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Bronchoscopy guided by high-resolution computed tomography for the diagnosis of pulmonary infections in patients with hematologic malignancies and normal plain chest X-rays

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ABSTRACT

Background and Objectives. **High-resolution computed tomography (HRCT) of the chest is able to demonstrate the presence of pulmonary infiltrates in febrile neutropenic patients with normal chest X-rays. Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) is a safe procedure for the etiological diagnosis of pulmonary infiltrates in oncohematologic patients. The objective of this study was to determine the diagnostic yield and subsequent therapeutic changes of a protected BAL (p-BAL) guided by HRCT in febrile oncohematologic patients unresponsive to broad-spectrum antibiotics with a normal chest X-ray.**

Design and Methods. **Twenty-two episodes from 20 oncohematologic patients were included: group A, 9 episodes (8 patients) with no respiratory symptoms and group B, 13 episodes (12 patients) with signs or symptoms of pulmonary infection. HRCT and p-BAL were performed in all episodes within the first 24 hours.**

Results. **HRCT showed abnormalities in all 22 episodes (bilateral abnormalities in 14 of the 22 episodes [64%]) and the most frequent pattern was ground-glass infiltrate (7 out of 22 episodes). An infectious agent was isolated in 12 of the 22 episodes, 5 in group A and 7 in group B with a diagnostic yield of 54%. Antimicrobial therapy was modified in 12 of the 22 episodes (54%): 5 in group A and 7 in group B. In 6 episodes, treatment was changed according to HRCT results and in the remaining 6 due to positive microbiological results. Modifications in empirical therapy were associated with a favorable response in 44% episodes of group A and in 31% of group B.**

Interpretation and Conclusions. **Oncohematologic patients with fever of unknown origin unresponsive to empirical antibiotics and with a normal chest X-ray can be candidates to undergo a HRCT. This subgroup of high-risk patients can benefit from a combined strategy consisting of BAL guided by a previous HRCT.**

Key words: bronchoscopy, high-resolution computed tomography, pulmonary infections

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Pulmonary infections represent an important cause of morbidity and mortality in oncohematologic patients treated with chemotherapy. Prolonged neutropenia due to intensive antineoplastic treatments exposes patients to infectious complications, pulmonary among others. In fact, pneumonia is the main cause of mortality not due to the underlying disease in these patients. Serial chest X-rays are often requested to detect pulmonary disease, but faint opacities on chest roentgenograms may be difficult to detect, especially in patients who are unable to inspire fully. Furthermore, neutrophil counts are often low, and this may result in a poor inflammatory response, which may further decrease the sensitivity of the chest X-rays. Some groups of investigators[1,2] have recently shown that high-resolution computed tomography (HRCT) of the chest is able to demonstrate the presence of pulmonary infiltrates in febrile neutropenic[2] or bone marrow transplant patients[1] with normal or non-specific chest X-rays.

Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) has been shown to be a safe and easy procedure for the etiological diagnosis of pulmonary infiltrates in oncohematologic patients,[3-6] with a yield ranging from 50 to 70%, depending on the type of pneumonia and the patient population analyzed.[3–8.] Although the role of BAL in the investigation of new pulmonary infiltrates has been extensively studied, little research has been done in oncohematologic patients who have normal chest X-rays.

The purpose of this study was to determine the diagnostic yield and subsequent therapeutic changes of a protected BAL (p-BAL) guided by HRCT in oncohematologic patients with fever of unknown origin not responsive to broad-spectrum antibiotics and with a normal chest X-ray.

Design and Methods

Patients

Twenty-two episodes from 20 oncohematologic patients were included in the study. The patients' characteristics are shown in Table 1. There were 11 males and 9 females with a median age of 42 years (range 16 to 65). Inclusion criteria were fever of unknown origin not responsive to a 5-day course of broad-spectrum intravenous antibiotics and a normal chest X-ray. The patients were divided into 2 groups depending on the presence or not at the moment of entry into the study of symptoms and/or

Table 1. Characteristics of the patients included in the two groups. Group A: patients without respiratory signs or symptoms. Group B: patients with a clinically suspected respiratory infection.

