Michał Zieliński[1], Piotr Sitek[2], Dariusz Ziora[1]

[1]Department of Lung Diseases and Tuberculosis, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia in Katowice, Poland
[2]Pulmonology Department, Public Clinical Hospital No. 1 in Zabrze, Medical University of Silesia in Katowice, Poland

Idiopathic pulmonary fibrosis coexisting with lung cancer

Abstract

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with poor prognosis. Although the underlying mechanisms are not fully understood, IPF is connected with lung cancer development, which farther worsens the prognosis. Various papers report IPF and cancer coexistence in 9.8% to over 50% of patients depending on observation period. Contrary to already established guidelines in the general population, there are no widely accepted recommendations on lung cancer treatment in IPF population. At the same time, various oncologic interventions can result in acute exacerbation of IPF. In this paper authors tried to revise the available data on lung cancer in patients with preexisting IPF.

Key words: idiopathic pulmonary fibrosis, lung cancer, intersititial pneumonitis

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Introduction

Idiopathic pulmonary fibrosis is the most commonly observed form of idiopathic interstitial pneumonia, yet as with other interstitial lung diseases, it could be frequently unrecognised [1–3]. It manifests itself as a usual interstitial pneumonia (UIP) pattern in the radiological and histopathological examination. IPF is the most prevalent in the population of older males with smoking history. The chronic and progressive character of the disease accounts for a poor survival rate. The available treatment options are scarce and offer only a partial reduction in the decline of the lung function.

The first widely accepted diagnostic criteria for IPF were published on the basis of a consensus of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2000 [4]. A revision of those criteria based on the current state of knowledge was published in 2011 and 2018 [5, 6]. In the same year Fleischner Society proposed its own updated criteria [7]. The lack of an international consensus concerning the IPF diagnosis before the aforementioned guidelines causes difficulties in comparing novel data with the ones issued before the guidelines publication.

The available data show that IPF is associated with a high risk of lung cancer comorbidity, which further affects a poor survival prognosis [6]. Moreover, former smokers diagnosed with coexisting lung emphysema (Combined Pulmonary Fibrosis and Emphysema, CPFE) are at an even higher risk of lung cancer [8]. Although the link between IPF and carcinogenesis has been proven, the available data have not allowed to develop widely accepted diagnostic and management protocols for patients with both diseases.

Pathogenetic link

Despite the fact that IPF is associated with lung cancer development, the common underlying mechanisms connecting both conditions are poorly understood.

Address for correspondence: Michał Zieliński, Department of Lung Diseases and Tuberculosis, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia in Katowice, Poland, e-mail: michal.zielinski1@interia.pl
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Histologically, UIP is characterised by fibroblastic foci. The pattern of proliferation and 'invasion' of a normal lung tissue bears similarity with the cancer tissue proliferation. Simultaneously, the cells forming those foci lack monoclonality, characteristic of preneoplastic, and, to some extent, neoplastic processes and the ability to metastasise [9].

Suggested similarities in pathogenetic mechanisms on molecular levels include mutations of tumour suppressor genes, like p53 [11], or the fragile histidine triad gene (FHIT) [12], hipermethylation of the Thy-1 promotor region [13], changes in the expression of microRNA during epithelial-mesenchymal transition [14] culminating in cellular and intercellular abnormalities. Analogical changes observed on molecular, cellular and histological levels coupled with an ability to uncontrollably proliferate, and the signs of tissue invasion allowed some authors to advocate the view of IPF as a neoproliferative lung disorder, which can possibly link it with lung cancer [15].

