Lung cancer in idiopathic pulmonary fibrosis

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Abstract Lung cancer appears to be more common among patients with idiopathic pulmonary fibrosis (IPF). The exact prevalence is unclear but is likely to be in the range 5–17 %. Risk factors for lung cancer in IPF include age, greater smoking history, and male gender. Squamous cell lung cancer may be more common in IPF than in the general population. The lung cancers are more often at the periphery and bases, although these findings are not universal. The pathogenesis behind this increased association is unknown but may be because of increased cell turnover and DNA damage. The development of lung cancer often is a late complication and the effect of this diagnosis on an individual's outcome is unknown. However, IPF affects patients' therapeutic options, both their ability to tolerate intervention and because of a significant risk of acute exacerbation after the intervention.

Keywords Lung cancer · Idiopathic pulmonary fibrosis · Prevalence · Relative risk · Risk factors · Prognosis · Therapy · Acute exacerbation

Introduction

Although most patients with idiopathic pulmonary fibrosis (IPF) will die from respiratory failure as a result of their disease [1], lung cancer is a not infrequent complication and competing cause of death [2]. Therefore the clinician caring for the patient with IPF must be aware of the risk and the implications of this additional diagnosis.

Case vignette (Fig. 1)

A sixty-one-year-old former smoker with IPF newly diagnosed on the basis of CT criteria underwent evaluation for transplant. A growing left upper lobe nodule was detected on HRCT (Fig. 1). A transthoracic needle biopsy confirmed the presence of squamous cell carcinoma. He underwent surgical resection for his Stage IIb lesion. He suffered a post-operative exacerbation of his IPF. He survived the exacerbation but suffered a significant decline in lung function. After recovering to his new baseline he was started on chemotherapy. He then experience another acute exacerbation after his third infusion. He became progressively hypoxemic and was ultimately intubated for respiratory failure. After a week without significant improvement his family advanced his code status to comfort care and he was terminally extubated. He died six months after his initial cancer diagnosis.

Epidemiology

Prevalence (Table 1)

Over the years multiple case series and cohort studies have sought to answer the question of how commonly lung cancer occurs in patients with IPF. As demonstrated in Table 1, estimates based on these studies have varied greatly, from 3 to 48 %. The wide differences in estimates are likely due to how studies accrued their cases and where the studies were performed. In general, studies that relied on autopsy material for their cases tend to produce the highest estimates whereas studies relying on death certificate coding had the lowest. This may indicate that a significant number of patients with IPF may die with lung cancer present but the attending physicians at the

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Fig. 1 Fifty-one-year-old man with IPF and with nodule detected during transplant evaluation

time of death may not have either detected it yet or did not feel that it was a major contributor to their ultimate cause of death. In addition, a preponderance of the studies were performed in Japan where estimates of the prevalence of lung cancer are higher and may suggest an additional either genetic or environmental predisposition above and beyond that imposed by IPF alone.

Relative risk

Another important question, beyond the frequency of lung cancer, is whether the risk of lung cancer in IPF is greater than for other lung diseases or greater than that for patients without

lung disease. Several studies have sought to answer this question but their results have been somewhat contradictory. Two studies relied on death certificate data to compare patients with IPF and other lung diseases and their prevalence of lung cancer. Wells et al. examined US death certificates from 1979 to 1991 seeking subjects for whom pulmonary fibrosis and lung cancer were listed as the underlying cause of death and/or a contributing cause of death [3]. Similarly, the relationship between chronic obstructive pulmonary disease (COPD) and asbestosis and lung cancer were examined. It is important to note that this study was published before our current classification scheme [4] and, thus, may have included patients with other fibrotic lung diseases that we would now not include in our categorization of IPF. In their study Wells et al. found that lung cancer was listed on the death certificates of 4.81 % of patients with IPF whereas it was noted for 10.06 % of patients with COPD, 26.6 % of those with asbestosis, and 6.48 % of the general population. Therefore, they concluded that the risk of lung cancer was actually not increased in IPF. A similar study was performed in England and Wales by Harris et al. [5]. They examined death certificates from 1985 to 1986 that coded for asbestosis, silicosis, coal workers pneumoconioses, and cryptogenic fibrosing alveolitis and then sought those that also contained the codes for lung cancer. They found lung cancer on 43 % of the death certificates of patients with asbestosis, on 7 % of those of patients with silicosis, on 8 % of those of coal workers with pneumoconioses, and on 6 % of those of patients with cryptogenic fibrosing alveolitis. Although this study did not compare prevalence with that of a general population, it was noted that the magnitude was much lower than in a setting