	Group A	*Group B*	*Total*
Patients, number	8	12	20
Episodes, number	9	13	22
Median age, years (range)	37 (19-65)	47 (16-62)	42 (16-65)
Sex, male/female	5/3	6/6	11/9
Underlying disease			
Acute leukemia/MDS	6	7	13
Chronic leukemia	0	3	3
NHL	1	1	2
Breast cancer	1	1	2
Previous treatment			
Conventional chemotherapy	5	8	13
First-line	5	5	10
Salvage	0	3	3
HSCT	3	4	7
Allogeneic	2	2	4
Autologous	*1*	*2*	*3*
Duration of neutropenia before HRCT/BAL (<0.5x10⁹/L), median in days (range)	18 (7-70)*	10 (0-25)*	14 (0-70)
Duration of fever before HRCT/BAL, median in days (range)	8 (6-22)	11 (3-18)	9 (3-22)
Antimicrobials at HRCT/BAL			
No antimicrobials	1	0	1
BSA only	5	4	9
BSA + amphotericin B	3	9	12

*MDS: myelodysplastic syndrome; NHL: non-Hodgkin's lymphoma; HSCT: hematopoietic stem cell transplantation; HRCT: high resolution computed tomography; BAL: bronchoalveolar lavage; BSA: broad spectrum antimicrobials. *p= 0.057 with Mann Whitney' s U-test.*

signs of pulmonary infection: group A, 9 episodes (8 patients) with no respiratory symptoms and group B, 13 episodes (12 patients) with signs or symptoms of pulmonary infection such as cough, dyspnea, abnormal blood gases or abnormal pulmonary auscultation and a normal chest X-ray. At the moment of inclusion in the study, all patients but one were severely neutropenic (granulocytes < 0.5×10^9/L) and in 21 of the 22 episodes the patients were receiving antimicrobial therapy (broad-spectrum intravenous antibiotics in 9 episodes and broad-spectrum antibiotics plus amphotericin B in the remaining 12).

Methods

After including the patient in the study, a HRCT followed by fiberoptic bronchoscopy and p-BAL were performed within the first 24 hours.

HRCT technique. All patients underwent plain chest radiography performed on the same day as the HRCT examination. Chest X-rays were examined by two independent radiologists and infiltrates, cavitations, consolidation areas and ground-glass opacities suggesting pulmonary infection were ruled out. In cases of doubt, chest X-rays were compared with previous films of the patient. All HRCT examinations were performed with a Toshiba 900 CT unit (Toshiba Medical Systems, Tokyo, Japan). Thin-collimation (2 mm) sections were obtained at 10-mm intervals, extending from lung apices to below the costophrenic angles. A 350-mm field of view and a 512×512 reconstruction matrix were used. Images were reconstructed with a high-spatial frequency algorithm for parenchymal analysis and a standard algorithm for mediastinal evaluation. HRCT scans were obtained at the suspended end-inspiratory volume with an imaging time of 2 sec. Patients were scanned in the supine position, with additional scans obtained in the prone position, when necessary, to demonstrate the reversibility of dependent areas of attenuation. No intravenous contrast material was used. All images were obtained at window levels appropriate for lung parenchyma (window width, 1700 H; window level -600 H) and mediastinum (window width, 350 H; window level, 50 H).

The HRCT scans were analyzed by two thoracic radiologists for perfusion and type of parenchymal abnormalities. Ground-glass opacities, ill-defined nodules, consolidation, cavitations, and poorly defined linear opacities were considered highly indicative of inflammation or pneumonia.[9-11] If at least one of these findings was present, the study was classified as suggestive of pneumonia. In case of ground-glass pattern, other causes such as apiration, graft-versus-host disease (GVHD) or hyperhydration were ruled out on the basis of clinical data (type of bone marrow transplant, increasing weight, central venous pressure measurements...).

Bronchoalveolar lavage. Bronchoscopies were performed with an Olympus BF-P20 fiberoptic bronchoscope. The bronchoscope was inserted into the chosen bronchus and p-BAL was done through the external catheter of a telescoping double plugged catheter (Combicath) with 5 boluses of 20 mL of sterile saline solution; the last four instillations were used for cytologic and microbiological analysis whereas the first one was discarded. All bronchoscopies were performed at the bedside with local anesthesia and supplemental oxygen. The procedure was well tolerated in all patients and no complications were recorded.

Microbiological processing. Samples were centrifuged for 15 to 20 minutes at 1,500-1,800 g and the supernatant was eliminated. The resultant pellet was resuspended in 10 mL of physiologic saline. One milliliter of the resulting material was used for bacterial cultures: rapid detection of bacteria was performed by means of a Gram stain. Several culture media were used for the diagnosis of aerobic and anaerobic bacteria including selective media for *Legionella spp.* and *Nocardia spp*. The methenamine silver stain was performed to detect *Pneumocystis carinii*. The presence of fungi including *Aspergillus spp.* was ruled out by means of a Giemsa stain as a quick method and other midterm specific culture media. A sample of 4 mL of the initial resuspended material was treated with antibiotics and seeded in several cell lines for viral analysis; detection of the early viral antigen of CMV was performed by means of specific monoclonal antibodies. The remaining 5 mL were used for mycobacterial isolation employing both Lowenstein and Bactec media and the Ziehl-Neelsen technique as a quick stain.

