Original article

Pulmonary fungal infections in patients with acute myeloid leukaemia: is it the time to revise the radiological diagnostic criteria?

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Summary

The definition of pulmonary fungal infections (PFI) according to the EORTC-MSG criteria may lack diagnostic sensitivity due to the possible presentation of PFI with different radiological pictures. We evaluated the hypothesis to apply less restrictive radiological criteria to define PFI in patients with acute myeloid leukaemia (AML) submitted to chemotherapy. Overall, 73 consecutive episodes of pulmonary infiltrates associated to positive serum galactomannan test or fungal isolation or galactomannan detection from respiratory specimens were considered. CT scans acquired at the onset of symptoms (time-0) and within 4 weeks (time-1) were analysed to identify specific (group A) or aspecific radiological signs (group B). Pulmonary infiltrates fulfilled the EORTC-MSG criteria in 49 patients (group A), whereas in 24 patients (group B) they did not reach the criteria due to aspecific CT findings at time-0. Eleven of 21 (52.4%) patients of the group B evaluable for the evolution of the radiological findings fulfilled EORTC-MSG criteria at time-1. All the analysed clinical and mycological characteristics, response to antifungal therapy and survival were comparable in the two groups. Our study seems to confirm the possibility to extend the radiological suspicion of PFI to less restrictive chest CT findings when supported by microbiological criteria in high-risk haematological patients.

Key words: Pulmonary fungal infections, acute myeloid leukaemia, definition, radiological findings.

Introduction

Pulmonary fungal infections (PFI), in particular invasive pulmonary aspergillosis (IPA), are a major cause of morbidity and mortality in patients affected by acute myeloid leukaemia (AML).[1–3] The European Organization for Research and Treatment of Cancer (EORTC) and the Mycosis Study Group (MSG) developed consensus definitions for the diagnosis of invasive fungal diseases (IFD) in immunocompromised patients to facilitate the identification of reasonably homogeneous groups of patients for clinical and epidemiologic research and to foster communication between international researchers.[4,5] Proven diagnosis of PFI necessitates tissue microscopic visualisation of fungi. However, the poor candidacy of many patients with suspected PFI for invasive diagnostic procedures has prompted interest in non-invasive means for diagnosis and most of cases of PFI are documented at a level of probable infection by radiological and microbiological findings. According to the updated EORTC-MSG definitions published in 2008, a diagnosis of probable PFI is based on the documentation of at least 1 of 3 specific radiological findings (dense, well-circumscribed lesions with or without halo sign, air crescent sign or cavity) associated with fungal isolation or galactomannan (GM) detection from respiratory tract and/or positive

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serum GM or beta D glucan (BDG) assay.[5] Although the introduction of definitions for IFD has greatly facilitated the conduction of clinical trials on diagnostic and therapeutic modalities, their diagnostic performance in the clinical practice is low when compared with autopsy examination.[6–9] The application of specific but not very sensitive diagnostic radiological criteria may determine an underestimation of these severe complications as shown in recently published retrospective studies in patients affected by various haematological diseases.[10,11] As a consequence, the revision of the EORTC-MSG definitions with the inclusion of less specific radiological images in addition to the three above findings in the diagnosis of PFI, when supported by proper microbiological exams, has been proposed.[10–12] The objective of our study was to expand the above experiences to a large homogeneous population of high-risk AML patients submitted to standard intensive chemotherapy.

Patients and methods

We retrospectively evaluated all consecutive patients older than 18 years with a newly diagnosed non-M3 and BCR-ABL-negative AML, who underwent intensive remission-induction chemotherapy at the Hematology Departments of the Policlinico Umberto I of the Sapienza University of Rome from February 2006 through December 2013. Informed consent for the use of clinical data for scientific purposes had been obtained from the patients. This was a non-interventional retrospective study and the collection and storage of data were performed by the investigators directly involved in patient care using current techniques of privacy assurance.

