

Interstitial lung disease in Malta

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Abstract

Aim: To establish the prevalence, management and response to treatment of interstitial lung disease (ILD) in Malta.

Methodology: The personal files of 102 living and 26 deceased patients with ILD under the care of 4 respiratory physicians were reviewed retrospectively. The investigations utilised for reaching the diagnosis, patient management and response to treatment were analysed.

Results: The prevalence of ILD was estimated at 24.9 per 100,000 population. Pulmonary function tests were performed at least once in 109 patients ($n=128$, 85%), and pletysmography and exercise oximetry in 36 patients ($n=128$, 28%). A chest x-ray (CXR) was performed in 120 patients ($n=128$, 93.7%), of which 8 ($n=120$, 6.66%) were normal, a computed tomography scan of the thorax in 113 patients ($n=128$, 88.3%), all of which showed fibrotic changes and a DTPA scan in 17 patients ($n=128$, 13.3%). Regarding more invasive investigations, bronchoalveolar lavage was performed in 10 patients ($n=128$, 7.8%), open lung biopsy in 4 patients ($n=128$, 3.1%), video-assisted thoracoscopic surgery in 4 patients ($n=128$, 3.1%) and transbronchial lung biopsy in 7 patients ($n=128$, 5.5%). Corticosteroids were the most common drugs prescribed in 64 patients ($n=128$, 50%) followed by azathioprine in 23 patients ($n=128$, 18%) and cyclophosphamide in 3 patients ($n=128$, 2.3%). There was a definite worsening in lung function associated with increasing age. There was no standardisation of follow up for these patients.

Conclusion: The method of diagnosis, management and follow up of patients with ILD locally requires improvement to optimise standards of care and hence compare with proposed international guidelines.

Keywords

Interstitial lung disease, respiratory physicians, Mater Dei Hospital, diagnostic measures

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Introduction

Interstitial lung disease (ILD) represents a heterogeneous group of distinct parenchymal pulmonary disorders with variable degrees of inflammation and fibrosis, based on similarities of various clinical features. However, there are significant differences in aetiology, radiological and histological features, and also in the clinical course, prognosis, treatment and response to treatment. ILD has always posed a challenge to respiratory physicians with regards to the differential roles of the main diagnostic tools and methods of assessing disease progression.

The delivery of medical treatment according to guidelines is increasingly viewed as the preferred model of clinical practice. A major difficulty in developing guidelines in ILD is the necessity of incorporating recommendations relating to a heterogeneous group of rare disorders. While as a group the various forms of ILD form a significant proportion of respiratory morbidity in the community, individually they are uncommon leading to a lack of expertise in their diagnosis and management. The failure to adopt uniform disease definitions and treatment protocols, have made the interpretation of results confusing and therefore incorporation of the evidence into guidelines difficult.¹ An international study reveals that in the United States, the large majority (75%) of patients suffering from nonspecific ILD had no evidence of having undergone diagnostic testing and when persons with ILD are thoroughly evaluated at referral centres, a substantial proportion (more than 50%) are found to have idiopathic pulmonary fibrosis (IPF).²

To date, no data are available locally. The purpose of this initiative is to evaluate the prevalence, method of diagnosis, management and response to treatment of such patients locally and compare these to proposed international guidelines.

Methodology

The medical records of 102 living and 26 deceased patients, suffering from ILD under the care of respiratory physicians in Malta, were reviewed between February and September 2009. Approval was obtained from the Head of the Department of Medicine, all consultant respiratory physicians and the data protection officer at Mater Dei Hospital. An audit form was compiled. Demographic data, bird exposure, smoking history, drug history, symptoms and signs at presentation, and investigations utilised were collected. The patients' management was reviewed. Response to treatment was analysed from the trend in consecutive spirometry readings. Data were transferred

from the audit forms to a Microsoft Excel sheet and results were compiled.

Results

A total of 128 patients were included with 65 (50.8%) males and 63 (49.2%) females, 102 (79.7%) of who were alive and 26 (20.3%) deceased at the time of auditing. The mean age at presentation was 62 years and ranged between 22 and 83 years. The mean age between diagnosis and review of the data in the live patients was 4.4 years and ranged between 1 and 18 years. At the time of diagnosis there were 14 patients ($n=128$, 10.9%) who were current smokers, 63 ($n=128$, 49.2%) who never smoked and 47 ($n=128$, 36.7%) ex-smokers.

