAL
			Obstructive, pseudomembranous or ulcerative tracheobronchitis on bronchoscopy
			Imaging features: bronchial wall thickening, clusters of centrilobular nodules, peribronchial consolidations, mucus plugs, segmental or lobar collapse

ABPA Allergic bronchopulmonary aspergillosis, *AIDS* acquired immunodeficiency syndrome, *BAL* bronchoalveolar lavage, *CCPA* chronic cavitary pulmonary aspergillosis, *CFPA* chronic fibrosing pulmonary aspergillosis, *CPA* chronic pulmonary aspergillosis, *COPD* chronic obstructive pulmonary disease, *CTD* connective tissue disease, *HSCT* hematopoietic stem cell transplantation, *IPA* invasive pulmonary aspergillosis, *NTM* non-tuberculous mycobacteria, *SAIA* subacute invasive aspergillosis

aspergillomas are essential to be depicted because of the destructive nature, which may lead to severe hemoptysis. Usually, patients present with chronic constitutional symptoms [21, 23].

Aspergillus nodule: one or more nodules are an uncommon presentation of CPA. Usually, the nodules measure less than 3 cm and tissue invasion is not evident (Fig. 2). Central necrosis, better iddentified on post-contrast CT studies, and cavitation may be present, especially in nodules bigger than 3 cm. The nodules can be round or have spiculated edges. *Aspergillus* nodules mimic several other conditions, and the definitive diagnosis is usually made on histology: lung carcinoma, metastases, rheumatoid nodules, cryptococcosis, coccidioidomycosis or other pathogens [13].

Allergic bronchopulmonary aspergillosis—ABPA: it is caused by a complex immune reaction to antigens released by *Aspergillus* species that colonize the tracheobronchial tree, especially in patients with asthma. Asthma-induced mucosal damage facilitates the proliferation of the fungus, causing additional mucosal injury, bronchiectasis, and mucus production. ABPA also occurs in patients with cystic fibrosis, lung transplantation, or Kartagener's syndrome [28]. Chest radiographs reveal tubular, finger-in-glove opacities in a bronchial distribution, predominantly involving the upper lobes. CT depicts central and upper lobe predominant bronchiectasis, mucoid impaction, centrilobular nodules, parenchymal scarring, mosaic perfusion, air trapping on expiration, and lobar and segmental collapse. The mucous plugs are generally hypodense but can also be hyperdense in about 28% of the patients, resulting from the presence of calcium salts, metals, and desiccated mucus. The occurrence of hyperdense mucous plugs on non-contrast CT studies, i.e., an attenuation higher than the paraspinal skeletal muscle or > 70 HU, is considered a pathognomonic feature of ABPA [29, 30]. Magnetic resonance imaging (MRI) is also a useful imaging modality with great correlation with CT findings, particularly in children, patients with a need for repeated imaging, pregnant women, and as a problem-solving tool for the exclusion of other pathologies. The evidence of both high T1 and low T2 signal intensities correlates well with the hyperdense mucus plugs on CT, allowing a

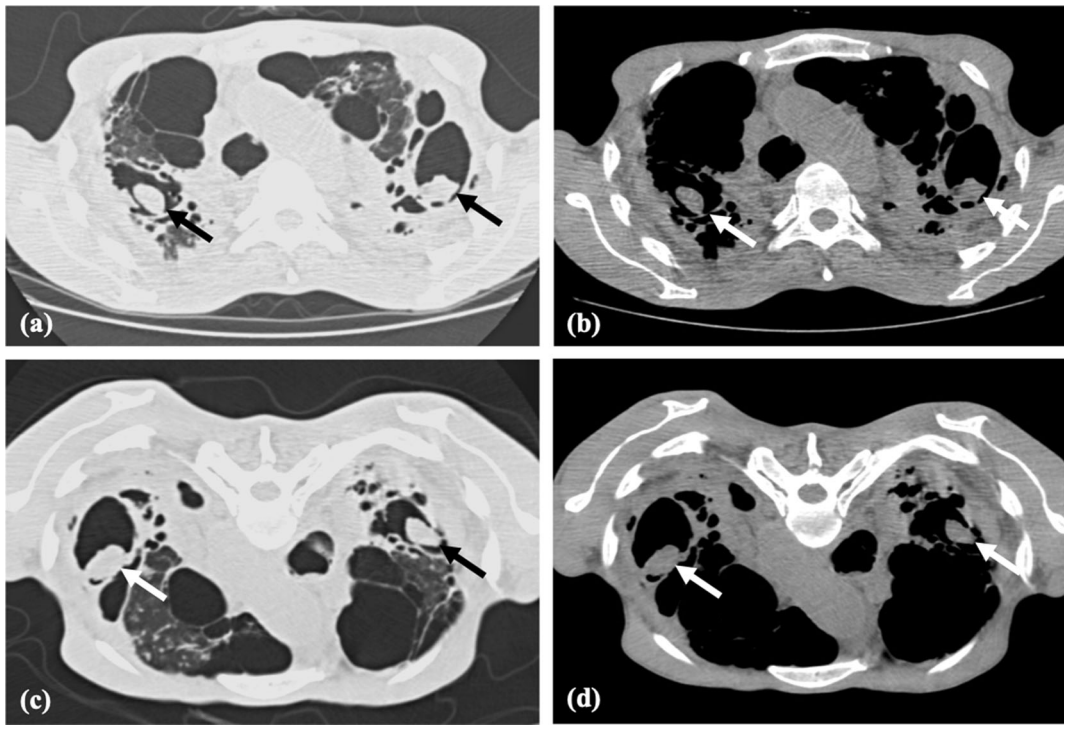

Fig. 1 Fungal balls. Cavitary sequelae of tuberculosis with bilateral aspergillomas in a 78-year-old male patient presenting with mild cough and sporadic hemoptysis. CT images (lung and mediastinal windows) on supine (**a**, **b**) and prone (**c**, **d**) positions depict mobile fungal balls settled in the dependent position (arrows)

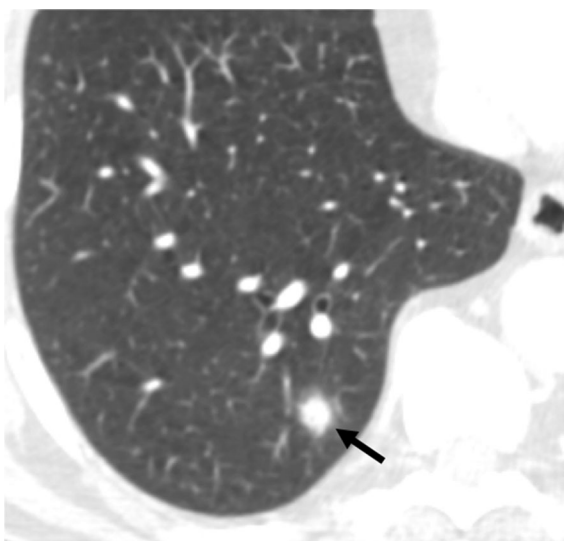

Fig. 2 Axial view of lung window at the level of the right lower lobe. Nodule with irregular borders and mild halo sign that was proven to be an *Aspergillus nodule* on biopsy (arrow)

confident diagnosis of ABPA (Fig. 3). Additionally, the absence of enhancement in post-contrast studies permits the exclusion of other potential causes, such as pulmonary masses [31–33]. Differential diagnoses include endobronchial lesions and bronchial atresia [30].