Among hypotheses trying to explain the pathogenetic connection between IPF and cancer, a common factor or co-factor participating in the development of both diseases was proposed. Among possible agents, exposition to tobacco smoke is often postulated because of a high prevalence of smokers among patients diagnosed with IPF [16, 17]. It is hypothesised that although tobacco smoking is generally associated with lung fibrosis, which significantly differs from IPF, the permanent inflammatory response in the lung tissue caused by tobacco smoke may augment the reaction to other, more direct causative factors ending in IPF development [18, 19]. There are four case series studies which explored the connection between occupational exposures and IPF. A study on 40 cases of cryptogenic fibrosing alveolitis found a significant connection between the disease development and occupational exposures to organic and inorganic dusts, yet failed to prove one with smoking history [20]. On the other hand, a larger study including 248 cases of IPF diagnosed on the basis of radiological and pathological examinations showed the odds ratio of 1.6 (95% CI 1.1–2.4) for patients with the history of smoking. The odds elevated even further when only former smokers or smoking history of more than 20 pack-years were considered [18]. Another study with a studied group of a similar size gave comparable results — the odds ratio of 1.57 (95% CI 1.01–2.43), yet the increase of the odds with pack-years was not proven. [21] The fourth research investigated IPF risk-factors on the basis of 86 patients. It reported the risk ratio of 2.9 for smoking [22]. Therefore, the data from available studies seem to support the existence of an association between IPF development and tobacco smoking, which can constitute a link to carcinogenesis in the lung tissue.

Epidemiology

Several studies published before the first ERS/ATS diagnostic consensus statement analysed the association between IPF and lung cancer. In an investigation of a series of patients from a single centre in London, lung cancer was diagnosed in 9.8% of subjects with IPF, termed cryptogenic fibrosing alveolitis then. If a patient was followed till death, the proportion rose to 12.9% [23]. Another series from the United Kingdom adjusted for tobacco smoking examined the common risk factor of both diseases. The authors reported the rate ratio of 7.31 after excluding the risk connected with smoking history [24].

Two Japanese studies analysed prevalence rates of lung cancer in patients with a histopathologically proven UIP pattern based on autopsy findings. The first research reported prevalence rates of 48.2 % of lung cancer in UIP patients in comparison to 9.1% in an age-matched population without UIP [25]. The second study showed prevalence of 45.7%. The occurrence of squamous metaplasia in the analysed material from patients with both lung cancer and the UIP pattern was more frequent than in the UIP group without the neoplastic process [26]. However, the UIP pattern in histopathological specimens can be observed as a final stage of various interstitial diseases or other inflammatory processes like connective tissue diseases, radiation pneumonitis, or various drug adverse reactions. Histopathological examination alone cannot diagnose IPF without consideration of other clinical data. Therefore, investigations based on autopsy findings tend to overestimate the prevalence of IPF, and, consequently, its possible connection with cancer development.

On the other hand, the study approach based on the findings that mentioned both lung cancer and pulmonary fibrosis on death certificates showed different results. There were two such studies, one from the United States covering the years 1979–1991, the second was based on data from England and Wales in the years 1985–1986. Findings of both researches did not show any association between IPF and lung cancer. The methodology used to assess the coexistence of both

disorders was criticised as pulmonary fibrosis tends to be underreported in certificates of multiple causes of death. Moreover, the definition of 'pulmonary fibrosis' in those studies differs from the presently used diagnostic criteria [27–29].

Most of the investigations analysing epidemiology of lung cancer in IPF are retrospective by design, and the reported incidence does not allow to recognise the changes in incidence in accordance with the follow-up duration. A Japanese retrospective longitudinal cohort study was designed to allow the calculation of the cumulative incidence. IPF was diagnosed according to the criteria proposed by the American Thoracic Society and the European Respiratory Society. The cumulative incidence of lung cancer rose from 3.3% in the first year of the follow-up to 54.7% in the tenth year, the median duration to the cancer diagnosis was 120 months from the diagnosis [30]. In contrast, another study from Japanese authors showed lung cancer development rates of 12.2% and 23.3% after 5 and 10 years, respectively. However, the routine lung cancer screening was not implemented in the studied group, which can account for the discrepancies with other data from the Japanese population [8]. A similar study was based on a group of patients from Italy, where all cases of lung carcinoma were incidental findings. Among IPF patients with coexisting lung cancer, the cumulative incidence was 41% and 82% after 1 and 3 years, respectively [31]. On the other hand, a Chinese study using the ATS/ERS IPF diagnostic criteria reported a 17.16% incidence of lung cancer in the studied population. 95.65% of cases of cancer were diagnosed at the same time as the IPF diagnosis was established. The authors suggest the cultural background leading to late reporting to the medical professionals as a cause [32]. Similar results were reported basing on a South Korean study sample, where lung cancer prevalence in IPF patients was 6.8%. Among 89 IPF subjects, a simultaneous diagnosis of lung cancer and IPF was established in 78.1% of cases [33].