The prevalence of patients diagnosed with ILD was estimated at 24.9 per 100,000 population. The patients were grouped into the distinct forms of ILD according to the information available in the clinical notes.

Diagnostic methods utilised included spirometry and flow volume loops, radiological and histological investigations, and serology. PFTs were never performed in 15 patients ($n=128$, 11.9%) and performed at least once in 113 patients ($n=128$, 89.7%). Pletysmography and exercise oximetry were performed in 36 patients ($n=128$, 28%). A CXR was performed in 120 patients ($n=128$, 93.7%) of which, only 8 ($n=128$, 6.2%) showed no fibrotic changes and a CT thorax in 113 patients ($n=128$, 88.3%) all of which showed fibrotic changes. A bronchoalveolar lavage was performed in 10 patients ($n=128$, 7.8%), an open lung biopsy in 4 patients ($n=128$, 3.1%), VATS in 4 patients ($n=128$,

Figure 1: The number of patients per heterogenous form of pulmonary fibrosis diagnosed locally

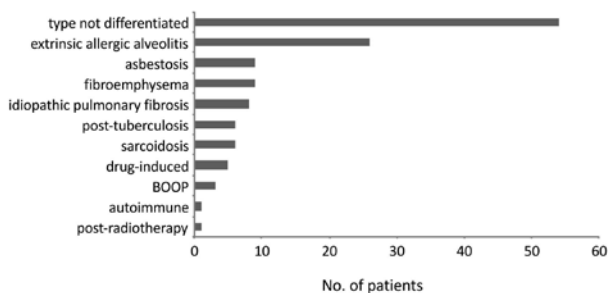
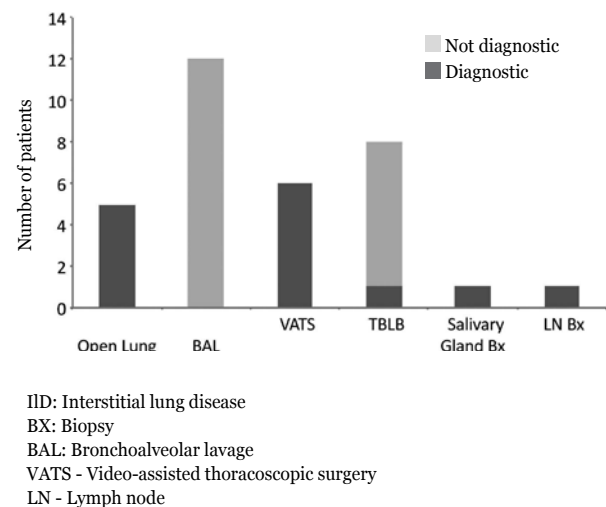


Table 1: Causes of death obtained from available death certificate

Cause	Number of patients	Percentage number of patients
Respiratory failure secondary to pulmonary fibrosis	10	38.5 %
Chest infection	3	11.5
Lung malignancy	3	11.5
Extra-pulmonary	2	7.8
Unavailable death certificate	8	30.8

Figure 2: Results of the different tissue samples obtained and their contribution to differentiating the heterogenous forms of ILD



3.1%) and a transbronchial lung biopsy in 7 patients ($n=128$, 5.5%). A DTPA scan was performed in 17 patients ($n=128$, 13.3%). DTPA scan results included 12 ($n=17$, 71 %) having increased alveolar permeability or active alveolitis and the remaining 5 ($n=17$, 29%) being normal. Serology screening was reviewed. Serum anti-nuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) and rheumatoid factor (RF) levels were performed in 57%, 27.3% and 57.8% respectively and were positive in 18 patients ($n=73$, 25%), 2 patients ($n=35$, 5.7%) and 16 patients ($n=74$, 21.6%) respectively. Serum angiotensin converting enzyme (ACE) levels were significantly raised in 4 patients ($n=31$, 13%). Avian precipitins were positive in 34 patients ($n=65$, 52%). Of these, only 18 ($n=34$, 52.9%) had a history of prolonged avian exposure.