Patients were hospitalised in double-bed rooms without air filtration or positive pressure. All patients underwent a baseline chest CT scan at leukaemia diagnosis and before any chemotherapy treatment. Antibacterial prophylaxis consisted of oral ciprofloxacin (500 mg bid^{-1}). Until March 2007 patients did not receive any mould active systemic antifungal prophylaxis, while since April 2007 primary antifungal prophylaxis with oral posaconazole (200 mg tid^{-1}) was administered from the end of chemotherapy administration to the recovery of neutropenia, with the exception of those treated with midostaurin, a selective inhibitor that targets the fms-like tyrosine-kinase 3 (FLT3) activating mutations frequently found in AML, in view of a possible drug–drug interaction with triazoles.[13]

Since February 2006, a survey of IFDs in AML patients undergoing intensive chemotherapy has been prospectively conducted by a predefined diagnostic strategy.[14] A microbiological laboratory and a radiological service dedicated to patients with haematological diseases were available at our centre. In the event of febrile neutropenia (temperature >38 °C recorded twice or >38.5 °C recorded once), a baseline diagnostic work-up (BDWU) based on three blood cultures (Sygnal System, Oxoid, Hants, UK) and other microbiological and radiological exams, if clinically indicated, was performed. Empirical antibacterial therapy was started and eventually modified according to the microbiological or clinical data. Patients with persisting fever after 4 days of antibacterial therapy or patients with fever relapsing after 48 h of defervescence, as well as patients with other clinical findings possibly related to an IFD, underwent an intensive diagnostic work-up (IDWU) that included three blood cultures, GM serum detection by Platelia *Aspergillus* assay (Bio-Rad Laboratories, Marnes-La-Couquette, France) over three consecutive days, CT of the chest and other exams as indicated. In the event of a negative IDWU and persistent fever, the IDWU was repeated. A positive GM test result was defined as an optical density index of ≥0.5 in two consecutive samples or ≥0.7 in a single sample in serum and ≥1 in bronchoalveolar lavage.

In patients with radiological evidence potentially related to a PFI and negative microbiological exams (cultures and GM), they were repeated from serum or respiratory specimen as indicated. Mould-active antifungal therapy (voriconazole or liposomal amphotericin B) at standard recommended doses was started on first documentation or suspect of PFI. Response to antifungal therapy was defined as complete or partial if a >90% or between 50% and 90% reduction in size of the pulmonary lesions was obtained within 3 months from the diagnosis respectively.[15]

All patients fulfilling the following criteria were considered in the analysis:

- Documentation at BDWU or IDWU of any type of pulmonary lesion at CT examination. The lesion should not have been already documented at the baseline CT scan.
- Cultural isolation of filamentous fungi or *Geotrichum capitatum*[16] from BAL or sputum and/or GM detection from serum or BAL.
- No microbiological evidence of other pathogens potentially related to the pulmonary infection.

The Standard glossary of CT imaging definitions was used to classify pulmonary lesions.[17] According to revised EORTC/MSG definitions only dense and well-circumscribed lesions with or without halo sign, air

crescent sign or cavity were considered specific for a diagnosis of probable PFI.[5] Conversely, not well-circumscribed consolidations, ground glass opacities and small airways lesions were not considered specifically diagnostic for a probable PFI. With regard to nodules, although the revised EORTC/MSG definitions did not differentiate the pulmonary lesions according to their size, there is no general agreement in considering micronodules (<1 cm in diameter) as radiological findings fulfilling the EORTC-MSG criteria.[11] Therefore, in our analysis we considered single or multiple millimetre pulmonary lesions as aspecific radiological findings.

Two independent radiologists (FM and SV), blind of the clinical and radiological results, randomly re-evaluated all CT Scans at first documentation of PFI (T0) and classified the radiological findings. Cases were considered 'probable PFI' (group A) when radiological findings fulfilled the EORTC-MSG criteria[5] or 'presumed PFI' (group B) when other aspecific radiological findings were documented. Then the two observers blindly re-evaluated the CT exams performed in patients of groups B within 4 weeks from T0 (T1), when available, to monitor the possible evolution of the aspecific pulmonary lesions in specific lesions. In case of disagreement (for both T0 and T1) a consensus was reached after discussion.

