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Clinical and radiological criteria for the differential diagnosis between asbestosis and idiopathic pulmonary fibrosis: Application in two cases

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Abstract

Introduction: *Idiopathic pulmonary fibrosis (IPF) and asbestosis are pulmonary interstitial diseases that may present overlapping clinical aspects in the full-blown phase of the disease. For both clinical entities the gold standard for diagnosis is histological examination, but its execution poses ethical problems, especially when performed for preventive or forensic purposes.* **Objective:** *To evaluate the application of internationally accepted clinical, anamnestic and radiological criteria for differential diagnosis between asbestosis and IPF, and to assess the ability to discriminate between the two diseases. Even if clinically similar, the two diseases present extremely different prognostic and therapeutic perspectives.* **Methods:** *Two clinical cases of IPF are reported, in which the differential diagnosis was made by studying occupational exposure to asbestos, the onset and progression of clinical symptoms, and the identification of specific radiological elements by means of chest High Resolution Computed Tomography (HRCT).* **Results:** *The diagnosis of IPF could be made on the basis of the absence of significant exposure to asbestos, the early onset and rapid progression of dyspnea and restrictive ventilatory defects, in association with a pulmonary radiological pattern characterized by peculiar elements such as honeycombing.* **Discussion:** *The diagnostic procedure adopted to make a differential diagnosis with asbestosis provides practical clinical elements facilitating the differentiation between the two forms of pulmonary fibrosis, a fundamental aspect of the activity of the occupational physician.*

Introduction

Idiopathic pulmonary fibrosis (IPF) belongs to the group of interstitial pneumonia of unknown aetiology. It is an irreversible disease, whose progression from diagnosis, according to different authors, results in a survival of 3 - 5 years (1, 2). The clinical symptoms and signs that characterize the clinical picture are chronic dyspnea, late inspiratory crackles in the mid-basal fields, severe impairment of respiratory function and presence of honeycombing with or without bronchiectasis or peripheral traction bronchioloectasis, with a prevalently basal or subpleural distribution. The median time between

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the onset of dyspnea and the achievement of the claimed clinical picture is 24 months (3, 4).

Asbestosis is pneumoconiosis, defined as diffuse interstitial fibrosis of the lung, with onset from the lung bases, caused by the inhalation and retention of a considerable number of asbestos fibers, generally after prolonged occupational exposure. In the more advanced stages of the disease, it may have the same anamnestic, clinical, functional respiratory and radiographic features of IPF, thereby posing problems of differential diagnosis (5). Although the use of asbestos has been banned in many countries worldwide, in Italy since 1992, new diagnoses of asbestosis as an occupational disease are still being made (6).

For both these pulmonary diseases the gold standard for diagnosis is the histological examination of the lung tissue, which is invasive and posing ethical problems for its execution, especially when performed for preventive or forensic purposes. It can be replaced by chest High Resolution Computed Tomography (HCRT), which can provide specific information about the degree of inflammation and interstitial fibrosis (7, 8).

Two cases of IPF are described, investigated by the occupational physician to assess a forensic diagnosis of asbestosis. The information concerning occupational asbestos exposure and clinical-anamnestic features of the two cases was retrieved from administrative and health documentation contained in the respective court files.

Description of the cases

Case I. Male, died in 2012 at the age of 64. He worked at the steel production department of a steelwork plant: from 1971 to 1996 as a mechanic repairman, and from 1996 to 2000 as first operator in the water and sludge treatment area. For the first job, the steel plant estimated, from 1971 to 1992, exposure to asbestos ranging between 0.001 and 0.092 ff/ml. The last periodic medical examination carried out in February 2000, according to Legislative Decree 626/94 and subsequent modifications and integrations (s.m.i.), showed the absence of any subjective symptoms or objective respiratory signs, normal spirometry and chest radiography. For the period 1971-1992, the Italian Compensation Authority (INAIL) recognized exposure to asbestos of the worker to obtain social security benefits under Law 257/92 and s.m.i. On October 2011, he submitted to INAIL the first medical certificate of occupational disease for 'Pulmonary fibrosis with severe respiratory deficit and asbestosis'. INAIL rejected the application for lack of a clear causal association with the exposure, and therefore the heirs appealed to the Labor Court Judge.