Chronic cavitating aspergillosis: CCPA is the most common form of CPA. The clinical and radiological evolution over time is typically slower and more indolent than in cases of semi-invasive or IPA. However, if untreated, it may progress to severe pulmonary fibrosis. The typical features consist of unilateral or bilateral consolidations, expanding thick-walled cavities, perhaps containing intraluminal debris or aspergillomas, perilesional fibrosis, and pleural thickening (Fig. 4). The findings are usually located in areas with pre-existing lung disease. CFPA is the terminal evolution of CCPA coursing with severe fibrotic destruction involving at least two lobes, multiple cavities, and gross volume loss. The imposing differential diagnosis is mycobacterial infection

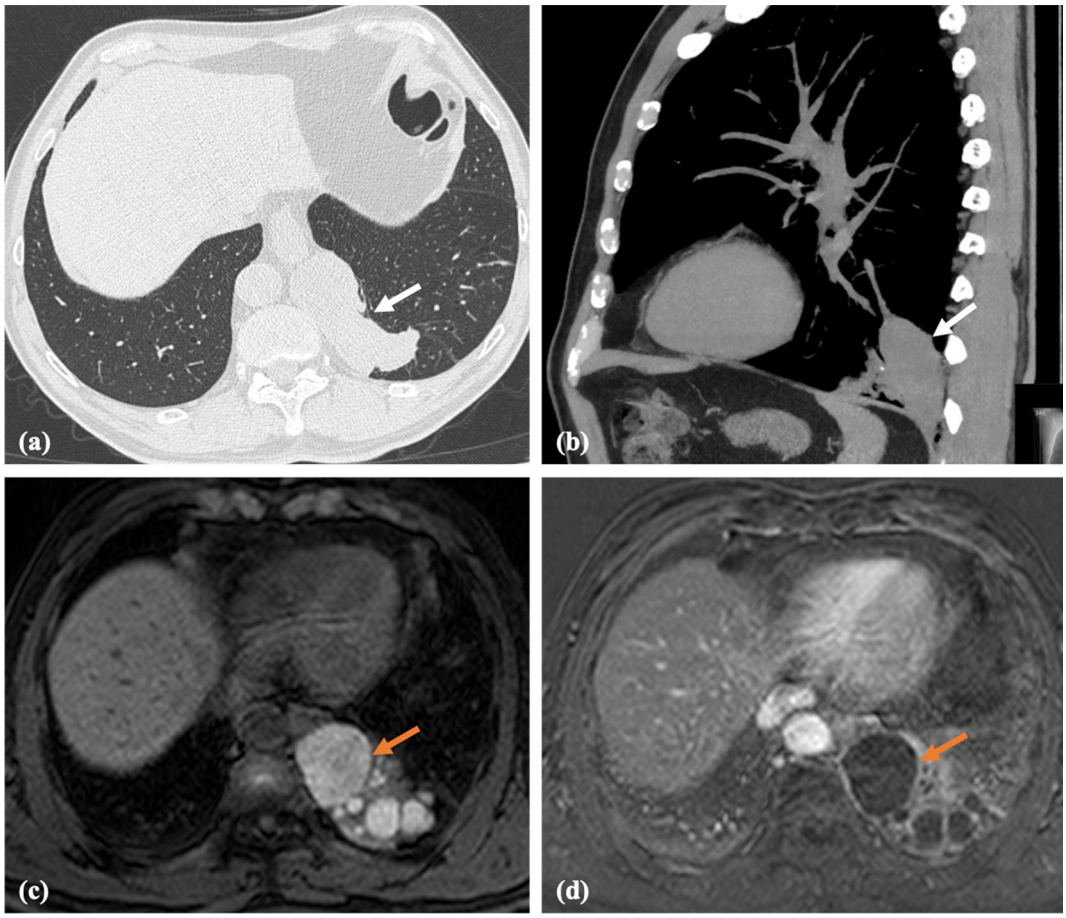

Fig. 3 78 year-old-male with ABPA and previous history of tuberculosis. Axial (**a**) and sagittal (**b**) chest CT depict an elongated opacity in the left lower lobe consistent with saccular bronchiectasis packed with dense mucus plugs (white arrows). Non-contrast magnetic resonance T1-weighted fat-saturated image (**c**) depicts the high-intensity mucus plugs without enhancement on post-contrast subtraction image (**d**), supporting the diagnosis of ABPA (orange arrows)

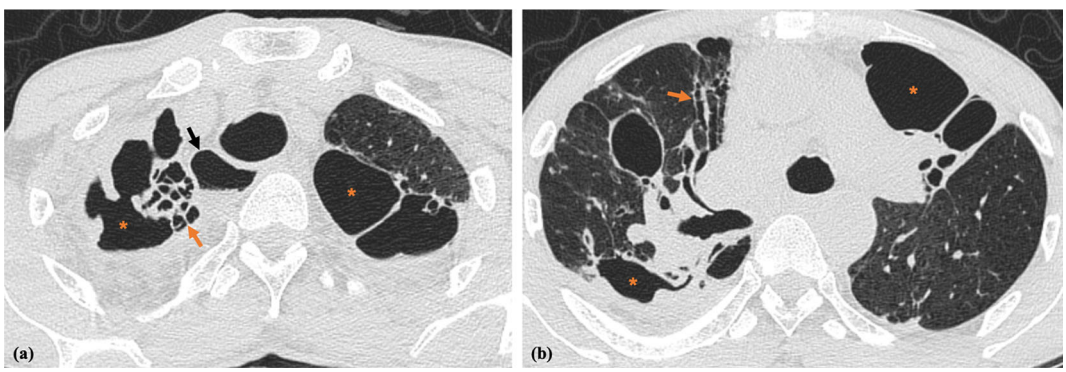

Fig. 4 Chronic cavitating aspergillosis in a 58-year-old patient with a clinical history of tuberculosis several years ago and alcoholism, now presenting with low-grade fever and cough for more than three months. CT scan in lung window from an upper (**a**) and lower level (**b**) reveals multiple bilateral cavities (orange asterisks), perilesional consolidations, bronchiectasis (orange arrows) and thickening of the pleura. The black arrow in **a** shows the esophagus. The bronchial washings depicted *Aspergillus*, and the serum immunoglobulin IgG antibodies to *A. fumigatus* were positive

(TB or NTM), as the diagnosis of one entity does not exclude the other because these pathologies may precede, follow, or coincide. Pulmonary samples for smear, culture and mycobacterial nucleic acid amplification are essential components of the complex differential workup of CPA. Furthermore, conventional bacteria (i.e. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, anaerobic bacteria and *Pseudomonas aeruginosa*) may also infect the pulmonary cavities. Other differential diagnoses include actinomycosis, histoplasmosis, necrotizing lung cancer, pulmonary infarct, and vasculitides [1, 3, 13, 34, 35].