Corticosteroids were prescribed in 64 patients ($n=128$, 50%) at some stage of the disease, with a large proportion in the less than 60 age group, followed by azathioprine in 23 patients ($n=128$, 18%) and cyclophosphamide in 3 patients ($n=128$, 2.3%). Of the patients who were prescribed azathioprine, 87% of them were also prescribed corticosteroids. Three patients

Figure 3: Treatment prescribed for the heterogenous types of IPF

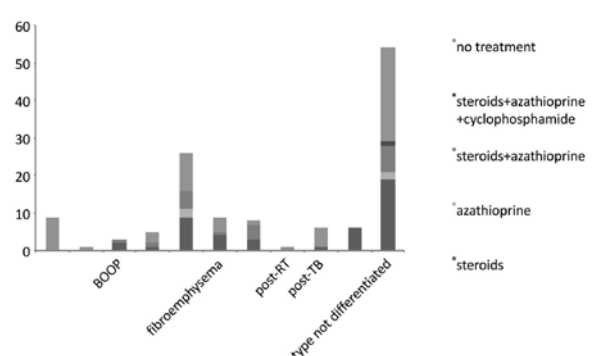
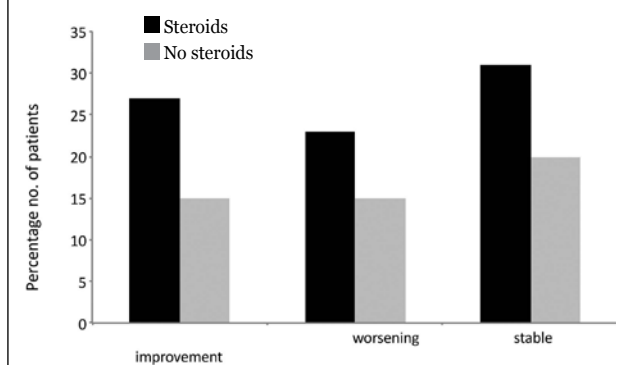


Figure 4: Percentages of pulmonary function trends in patients treated with steroids as opposed to those who were not

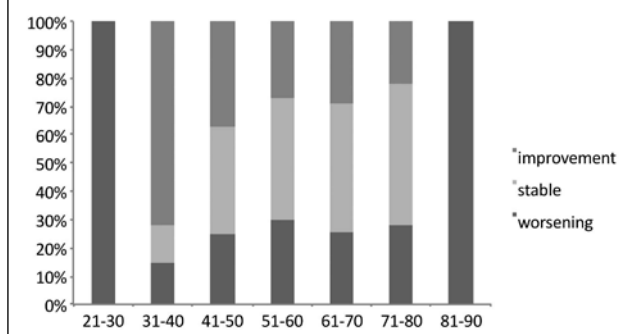


($n=128$, 2.3%) were on amiodarone at the time of auditing. Four patients were diagnosed with amiodarone-induced ILD. Only 1 patient had methotrexate-induced ILD.

Of the patients treated with azathioprine ($n=23$), there were 21% who showed improvement in pulmonary function, 27% with worsening and 21% who were stable. The rest of the patients did not have sufficient spirometries performed to analyse the trend. Patients treated with cyclophosphamide were too small a number to analyse.

Analysis of the results of the deceased patients showed a mean time from diagnosis to death of 5.57 years which ranged between 1 and 12 years. Twelve of these patients had received corticosteroids only, 2 received solely azathioprine, 6 received both and the rest, 6 patients, were never prescribed any form of treatment for ILD.

Figure 5: Percentage of patients and their lung function trend in association with age



Discussion

The prevalence of ILD calculated may be an underestimate since patients included in this audit were only those under the care of respiratory physicians. However, this is likely to be a good estimate as there is a tendency for other physicians to refer such patients to a respiratory specialist. Patients with pulmonary fibrosis secondary to connective tissue diseases or those under the care of other physicians were not included. Despite the guidelines for diagnosis with clearly described

criteria, ILD remains a diagnosis of exclusion requiring extensive investigation, which is seldom possible. Hence, it is not possible to precisely estimate the incidence and prevalence rates of ILD.³ Unfortunately, the worldwide prevalence of fibrotic lung diseases is difficult to determine because of lack of studies performed.⁴ Having the correct specific diagnosis helps clinicians have a clear plan of management of the disease. Since the diagnosis of the specific type of ILD was not made in 54 patients (42.2%), optimal management was limited. Age and late presentation were factors that contributed to a lack of diagnosis. Poor general health precluded invasive investigation. Some patients with minimal symptoms and mild disease were amongst those who were not investigated further. Others were also lost to follow up.