The onset of the IPF occurred in June 2006 with the onset of rapidly progressive exertional dyspnea in the following months. In May 2009, he performed chest X-ray at a Hospital, which highlighted interstitial abnormalities with a more evident reticular-micronodular pattern at the lung bases. In June of the same year, he was admitted to the Pneumology Department of a University Hospital where, in addition to dyspnea at rest, the clinical picture was characterized by bilaterally mid-basal crackles, digital clubbing, spirometry with preserved ventilatory volumes, DLCO reduced to 81.6%. The walking test showed O_2 saturation at rest of 93% and 76% at the end of the exertion test, interrupted after 1 minute, and absence of fibers and asbestos bodies in the broncho-alveolar lavage (BAL). Moreover, the chest HRCT showed morpho-structural changes of the lung parenchyma due to the presence of fibrotic stranding, thickening of the bronchial walls, bubbles and initial honeycombing at the lower lobes, especially in the posterior-basal segments, the absence of hilar or mediastinal lymph nodes, resulting in a discharge diagnosis of 'diffuse interstitial disease of the pulmonary parenchyma, hypoxemic respiratory distress'.

In October 2010, admission to the Pneumology Department of a University Hospital reported a positive history of previous smoking habit for about three years (packs/year: 40), not previously reported, dyspnea at rest, reduced vesicular murmur associated with velcro-like crackles bilaterally in the mid-basal pulmonary region and compromise of pulmonary perfusion at 50%, with a discharge diagnosis of 'Usual interstitial pneumonia'. In December of the same year, a new admission to a Hospital Pneumology Department showed a slight restrictive ventilatory defect and reduced DLCO, at 86%, yielding a discharge diagnosis of 'Chronic respiratory failure,

pulmonary fibrosis associated with bullous emphysema, listed for single left lung transplant'.

He died of chronic broncho-pneumopathy, interstitiopathy, acute respiratory failure.

Case II. Male, aged 72. He worked as a machine repairman in a steelwork plant: in the tube mill (1970-1973), in the rolling mill (1974-1980) and again in the tube mill (1981-2000). No quantifiable exposure to asbestos was estimated by the steelwork plant for the period 1970 to 1992 for the work carried out in the two departments. Nevertheless, INAIL, for the period 1970-1992, recognized exposure to asbestos to obtain social security benefits under Law No 257/92 and s.m.i. The last periodical medical examination carried out, according to D. Lgs 626/94 and s.m.i., on 04 April 2000 showed absence of subjective and objective respiratory symptoms and signs, and normal spirometry and chest X-ray. On May 2018, the worker appealed to the Labor Court Judge, asking for recognition of 'Pulmonary fibrosis with COPD and reticular-nodular thickening of the interlobular and subpleural interstitium', as an occupational disease due to exposure to asbestos. The onset of symptoms dates back to 2009, with progressive exertional dyspnea and recurrent fever episodes. In January 2013, following the onset of dyspnea and fever, inspiratory crackling at the lung bases were detected at a Hospital Emergency Department at chest auscultation, and chest X-rays showed 'diffuse reticular thickening of the lung interstitium, more evident at the bases where a slight reduction of parenchymal lucency was also observed. Some parenchymal stranding is visible in the right apex (fibro-retractive thickening?). The pulmonary hila are moderately prominent.' In October of the same year, he was admitted to the Internal Medicine Department of a private Hospital, where dyspnea after moderate exertion and persistent coughing, basal crackling bilaterally, and an initial spirometric restrictive defect were detected. Histological examination of the bronchial biopsy showed mild chronic inflammation, fibrosis and the absence of giant cells, while chest HRCT showed thickening of the sub-pleuric interstitium, bilaterally in the subpleural area and especially at the bases, with multiple micronodules, some even calcific; imbibition of fissures; presence of clustered lymph nodes with diameters ranging between 18 and 28 mm in the paratracheal site, Barety's lodge, aortopulmonary, inter-tracheobronchial and sub-carenal windows; sub-centimetric bilateral axillary lymph nodes were also visible. The discharge diagnosis was 'Pulmonary fibrosis, chronic obstructive emphysematous broncopneumopathy'.