Subacute invasive aspergillosis—SAIA: it represents mildly invasive aspergillosis of the parenchyma with a more rapid and subacute (1–3 months) clinical and radiological progression compared to CCPA. Radiological findings include unilateral or bilateral nodules/masses or consolidations that may show necrosis and cavitation, pulmonary infiltrates and pleural thickening (Fig. 5). Due to the aggressive nature of the lesions, SAIA may be complicated by bronchopleural fistula, thoracic wall invasion, pneumothorax and empyema. The findings of SAIA overlap with those seen in CCPA. Consequently, further data on progression over time, serial imaging, exclusion of other diagnoses and pathological results showing evidence of invasion are usually essential to establish the final diagnosis [1, 13, 14].

Radiological diagnosis and follow-up of CPA: chest radiograph is commonly the first imaging modality and remains helpful in raising suspicion or excluding CPA. High-resolution chest CT provides further detailed information regarding the location, distribution and extension of imaging abnormalities. Intravenous contrast administration is usually not required. However, contrast may be valuable if there are concerns about complications, such as chest wall involvement, abscesses, empyema, new hemoptysis, and in case of therapy failure. During the follow-up,

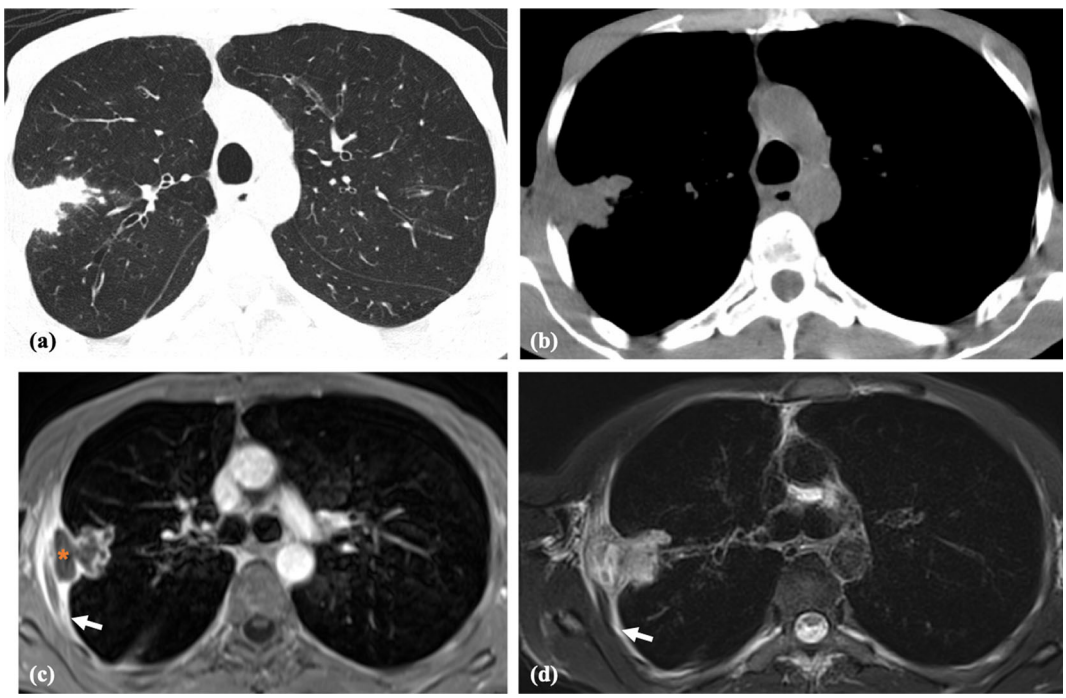

Fig. 5 SAIA in a 46-year-old male diagnosed with AIDS presenting with constitutional symptoms, dry cough and chest pain for about two months. Axial CT in lung (**a**) and mediastinal (**b**) windows depict an irregular and spiculated mass in the right upper lobe associated with pleural thickening. Post-contrast T1FS (**c**) and T2FS (d) MRI images reveal the necrotic nature of the mass, lacking enhancement in the center (orange asterisk) and with hyperintense signal on T2-weighted image. MRI also highlights the invasion of the pleura adjacent to the mass (arrows), showing thickening, hyperenhancement and hyperintensity on T2-weighted image. Sputum smear and bronchoalveolar lavage revealed growth of *A. fumigatus*. Transthoracic biopsy confirmed the diagnosis of SAIA

chest radiographs and CT are complementary imaging modalities. Low dose techniques are optimally used for follow-up. Imaging is recommended every 3–6 months after treatment and then less often. The radiological changes are slow, and very little change is visible in less than 3 months on CT scans or chest radiographs. Imaging findings of improvement include a smaller nodule or cavity, thinner and smoother cavity wall, less material or fluid in a cavity, reduced pleural thickening and pleural fluid, and smaller pericavitary consolidation. Radiological signs of treatment failure include new cavities, expanding and coalescing cavities, progression or appearance of new consolidations and infiltrates, and formation of an aspergilloma [13].

Invasive pulmonary aspergillosis

IPA is a common pulmonary complication in severely immunocompromised patients, such as those with hematopoietic stem cell or solid organ transplantation and hematologic malignancies. A major predisposing factor is severe neutropenia (absolute neutrophil count of < 500 cells/L). This manifestation of *Aspergillus* infection can be rapidly fatal, and early initiation of antifungal therapy is critical [36].