As the majority of ILDs involve varying degree of inflammatory or fibrotic infiltration of alveolar walls, they share common restrictive physiological abnormality on pulmonary function testing.⁵ Pulmonary function tests (PFTs) are cheap, non-invasive and contribute to quantifying disease severity, monitor disease progression and help identify variables most strongly predictive of mortality. Unfortunately, studies of these important aspects of routine management are largely confined to IPF. Therefore, it is advised that all patients with ILD should have a resting spirometric and gas transfer measurement at presentation, which together provides a reasonable measure of disease severity. Possibilities as to why PFTs were not performed include uncooperative patients, contra-indications to PFTs, and possibly lack of insight of the importance of such a tool. According to graph 5, there is a definite worsening in lung function associated with increasing age, as would be expected in a chronic condition. Progression of the disease was followed up by performing regular spirometries in some, especially those who were receiving treatment, and these patients were also followed up more regularly at the out-patients clinics. However, there was no standardisation as to the regular performance of pulmonary function tests (PFTs), exercise oximetry and pletysmography. Change in forced vital capacity (FVC) has emerged as the serial lung function measurement most consistently predictive of mortality. A change in FVC of only 10% is needed to identify a true change in disease severity.² Unfortunately, the carbon monoxide transfer factor (TLCO) could not be measured as it was not available locally until very recently.

Recent literature suggests that exercise testing provides diagnostic and prognostic value in ILD. When normal, it is useful in excluding clinically significant diffuse lung disease. Exercise-induced hypoxia may be an early indicator of disease before the development of pulmonary function abnormalities. Desaturation during the 6 minute walk test at presentation is a stronger prognostic determinant in IPF than resting lung function, but probably adds little in assessing the severity of ILD owing to the absence of a "gold standard" to quantify disease severity.^{6,7} Despite it being a cheap, non-invasive tool, it was not often requested locally. Possible explanations include

immobility or lack of physician awareness of its importance.

Despite the limitations of chest radiography and the paucity of published evidence to support its use, it is widely used for patients with ILD. Locally, a CXR performed at presentation, aided in confirming the diagnosis in most cases. In conjunction with clinical and laboratory findings, it may allow a confident diagnosis to be made. It is also useful, but often non-specific for detecting secondary pulmonary complications. However, PFTs usually reflect the severity of disease more accurately than chest radiography.⁶ High resolution computed tomography (HRCT) scanning is significantly superior to CXR in identifying and determining the correct diagnosis of ILD. With its greater ability to visualise fine detail within the lung, HRCT scanning has replaced conventional chest radiography as the preferred imaging method for ILDs. It has been found useful in the evaluation of ILDs in the following areas: identification of the presence of disease, evaluation of the extent of disease, characterisation disease patterns, narrowing the differential diagnosis, as a guide to the site of biopsy, and assessing the clinical course of the disease and response to therapy.⁸ Investigators have identified the key features that allow HRCT scanning to provide highly disease-specific information leading to a confident, definite diagnosis with a sensitive means of staging disease severity. PFTs complement HRCT, helping the clinician to discount trivial disease on HRCT scans but to recognise, especially with estimation of gas transfer, that HRCT may underestimate widespread and clinically important pulmonary infiltration.⁶ Most patients with clinically significant ILD have an abnormal HRCT scan but a normal HRCT scan does not exclude it.^{6,8} Radiologists interpreting HRCT scans should have experience in the technique and be responsible for quality assurance. Locally, none of the CT scan reports gave a diagnosis of the ILD type. Most reports were vague and non-specific. A proportion of images were difficult to interpret in view of movement artefacts. One must also consider that patients' dyspnoea will interfere with sufficient co-operation to carry out the study. Bronchoalveolar lavage (BAL) is a well-tolerated procedure and plays an important role in the diagnostic evaluation of new onset ILDs in patients with clinical features and HRCT appearances not typical of IPF. The decision to perform bronchoscopy and BAL should be guided by clinical presentation, the patient's functional status as well as technical expertise, both in performing the procedure and in interpreting the BAL cellular component. In some ILDs such as hypersensitivity pneumonitis, positive findings by BAL analysis may be sufficient to formulate a specific diagnosis, thus avoiding the need for more invasive procedures.⁷ Locally, BAL, when performed, did not contribute to differentiating the types of ILD, but aided in exclusion of malignant conditions such as bronchoalveolar cell carcinoma.