In May 2016, he was examined at a specialized University Pneumology Department, showing exsmoker conditions, slightly worse exertional dyspnea compared to 3 years before, the presence of fine bilateral basal crackles, a slight restrictive defect at spirometry, reduced DLCO at 55%, walking test saturation value of 84% at rest and 87% at the end of the test. The subject was a former smoker (pk/y: 39). The discharge diagnosis was 'Pulmonary interstitial disease undergoing definition'.

Chest HRCT performed in June 2017, revealed widespread and irregular reticulonodular thickening of the interlobular and subpleural interstitial septa, more evident in correspondence with the bilateral basal lung; presence of numerous traction bronchiectasis foci, partial distortion of the scissural planes, with an initial honeycombing appearance. The focal thickening of the parietal pleura and the peribronchial micronodules, partially calcific, distributed in all lung fields, the small parenchymal consolidation area at the apical segment of the right upper lobe in the subpleural region and the small nodule (7 mm) on the lower blade of the left fissure remained unchanged. Paraseptal emphysema was detected. Substantially unmodified the several lymph nodes in the anterior-superior mediastinum, in the hilar and bilateral paratracheal, para aortic and sub-carenal sites (short axis maximum 2 cm).

Outpatients check-up in September 2018 at a Pneumology University Centre found: FVC 78% and FEV1 84% compared to the theoretical values; reduced DLCO with a value of 65%; significant desaturation at the walking test, with a discharge diagnosis of 'Idiopathic pulmonary fibrosis'.

For both workers, the laboratory and instrumental tests performed during hospitalization in a Pneumology Department excluded that the pulmonary fibrosis detected was related to known occupational and environmental causes, connective, immune,

infectious and rheumatic cardiovascular disease or sarcoidosis, drugs, or ionizing radiation.

Discussion

In the two cases examined, the possibility that the pulmonary interstitial disease they were suffering from could be asbestosis was firstly verified, and then the clinical elements valid for making the differential diagnosis between asbestosis and IPF were analyzed (Table 1).

According to Roggli et al. (9), the clinical diagnosis of asbestosis, in the absence of histological confirmation, is based on the presence, mandatory and contemporary, of a history of moderate to high occupational exposure to asbestos and diffuse reticular-linear opacity in the lower lung fields on chest X-ray examination.

These two criteria can be associated, in decreasing order of importance, with the presence of pleural plaques or diffuse pleural fibrosis, late inspiratory crackles especially in basal lung fields, and a restrictive respiratory functional defect. Of these criteria, those that fundamentally allow to qualify a pulmonary interstitial disease as asbestosis are represented by the presence in the working history of sufficient cumulative exposure to asbestos to cause the clinical picture, and the presence of pleural plaques or dif-

Table 1. Clinical and radiological features supporting the differential diagnosis between asbestosis and idiopathic pulmonary fibrosis.

Clinical and radiological features (references)	Asbestosis	Idiopathic pulmonary fibrosis
Occupational history (5, 9, 11)	Positive for moderate to high asbestos exposure (>25 ff/ml/years)	Occasionally positive for moderate or mild asbestos exposure
Smoking habit (22, 24)	Occasionally reported	Often reported
Dyspnea (9, 16, 24)	• Exertional initially, then at rest in the advanced stages of the disease; • slow progression.	• Present at the clinical onset; • rapidly worsening progression.
Fever (2, 9, 18)	Absent	Frequent, during re-exacerbation
Basal late inspiratory crackles (7, 8)	Present	Present
Digital clubbing (2, 9, 10)	Rarely present	Often present
Restrictive ventilatory defect (9, 10, 18)	Present at advanced stages	Present at advanced stages
Diffuse reticular-linear opacities in the lower lung fields (10, 19)	Present	Present
Pleural plaques/thickening (7, 8)	Often present	Rarely present
Bronchiolar obstruction (14, 15)	Present	Absent
Peribronchiolar fibrosis (14, 15)	Present	Rarely present
Parenchymal bands and subpleural curvilinear lines (11)	Present	Absent
Mosaic attenuation (14, 15)	Frequently present	Absent
Honeycombing (13, 14, 21)	Rarely present	Very often present
Ground-glass opacity (5, 10)	Often present	Occasionally present, associated with a superimposed reticular image
Bronchiolectasis and traction bronchiectasis (13, 14, 21)	Generally absent	Very often present
Mediastinal lymphadenopathies (10)	Absent	Frequently present
Pulmonary nodular calcifications (10)	Absent	Often present
DLCO (1, 4, 14, 20)	Reduced in late stages of disease	Reduced in the early stages of disease
SpO_2 (9, 10, 18)	Reduced after exertion in the advanced stages of disease	Reduced after exertion in the early stages of disease

fuse pleural fibrosis, being the expression of low and high exposure to asbestos, respectively (7, 8).