The isolation ≥ of 10^4 CFU/mL of a specific micro-organism in the p-BAL was considered diagnostic.

Statistical analysis

Results are expressed as median and range. Qualitative variables were compared by means of the Mann Whitney U-test. A p value < 0.05 was considered statistically significant.

Results

Results of HRCT/BAL and the clinical outcome of the 22 episodes analyzed are shown in Table 2. HRCT showed abnormalities in all 22 episodes, independently of the presence or not of respiratory symptoms and/or signs at the time of entry into the study. Bilateral abnormalities were demonstrated in 14 of the 22 infectious episodes (64%), and the most frequently observed pattern was ground-glass infiltrate (7 out of 22 episodes), without differences between patients with respiratory symptoms and those with no symptoms. In cases in which HRCT was not strongly suggestive, no invasive procedures such as transbronchial biopsy were performed due to the high risk of hemorrhagic complications in these severely thrombocytopenic patients. Overall, an infectious agent was isolated in 12 of the 22 episodes analyzed, 5 in group A (55%) and 7 in group B (55%) for an overall yield of 54%. Pathogenic bacteria or *Pneumocystis carinii* were isolated in 3 episodes, while viral infections were detected in 6 episodes. We were not able to find differences in pathogenic micro-organisms between the two groups of patients, but the numbers were very low. In 3 episodes, a non-pathogenic micro-organism was found: there was one case of CMV isolated in a non-transplant recipient and 2 cases of *Candida albicans* and mixed flora of the upper respiratory tract which were considered to be contaminants.

Antimicrobial therapy was modified upon entering the patient in the study in 12 of the 22 episodes (54%): 5 (66%) in group A and 7 (53%) in group B. In 6 episodes treatment was changed according to the results of HRCT, and in the remaining 6 due to the identification of pathogenic micro-organisms in the BAL. Cytology of BAL showed low numbers of polymorphonucleate cells in all cases as previously reported in the literature[6] and did not help in the differential diagnosis; only in one case did the initial result of cytology, showing cells with changes suspicious of CMV infection, cause the addition of gancyclovir to the treatment. Patients in whom therapy was modified are shown in Table 3. Modifications in empirical therapy were associated with a favorable response and clinical improvement in 44% of episodes in group A and in 31% in group B. In 14 (63%) episodes patients survived, 4 (44%) in group A and 10 (76%) in group B. In 3 episodes (2 from group A and 1 from group B), death was due to the pulmonary infection. Causes of death and relation to results from the combined approach of HRTC-BAL in patients with an unfavorable outcome are shown in Table 4.

Discussion

The results of this study highlight the role of HRCT in the diagnosis of pulmonary infections in oncohematologic patients with fever unresponsive to broad-spectrum antibiotics, with or without respiratory symptoms and a normal chest X-ray. Abnormal findings were found by HRCT in all infectious episodes analyzed, independently of the presence or not of respiratory symptoms. Several other groups have also analyzed the role of HRCT in this setting: Barloon *et al.*,[1] in a prospective analysis of 36 febrile episodes occurring in 33 bone marrow transplant recipients, found that in 3 out of 14 episodes with a normal chest X-ray and in 17 out of 22 episodes with non-specific chest roentgenogram changes, CT scanning resulted in a change in clinical management or in added confidence about the diagnosis. Heussel and coworkers[2] recently presented their data on 188 HRCT studies performed in 112 neutropenic patients with fever lasting more than 48 hours under broad-spectrum antibiotic coverage; 112 (60%) HRCT studies showed pneumonia when chest X-rays were normal and documentation was possible in 61 cases by chest X-rays or micro-organism detection (54%) during follow-up. Different sensitivities and specificities have been associated with the different radiologic

Table 2. Results of the tandem protocol HRCT/BAL.