Lung emphysema is prevalent in patients with IPF because the conditions share common risk factors. Since the 1990s the coexistence of both pathological entities was described and authors suggested the existence of a syndrome — CPFE [34]. Both pathologies constitute a risk factor for the development of lung cancer. In a study from South Korea, the authors concluded that CPFE patients had a higher risk of lung cancer development than patients with emphysema alone. The risk was similar to individuals diagnosed only with IPF [35].

Lung transplantation is one of the possible therapies for IPF. The immunosuppressive therapy employed after the transplant contributes to the increase of the incidence of solid tumours in the transplant recipient. In the majority of cases lung cancer develops in the native lung. Although screening for malignancies is employed before the transplantation, there are cases in which cancer was found in the explanted lung tissue [36]. A higher incidence of bronchogenic carcinoma was reported in the general population of lung and other solid organ transplant recipients [37]. In patients with lung fibrosis after single lung transplants, the frequency of lung cancer development in the native lung equalled 4%, which was higher than in the group with emphysema (2%) [38].

Another possible therapeutic option considered in IPF is the antifibrotic therapy. There is one Japanese study comparing patients receiving pirfenidone (one of the two available antifibrotic drugs) and patients without the antifibrotic treatment. Pirfenidone significantly reduced the risk of lung cancer development (2.1% in the treated group versus 22% in the non-treated group), yet it had no influence on the survival rate [39]. A possible explanation of the anticancer action of pirfenidone is the induction of cancer-associated fibroblasts apoptosis by the drug, demonstrated both in the *in vitro* model and in the mouse model *in vivo* [40].

When considering the risk of developing lung cancer in patients with IPF, one must take into account the competing risk events. IPF is generally associated with a poor prognosis. Because of that, a patient may die from other causes before cancer becomes clinically significant. Japanese authors in their paper on the incidence of lung cancer in IPF patients showed that IPF patients with lung cancer were younger and their pulmonary function was better than in the group without lung cancer [8]. Similarly, in the aforementioned pirfenidone study, a higher lung VC (vital capacity) was also associated with a higher risk of lung cancer development [40]. Therefore, poor prognostic factors may lower the risk of the lung cancer diagnosis because of the shorter survival time.

Histopathology

An autopsy study reported the peripheral lung area as the main location of cancer, adjacent to the areas where non-fibrotic and fibrotic tissues border. It suggests remodelling as a process connected with lung cancer development [25].

Another autopsy study also documented peripheral areas of the lung as the main location of cancer. The aforementioned fibrotic/non-fibrotic border, as well as the honeycomb areas showed a topographical association with cancer [26]. Likewise, studies using the radiological examination report a peripheral lung cancer location, adjacent to areas with the radiological UIP pattern [16, 33, 41]. The involvement of lower lobes is significantly more frequent in the neoplastic process connected with IPF than in patients without IPF [42].

Most studies announce squamous cell carcinoma as a dominating histological type of lung cancer in IPF [30, 16, 42, 43]. One Chinese investigation found adenocarcinoma as the most frequently occurring type of cancer [32]. An analysis of lung cancers in resected surgical specimens showed a similar incidence of squamous cell carcinoma and adenocarcinoma. However, for obvious reasons, the studied group included only patients with lung carcinoma of up to stage IIIa [44].