Concerning the number of asbestos fibers that penetrate the lung and can cause asbestosis, extensive literature reviews and international consensus documents agree that a cumulative exposure of at least 25 ff/ml/year is required. Achieving this cumulative exposure is the condition that the risk of asbestosis becomes 2, compared to 1 attributed to the general population not exposed to asbestos, with the risk increasing by 4% for each year of exposure to 1 ff/ml. In the literature, however, cases of asbestosis are reported for cumulative exposures to even lower concentrations, up to 5 ff/ml/year (8, 10).

To assess the asbestos exposure history of the two workers, the estimates of asbestos exposure were taken into account. An initial evaluation, prepared by the steelwork plant, refers to exposure linked to the tasks performed from hire until 1992, the year when the use of asbestos in Italy was ended by Law (257/92). For Case I, the estimated exposure ranged from 0.001 to 0.092 ff/ml in the period 1971-1992, while for Case II (1970-1992) no quantifiable exposure was defined. The second estimate concerns the assessment by the Compensation Authority agency (INAIL Contarp), which recognized to both worker exposure to asbestos in the above-mentioned periods of 0.1 ff/ml, valid to obtain the social security benefits provided by the Law mentioned above, and which represents the limit value for asbestos reported in Legislative Decree 81/08 and subsequent modifications and integrations (11, 12).

The cumulative exposure, calculated for the above mentioned periods, was 2.1 ff/ml/year for Case I and 2.2 ff/ml/year for Case II, assuming that they had constant exposure to these concentrations. Moreover, a non-continuous exposure to asbestos could be supposed, according to the jobs performed by the two workers. The resulting risk index was close to 1.0 (1.08 for Case I and 1.09 for Case II) (9). Thus, the risk was similar to that of the general population. It emerges that the cumulative asbestos exposure estimated for the two workers is very far not only from 25 ff/ml/years but also from 5 ff/ml/years (8).

Moreover, the search for asbestos fibers and bodies for Case I, performed in BAL fluid, was entirely negative, as expected given the long time that had elapsed since the last exposure.

As regards the presence of pleural plaques and diffuse thickening of the visceral pleura at the chest HRCT, both workers did not show these radiological features. Case II showed focal thickening of the costal pleura, which were not well defined in location and size, and it could be related to the frequent inflammatory pulmonary phenomena that characterized the IPF in this worker. Moreover, several studies have shown that workers exposed to asbestos might have pleural thickening caused by agents other than asbestos (13). The peculiar radiographic elements of asbestosis, such as bronchiolar obstruction, peribronchiolar fibrosis, parenchymal bands, sub-pleural curvilinear lines and mosaic perfusion patterns, were not evident at the HRCT of both workers (14, 15). Also ground-glass opacities, a typical diagnostic element of asbestosis, are absent in both cases, and, although they may be present in IPF, they are not a dominant feature and are usually associated with an overlapping reticular pattern (10). On the contrary, the presence in both cases of honeycombing in the posterior basal segments is the most specific elementary radiological lesion characterizing IPF (5).

Therefore, the absence of adequate cumulative exposure to asbestos and of radiographic signs of previous low or high exposure to asbestos, and in Case I also of asbestos fibers or asbestos bodies in BAL, makes it possible to exclude with a high degree of probability that the interstitial pulmonary diseases of which they are affected are asbestosis. On the contrary, the clinical and radiological information suggests a diagnosis of IPF, as repeatedly confirmed after various hospitalizations in Pneumology Departments (8, 10).