Variables considered included age, sex, antifungal prophylaxis, type of chemotherapy cycle, radiological and microbiological findings, response to antifungal therapy and survival at 1 and 3 months. The endpoint of this study was to compare the variables of the group A and of the group B. Categorical data were analysed using χ^2 or Fisher's exact tests as appropriate, and continuous variables were compared using *T*- test. Cumulative survival curves was calculated using the Kaplan–Meier method and compared by the log-rank test, taking into account the date of diagnosis of PFI and the date of death or last follow-up, censored at 3 months after the diagnosis of PFI. All analyses were performed using SPSS statistical software, version 17.0 for Windows (SPSS, Armonk, NY, USA). $P \leq 0.05$ was considered to be statistically significant. Inter-observer agreement between the independent reading of the two radiologists was calculated for both T0 and T1.

Results

During the 8-year period, 265 consecutive patients were diagnosed with AML and submitted to intensive chemotherapy. Out of 138 patients with a pulmonary infiltrate documented at CT examination, 73 patients fulfilling the above criteria of Group A or Group B PFI were considered for the analysis. In all cases the infection was documented within 3 weeks from the administration of chemotherapy while the patient was severely neutropenic (absolute neutrophil count < 100 cmm^{-1}). The demographic, clinical, radiological and microbiological manifestations, and 1 and 3 month survival of patients from the first evidence of PFI are detailed in Table 1.

Overall, 24 (32.9%) patients presented at first evidence of PFI with radiological findings not fulfilling the EORTC-MSG definitions (group B). No statistically significant difference was observed for all the analysed characteristics between the two groups, with the exception of infection by mucormycetes which were observed only in the group B (3 of 24 vs. 0 of 49, $P = 0.03$). The radiological findings more frequently observed at diagnosis in group A were macronodules or well-circumscribed consolidations with halo sign (27 of 49 cases, 55.1%), whereas not well-circumscribed consolidations were found in the majority of group B (13 of 24 cases, 54.2%). We found no correlation between the type of microbiological documentation (GM from serum, GM from BAL, *Aspergillus* culture isolation) and the different radiological findings of cases of IPA.

Voriconazole was the most frequently used primary treatment for PFI and treatment practices did not differ in the two groups. The 3 months response to antifungal therapy and cumulative survival of the two groups at 1 and 3 months evaluation were comparable.

Evolution of radiological aspecific findings was monitored in 21 of 24 patients of the group B (in 3 patients who early died radiological control was not performed). The early aspecific radiological findings (T0), at a repeat imaging (T1) changed into specific findings diagnostic of probable PFI in 11 (52.4%) patients, a median of 10 days (range, 5–28 days) after T0 (Table 2) (Fig. 1). Macronodule/well-circumscribed consolidation without halo sign represented the most frequent radiological finding specific of PFI at Time 1. An evolution in cavity or air crescent sign lesions was observed in 2 of 13 (15.4%) consolidations and in 2 of 4 (50%) micronodular lesions. In the 21 patients of the group B evaluable for radiological evolution, we found no difference (considering age, sex, previous antifungal prophylaxis and leukaemia phase) between the 11 patients who later developed specific radiological findings and the 10 patients who did not. Furthermore, in 17 patients of the group B with a diagnosis of probable aspergillosis, we found no correlation between previous antifungal prophylaxis, microbiological characteristics, antifungal therapy and radiological evolution (Table 3).

Table 1 Clinical, radiological and microbiological findings among patients with acute myeloid leukaemia and pulmonary fungal infection (PFI): comparison of cases by EORTC-MSG prespecified radiological criteria (Group A)[1] vs. cases without prespecified radiological findings (Group B) at diagnosis.