Japanese and Korean authors showed the distribution of lung cancer subtypes in their series of patients with IPF similar to that of the general population with lung cancer in Japan [43, 44]. In contrast, a French study from 2017 compared two groups of patients with cancer developed in a fibrotic lung — one with underlining IPF and the other with fibrosis of a different background. In this series, a comparison of both groups revealed a frequency of histological types in the non-IPF group similar to the general population. Squamous cell carcinoma was predominant in the IPF group, which showed a different distribution in this group in comparison to the previously mentioned Japanese results [16].

Most of the available literature focuses mainly on histology and location of IPF-associated cancer; therefore, the available data on the immunohistological and molecular characteristics are scarcer. It is hypothesised that cancer in IPF arises from pathologically proliferating bronchiolar epithelium in areas affected by honeycombing, which should influence the expression of immunohistochemical markers. There is one study comparing immunohistochemical markers in adenocarcinoma from the general population and a group with IPF. IPF-associated adenocarcinomas lacked the expression of TTF-1, napsin-A, and surfactant protein A, which were characteristic of adenocarcinoma in the control, IPF-unassociated group. The MUC5AC (goblet cell marker) expression was significantly more often encountered in IPF adenocarcinomas. The results demonstrate striking differences in the immunohistochemical pattern in adenocarcinoma from IPF patients [41]. The available data on genetic mutations in cancer in IPF generally concern adenocarcinomas. Papers point to a lower frequency of EGFR (epidermal growth factor receptor) gene mutations [45, 46]. The frequency of mutations of ALK (anaplastic lymphoma kinase) gene does not differ from the one encountered in the general population [46]. Data on the KRAS gene mutations are inconclusive. The available results show either a high prevalence of mutations or no differences with adenocarcinomas not related to IPF [45, 46].

Diagnostics, possible screening options

Although lung cancer worsens the already poor survival of IPF patients, there are no official guidelines issued by international organisations concerning screening for lung cancer in the population with IPF [5, 47]. The recommendations developed for the general population cannot always be safely applied in IPF patients. For example, IPF patients can react with acute exacerbation when surgical intervention is performed, such as for example an open lung biopsy [48]. A group of Greek authors suggested an annual HRCT scan as the basic screening protocol. In their opinion nodules less than 8mm should be followed-up every 3–6 months. A noticeable progression or the base diameter of more than 8mm should encourage PET -CT. Results suggestive of the neoplastic process should be followed by a minimally invasive biopsy [47]. The National Comprehensive Cancer Network lung cancer screening guidelines from 2012 consider pulmonary fibrosis an additional risk factor. The additional risk factor in patients > 50 years and smoking history above 20 pack-years justifies screening with the baseline low-dose computed tomography. If the presence of lung nodules is not detected, an annual CT for 3 years is recommended. There is no difference in the general population in terms of further evaluation of detected nodules [49].

Therapeutic options

Common therapeutic options employed in the lung cancer treatment in the general population include surgery, chemotheraphy, and radiotheraphy. Nowadays, the targeted therapy and immunotherapy grow in significance. Those conventional treatment strategies can prove difficult in IPF patients because of the initial poor lung function results connected with the disease and the possibility of triggering an acute exacerbation of IPF, which has high mortality rates.