In the last century, it was widely accepted that the diagnostic "gold standard" for ILD was a histological diagnosis made on a surgical biopsy. However, the limitations of diagnoses relying solely on histology are increasingly recognised. In

many patients, the disease is too advanced or co-morbidity too severe to allow a surgical biopsy to be performed. The procedure is highly unattractive to patients and physicians alike. Also, there is significant interobserver variation in histological reports and the problem of "sampling error."⁶ Its use in the evaluation of suspected IPF was discussed by the joint ATSIERS/JRS taskforce in 2009. Based on the additional morbidity of transbronchial lung biopsy in these patients and a low diagnostic specificity, it has not been recommended. Despite this, diagnoses made from such investigations were varied and included bronchiolitis obliterans organising pneumonia (BOOP), desquamative interstitial pneumonia, extrinsic allergic alveolitis (EAA), sarcoidosis and usual interstitial pneumonia, hence the possibility of targeting treatment. Multiple multilobe lung biopsies are easier by video-assisted thoracoscopic surgery (VATS) than by open lung biopsy. VATS is also associated with less early postoperative pain than open lung biopsy. Pulmonary complications are well recognised in connective tissue diseases and ILD has been described as the sole initial clinical manifestation of connective tissue diseases. The ATSIERS/JRS taskforce in 2009 recommends that serological testing for connective tissue diseases should be performed in the evaluation of IPF even in the absence of signs or symptoms of connective tissue diseases. These serological tests include RF, anti-cyclic citrullinated peptide, and ANA titre and pattern. The routine use of other serological tests is of unclear benefit.⁹

With regard to IPF in particular, the last 3 years have seen more studies of treatment than in the previous history of the specialty, yet there is no universally accepted "best current treatment."⁶ However, targeting treatment to the correct diagnosis is advisable. A larger proportion of patients showed stable or improved lung function when treated with corticosteroids compared to those who were not, indicating the positive response of some ILDs to corticosteroids. However, the larger percentage of patients who had worsening pulmonary function despite corticosteroids could reflect that patients have more extensive or more rapidly progressive disease. All patients who were receiving amiodarone at the time of auditing had all been diagnosed with a differential type of ILD-EAA, BOOP and asbestosis. There was a large variation in the amount of information documented on follow up visits for different patients. Important symptoms such as exertional dyspnoea and exercise tolerance were often not mentioned, hence making it difficult to monitor symptomatic improvement or deterioration over time. A standard template for symptom scoring could be filled by patients while waiting at the out-patient clinic and any worsening could alert the physician to the need of a change in management.

The fact that 77% of deceased patients had received drugs at some point since diagnosis may be explained by the fact that their deterioration necessitated treatment to slow down disease progression.

The reported frequency of lung cancer in the setting of diffuse pulmonary fibrosis varies greatly, depending on the

country of origin and the type of study. Frequency ranges from 4.8% in the United States to 48.2% in Japan. The molecular and genetic mechanisms governing the development of lung cancer require additional study.¹⁰

Conclusion

Improving our knowledge on disease classification, understanding pathogenesis of the disease and updating ourselves with novel therapies are important in order to achieve an accurate diagnosis and hence plan further management. We have concluded that the diagnosis and management of pulmonary fibrosis locally requires improvement in order to compare with international guidelines. The adoption of clinical guidelines that utilise standardised disease definitions, and which target the investigation and management, would help to standardise care and hopefully improve patient outcomes. We strongly recommended that a multidisciplinary team consisting of respiratory physicians, radiologists and pathologists should be used in the evaluation of ILD. Introducing measurement of the carbon monoxide transfer factor locally promises to be an important tool to optimise monitoring of these patients.

Limitations of the audit

The CT scan reports were often a strong limiting factor since the heterogeneous types of pulmonary fibrosis could not be distinguished from the report. Haphazard follow up of these patients and irregular use of pulmonary function tests made it difficult to assess the rate of progression of the disease. Documentation was at times incomplete. A proportion of patients did not have a working diagnosis, making follow-up and management more difficult for different physicians reviewing these patients.

Further studies

We suggest reviewing the management and progression of patients suffering from pulmonary fibrosis secondary to connective tissue disorders. These patients are more likely to be treated with corticosteroids and other immunosuppressive agents.

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