	Group A (N=9)	*Group B (N=13)*	*Total (N=22)*
HRCT findings			
Single nodule (>1 cm)	1	2	3
Multiple nodules (> 1 cm)	1	2	3
Ground-glass infiltrates	4	3	7
Alveolar infiltrates	-	2	2
Others°	3	4	7
Bilateral lesions	7	7	14
Positive micribilogy in BAL			
Pathogenic bacteria	1	2	3
Fungal hyphae	1	-	1
P. carinii	1	-	1
CMV	-	1	1
HSV-1	1	-	1
Influenza A	-	1	1
Enterovirus	-	1	1
Non-specific/non-pathogenic Micro-organisms in BAL	1	2	3
Change in therapy due to HRCT/BAL			
Due to HRCT findings only*	2	4	6
Due to positive BAL results	3	3	6
No changes	4	6	10
Outcome (of episode)			
Died of respiratory infection	2	1	3
Died of another cause	3	2	5
Survived	4	10	14

*BAL: bronchoalveolar lavage; HRCT: high resolution computed tomography; CMV: cytomegalovirus; HSV-1. Type 1 herpes simplex virus. *These cases had negative microbiologic findings in BAL except for one patient who had a non-pathogenic micro-organism. °Others: 3 cases with a pattern characterized by ill-defined small nodules, 2 with pleural effusions, 1 bronchiolar pattern and 1 case with a scarring image.*

Table 3. Modifications of antimicrobial therapy and clinical outcome.

Patient	*Group*	*Diagnosis*	*HRCT findings*	*BAL*	*Previous treatment*	*Changes in treatment*	*Cause of the change*	*Outcome*
CGA	A	AML	Ground-glass	*E. coli* + *K. Pneumoniae*	No	Start tazocel +amikacin	BAL	Died
FRC	A	ALL	Ground-glass	CMV + *P.carinii*	Ciprofloxacin	Change to cotrimoxazole +foscarnet	BAL	Died
MRA	A	AML	Ground-glass + Small nodules	Negative	Cefepime + amphotericin B	Change to imipenem + erythromycin	HRCT	Survived
APM	A	ALL	Small nodules	HSV-1	Imipenem + amikacin	Addition acyclovir	BAL	Survived
RFD	A	Breast cancer	Single nodule	Negative	Imipenem + teicoplanin	Addition amphotericin B	HRCT	Survived
DMG	B	AML	Alveolar diffusse pattern	Negative	Meropenem + amphotericin B	Start cotrimoxazole	HRCT	Died
FCR	B	ALL	Multiple nodules	*P. cepacea* + *S. Coagulase* neg.	Imipenem + abelcet	Change to tazocel + amikacin	BAL	Survived
MCI	B	CLL	Single nodule	Negative	Cefepime + vancomycin	Start amphotericin B	HRCT	Survived
APG	B	CML	Small nodules	CMV (Ag)	Cefepime + foscarnet + abelcet	Addition gancyclovir	BAL	Died
JSL	B	AML	Single nodule	Non-pathogenic	Meropenem	Change to tazocel B + amphotericin	HRCT	Survived
RTF	B	AML	Ground-glass	Negative	Amphotericin B	Start clarithromycin + cotrimoxazole	HRCT	Survived
JTS	B	Breast cancer	Cicatricial image	Negative	Imipenem + amikacin	Start gancyclovir	Cytology of BAL	Survived

HRCT: high resolution computed tomography; BAL: bronchoalveolar lavage; AML: acute myeloblastic leukemia; ALL: acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; CMV: cytomegalovirus; HSV-1: type 1 herpes simplex virus.

Table 4. Results of BAL and causes of death in patients with an unfavorable outcome.

Age/sex	*Group*	*Result of BAL*	*Cause of death*
19 M	A	Fungal hyphae	Pulmonary infection
32 M	A	*E. coli, K. pneumoniae*	GvHD
42 M	A	*P. carinii*, CMV	Pulmonary infection
43 F	A	Negative	GvHD
34 F	A	Negative	Progression/GvHD
54 M	B	Negative	Progression
53 F	B	Negative	Pulmonary infection
23 M	B	CMV	Brain toxoplasmosis

M: male; F: female; GvHD: graft-versus-host disease; CMV: cytomegalovirus.

patterns obtained in the HRCT.[2,11,12] In our series, the ground-glass appearance was the most frequent pattern found (7 out of 22 episodes). Ground-glass opacities are known to be a pattern of low specificity[11,12] and they can reflect disturbances of ventilation, temporary overhydration, aspiration, graft-versus-host disease or disturbances of perfusion.[2] All these clinical circumstances were carefully ruled out in all the episodes reported in this study. Moreover, the fact that in more than 60% of the episodes HRCT changes were bilateral makes the diagnosis of infectious pneumonia associated with ground-glass opacities more reliable.[6]

