LETTER TO THE EDITOR

MULTIPLE PULMONARY NODULES AND UNEXPLAINED FEVER: WHEN THE PULMONOLOGIST FAILS

M. MINCARINI, D. BAGNASCO, M.G. FERRANTINO, F. BALBI and G. PASSALACQUA

Respiratory Diseases, IRCCS S.Martino Hospital-IST, University of Genoa, Italy

Received January 14, 2014 - Accepted May 19, 2014

We describe herein a difficult case of persistent and refractory fever, associated with multiple lung nodules, progressive respiratory failure and general deterioration. Our patient was carefully investigated for the possible causes of his symptoms, using current and advanced diagnostic procedures, either serological or by imaging. The confirmatory diagnosis of anaplastic T-cell lymphoma, was obtained only after an invasive procedure (with severe pneumothorax), although it was too late. This suggests that also very rare diseases should be considered in the presence of unexplained signs/symptoms, and that in such cases, aggressive diagnostic procedures should be applied as early as possible.

The detection of multiple parenchymal lung nodules, in the presence of non-specific signs and symptoms, including refractory and persistent fever, may represent a difficult diagnostic challenge. Infectious and malignant diseases are to be firstly ruled out, including tuberculosis, sarcoidosis, interstitial diseases, opportunistic infections. Nonetheless, in rare cases, a more extensive approach is needed, since non respiratory or systemic diseases can cause some of the signs/symptoms observed. We describe herein a case of malignant and fatal lymphoma with an isolated respiratory onset.

A 53-year-old male, referred to our clinic by his general practitioner because of persistent fever, weight loss and asthenia, lasting at least 2 months. The physician had prescribed, in addition to routine biochemistry, a chest X-ray, that showed multiple bilateral pulmonary nodules. The patient was febrile (37.8°C), with an oxygen saturation of 94%, profoundly debilitated and dehydrated, despite a substantially negative physical examination, thus he was hospitalized. The clinical history was not relevant (non-smoker, no professional harm), except for anxious depression (treated with serotonine reuptake inhibitors), and a previous episode of tibial osteomyelitis. The whole body computerized tomography (Fig. 1) confirmed the presence of multiple parenchymal lung nodules (maximum diameter 1.5 cm), some with cavitation, and also evidenced mesenteric lymph-nodes, with no gross abdominal abnormality. The blood cell count was normal (WBC 4.44/nL, RBC 4.7/fL, red blood cell volume 84.9 fL), with no alteration in the differential count and no eosinophilia. Routine biochemistry parameters, urinalysis, pulmonary function, carbon monoxide diffusion, and C-reactive protein (8 mg/L) were normal. Although the patient appeared not immune-suppressed, we initially suspected disseminated tuberculosis (1), sarcoidosis/interstitial diseases (2), secondary malignancy, or opportunistic infection (3). The fiberoptic bronchoscopy was negative. No evidence of mycobacteria, fungi, pathogens, or neoplastic cells was found in the bronchial lavage. In the meantime, all the assays for

Key words: multiple pulmonary nodules, persistent fever, diagnosis, lymphoma

Mailing address: Giovanni Passalacqua MD,
Allergy and Respiratory Diseases,
IRCCS – S.Martino Hospital – IST,
University of Genoa,
Pad. Maragliano, L.go R. Benzi 10,
16132 Genoa, Italy
e-mail: passalacqua@unige.it

0394-6320 (2014)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

autoantibodies (including anti-neutrophil cytoplasm antibodies) and tumoral biomarkers provided negative results. Positron Emission Tomography displayed a slight accumulation of the tracer in some of the pulmonary nodules, in the tibial bone (previous osteomyelitis) and at duodenal level. Gastroscopy displayed a non-specific duodenitis and no evidence of malignancy.

The clinical conditions rapidly worsened, despite an appropriate nutritional support. The temperature peaked over 40°C, with a septic profile, but repeated blood cultures were negative. The temperature could not be fully controlled by paracetamol, noramidopyrine, indomethacin or intravenous steroids, alone or variously associated. According to our infectivologists we started "ex adjuvantibus" amoxycillin-clavulanate (2 g t.i.d.) plus clarithromycin (1 g/day), without benefit. These were then replaced after few days by levofloxacin (750 mg/day), then linezolid, then rifampicin (600 mg/day). The patient's condition progressively worsened, with vomiting, diarrhea, dehydration, weight loss, decrease in oxygen saturation and arterial oxygen. The brain TC was negative for focal lesions. The haematologists excluded a pertaining disease. A trans-thoracic, computer tomography-guided biopsy was attempted, within 10 days from hospitalization, resulting in a non-significant specimen, and followed by pneumothorax. After draining pneumothorax, another biopsy was carried out about 1 week later. This showed a lymphocytary alveolar infiltrate, and multiple necrotic areas, suggesting a differential diagnosis between Hodgkin lymphoma and non-Hodgkin large-cell anaplastic lymphoma (ALCL). After the appropriate immunostaining, the diagnosis of ALCL ALK was finally established. The patient further worsened, with anemia (hemoglobin from 10.2 g/dL to 8.6 g/dL), neutropenia (0.4/nL), hyponatremia (120 mEq/L), pleural effusion and hypercapnic respiratory failure (ventilated). The patient was then moved to the Hematology division for a rescue chemotherapy, but he died within two days.

