Chronic pulmonary aspergilloses: do they exist?

Le aspergillosi polmonari croniche: esistono?

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In an editorial of this journal in 2006, Professor de Marinis made a heartfelt appeal to Italian pulmonologists to become more active and involved in the field of lung tumors [1]; today we find ourselves in the same situation regarding pulmonary mycoses with, we fervently hope, more chance of success. Recently, within the span of one month two eminent clinicians as well as a biologist, expert in the field of mycoses, contested the existence of chronic pulmonary aspergilloses [2]; in the same period four patients were admitted with this diagnosis to the Pulmonary Aspergillosis Outpatient Clinic of Niguarda Hospital in Milan. Hence it is justified to ask ourselves the question if these diseases exist or not and, if the answer is yes, to enquire about their incidence, diagnosis and the related therapy.

That pulmonary mycoses and – of particular interest for pulmonologists – the aspergilloses exist has been known since the '50s and they have always posed a problem at diagnostic and therapeutic level; but the problem mainly interested hematologists, mycologists and infectivologists, and not only in Italy (in contrast to the lung cancer issue which is a strictly Italian question). In particular, chronic pulmonary aspergilloses – formerly known as 'chronic necrotizing aspergillosis' - were well defined back in the '90s by G. A. Sarosi [3].

Pulmonary mycoses are diseases caused by microscopic fungi that, according to the patient's immunity status – due to deficiencies at both local (e.g. of mucociliary clearance) and general level (acute and chronic diseases, assumption of immune suppressors), can involve the respiratory system to a more or less severe degree [4]. In Europe, in particular in Italy, *Aspergillus* and *Candida* are the fungi responsible in absolute terms for the most number of infections, in contrast to other continents where other fungi have a significant incidence. While the acute forms caused by *Candida* and *Aspergillus* have been well investigated and classified as to the therapy and the pulmonologist is normally required only from the diagnostic-instrumental point of view – to perform the fibrobronchoscopy – the allergic (asthma and allergic bronchopulmonary aspergillosis) and chronic forms (chronic pulmonary aspergillosis) should be the prerogative of the pulmonologist: they are the specialists that normally visit these patients. But the role of the internal medicine specialist should also not be overlooked: they can encounter these diseases in the context of their work, especially in hospital.

But how significant is this problem for pulmonologists? According to a brief epidemiological survey carried out at the Niguarda Hospital in Milan over a period of 4 consecutive months in which 2,440 first-time patients referred for respiratory symptoms of the lower airways were screened, 20 patients were found affected by pulmonary aspergillosis (chronic or allergic): approximately 0.82% [2]. In contrast, according to anglosaxon authors, about 10% of patients affected by chronic respiratory diseases have an underlying *Aspergillus* infection [3-5], while data from the Lombardy Region (Dr. Bersani at the "4th Workshop Focus on Aspergillosis: an Update 2011") show an average of 320 cases/year, equivalent to 4/10,000 for the potential patients affected by chronic pulmonary diseases. Further, the same author observed that 40% of all diagnoses of aspergillosis in the Lombardy Region had been made in only 3 hospitals (Niguarda Hospital, University Polyclinic of Milan and San Matteo of Pavia) [6]. These data – although of an approximate

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and discordant nature – lead to three conclusions:
- the pulmonary aspergilloses constitute a real and, numerically speaking, far greater problem than other rare diseases and should thus receive more attention, both from pulmonologists in the first instance, but also from internal medicine specialists and infectivologists;
- their identification and diagnosis depends on how sensitized physicians are to detect them;
- their incidence should be adequately evaluated by a specific joint national epidemiological survey involving AIMAR, AIPO and SIMeR.

In this issue of *Multidisciplinary Respiratory Medicine* the article by Luo et al. [7] is particularly to be appreciated, even if somewhat "rough" compared to current articles written by expert western mycologists. It is notable above all for its sincerity and humility of thought: the authors posed the question if pulmonary mycoses exist and what importance they have. To answer the question, the Chinese pulmonologists utilized the oldest methodology of "modern" medicine: anatomical pathology. They verified in retrospect – over a time span of one decade – the histological specimens (from diagnostic or interventional surgery and needle biopsy) and correlated these with clinical, radiological and laboratory data. The importance of this approach should be underscored: histological data reported in the literature in the field are in fact rather modest and sporadic.

The pulmonologists from the University of Xiang Ya verified that "in more than 76% of cases the diagnosis was made by the anatomopathologist" – hence only at the act of biopsy – confirming the difficulty of making correct mycological diagnoses in life through the common laboratory, radiological and clinical means. Hence, late and occasional diagnoses. And they found, also in their continent, a greater incidence of pulmonary aspergillosis among mycoses as a whole – as in Europe – with a significant percentage of cryptococcosis, in contrast to Italy; while candidiasis was not evaluated because it is not in general susceptible to surgery.

This article is noteworthy for the fact that it was conceived and written by pulmonologists, an exceptional event in the literature worldwide; the Chinese pulmonologists have significantly affirmed their presence also in this field: it is the first time that a school of specialization in pulmonology, and not a single individual, has entered this field, and it is likely that their effort will "infect" other Chinese pulmonologists.

All pulmonologists should imitate this example, i.e. show interest in a disease that is rare, precisely because it is not well known and thus not recognized. Difficulties of diagnosis certainly exist, because the diagnosis is first suspected with clinical intelligence and then confirmed with instrumental methods. But at least the doubt should arise each time a chronic pulmonary disease, even if correctly treated, does not respond to the treatment: three simple examinations can be of help, i.e. total IgE, RAST for *Aspergillus* and anti-*Aspergillus* antibodies for immunodiffusion, as well as the Prick test. Positivity on one of these tests should lead one to pose in differential diagnosis an aspergillar disease. Recently the use also of positron-emission tomography (PET) has been proposed as an important complementary test: a positive finding may demonstrate, in the context of areas considered fibrotic from the CT scan, areas of inflammation confirming the diagnosis in the case of presence of anti-*aspergillus* antibodies, or of cultural findings of *Aspergillus spp.* or justify the performance of a fine-needle aspiration biopsy [8].

From the therapeutic point of view, fortunately the number of treatments available in Italy has expanded, but so also unfortunately has the number of side effects and in particular of pharmacologic interactions, with the result that prescription of antiblastics and immune suppressors has become more difficult: of voriconazole, in particular, and more recently of posaconazole as well as echinocandin.

These diagnostic and therapeutic difficulties suggest the need for a telematic network to be set up as a reference point for specialized Centers and other facilities, as recommended at the recent congress on aspergilloses: it is our hope that Italian pulmonologists will be able to create such a network.

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