Characteristic at diagnosis	Group A (n = 49)	Group B (n = 24)	P
Sex, no. of male (%)	31 (63.3)	14 (58.3)	0.8
Age, median years (range)	53 (24–73)	54 (30–72)	0.9
Type of chemotherapy, no. of cases (%)			
First induction	37 (75.5)	17 (70.1)	0.7
Consolidation	6 (12.2)	2 (8.3)	
Re-induction/salvage therapy	6 (12.2)	5 (20.1)	
Microbiological diagnosis			
Aspergillus	46 (93.9)	19 (79.2)	0.1
Mucormycetes	0	3 (12.5)	0.03
Geotrichum capitatum	1 (2.2)	2 (8.3)	0.2
Aspergillus plus Mucormycetes	1 (2.2)	0	1
Aspergillus plus *G. capitatum*	1 (2.2)	0	1
Posaconazole prophylaxis, no. of cases (%)	21 (42.9)	10 (41.7)	1
Radiological findings, no. of cases (%)[2]			
EORTC-MSG-specific findings			
Macronodule/well-circumscribed consolidation with halo sign	27 (55.1)	0	NP
Macronodule/well-circumscribed consolidation without halo sign	18 (36.7)	0	
Cavity or air crescent sign	4 (8.2)	0	
Aspecific findings			
Not well-circumscribed consolidation	0	13 (54.2)	
Ground-glass opacity	0	4 (16.7)	
Micronodules	0	6 (25.0))	
Tree in bud	0	1 (4.2)	
Mycologic criteria, no. of cases (%)			
GM from serum	40 (81.6)	17 (70.8)	0.4
GM from BAL or sputum	5 (10.2)	4 (16.7)	0.5
Culture from BAL or sputum	6 (12.2)	6 (25.0)	0.2
Serum GM peak, median value (range)	1.1 (0.6–4.4)	1.0 (0.5–5)	0.7
Primary antifungal treatment, no. of cases (%)			
Voriconazole	37 (75.5)	15 (62.5)	0.3
Liposomal Amphotericin B	10 (20.4)	6 (25.0)	0.8
No antifungal therapy due to early death	2 (4.1)	3 (12.5)	0.3
Complete/partial response after 3 months antifungal therapy; no. of cases (%) out of pts who received antifungal therapy	36 (73.5)	19 (79.2)	0.8
1 month cumulative survival, %	77.5	83.3	0.5
3 month cumulative survival, %	67.3	75.0	0.4

GM, galactomannan; NP, statistical comparison was not performed because by definition the two groups had been stratified according to different radiological findings.

[1]EORTC-MSG radiological criteria of pulmonary fungal infection were: dense, well-circumscribed lesions with or without halo sign, air crescent sign and cavity.

[2]In each patient more than one radiological finding may have been observed at CT examination but only the predominant finding was indicated.

Overall, radiological findings fulfilled the EORTC-MSG criteria in 49 of 73 (67.1%) patients at T0 and in 60 of 70 (85.7%) evaluable patients considering also T1. In the remaining 10 evaluable patients of the group B without a specific radiological evolution, a complete or partial regression of pulmonary lesions with antifungal therapy was obtained in six cases. In three patients with large pulmonary consolidations and isolation of mucormycetes, the diagnosis was confirmed histologically (in 2 cases at autopsy) but the radiological findings continued to not fulfil the EORTC/MSG criteria at the following radiological controls.

Inter-rater agreement between the two Radiologists was very good: at T0 k was = 0.858 (SE 0.061, 95% CI 0.739–0.978); at T1 k was 0.915 (SE 0.048, 95% CI 0.821–1.000). At T0 discordance was found in five cases, at T1 discordance was

Table 2 Evolution of radiological findings at a repeat imaging in 21 patients with pulmonary infiltrates not fulfilling the EORTC-MSG radiological criteria at diagnosis of presumed pulmonary fungal infection.

	Evolution of radiological findings, *n* (%)			
Radiological findings at diagnosis	Macronodule/well-circumscribed consolidation	Macronodule/well-circumscribed consolidation with halo sign	Cavity or air crescent sign	No specific evolution
Not well-circumscribed consolidation, 13 pts[1]	4 (30.8)	0	2 (15.4)	7 (53.8)[1]
Micronodules, 4 pts	1 (25)	0	2 (50)	1 (25)
Ground glass. 3 pts	1 (33.3)	0	0	2 (66.6)
Tree in bud, 1 pt	1 (100)	0	0	0

[1]3 pts with a diagnosis of presumed pulmonary mucormycosis (later histologically proven): no specific evolution in all cases.