Angio-invasive pulmonary aspergillosis: it is the most common form of IPA. The infection invades and occludes small to medium-sized pulmonary arteries with resultant hemorrhage and necrosis. Radiological findings comprise scattered nodules and masses or infarct-shaped consolidations. Well-circumscribed nodules represent the main radiologic finding of IPA. The classic CT finding of angio-invasive aspergillosis is the halo sign, characterized by a ground-glass opacity signifying hemorrhage and coagulative necrosis surrounding a solid pulmonary nodule, mass, or consolidation. Despite this sign being nonspecific and may be appreciated in other pathologies, such as infections, malignancies and vasculitides, its evidence in the appropriate clinical scenario is a crucially early indication of IPA with high sensitivity and specificity [3, 7, 37]. The halo sign is transient and is present in the first ten days of angioinvasion, after which it disappears. Likewise, the reversed halo sign, defined as central ground-glass opacity surrounded by a crescentic consolidation, is also a highly suggestive sign of early infection by an angioinvasive fungus. So, prompt CT studies in symptomatic, severely immunocompromised patients may be of fundamental value in depicting these early signs. Usually, the nodular and mass-like infiltrates with the halos subsequently develop internal hypodensity areas seen in the mediastinal window and post-contrast CT studies, and progress to cavitation and air crescent formation, frequently at the time neutrophil counts increase. Air crescents are a later sign, usually seen after two weeks of disease onset. This sign is also nonspecific and perceived in several other diseases. However, when present in the appropriate clinical context, it is very characteristic and has prognostic value, suggesting improvement of the immune response [3, 7, 21–23, 38, 39]. Figure 6 depicts characteristic findings of angio-invasive aspergillosis. MRI correlates well with CT for detecting nodules larger than 10 mm, consolidations, and GGO. MRI and CT are concurrent in depicting nodular margins, halo signs and pleural effusions. MRI may detect nodules with high signal on T1-weighted images at early stages of infection that correspond to hemorrhages. At later stages, usually after 10 days from symptoms onset, the target sign, defined as a hyperintense rim of gadolinium enhancement surrounding an isointense center on T1-weighted images and the reversed target sign, or a lesion with a hyperintense center and a rim of intermediate signal intensity on T2-weighted images are strongly suggestive of IPA. However, MRI lacks reliability for detecting nodules smaller than 10 mm and delineating small areas of air in the nodules or consolidations. Because cavitations are significant findings that can suggest the fungal nature of the infection, this represents an important disadvantage of MRI [40, 41].

Airway-invasive pulmonary aspergillosis: also known as bronchopulmonary aspergillosis, it accounts for 14–34% of IPA [42]. The diagnosis is based on the evidence of organisms deep to the basement membrane of the airways. The clinical manifestation can range from acute tracheobronchitis to bronchiolitis and bronchopneumonia. Imaging findings are nonspecific and indistinguishable from bronchopneumonia caused by other common microorganisms (bacterial and viral infections). Patients with acute tracheobronchitis usually have normal imaging findings; however, they may present with tracheal and bronchial wall thickening, narrowing, and luminal secretions (Fig. 7). Bronchiolitis is characterized by

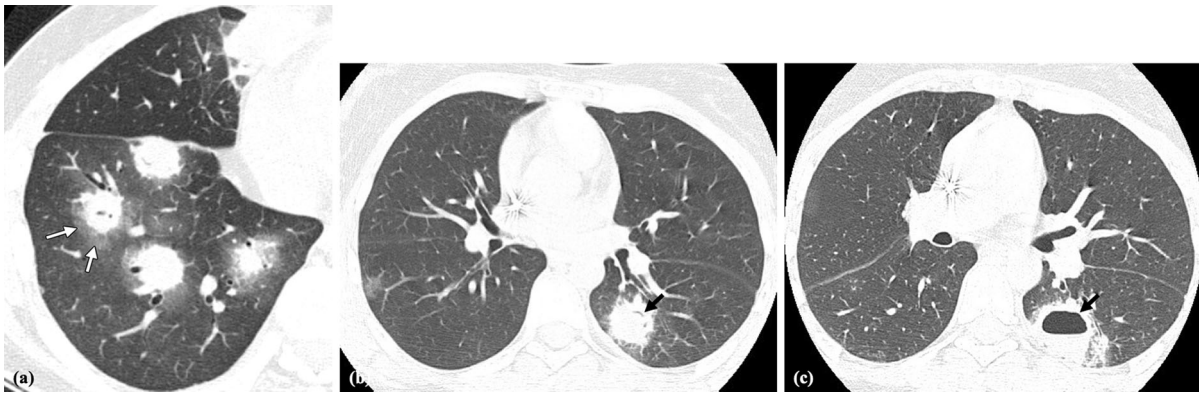

Fig. 6 Angio-invasive aspergillosis in different severely immunosuppressed patients. Image **a** reveals multiple nodules in the right lower lobe with surrounding ground-glass opacities (white arrows) or the halo sign. Images **b**, **c** in a different patient show a left lower lobe mass with mild surrounding ground-glass opacities with increasing breakdown and air-crescent (black arrows) over 16 days

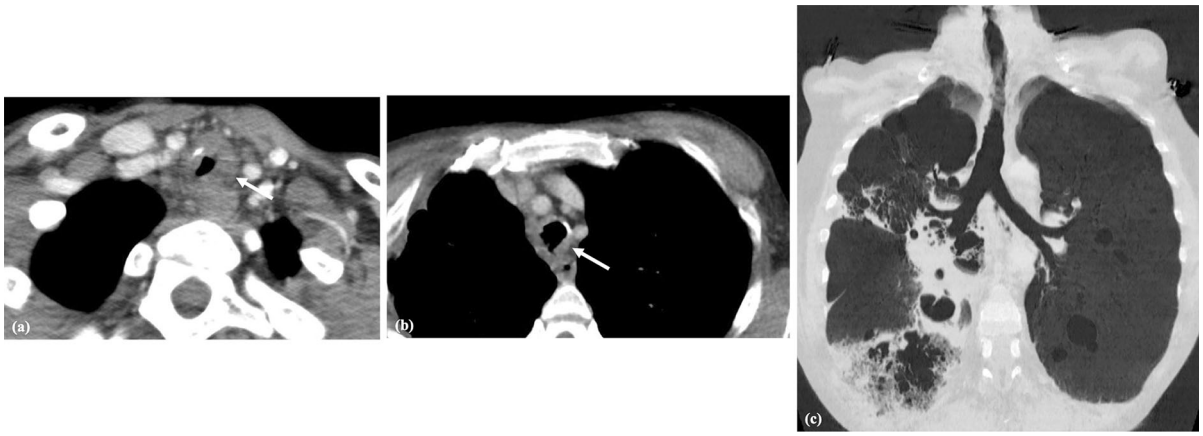

Fig. 7 54-year-old male patient with a previous history of hepatic transplantation, presenting with cough and fever. Axial CT from upper (**a**) and lower (**b**) levels reveal concentric thickening of the tracheal walls (white arrows). **c** Coronal minimum intensity projection (MinIP) reconstruction shows tracheal narrowing and peribronchovascular consolidations in the right lung. Bilateral centrilobular and paraseptal emphysema is also depicted. The diagnosis of *Aspergillus tracheobronchitis* was confirmed by bronchoscopy and biopsy

patchy centrilobular nodules with a tree-in-bud appearance, and bronchopneumonia is demonstrated as areas of peribronchovascular consolidation and ground-glass (Fig. 8). Occasionally, lobar consolidation may also be found [1, 39, 42]. Lung transplantation is the most common predisposing risk factor for airway-invasive aspergillosis, accounting for nearly 40% of cases [43–46]. Ischemic injury at the anastomotic sites, deficiency of mucociliary clearance due to the absence of the cough reflex, chronic airway inflammation secondary to rejection episodes, and more important requirement of immunosuppression compared to other solid organ transplantations are some of the specific factors that might favor airway colonization and invasive disease in these patients [47, 48]. Necrotizing and pseudomembranous tracheobronchial aspergillosis is a form of infection specific to lung transplants, confirmed on bronchoscopy with evidence of airway ulcerations and formation of pseudomembranes [49, 50].