Even if in the later stages of asbestosis, the clinical picture is quite similar to that of IPF, it must be considered, however, that the ways of onset and progression of symptoms are entirely different in the two interstitial diseases, and that these clinical features are essential elements that must be considered in differential diagnosis between the two lung diseases. In asbestosis, for example, dyspnea is not always the first symptom of the disease, being initially caused by exertion, and only after many years

and a slow progression does it appear even at rest, when the disease reaches the full clinical picture. On the contrary, the occasional finding of pulmonary interstitial disease in the mid-basal fields of the HRCT, or the presence of late inspiratory crackles in the mid-basal chest fields, can characterize the clinical picture of asbestosis onset. In IPF, on the other hand, the rapid development of exertional dyspnea within a median time of 24 months from the onset of symptoms, and the simultaneous presence of severe clinical, functional respiratory and radiographic disorders, allows us to make a differential diagnosis with asbestosis, in which these disorders tend to appear more slowly and progressively over time, depending on the cumulative dose of exposure to asbestos (9, 16, 17).

In the two workers examined, dyspnea, initially due to exertion, was rapidly progressive and appeared almost immediately also at rest, with a latency time between its appearance and the full-blown IPF of 3 years in Case I and of 4 years in Case II. These periods fall within ranges reported in the literature for IPF, while there is no such evidence for asbestosis. It should also be noted that in the two cases, exertional dyspnea appeared several years after the hypothetical end of asbestos exposure in 1992 and the end of work in 2000 (14 and 6 years in Case I and 17 and 9 years in Case II, respectively). During these periods and until the health surveillance checks carried out in 2000 neither worker presented any subjective, objective or instrumental signs of disorders of the respiratory system, thus eliminating any causal link between exposure to asbestos and the onset of exertional dyspnea (8, 16, 17). These evidences at the end of the occupational health surveillance, therefore, contributed to exclude a possible asbestosis.

Less relevant for the differential diagnosis between IPF and asbestosis is the finding of chest late inspiratory crackles in the mid-basal fields, as these can be present early in both interstitial diseases. This objective clinical sign was found in the overt clinical picture of IPF in both workers. It also plays a secondary role in the clinical diagnosis of asbestosis, as reported by Roggli et al. (9).

Considering the functional respiratory disorders, the spirometry examination in the full-blown phase of IPF of the two workers showed only a slight restrictive ventilatory defect in both cases. This type of ventilatory defect is considered by Roggli et al. as a secondary sign of asbestosis, too, but it cannot be used for the differential diagnosis between this and IPF, as it could be present early in both diseases.

DLCO and exertion O_2 saturation, which may be impaired in the late full-blown stage of asbestosis, appeared early and were significantly impaired in the full-blown stage of IPF. The DLCO was always reduced (81.6% and then 86% in Case I, and 55% and then 65% in Case II, respectively), and a severe exertion O_2 desaturation was also present in both workers. The simultaneous, severe impairment of these two oxygenation indicators, characterizing the clinical picture of lung interstitial diseases observed in the two workers at a short distance from the onset of a rapidly worsening dyspnea, is almost exclusively indicative of IPF (9, 10, 18).

At the chest X-ray examination, the presence of diffuse reticular-linear opacities in the lower areas of the lung fields, lesions that, according to Roggli et al., are a fundamental early sign for the clinical diagnosis of asbestosis, was observed in both workers in the overt phase of IPF. These radiographic images also appear early in IPF, but associated with other images characterizing the HRCT picture of this lung disease (18, 19). Among these, there is first of all the presence of honeycombing, typically located in the dorsal, basal and subpleural regions, while it is described only in the very late stages of asbestosis, typically located in the middle lung fields (20). Both workers showed, at HRCT, the presence of honeycombing, typically located at the lower lobes, especially in the posterior basal segments (3, 10). Also, both HRCT, in association with honeycombing, showed images indicating the presence of a reticular pattern, interstitial-intralobular thickening, bronchiolectasis with consolidation at predominantly sub-pleural and centrilobular localizations and traction bronchiectasis, typical radiographic aspects of IPF and unlikely in asbestosis (13, 14, 21). In some cases, however, an initial fibrosis not evident at X-ray images has been described at autopsy in asbestos-exposed workers (22).

