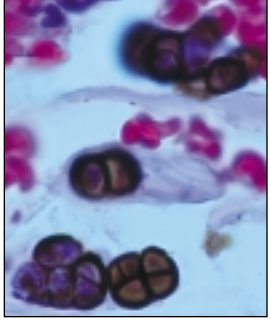

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CONVENTIONAL CHEST RADIOGRAPHY IN THE INITIAL ASSESSMENT OF ADULT CANCER PATIENTS WITH FEVER AND NEUTROPENIA

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Introduction

Infection continues to be a leading cause of morbidity and mortality in patients with neoplastic disorders who are treated with myelosuppressive chemotherapy.[1] In a granulocytopenic patient, fever may be the first and only sign of infection.[2] Other clinical signs and symptoms that often indicate an infectious process may be blunted or missing in the presence of neutropenia. Thus, treating all febrile neutropenic patients with broad-spectrum antibiotics has become the standard of care. Initial evaluation of such patients usually includes a complete history, physical examination, blood culture, urinalysis, urine culture, and chest radiography.[3] Some investigators advocate routine chest radiography to detect signs and symptoms of pneumonia that may be absent in the neutropenic host despite the presence of a consolidate pneumonic process.[2] Others report that the yield of abnormal findings on a diagnostic chest radiograph in febrile neutropenic children is low in the absence of clinical signs of pneumonia.[4-6]

In a retrospective review of adults who were hospitalized for fever and neutropenia, Donowitz et al[7] found that only 10% of patients who had no respiratory findings on examination had abnormal chest radiographs. This issue has not yet been prospectively evaluated in a population of adult patients with cancer. However, patients with fever and neutropenia are not a homogeneous group. In recent years, the concept of risk assessment during the initial phases of a febrile episode has been introduced and evaluated.[8] Several recent trials have demonstrated the safety and efficacy of oral antibiotic therapy in febrile patients with low-risk neutropenia.[9,10] Therefore, it is important to consider the risk of neutropenia when determining the best therapeutic approach to the patient. To examine the value of routine chest radiography, we conducted a study in a series of consecutive hospital consultations for fever and neutropenia in adult patients treated with standard chemotherapy.

Materials and Methods

During 14 months, 113 adult patients with malignant diseases had 130 medical appointments at the Angel Roffo Oncology Institute of the University of Buenos Aires due to fever in the presence of neutropenia. All data were collected prospectively. Fever was defined as having a single axillary temperature of 38.5ºC (101.3ºF) or higher or having a temperature of 38ºC (100.4ºF) or higher for at least 1 hour. Neutropenia was defined as an absolute neutrophil count (ANC) of 500/µL or less. Febrile patients whose ANC levels were expected to drop below 500/µL within 24 hours were also admitted to the study.

At first consultation, all patients underwent a complete history and physical examination, and the following laboratory tests were performed: complete blood count, peripheral blood culture, blood culture from the central line (if present), urinalysis, urine culture, and chest radiograph. Additional cultures and other laboratory tests were obtained as clinically indicated.

The risk assessment was performed using criteria developed by Talcott et al,[8] which we slightly modified for patients considered to be in group III.[11] Patients were placed in three high-risk groups, based on their status at diagnosis of fever and neutropenia. Group I included patients who were already inpatients. Group II included outpatients who demonstrated serious concurrent comorbidity within 24 hours of presentation. Group III consisted of outpatients without serious concurrent comorbidity but with uncontrolled cancer. For this third group, we considered only those patients with solid neoplasms who were progressing after the last course of chemotherapy, those with clinically relevant liver, lung, or brain metastases, patients with stage III or IV lymphomas not in response, and leukemia patients who were not in remission. The remaining patients who had none of these high-risk features comprised group IV (low-risk group). The chest radiograph findings were not taken into account for the risk assessment.

Patients started antibiotic treatment immediately after the initial laboratory test (including chest radiograph). Those in the high-risk groups were treated in an inpatient setting with ceftazidime monotherapy and other antibiotics if needed. Low-risk patients were treated with either short-term intravenous ceftazidime followed by oral ciprofloxacin plus amoxicillin-clavulanate or oral ciprofloxacin plus amoxicillin-clavulanate from the beginning. Patients using oral antibiotics were discharged if they had good oral tolerance, lived closer than 1.5 hours from the hospital, had access to a telephone, and had help available at home. Antibiotic coverage was modified if clinically indicated. None of the patients were receiving oral prophylaxis with antibiotic, antiviral, or antifungal medications.