Viral induced pulmonary aspergillosis: IPA has been increasingly described in critically ill patients with viral pneumonia due to two viruses: influenza (predominantly influenza A) and severe respiratory syndrome coronavirus 2 (SARS-CoV-2). Influenza-associated pulmonary aspergillosis (IAPA) affects

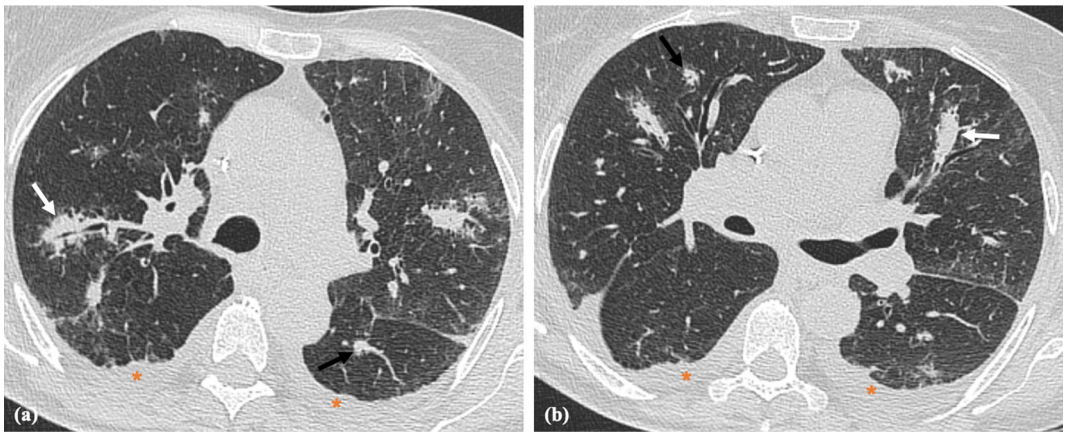

Fig. 8 Airway-invasive pulmonary aspergillosis in a 56-year-old female with non-Hodgkin lymphoma undergoing chemotherapy. Sputum examination demonstrated actively multiplying colonies of *A. fumigatus*. Serum was also positive for galactomannan. CT scan from upper (**a**) and lower (**b**) levels reveals multifocal and bilateral peribronchial consolidations (white arrows) and ground glass opacities, and centrilobular nodules (black arrows). Bilateral small pleural effusions are also seen (orange asterisks)

patients in the intensive care unit (ICU) with severe influenza and portends a high mortality of 45–61% compared to 20% in patients without IAPA. IPA has also been increasingly reported in patients with COVID-19. COVID-19-associated pulmonary aspergillosis (CAPA) is described in 4–33% of patients with COVID-19 and has a mortality of 44–71%, higher than 19–37% in patients with COVID-19 without CAPA. IAPA tends to develop early, with a median of three days after ICU admission, although CAPA develops after a median of 4–8 days after ICU admission or intubation. Furthermore, complicating the picture is also the fact that the classical risk factors and the typical imaging features of IPA are frequently absent in patients with CAPA and IAPA, with the majority of cases occurring in previously immunocompetent individuals [51]. CAPA patients have an atypical appearance for COVID-19 on CT studies in 40% of cases. The features not explained by COVID-19 include cavities, solid nodules, consolidation without ground-glass opacities (GGO), centrilobular nodules, and tracheal and bronchial wall thickening. The most frequent IPA pattern is the airway-invasive pattern (approximately 57% of the CAPA patients), with an angio-invasive pattern in only 7% of the patients. The most common findings are cavities and solid nodules, predominant in the upper lobes and frequently along the peribronchovascular bundles. The presence of the halo and reverse halo signs is of limited value due to the underlying GGO of COVID-19 pneumonia. Also, the crescent sign is uncommon in CAPA. Findings of tracheobronchitis may also be encountered and should raise the possibility of aspergillosis, coursing with diffuse bronchial wall thickening and thickening and irregularity of the internal wall borders of the trachea. The evidence of cavitations in COVID-19 pneumonia should raise the possibility of co-infection, including aspergillosis, nocardiosis, actinomycosis, pulmonary tuberculosis, septic emboli, and also other etiologies such as malignancy and vasculitis [52]. The principal findings in IAPA include tracheobronchitis, nonspecific bilateral and multifocal consolidations and solid nodules with or without cavity or GGO. The cavitary lesions, halo, or crescent signs are typically more common in immunosuppressed patients, such as neutropenic and transplant patients. Bacterial superinfection is a well-described and more frequent complication of influenza infections, and this possibility should also be included in the differentials [53, 54].

Imaging work-up of invasive aspergillosis: imaging has a role in early detection and helps further testing. While the presence of specific lesions increases the probability of IPA, such as the halo sign, reversed halo sign, hypodense sign, and crescent sign, the diagnosis by imaging lacks specificity. Furthermore, conclusions regarding imaging manifestations are drawn based on possible or probable IA. Chest X-ray has low sensitivity and contrast resolution, especially in the

detection of early pneumonia and small nodules below 10 mm; thus, the utility of X-ray is limited for the diagnosis of IPA. High-resolution CT is the method of choice. Intravenous contrast may be used, but it is frequently not necessarily due to the inherently high contrast of the lung tissue. Also, it is associated with potential adverse effects such as nephropathy and anaphylactic reactions. Modern acquisition techniques using model-based noise reduction algorithms permit a low dose acquisition that is only around 5 times higher than the X-ray dose. CT can detect typical lesions for the diagnosis of IPA and further monitor the disease evolution, complications and later findings linked to therapeutic response. The principal benefits of MRI are the absence of ionizing radiation, which is especially useful for pregnant women and children, and greater resolution in solid organs. The important disadvantages include the intrinsically low signal-to-noise ratio of the lungs, cardiac and respiratory motion, susceptibility artifacts related to air-tissue interfaces, time acquisition of 20–30 min, and sufficiently cooperative patients able to hold their breaths 20–50 times for 10–20 s during table time. The most common contraindications are claustrophobia and the presence of implantable devices. MRI is an essential alternative, with sensitivity and specificity comparable to CT for the diagnosis of IA [41].