Pneumonia in oncohematologic patients who are receiving chemotherapy or bone marrow transplantation is frequent and has a high mortality. The earliest possible detection of causative pathogens is required so that specific treatment can be started immediately. Procedures such as transbronchial biopsy, transthoracic fine needle aspiration or open-lung biopsy are associated with a high risk of complications in this population of patients because most of them have severe thrombocytopenia. Non-invasive bronchoscopic techniques such as BAL or p-BAL have been shown to be safe and sensitive procedures to evaluate lung infiltrates in neutropenic oncohematologic patients.[3-5] BAL has an overall diagnostic yield ranging from 16 to 60%[3-6] being more helpful when chest X-rays show diffuse infiltrates.[6] The tandem association of HRCT and a guided bronchoscopy with a BAL or p-BAL performed within the first 24 hours after HRCT could possibly increase this yield. In our study of 22 episodes an infectious agent was isolated in 12. Although this figure does not initially seem significantly different from what has been previously reported in the literature, it must be taken into account that in half of the episodes analyzed the patients did not present with respiratory symptoms and had a normal plain chest X-ray, which makes this diagnostic yield of 55% of strong interest for the early diagnosis of a pulmonary infiltrate. Moreover, the majority of the patients included in our study were neutropenic and had been previously treated with

broad-spectrum intravenous antibiotics (n = 9) or amphotericin B (n = 12), factors that may decrease the yield of a BAL.[2,4,6] The use of protected BAL as the only bronchoscopic diagnostic procedure without a bronchial brush may also have decreased the diagnostic yield. Some authors claim that the combined use of these techniques has higher sensitivity than each single method in the microbiological diagnosis of pulmonary infiltrates in immunocompromised patients.[4] Nevertheless, our group has previously demonstrated that p-BAL alone can substitute the combined use of protected brush and BAL in immunocompromised patients and obtains a higher sensitivity than protected brush in diagnosing bacterial pneumonia.[13]

As expected, the number of bacterial isolates is low (3 out of 9, 33%); as previously stated by other authors[3,4,6,13,14] the use of broad-spectrum antibiotics before endoscopy significantly decreases the positivity of BAL and all but one of the patients included in the study were under antibiotics at the time of entry. On the other hand, viruses were frequently isolated in our series. Although some authors have tried to associate different radiologic patterns obtained with a HRCT with different microbiological isolates,[2] the low number of episodes in this study did not allow of any type of relationship to be established.

HRCT findings led to modification of the empirical treatment in 6 episodes, and microbiological results from BAL led to antimicrobial changes in another 6 episodes (>30% of the episodes included), thus making this tandem procedure worthwhile in this clinical situation. This approach is, in our opinion, a good method for limiting the empirical therapies used in routine practice. Changes in empirical treatment due to this approach resulted in a good clinical response in 44% of the episodes in group A and 31% in group B. Only 3 patients died from respiratory infection: 2 from group A and 1 from group B.

From this study, despite the low number of patients, we conclude that oncohematologic patients with fever of unknown origin unresponsive to empirical antibiotics and with a normal chest X-ray can benefit from a tandem strategy consisting of p-BAL guided by a previous HRCT. Further prospective randomized studies including larger number of patients are needed to assess the sensitivity and specificity of this approach.

Contributions and Acknowledgments

AS had the initial idea of performing this study. She contributed to the study design, interpretation of the data and writing of the manuscript. RM also contributed to the study design, interpretation of the data and reviewed the final version of the manuscript. AS and ER collected and analyzed the data and prepared the first draft of the manuscript. GP also collected data and contributed to the analysis of the results. TF was the responsible for the high resolution computed tomography procedures and CP for the bronchoscopies. JS is the head of the Unit and critically corrected the different versions of the manuscript.

The order of the authors tries to take into account the time, work and scientific contribution given by all the authors, the second author being the idea promoter and the last the senior member of the research group.

Disclosures

Conflict of interest: none.

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Potential implications for clinical practice

- HRCT is abnormal in a high percentage of oncohematologic patients with fever of unknown origin unresponsive to empirical antibiotics and with a normal chest X-ray.
- The tandem strategy consisting of p-BAL guided by a previous HRCT in this subset of patients allowed modifications of the empirical antibiotic treatment in more than one third of the infectious episodes included in the protocol.
- Changes in empirical treatment due to the strategy applied in this study resulted in favorable clinical responses in a significant proportion of patients.

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