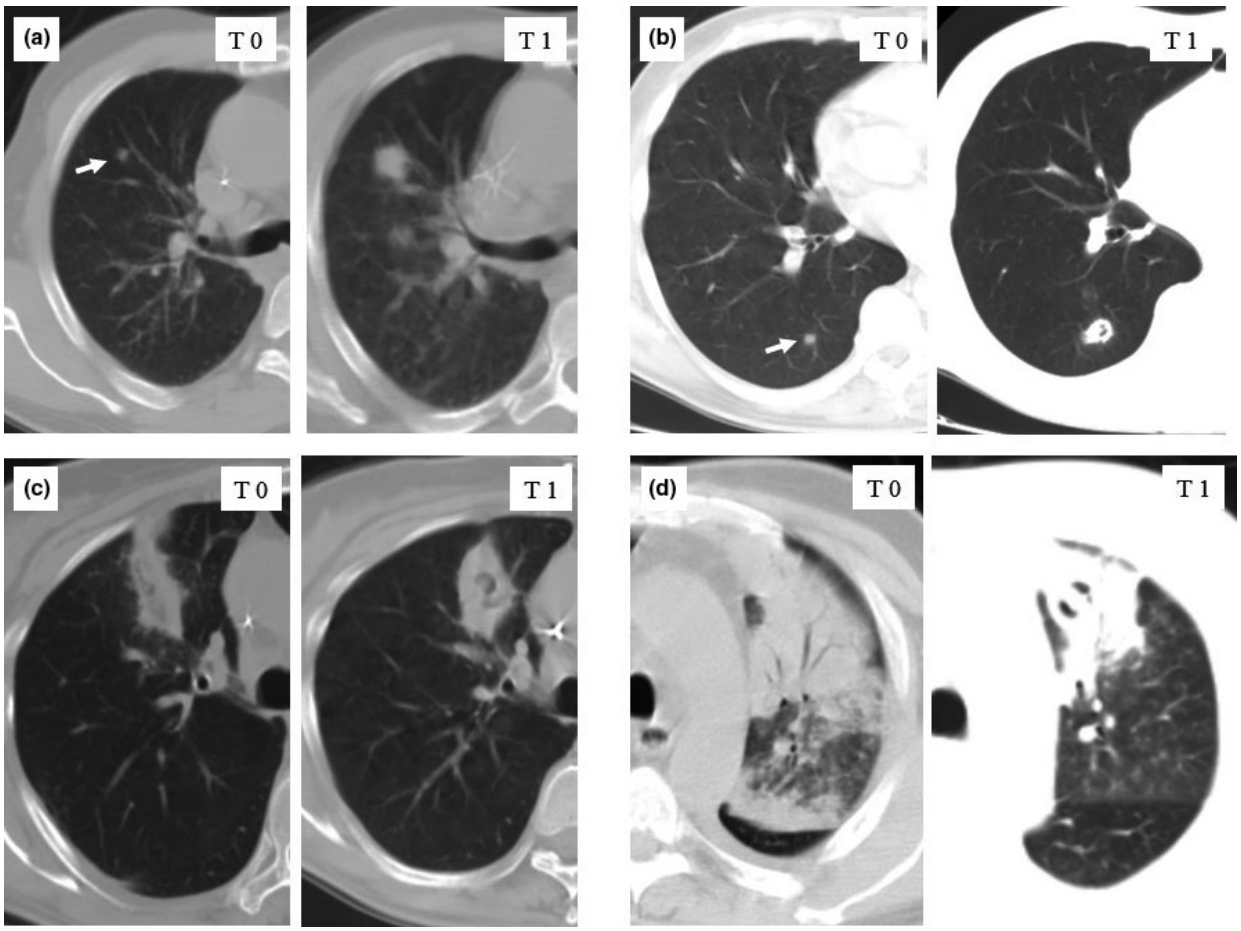

Figure 1 Cases of pulmonary fungal infections with aspecific radiological findings at first documentation (T0) and evolution in specific radiological findings at re-evaluation (T1). (a) A micronodular lesion at T0 (arrow) and a nodular lesion at T1 (day +5). (b) A micronodular lesion at T0 (arrow) and an air crescent sign lesion at T1 (day +8). (c) A consolidation at T0 and an air crescent sign lesion at T1 (day +9). (d) A mass with air bronchogram at T0 and a cavity lesion at T1 (day +11).