Extra-pulmonary aspergillosis

Central nervous system (CNS) aspergillosis: it results from angio-invasive infection of the CNS by *Aspergillus* spp. It is one of the most common fungal opportunistic infections of the CNS, along with those caused by *Candida* and *Cryptococcus*. The clinical presentation is often understated, making initial diagnosis difficult, and may include fever, altered mental status, headache, seizures, and focal neurological signs (including hemiparesis and dysarthria). There are two mechanisms of infection spread to the CNS: dissemination from pulmonary angio-invasive infection (25–50% of cases) and direct spread via paranasal sinuses. CNS aspergillosis has a worrying prognosis in immunocompromised patients, with a mortality rate approaching 100%. So, prompt recognition and treatment of pulmonary aspergillosis before it reaches the CNS are crucial for patient prognosis. The infection starts to invade the walls of both small and large vessels and then reaches the brain tissue, causing septic infarcts, abscesses, mycotic aneurysms, and hemorrhage. The most characteristic radiological features of both CT and MRI studies are the presence of multiple brain infarcts with or without hemorrhage and varying degrees of inflammatory changes, predominantly located in the cerebral hemispheres, thalami, basal ganglia, cerebellum, brainstem, and corpus callosum. Lesions in the subcortical territories of cerebral hemispheres are common. The distribution of findings contrasts with pyogenic infections and thromboembolic infarcts and is thus suggestive of the diagnosis. Most lesions have intermediate signal-intensity centers related to coagulative necrosis with surrounding areas of high signal on T2-weighted and proton-density images. The evidence of areas of high signal on T1 and low signal on T2-weighted images is commonly present and are related to hemorrhage. Diffusion-weighted MRI is a valuable tool for depicting early ischemic lesions. In severely immunocompromised patients, there is little or no evidence of contrast enhancement on CT and MRI studies due to the absence of inflammatory response. In contrast, in patients without severe immunosuppression, ring or nodular enhancement is typically seen and consistent with the development of an abscess or granuloma (Fig. 9) [55–59].

Abdominal aspergillosis: aspergillosis may disseminate to the abdomen involving the gastrointestinal tract, solid organs, lymph nodes, or the abdominal wall [19]. The gastrointestinal tract is the second most common location of invasive aspergillosis, and the small intestine is the most affected organ [60, 61]. The gastrointestinal tract may also be the primary site of infection due to drugs that may alter the normal mucosal barriers, such as chemotherapeutic and immunosuppressive drugs [62, 63]. Clinical manifestations include fever, abdominal pain, ileus, peritonitis, bloody diarrhea, or hematochezia. Imaging findings may course with bowel ischemia and perforation, secondary to the invasion of the mesenteric arteries and intravascular thrombosis. Bowel wall thickening with adjacent mesentery inflammation, bowel obstruction and distention, and toxic megacolon are additional imaging findings [60, 61]. Aspergillosis is also a recognized infection implicated in typhlitis, coursing with concentric bowel wall thickening involving the terminal ileum and cecum [19]. Imaging features involving the solid organs include diffuse or

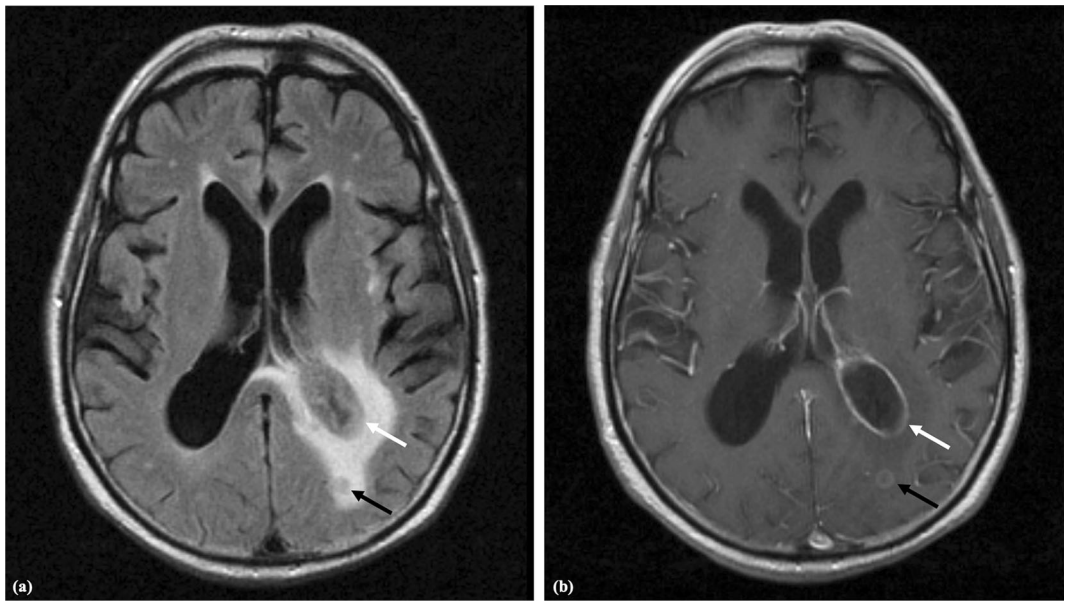

Fig. 9 52-year-old female patient with prior history of heart transplantation and headache. Axial T2-weighted-fluid-attenuated inversion recovery (FLAIR) (**a**) and T1-weighted postcontrast (**b**) images demonstrate a small abscess in the left occipital lobe, with intermediate signal-intensity and ring enhancement (black arrows), surrounded by edema. The images also reveal layering debris on T2-FLAIR in the occipital horn of the left lateral ventricle with a thin enhancement of the walls (white arrows), consistent with ventriculitis. Histopathological examinations demonstrated the final diagnosis of CNS aspergillosis