Japanese investigators examined the effects of lobectomy and a partial lung resection without the lymph node dissection on lung cancer and IPF or CPFE patients. The surgical treatment was connected with cardiopulmonary complications in 20% of IPF patients and 38% of CPFE subjects. An acute exacerbation was diagnosed in 6% of patients and became a cause of death in most of the cases. More than half of the treated individuals experienced a relapse in 5-years' time in both groups [50]. A broader approach to surgery was examined by a team of researchers from Korea. They investigated procedures covering less invasive procedures, like wedge resection and segmentectomy, and wider resections up to pneumonectomy. The sublobar procedures were connected with a statistically insignificant lower in-hospital mortality rate. Sublobar resections were associated with less frequent respiratory complications, yet the local recurrence rate was as high as 20%. As the overall survival did not differ between the groups, the authors concluded that sublobar resection could become another treatment option in IPF subjects [44]. Even in pathologic stage IA patients, surgical treatment is connected with a 10.7% chance of an acute exacerbation, which constituted a half of the respiratory failure- related fatal cases [51]. As seen from the above mentioned data, an acute exacerbation of IPF constitutes an important factor limiting the efficacy of the surgical treatment. Although the acute exacerbation usually proves fatal, there are no established treatment regimens or prevention measures [48, 51]. Because of that, a phase II trial conducted in Japan investigated perioperative pirfenidone in the prevention of a post-resection acute exacerbation. In preparation for surgery pirfenidone was administered at least for 2 weeks at a dose of 1200 mg/day, which was continued at least until the 30th day after surgery, with the dose escalation to 1800 mg/day, if viable. The results confirmed safety of perioperative pirfenidone administration and, in comparison to historical controls, a lower chance of an acute exacerbation with the pirfenidone regimen [52]. As further investigations in comparison to other medication regimens are needed, the surgery selection criteria still hold importance. Low values of preoperative %FVC were proven to predispose to higher rates of a postoperative acute exacerbation [53]. A similar relationship was reported for a lower diffusion capacity for carbon monoxide, the diffusion capacity for carbon monoxide corrected for the alveolar volume, and a higher composite physiological index (value quantifying the IPF severity, derived from FVC, FEV_1, and diffusion capacity for carbon dioxide) [54].

In advanced lung cancer unsuitable for surgery or in patients with the post-operative recurrence, chemotherapy is one of the feasible treatment options. In patients with IPF receiving chemotherapy, an acute exacerbation becomes a concern, as with patients undergoing surgery. The preferred chemotherapy regimens in this group of patients still remain controversial, and small groups of patients with IPF in various cohorts further hinder obtaining quality data. A study conducted on a Japanese population with idiopathic interstitial pneumonias (including IPF) investigated safety and efficacy of combined carboplatin (AUC 5) with paclitaxel (100 mg/m^2) in non-small cell lung cancer. One patient with proven IPF out of six enrolled in the study developed a fatal acute exacerbation due to chemotherapy. Other treatment-related grade 3 or 4 toxicities included neutropenia, hypersensitivity, and cerebral infarction. The overall response rate reached 61%, with the median survival time of 10.6 months [55]. Another study explored the influence of regimens constructed with carboplatin, paclitaxel, docetaxel, and vinorelbine. The resulted overall response rate was similar to the general population, yet the number of acute exacerbations reached 43% [56]. It could be partially explained by other results, which found a statistically significant link between the inclusion of docetaxel in the chemotherapeutic regimen and a chance of an acute exacerbation. The same effect was absent for pemetrexed, paclitaxel, and nab-paclitaxel-based regimens [57].

Among two drugs used in pharmacological treatment of IPF, nintedanib is used in conjunction with docetaxel as second line treatment of lung adenocarcinoma. It is shown that this regimen offers significant elongation of overall survival [58]. On the other hand, the aforementioned concerns about docetaxel toxicity in IPF patients can hinder the use of this combination in IPF-related cancer patients.

Small cell lung cancer is uncommonly diagnosed in IPF patients. The standard regimen of platin-derivate and etoposide was reported to induce 'a rapid deterioration' (which can comprise an acute exacerbation) in 36.4% of patients. Other authors reported a 12.5% chance of exacerbation after carboplatin with etoposide. The reported overall response rates ranged 63–88% [59, 60]. Basing on those results, IPF patients with small cell lung cancer may benefit from standard chemotherapy regimens; however, the possibility of an acute exacerbation cannot be neglected.