found in three cases. Disagreement was observed only in case with CT observation of well-circumscribed consolidation and macronodules: in all cases a final consensus was reached between the two radiologists.

Discussion

The definitions of PFI according to the EORTC-MSG criteria are considered a standard in the clinical trials and in the epidemiological studies, particularly in

Mycologic and therapeutic variables	Specific evolution of radiological findings, $n = 11$	No specific evolution of radiological findings, $n = 6$
Posaconazole prophylaxis, no. of cases (%)	4 (36.4)	2 (33.3)
Mycologic criteria, no. of cases (%)		
GM from serum	10 (91)	5 (83.3)
GM from BAL or sputum	2 (18)	1 (16.6)
Culture from BAL or sputum	1 (9)	1 (16.6)
Serum GM peak, median value (range)	0.9 (0.5–3.8)	1.2 (0.6–5)
Primary antifungal therapy, no. of cases (%)		
Voriconazole	9 (81.8)	5 (83.3)
Liposomal Amphotericin B	2 (28.2)	1 (16.7)

GM, galactomannan.

Table 3 Microbiological characteristics, antifungal treatment and evolution of radiological findings in 17 patients with pulmonary infiltrates not fulfilling the EORTC-MSG radiological criteria at diagnosis of presumed pulmonary aspergillosis.

immunocompromised populations at very high infectious risk such as AML patients.[4,5] The revised definitions published in 2008 restricted the radiological criteria of PFI as compared to those of the original definitions published in 2002 where any kind of pulmonary infiltrate was considered.[4,5] Indeed, it is common experience that the strict application of these definitions may exclude PFI with radiological findings other than well-circumscribed lesions with or without halo sign, air crescent sign and cavity, regardless of the microbiological documentation. The Consensus Group of the EORTC/MSG did not consider their definitions a substitute for complete clinicopathological descriptions and classifications of IFD, and acknowledged that the failure to meet the criteria for IFD does not mean that there is no IFD, only that there is insufficient evidence to support the diagnosis.[5] However, the EORTC/MSG Consensus Group suggested to apply them with the primary goal of fostering communication, furthering our understanding of the epidemiology and evolution of IFD, and facilitating our ability to test the efficacy of therapeutic regimens and strategies.[5] The use of restrictive, specific diagnostic criteria in studies aimed at the evaluation of the efficacy of new antifungal treatments may be acceptable considering the importance of a careful evaluation of alternative strategies in the management of severe IFDs and the comparability of clinical trials, but the application of insensitive diagnostic criteria in the detection of epidemiological trends or in the evaluation of prevention strategies is likely to lead an underestimation of the phenomenon with a potentially deleterious impact on some practices as the definition of the infectious risk and the indication for primary prophylaxis. It should be also considered that, in the absence of other shared criteria more suitable for clinical practice, the EORTC/MSG definitions represent a 'de facto' standard in the real life and in the daily communication between physicians.