Each chest radiograph was read by a staff radiologist. Abnormal radiographic results were later reviewed by a senior staff radiologist to confirm the abnormal findings. Each abnormal chest radiograph was compared with a previous chest radiograph of the patient. The findings of the chest radiograph were correlated with the presence or absence of symptoms of respiratory disease (cough, dyspnea, pleuritic pain, and expectoration) and/or pulmonary findings on physical examination (crackles/rales) at the time of the hospital consultation. Patients were moni-

Table 1. — Characteristics of Patients With Febrile Neutropenia at Initial Evaluation*

Characteristics	Number (130 Patient Admissions)
Mean age (range)	45 (16 - 81)
Male sex	61 (47%)
Mean neutrophil count (cells/mm^3)	309 ± 220
Mean neutropenia duration (days)	3.5 ± 1.2
Oncologic diagnosis:	
Non-Hodgkin's lymphoma	35 (27%)
Breast	32 (25%)
Germinal cell	25 (19%)
Other	38 (29%)
Neutropenia risk:	
High-risk (Talcott's groups I, II, III)	77 (59%)
Low-risk (Talcott's group IV)	53 (41%)
Positive cultures:	
Blood	20 (15%)
Sputum	6 (4.5%)
Urine	4 (3%)
Other	4 (3%)
Chest radiograph:	
Normal	87 (67%)
Abnormal	43 (33%)

* 113 patients comprised 130 patient admissions.

Table 2. — Relationship Between Initial Abnormal Chest Radiograph and the Presence of Respiratory Signs and/or Symptoms

Abnormal Chest Radiograph	Respiratory Signs/Symptoms Yes	No	Total
Pneumonia	18 pts	3 pts	21 pts (48.9%)
Primary/metastasis	10 pts	8 pts	18 pts (41.9%)
Pleural effusion/others	4 pts	0 pt	4 pts (9.2%)
Total	32 pts (74.4%)	11 pts (25.6%)	43 pts

pts = patients

tored throughout their hospital stay or their ambulatory daily visits for the development of respiratory infection, and additional chest radiographs were obtained if clinically indicated.

The 95% confidence interval around a proportion (exact binomial) was calculated using the Epi Info software (version 6.04a, 1996), designed by the Centers for Disease Control and Prevention.

Results

The characteristics of these patients are noted in Table 1. No patients had highly aggressive lymphomas/leukemias. The initial chest radiographic findings were abnormal in 43 (33%) of the 130 patient admissions. Of these 43 admissions, 18 (41.9%) showed one or more findings of known malignant disease involving the chest (2 primary, 11 metastatic, and 5 pleural effusions), 4 (9.2%) showed no known malignant disease, and 21 (48.9%) had pneumonia infiltrates. The relationship between initial chest radiographic abnormal findings (33%) and respiratory signs and/or symptoms are given in Table 2.

The overall incidence rate of radiologically confirmed pneumonia was 16%. Three patients with pneumonia were asymptomatic and had negative physical findings. Therefore, only 2.3% had a positive chest radiographic result for pneumonia that was not suspected by history or physical examination. The 95% confidence interval was 0.48% to 6.59%; therefore, the chance that pneumonia was present on chest radiograph but not suspected on the basis of history and physical examination was, at most, 6.59%.

The clinical features of three episodes of asymptomatic pneumonia are given in Table 3. Follow-up physical respiratory examinations at 24 hours (Patient 1) and at 48 hours (Patient 2) became positive with findings compatible with pneumonia (crackles). Patients 1 and 3 had uncomplicated hospital courses and were discharged on oral amoxicillin-clavulanate plus ciprofloxacin to complete a 10-day course of antibiotics. As already noted, Patient 2 had progressive chest infiltrates and required mechanical ventilation. Despite recovering neutrophils (day 4) and becoming afebrile (day 2), he died of a lung hemorrhage after a 10-day stay in the intensive care unit. No microorganisms were found in multiple blood and respiratory secretion samples. The coagulation tests and platelet count were normal.

Table 3. — Clinical Features of Three Patients With Asymptomatic Infiltrates on Chest Radiograph

Patient	Sex	Age	Tumor Type	Neutrophil	Cultures Count	Chest Radiograph Findings	Risk Group	Days Postchemotherapy
1	M	66 yrs	NHL	100	negative	RUL infiltrate	high	6
2	M	56 yrs	NHL	20	negative	RML infiltrate	high	11
3	F	65 yrs	NHL	500	negative	LUL infiltrate	high	12

NHL = non-Hodgkin's lymphoma
RUL = right upper lobule
RML = right medium lobule
LUL = left upper lobule

Invasive procedures or autopsy were not performed. Patient 3 showed no clinical symptoms or physical findings of pneumonia, and the infiltrate did not resolve with the recovery from neutropenia (on day 8) or in repeated chest radiographs on days 2, 7, 16, and 21. This patient died 2 months later of a progressive neoplasm without signs of adult respiratory distress syndrome. Repeated bacterial, mycobacterial, and fungal blood cultures after the episode of febrile neutropenia were negative, but invasive procedures to obtain respiratory material were not performed. All of these patients were initially treated with 2 g of ceftazidime t.i.d., and none had initial therapy modified based on the positive chest radiograph findings.

Thirteen patients had negative chest radiographic findings with positive ones on pulmonary examination (crackles in 6 patients) or had one or more symptoms (cough in 10 patients, expectoration in 7, and dyspnea in 1).