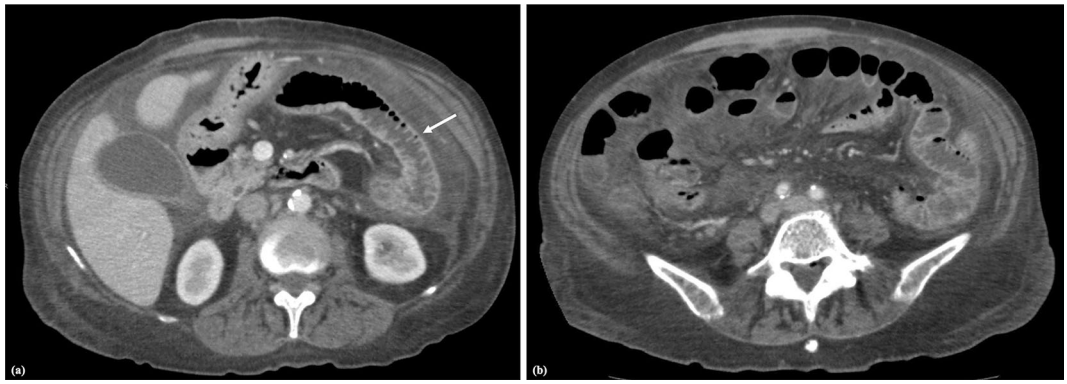

Fig. 10 21-year-old woman who received chemotherapy for acute myeloid leukemia. Contrast enhanced axial CT scans show **a** jejunal wall hyperenhancement (arrow), severe mesenteric infiltration (**b**) and moderate ascites. Laparoscopic evaluation revealed the diagnosis peritonitis secondary to aspergillosis

multifocal wedge-shaped infarctions with low attenuation on CT and lacking contrast enhancement and multiple tiny or round lesions like other fungal infections or pyogenic abscesses [19, 60, 61, 64, 65]. The evidence of miliary abscesses is the most common pattern of hepatic and splenic aspergillosis. *Aspergillus* peritonitis is rare and occurs most often in patients undergoing ambulatory peritoneal dialysis (Fig. 10) [19]. The diagnosis requires histopathological evidence of infection, such as direct microscopy of fluid or tissue specimens or galactomannan or (1,3) β-D-glucan assays [19, 60, 61].

Musculoskeletal aspergillosis: Aspergillus osteomyelitis, arthritis and spondylodiscitis are rare disorders and potentially debilitating infections. The most frequent clinical manifestations are pain and

tenderness in the affected regions, but also fever and neurologic deficits in relation to spinal cord compression. Osteomyelitis affects two or more non-contiguous bones in 56% of cases. The vertebral bodies are the most common sites of *Aspergillus* osteomyelitis and develop from contiguous pulmonary foci or hematogenous dissemination. Also, ribs, sternum and cranial bones are commonly afflicted sites of infection. The long bones and joints are less commonly infected. Most cases of costal and cranial bones aspergillosis develop through direct extension from the primary focus of infection. The final diagnosis is stablished most frequently by open or percutaneous biopsy or arthrocentesis in case of arthritis. The most common radiologic patterns of osteomyelitis are osteolysis, bone erosion, bone destruction, and extension of the infection into the soft tissues (Fig. 11). Less common findings are abscess and sequestrum formation. The most common changes of spondylodiscitis are decreased intervertebral space, endplate osteolysis, paraspinal abscess, epidural and subdural abscess, and spinal cord compression [66–69]. *Aspergillus* infection causing osteomyelitis or arthritis can also occur in immunocompetent patients, usually as an iatrogenic infection after surgery [66–70]. *Aspergillus*-induced myositis and muscle abscess are exceedingly rare conditions. MRI is the best imaging modality and commonly reveals nonspecific signs of inflammation, with increased signal on T2-weighted images and enhancement after contrast administration. Usually, the finding is limited to the muscle and the adjacent fascia but may also spread to neighboring tissues. Numerous superimposed abscesses may also be present, appearing as fluid collections with a high T2-weighted signal and a low signal intensity rim that enhances after contrast administration [71].

Invasive rhinosinusitis: invasive fungal rhinosinusitis is classified as acute, chronic, or granulomatous. The non-invasive forms are allergic fungal rhinosinusitis and fungal mycetoma. Chronic forms of invasive fungal rhinosinusitis occur over several months and generally in less severe immunocompromised and elderly patients. Acute invasive fungal sinusitis (AIFS) is the most severe form of fungal sinusitis, with mortality rates approaching 20% of the patients [72]. AIFS occurs predominantly in patients with profound immunosuppression, such as neutropenic patients, with a hyperacute presentation over several days. The infection starts in the nose and paranasal sinuses after inhalation of fungal spores, with further angioinvasion by the hypha and tissue necrosis. Spread to orbital and intracranial structures may occur through direct vascular invasion and occasionally embolic seeding. Imaging is critical in helping to stablish the diagnosis and guiding surgical planning for biopsy and debridement. A high

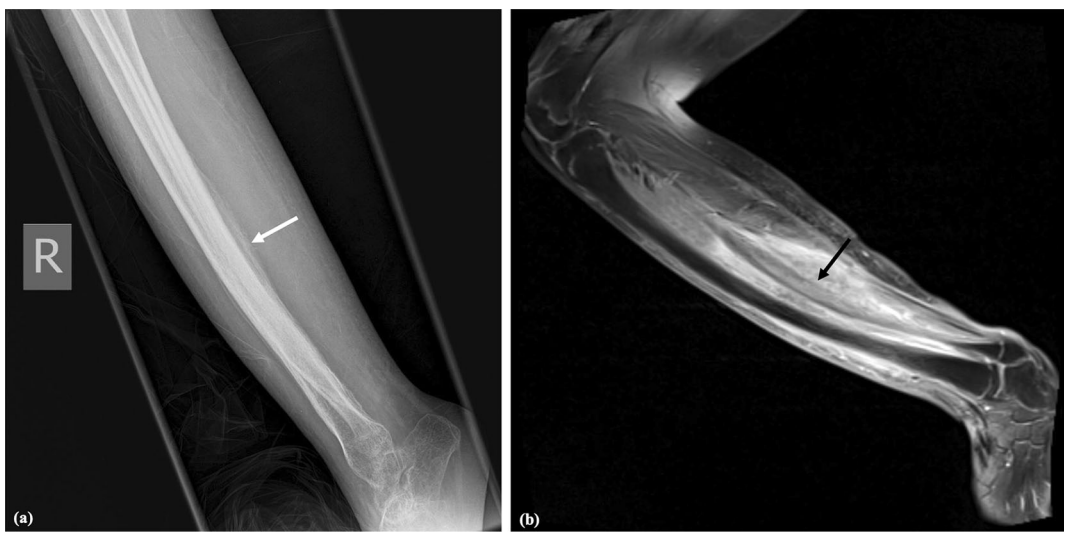

Fig. 11 5-year-old boy with leukemia undergoing chemotherapy presenting with pain in his right leg. Radiograph **a** reveals periosteal reaction and sclerosis of the fibular shaft (white arrow). Sagittal post-contrast T1-weighted image with fat saturation **b** shows exuberant contrast enhancement in the fibular shaft (black arrow) and surrounding soft tissues. A biopsy was performed later and revealed *Aspergillus osteomyelitis*