A revision of the EORTC-MSG definitions with the inclusion of a new category of IPA giving a greater weight to Aspergillus-specific microbiological criteria has been proposed by Nucci *et al.* [10] based on a retrospective study from the Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, which showed that the features of multiple myeloma patients with probable IPA according to the revised EORTC/MSG radiological criteria are comparable to those of patients without specific radiological findings. About 30% of 116 episodes of IPA, presented with radiological findings not fulfilling the above specific diagnostic criteria of probable IPA and no significant difference in the host, clinical and mycological characteristics, as well as in survival, was observed in the two groups. In a recently published experience from our Institution, we confirmed these results in 109 patients affected by various haematological malignancies or submitted to allogeneic stem cell transplant with pulmonary infections associated to culture isolation of Aspergillus and/or GM detection.[11]

In this study, which includes 46 AML patients already evaluated in the previous series, we expanded the population of AML patients and we considered also patients with isolation of non-Aspergillus fungi. A focus on the frequency and the evolution of some radiological pictures (i.e. not well-circumscribed consolidations, ground glass opacities, micronodules, tree in bud) different from those considered in the EORTC/MSG definitions was also performed.

Our results seem to further confirm that pulmonary infiltrates other than those defined specific for PFI, when associated to a microbiological documentation,

should be considered probably diagnostic of a fungal disease in high-risk AML neutropenic patients. The two PFI groups did not significantly differ in the host, clinical and mycological characteristics, in the response to antifungal therapy, and in the outcome. Half of pulmonary radiological pictures in the presumed PFI group (Group B), including micronodules, evolved in large well-circumscribed or cavity lesions after few days suggesting that these cases might be an early phase of the disease (Fig. 1), furthermore, three cases of mucormycosis, later confirmed hystologically, presented with large unspecific consolidations which maintained the same aspecific findings at the following radiological controls. Of interest, even though the inter-rate agreement between the two expert radiologists was very good, a slight discordance was still present between the two most frequently observed radiological findings: macronodules and consolidation. Thus, our results seem to show that the size and appearance of the pulmonary lesion does not represent a criterion for differentiating the diagnostic suspect of PFI. The two groups did not differ in the rate of previous posaconazole primary prophylaxis, furthermore, since we used posaconazole prophylaxis in AML patients at our institution, while observing a relevant reduction in the rate of PFIs, we did not detect significant changes in the clinical features of such complications. False-positive results may be observed when using the GM assay and serum positivity in absence of a proper clinical suspicion of PFI should be considered with caution. In our experience, GM assay was not used as a surveillance of asymptomatic patients along the period at risk but in the context of a clinically driven strategy. This approach proved to offer a 90% positive predictive value regardless of the use of antifungal prophylaxis.[18] The performance of the microbiological diagnostic strategy did not differ according to the radiological presentation of the pulmonary infiltrates. GM represented the main microbiological diagnostic tool and no significant difference in the serum level of the antigen was observed in the two groups.

In conclusion, our study shows that in AML patients submitted to intensive chemotherapy a large proportion of PFIs may present with radiological features not fulfilling the EORTC-MSG definitions, reflecting the fact that such fungal diseases may present in atypical form not only in patients with chronic lymphoprolipherative disorders but also in acute leukaemia.[10,11] The different radiological presentation of the pulmonary infiltrates (considering type, number and size) and their evolution was not associated to the use of antifungal prophylaxis and did not correlate with specific microbiological documentation or antifungal treatment.

Considerable uncertainty and controversy exists regarding the best method for establishing a diagnosis of PFI in high-risk haematological patients. We think that appropriate microbiological evidence of a fungal aetiology in high-risk patients may support the possibility to revise the current EORTC/MSG definitions extending the radiological suspicion of PFI to less traditional chest CT findings, including not well-circumscribed consolidations, micronodules, ground glass opacities and other small airway lesions. The more specific radiological criteria considered in the EORTC/MSG definitions, eventually with the addition of the recently described 'reversed halo sign' and 'hypodense sign',[19,20] should be probably preferred in clinical trials (i.e. primary or salvage antifungal therapy) where a high level of diagnostic accuracy is requested. On the other hand, more sensitive, although less specific, criteria are needed in other settings (i.e. epidemiological or prophylaxis studies) to avoid a misleading underestimation of diagnoses.

Authorship

All authors contributed to research design, or the acquisition, analysis or interpretation of data. The submitted, final version of the paper was approved by all authors. FM, SV and CG designed and performed the research study. CG and NA analysed the data. FM, SV and CG wrote the manuscript.

Conflict of interest

No conflict of interest or disclosure for all authors.

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