In the Case II chest HRCT images, there are two other elements typically associated with IPF, consisting of partially calcific peribronchial micronodules

distributed in all lung fields and numerous lymphadenomegalies in the anterior-superior mediastinum in the hilar and bilateral, para-aortic and sub-carenal paratracheal sites. Lynch et al. (10) showed mediastinal lymph node enlargement in 70% of subjects with IPF, and the possible presence of small nodular calcification foci within the areas of fibrosis, with a significantly higher prevalence in subjects with this lung disease than those with other pulmonary fibrotic diseases.

As regards the presence of specific clinical disorders associated with IPF and individually presented by the two workers, in Case I digital clubbing was evident. In Case II the disease had been characterized since its onset by persistent coughing and fever episodes, the expression of pulmonary inflammatory processes. While digital clubbing and coughing are clinical disorders that may also be present in the confirmed phase of asbestosis, even if after many years from the onset of the disease, the fever episodes are typically seen only in IPF, being characteristic of episodes of acute exacerbation of the disease. These episodes characteristically do not have an infectious, cardiovascular or embolic aetiology, and are associated with a rapid worsening of the spirometry and symptoms pattern (2). Therefore, also the presence of these clinical disorders in the two workers, considering their presence in the full-blown phase of IPF, represents an additional element supporting the differential diagnosis between the two interstitial diseases (9, 18).

The prognosis *quoad vitam* in asbestosis and IPF is quite different: median survival of 3-5 years from diagnosis characterizes IPF, whereas it is much longer in asbestosis. Case I had a rapidly evolving clinical course, as shown by the severely impaired DLCO, which caused death in 3 years, while in Case II the clinical course of the disease seems less progressive, as documented by the slower impairment of the DLCO in the course of time (1, 4, 20, 23).

Age and smoking habits are among the risk factors affecting the onset and progression of IPF. As regards age, men over 50 years are most commonly affected. Case I was 61 years old at diagnosis, and Case II was 65 years old. Both ages are very far from the beginning and the end of the estimated asbestos occupational exposure for the two workers. In particular, considering that the latency reported in the literature for the onset of asbestosis as a function of the cumulative dose of asbestos exposure is 15-20 years from the beginning, the first clinical signs of asbestosis should have appeared in the years 1985-1990, if they had had moderate to high exposure to asbestos whereas, as mentioned above, in 2000 the clinical conditions of their respiratory systems were perfectly normal. Consequently, in the two cases examined, the age of onset of IPF is an additional element supporting the differential diagnosis vs asbestosis (2).

Smoking habit, which is not a risk factor for the onset of asbestosis, is detectable in 60% of cases of IPF. Both workers examined were heavy smokers, having smoked 40 packs/year, Case I, and 39 packs/year, Case II. The action of cigarette smoke on their bronchopulmonary systems is detectable on the chest radiographic images, which showed signs of COPD with thickening of the bronchial walls and emphysema. Such signs did not seem to have any functional consequence, as the two workers showed only a slight restrictive and non-obstructive ventilatory defect, as is typical of COPD (2, 24).

Previous and unquantified occupational exposure to asbestos also has been suggested to play a role in the genesis of IPF. A recent review of the literature by Ranzieri et al. (24) shows that the relative risk for only subjectively reported or estimated exposure to asbestos ranged in the studies analyzed from 0.8 to 6.77, resulting higher than 1 in several studies. However, in all of them the 95% confidence interval included 1, indicating the absence of statistical significance. The Authors underline the need of further studies, based on known concentrations of asbestos exposure, to define the true ability of asbestos to cause IPF. The current available scientific evidences do not allow to sustain that a misunderstood exposure to asbestos only subjectively reported can be implicated in the genesis of IPF (4, 23, 24).

Conclusion

In conclusion, in the two cases examined, the absence of moderate to high exposure to asbestos, of radiographic signs of pleural plaques/thickening and, above all, the very rapid progression in just a

few years of interstitial pneumopathy from the onset of dyspnea to the clinical picture of chronic dyspnea, late inspiratory crackles in the mid-basal lung fields, severely impaired DLCO and O_2 desaturation on minimal exertion and radiographic pictures of severe alterations of the lung structure images, with diffuse sub-pleural and fibrotic striae and honeycombing, allowed to confirm the diagnosis of IPF and to exclude that of asbestosis. The illustrated methodology can help occupational physicians in the task to define a differential diagnosis between asbestosis and IPF.

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