Table 1 Studies estimating prevalence of lung cancer in IPF

Study	How cases identified	Country	# Cases of IPF	# Cases of Lung Cancer	Prevalence (%)
Fraire, Cancer, 1973 [11]	Autopsy	US	16	3	19
Kawai, Acta Pathol Jpn, 1987 [14]	Autopsy	Japan	47	8	17
Matsushita, Path Int, 1995 [8]	Autopsy	Japan	83	40	48
Hironaka, Path Int, 1999 [20]	Autopsy	Japan	70	32	46
Qunn, Virch Arch, 2002 [21]	Autopsy	Japan	72	31	43
Araki, Int Med, 2003 [26]	Autopsy	Japan (65+ years old)	86	15	17
Turner-Warwick, Thorax, 1980 [6]	Retrospective clinic cohort	England	205	20	10
Haddad, Am Jnl Med, 1986 [13]	Discharge diagnosis of IPF	US	8	3	38
Nagai, Tohoku J Exp Med, 1992 [16]	Hospital-based cohort	Japan	99	31	31
Rudd, Thorax, 2007 [33]	Death certificates	UK	398	69	17
Wells, South Med Jnl, 1996 [3]	Death certificates	US	107,312	5,162	5
Harris, J Epic Com Hlth, 1998 [5]	Death certificates	England, Wales	1,951	109	6
Harris, Thorax, 2010 [7•]	Death certificates of a cohort study	UK	488	46	9
Hubbard, AJRCCM, 2000 [9]	GPRD database	UK	890	39	4
Le Jeune, Resp Med, 2007 [34]	THIN database	UK	1,064	29	3
Ozawa, Respir, 2009 [10]	Prospective clinic cohort of incident cases	Japan	103	21	20

in which the increased risk of lung cancer was well established (asbestosis), raising the question of whether or not the risk of lung cancer is elevated.

Other authors have sought to answer the question of increased risk by performing case–control studies rather than relying on death certificate coding, which may be problematic. The first was reported in 1980 by Turner-Warwick et al. [6]. This was a clinic-based cohort of patients with cryptogenic fibrosing alveolitis (CFA) from the Royal Brompton Hospital followed between 1955 and 1973. The patients were followed for a minimum of four years. In their population 10 % of those with CFA (20/220 cases) were also diagnosed with lung cancer. They compared this with population-expected mortality based on previous studies by Doll and found an excess risk of 14.1 for male smokers and 6.7 for female smokers. Hubbard et al. examined cases of CFA identified in the General Practice Research Database in the UK from 1985 to 1986. They matched each case to six controls of the same sex, age, and practice. They found that the rate ratio for lung cancer was 7.31 for CFA versus controls. Adjustment for smoking status had little effect on the elevated rate (RR 8.25). Le Jeune et al. used a different database from the UK database and a more recent time period (up to 2004) and obtained similar results. The THIN (The Health Improvement Network) identified cases of CFA and matched them to non-CFA controls on the basis of age, gender, and practice; they found an increased rate ratio for lung cancer of 4.96. Again adjustment for smoking status had little effect on the estimate, suggesting that the disease state confers a risk above and beyond that of smoking alone. Finally, the results of the British Thoracic Society cohort of CFA patients accrued from 1990 to 1992 and then followed until 1996 or death, whichever occurred first, were recently published [7•]. In this cohort 9 % had lung cancer. This was again compared with expected survival based on national statistics, and they reported an increased standardized mortality ratio of 7.4 for lung cancer in CFA.

Risk factors

Relatively little is known about the risk factors for development of lung cancer among patients with IPF. The most consistently demonstrated risk factors include male gender, increasing age, and greater smoking history [6, 8–10]. For instance, Hubbard et al. revealed a dose response between the number of cigarettes smoked and the risk of lung cancer among those with IPF who were still actively smoking [9]. However, this dose response was not seen among former smokers. This may have been because of the difficulty of appropriate classification of the extent of previous smoking. Ozawa et al. found that age at the time of diagnosis of IPF was an independent risk factor for the development of lung cancer in IPF above and beyond the risk of smoking [10]. In addition, in their clinic-based cohort the incidence of lung cancer increased with

increasing duration of IPF follow up from 3.3 % at one year, to 15.4 % at five years, and 54.7 % at 10 years.