Multiple pulmonary nodules accompanied by fever, weight loss and non-specific signs of systemic inflammation represent a challenge for the pulmonologist, and for the physician in general. Of course, the primary suspect is oriented to infectious diseases (including tuberculosis, and opportunistic infections), neoplasms, or aggressive interstitial lung diseases (4),

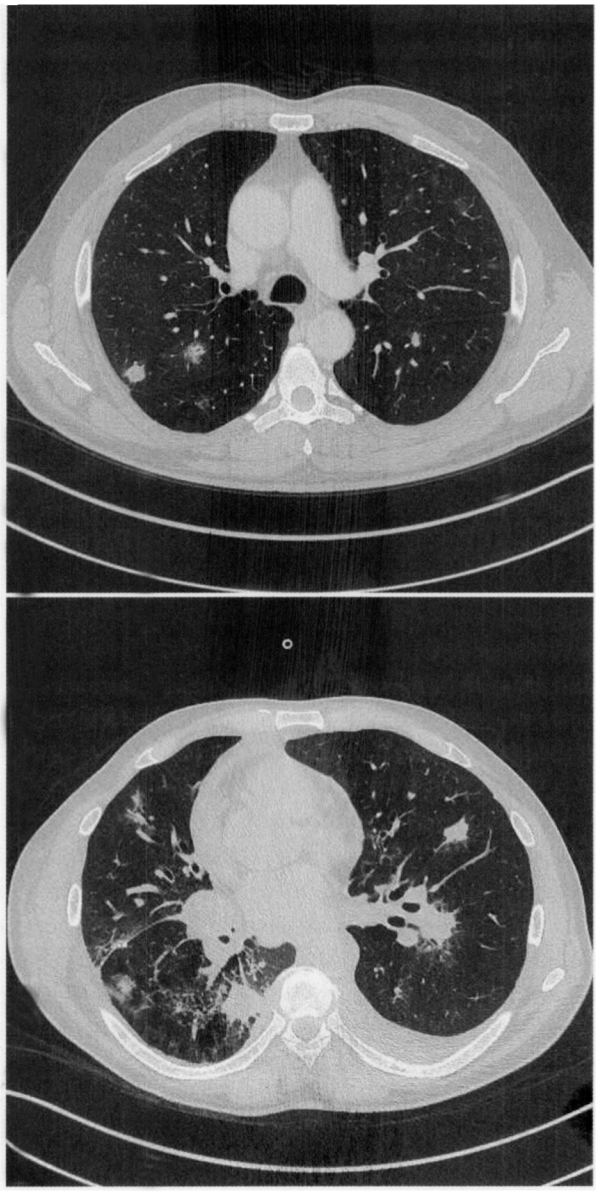

Fig. 1. *TC scans performed on admission (upper) and at the time of final diagnosis (lower).*

expecially if there is no evidence of extrapulmonary lesions. We have available many techniques to rule out the majority of those diseases (e.g. immunological assays, invasive approaches, and imaging) (5). Nonetheless, all those approaches are sometimes inconclusive, and a diagnosis can be made only by progressive exclusion of the best known causes. In the presented case, an aggressive malignant haematologic disease could not have been suspected on the simple basis of

clinical and standard diagnostic procedures. Indeed ALCL represents 2-3% of Non Hodgkin lymphoma (6, 7), characterized by the expression of CD30, a cell surface receptor present on activated T cells and B cells (7). Although rare, this disease can mislead or delay the correct diagnosis, even when all procedures are carried out by the specialist.

REFERENCES

1. Jacob JT, Mehta AK, Leonard MK. Acute forms of tuberculosis in adults. Am J Med 2009; 122:12-7.
2. Cottin V. Interstitial lung disease.Eur Respir Rev 2013; 22:26-32.
3. Alvarez B, Arcos J, Fernández-Guerrero ML. Pulmonary infectious diseases in patients with primary immunodeficiency and those treated with biologic immunomodulatingagents. Curr Opin Pulm Med 2011; 17:172-9.
4. Selman M, Pardo A. Update in diffuse parenchymal lung disease 2012. Am J Respir Crit Care Med 2013; 187:920-5l.
5. Nair A, Baldwin DR, Field JK, Hansell DM, Devaraj M. Measurement methods and algorithms for the management of solid nodules. A J Thor Imaging 2012; 27:230-39.
6. Savage KJ, Harris NL, Vose JM, et al. ALK-anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008; 111:5496-98.
7. Querfeld C, Khan I, Mahon B, Nelson BP, Rosen ST, Evens AM. Primary cutaneous and systemic anaplastic large cell lymphoma: clinicopathologic aspects and therapeutic options. Oncology 2010; 24:574-87.