Discussion

The initial assessment of patients with fever and neutropenia has not changed significantly in the past several decades. A careful history and physical examination remain imperative. Since neutropenic hosts have a decreased ability to manifest an inflammatory response, even subtle signs and symptoms should be considered as significant. On the other hand, lung infections are associated with a significant prognostic deterioration in patients with cancer.[12] Pneumonias represent the most unfavorable infectious complication occurring during the course of neutropenia in patients with cancer.[13] Admission chest radiograph in patient population has been recommended.[14-16]

In our study, chest radiographs were abnormal in 43 (33%) of the 130 patient admissions. Pneumonia was radiographically confirmed in 21 (16%) cases, 3 of whom had pneumonia in the absence of any respiratory symptom or sign at physical examination. Even though patients were considered to have no evidence of respiratory compromise at admission, Patient 1 and Patient 2 subsequently developed clear signs of pneumonia. Even if not done initially, the chest radiograph would have been performed in those two patients at 24 and 48 hours, respectively, when the signs and symptoms developed. In Patient 1, the infiltrates resolved within 1 month after a 10-day antibiotic treatment, but Patient 2 experienced progressive chest infiltrates and required mechanical ventilation. In spite of recovered neutrophils on day 4 and absence of fever, he died of a lung hemorrhage on day 10, as noted earlier. No microorganisms were found in multiple blood and respiratory-material samples. Due to the absence of risk factors for invasive aspergillosis — bone marrow transplantation (>15 days), profound neutropenia (<100/mm^3), long-term corticosteroid therapy, acute leukemia, high-grade non-Hodgkin's lymphoma, and chronic granulomatous disease[17] — an empiric antifungal therapy was not given. Patient 3 did not show clinical symptoms or physical findings of pneumonia, and the infiltrate did not resolve. For the analysis in our study, we assumed that this patient had a pneumonic infiltrate but, considering the clinical course, there could be other possible explanations for this infiltrate. Certain neoplasms, as well as treatments such as chemotherapy and radiotherapy, can produce clinical manifestations and radiographic lung images that are indistinguishable from those associated with pneumonia.[18] The patient presented the infiltrate 12 days after the completion of a regimen of chemotherapy with methotrexate, which may cause inflammatory interstitial pneumonitis.[18,19] However, this complication generally resolves with discontinuing use of the drug or, if this is insufficient, with corticosteroid therapy. A complete return to pretreatment lung function is the norm. Fever and a asymptomatic pulmonary infiltrate without mediastinal involvement caused by neoplastic invasion of the lung may sometimes occur, particularly in patients with non-Hodgkin's lymphoma.[20] These conditions often can be distinguished only by lung biopsy, but in the context of a progressive disseminated neoplasm, we can retrospectively assume that the infiltrate was not caused by pneumonia.

Our findings regarding asymptomatic pneumonia were consistent with previous studies involving neutropenic children,[6,14] but not surprisingly, we had a higher incidence of abnormal chest radiographs.

Cost of treatment of neutropenic febrile episodes has become a consideration when designing therapeutic strategies to be used in a large number of patients.[21] Although our study was not designed to test a cost-savings strategy, an initial analysis of the data led to the consideration that using our approach could reduce costs without impairing the care in this group of neutropenic patients.

Taking into consideration these points and our results, we believe that it is safe to perform a chest radiograph at admission only in adult cancer patients with solid tumors treated with standard chemotherapy who present respiratory signs or symptoms. However, our results most likely will not apply to other populations of neutropenic patients at higher risk of retention pneumonia or prolonged neutropenia (acute leukemias, bone marrow transplantation, myelodysplastic syndromes, and neutropenia for longer than 1 week).

Our study demonstrated that chest radiography provides limited yield for the early detection of asymptomatic pneumonia in neutropenic adult cancer patients. Recent studies suggest that pneumonia may be discovered earlier and more often with thin-section computed tomography (CT) scans than with chest radiographs.[22] Thus, thin-section CT might be considered in specific cases of febrile neutropenia with negative or questionable chest radiographs,[23] such as in patients at high risk of developing invasive fungal infection or in patients who may develop pulmonary infiltrates not necessarily associated with respiratory discomfort of pathologic findings at physical examination (eg, patients with T-cell lymphomas, patients who were treated with fludarabine or cladribine, or those who underwent total-body irradiation).

Conclusions

For patients with solid-tumor cancer treated with standard chemotherapy, chest radiography should be performed only if there are respiratory findings. In this context, the chest radiograph in conjunction with the clinical setting (physical examination, historical chest radiography, epidemiological data, duration and severity of neutropenia, underlying disease, and antineoplastic treatment) facilitates the diagnosis of pneumonia. When rapid and accurate diagnosis of pulmonary disease is required, other diagnostic tools such as thin-section CT could be considered.

Appreciation is expressed to Drs Ricardo Kirchuk, Oscar De Cristófaro, and Javier Castillo, the Clinical Oncology and Radiology residents for recruitment and follow-up of patients, nurses Juliana Trujillo and Elsa Gomez for their assistance with the patients, and Dr Miguel Korte for his assistance with the preparation of the manuscript.

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