Similar concerns about possible acute exacerbations and also radiation pneumonitis refer to radiotherapy. However, in contrast to chemotherapy and surgery, an official statement on radiotherapy in IPF was developed. The statement was published by the Czech Pneumological and Physiological Society and the Czech Society for Radiation Oncology, Biology and Physics in 2017, and is available in the Czech language. In patients with inoperable non-small cell lung cancer who potentially can be treated radically, the consideration of the stereotactic body radiation is suggested. In treated patients, the chance of pneumonitis amounting to 5.3% (after the median of 1 month after irradiation) should be taken into account. In patients with locally advanced non-small cell lung cancer and all patients with small cell lung cancer, a palliative chemotherapy before irradiation is suggested. In palliative cases, a greater consideration should be made because of the possible further damage to the lung and, consequently, diminished quality of life. In very selected cases, external radiotherapy of small targets like, for example, main bronchi or brachytherapy, can be considered [61]. The proton beam therapy was investigated separately in patients with idiopathic pulmonary fibrosis. Data from 16 patients with IPF and either primary lung cancer or lung metastases of lung cancer were analysed. After receiving 80Gy of the relative biological dose proton beam therapy, 19.8% of patients developed grade 3–5 pneumonitis. Simultaneously, grade 4––5 pneumonitis occurred only in 6.3% of patients. That value is significantly lower in comparison to data from other available studies, which reported a 19–53.8% chance of pneumonitis of this severity [62]. Although the analysed group was small and based on the experience of one centre, the achieved results suggest the proton beam therapy as a relatively safe procedure in IPF patients.

Lately, the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) have been growing in significance in the treatment of non -small cell lung cancer. As EGFR gene mutations are rarer in patients with IPF, the available data on their usefulness are scarce and based on single cases. Cases of a rapid deterioration are reported in patients receiving EGFR-TKI. Although the available evidence is weak, the use of EGFR-TKI should be associated with caution [56].

Prognosis, survival

IPF itself constitutes a risk factor for a poor prognosis. Various authors report the survival after IPF diagnosis ranging from 2.5 to 5 years, depending on the studied group [4, 6]. Lung cancer is similarly connected with short survival times. The available data point to a 5-year survival rate, independent from the disease stage, of 16.8% [63].

As IPF is a rare disease, all studies investigating lung cancer in IPF patients suffer from small sample sizes. One of the biggest groups, reaching 632 IPF patients, was accumulated in a cohort study by Eisuke Kato and co-authors. 70 patients developed lung cancer. If cancer was present at the stage of the IPF diagnosis, the all-cause mortality over 5 years reached 93%. In comparison, in a group with lung cancer diagnosed during the follow-up, the mortality over 5 years was 47%, in a group without lung cancer — it reached 40% [9]. Similar results were obtained by Korean researchers who analysed 70 patients with both IPF and lung cancer. The reported 5-year survival rate was 37.5% in patients with cancer in comparison to 72.5% [64]. On the other hand, Chinese data showed a far shorter median survival of 6.9 months in patients with both lung cancer and IPF, in comparison to 36.2 months in patients with IPF alone [32]. The data from the Italian group point to the median survival of 38.7 months in contrast to 63.9 months, if cancer was not diagnosed [31].

Conclusion

IPF is a disease with a poor survival rate, which is further diminished by a higher risk of developing lung cancer than in case of the general population. Although many hypotheses linking both diseases have been proposed, none has received a general recognition. Despite the fact that lung cancer has a profound negative impact on survival in IPF patients, screening protocols for general population can have limited usage, because of a higher risk of complications of diagnostic procedures in IPF subjects. Possible therapeutic options are scarce, and not backed by data from large studies. The available oncological treatment options may result in an acute exacerbation of IPF connected with a high risk of death. Therefore, further research should explore most efficient screening and diagnostic protocols.

Conflict of interest

The authors declare no conflict of interest.

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