suspicion with early imaging is crucial, especially in immunocompromised patients, as early presentation is often subtle or attributed to a less serious and more common viral or bacterial rhinosinusitis. AIFS is evaluated and diagnosed by CT and MRI. CT best evaluates osseous alterations, and soft tissue changes are better delineated by MRI. MRI is more sensitive than CT in detecting early changes of AIFS, however, the specificity and negative predictive value is equal to that of CT. Contrast administration to CT can better reveal periantral soft tissue changes and orbital and intracranial extension. The infection usually initiates as unilateral lateral nasal soft tissue thickening, typically with mucosal inflammation around the middle turbinate, and then spreads to the maxillary and ethmoid sinuses, followed by the sphenoid sinus. Most of the patients have only ipsilateral involvement of multiple sinuses. The CT findings comprise unilateral sinus opacification frequently with focal bone erosion, soft tissue thickening of the sinuses and lateral nasal wall mucosa, infiltration of the perimaxillary fat, and palatal erosions. The perimaxillary fat infiltration, secondary to fungal tissue infiltration or edema from vascular congestion, may occur before bone destruction. The evidence of bone destruction best depicted on CT is a comparatively late finding and signifies the extension of the infection beyond the sinus cavity. The secretions inside the sinus cavities are often heterogeneous on CT, although hyperdense secretions are more common in chronic invasive fungal rhinosinusitis due to the presence of metals such as manganese, high protein content, and the presence of fungal hypha. The findings that are more specific for AIFS are retroantral fat pad infiltration, bone erosion, and orbital and intracranial extension. Intracranial abscesses and leptomeningitis have also been reported [73–75]. MR findings include nonenhancing and hypointense turbinates (the "black turbinate sign"), absence of contrast enhancement in the sinonasal mucosa and extraocular muscles, sinus opacification and air-fluid levels, obliteration of the nasopharyngeal planes, variable intensity inside the sinus on T1 and T2-weighted images (frequently hypointense on T2), inflammatory changes in the periantral soft tissues and muscles, orbits and intracranial region [72, 74, 75]. The earliest finding that should raise suspicion of AIFS is fat stranding adjacent to the sinuses [76]. Therefore, the periantral fat pads and the overlying subcutaneous fat should be carefully inspected for these subtle changes. The "black turbinate sign" and the lack of sinonasal mucosal enhancement correlate with devitalized tissue secondary to infarction of smaller blood vessels, and these features have only been described in the setting of AIFS [74, 75, 77]. Due to the strong tendency of the organisms to angioinvasion, signs of vasculopathy may also be encountered, such as vasculitis, aneurysm and pseudoaneurysm, arterial narrowing, arterial and venous thrombosis, and infarctions [72]. MRI is better at demonstrating the subtle early findings of AIFS and is superior to CT in soft tissue contrast resolution. As a rule of thumb, a careful inspection should be paid for subtle perimaxillary fat infiltration that may occur before osseous destruction. Chronic forms of invasive fungal rhinosinusitis, such as chronic invasive fungal rhinosinusitis (CIFRS) and granulomatous invasive fungal rhinosinusitis (GIFRS), are slowly destructive processes that affect mildly immunosuppressed patients. CIFRS affects any sinus, however, the ethmoid and the sphenoid sinuses are most commonly affected. These chronic infections may also present as enlarging masses inflicting the paranasal sinuses, nose, cheek, and orbit [78–80]. Non-invasive fungal sinusitis forms, including allergic fungal rhinosinusitis (AFRS) and fungus ball, affect healthier and immunocompetent individuals. Allergic rhinosinusitis represents a hypersensitivity to fungi, and patients are often atopic with conditions like asthma and eczema. AFRS is best evaluated on noncontrast CT. There is often pansinusitis or bilateral involvement of multiple sinuses, with ethmoid involvement being the most frequent. The allergic mucin causes hyperdense opacification of the sinus lumen, with sinus expansion and bone remodeling. MRI is obtained when there is a concern of extension into the orbit and cranium. A fungus ball or mycetoma is an unusual form of fungal sinusitis [81–83]. The fungus ball often affects one sinus, may be ovoid or assume the sinus contour, with a hyperdense spot or calcifications in the center, and often with sclerosis of the adjacent bone (Fig. 12). The fungus ball demonstrates a low signal on both T1 and T2-weighted images due to the lack of free water and absence of contrast enhancement [84–86]. The non-fungal differential diagnosis of invasive fungal sinusitis includes complicated acute and chronic viral or bacterial rhinosinusitis, granulomatosis with polyangiitis, and malignancies, most commonly

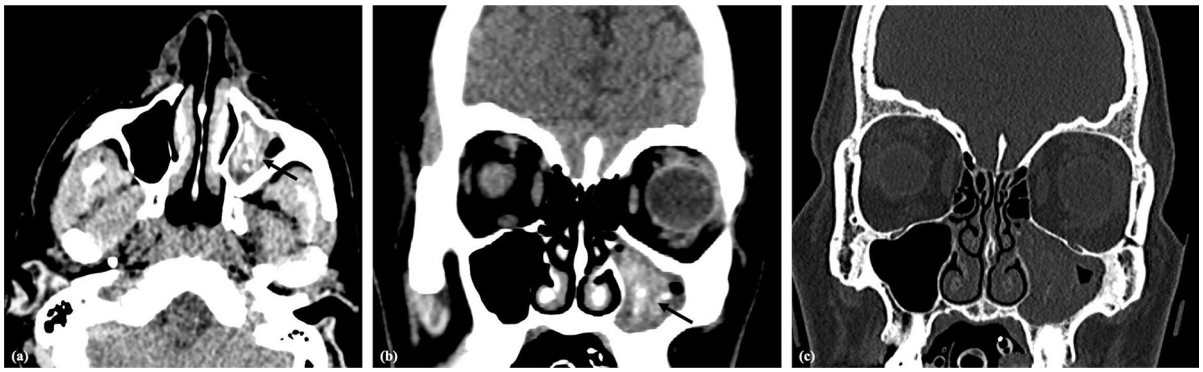

Fig. 12 38-year-old asthmatic patient with cough. Axial (**a**) and coronal (**b**) CT of the paranasal sinuses on soft tissue window demonstrate hyperdense material and calcifications inside the left maxillary sinus (arrows). Coronal CT on bone window **c** shows opacification of the left maxillary sinus with sclerosis of the sinus wall. The final diagnosis of the fungus ball was dictated by endoscopy

sinonasal squamous cell carcinoma and non-Hodgkin lymphoma [72].

Conclusion

Aspergillus species are ubiquitous fungi which almost everyone inhales. However, in susceptible patients, it can cause life-threatening infections. The clinical presentation depends on organism virulence and host variables, with immune deficiency and pre-existing lung disease as two of the most critical risk factors. Familiarity with the spectrum and the various distinctive imaging patterns of pulmonary and extra-pulmonary aspergillosis in the appropriate clinical settings can provide early diagnosis, life-saving management, and better prognosis in patient care.

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Declarations

Conflict of Interest The authors have no relevant financial or non-financial interests to disclose.

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