Cellular sub-types and location (Table 2)

Early series of lung cancer in IPF suggested that adenocarcinoma was the predominant cell type of lung cancer [11–14]. However, as seen in Table 2, more recent studies have not uniformly confirmed that finding. The study by Kawasaki et al. compared a cohort of patients with IPF and lung cancer with a group of lung cancer patients without IPF. They found significantly more squamous cell cancer in the IPF group. The Mayo clinic group reviewed their experience with IPF and lung cancer and similarly found increased occurrence of squamous cell cancer [15]. Interestingly, despite this increased squamous cell cancer, most studies suggest that the cancer occurs more often at the periphery and at the bases [8, 15–17] which is not typical of squamous cell cancer in the general population. Finally, some, but not all, series report that the cancers are often found in proximity to the fibrosis [18, 19] which may be relevant to the pathogenesis, as discussed below.

Multiple synchronous lesions

Some studies have suggested an increased risk of multiple synchronous lung cancers among patients with IPF. For instance, one series of autopsy cases from Japan from 1972 to 1992 found that 15 % of IPF patients had synchronous lesions whereas this was true for fewer than 1 % of the non-IPF lung cancer patients [8]. One report collected all reported cases of synchronous cancers and lone lung cancer in IPF published in Japan from 1980 to 1994 and compared them with a group of lung cancer without IPF [17]. They found that risk factors for multiple primaries included male gender, heavy smoking, small-cell carcinoma histologic cell type, and lower lobe and peripheral locations.

Pathogenesis

If the risk of lung cancer is indeed increased in IPF this could either be because idiopathic pulmonary fibrosis itself causes lung cancer or because a similar pathogenic risk factor (for example an environmental insult, such as smoking, or a genetic defect) causes both disease states.

The theory that IPF itself could cause lung cancer dates back to histological observations in the 1950s and 1960s of significant areas of metaplasia in regions of honeycombing. Furthermore, they noted that for some patients who had both IPF and lung cancer there was an increased amount/degree of metaplasia [12, 13, 20]. This led to the concept that recurrent

Table 2 Studies examining cellular subtypes and location of cancer in IPF

Study	Case source	Country	Cellular subtypes					Location		
			Adeno-carcinoma (%)	Squamous (%)	Small Cell (%)	Other (%)	Different from controls?	Peripheral (%)	Lower (%)	Proximate to honeycombing
Kawai, Acta Path Jpn, 1987 [14]	Autopsy	Japan	88	12	0	0	NR	100	87	NR
Nagai, Tohoku J Exp Med, 1992 [16]	Hospital-based cohort	Japan	32	45	13	10	NR	87	70	NR
Matsushita, Path Int, 1995 [8]	Surgery and autopsy cohorts	Japan	52	17	24	7	No	97	NR	NR
Mizushima, Chest, 1995 [17]	Cases from Japanese literature	Japan	35	39	14	12	No	91	53	NR
Lee, J Comm Ass Tom, 1996 [35]	Clinic database	Japan	22	56	19	3	NR	66	66	NR
Kawasaki, Jnl Surg Onc, 2001 [18]	Hospital cohort of surgical resections	Japan	46	46	2	7	Yes	NR	43	79
Park, Eur Resp Jnl, 2001 [36]	Hospital cohort	Korea	30	35	19	16	No	56	52	37
Aubry, Mayo Clin Proc, 2002 [15]	Clinic database	US	29	67	4	NA	Yes	56	42	NR
Kishi, J Com Ass, 2006 [19]	Clinic database	Japan	40	40	17	3	NR	NR	NR	56

NR not reported

injury and inflammation could lead to a progression from atypia to metaplasia to dysplasia and ultimately to frank cancer. More recent support for this comes from the observation of increased aneuploidy in hyperplastic epithelial foci in the honeycombing of patients who have both lung cancer and IPF [21]. This theory is further supported by the observation that many of the cancers do seem to occur in areas of fibrosis [8]. However, not all the cancers do, and this is unlikely to explain the entirety of the association.

The notion of a common pathogenic mechanism because of smoking is probably no longer viable. As noted above, multiple studies have controlled for smoking and the relationship for lung cancer and IPF remains and is not attenuated, arguing that there is something beyond the smoking itself. There is now increasing evidence of genetic defects common to both IPF and lung cancer. Whether the defects are a primary abnormality or a secondary occurrence in IPF is unknown. For instance, there is elevated expression of p53 and p21 in lung tissue in patients with IPF [22]. This may suggest, at the very least, that there is DNA injury, if not abnormal function, of these genes. These crucial tumor-suppressor genes are obviously important in many cancers also. In addition, microsatellite instability and loss of heterozygosity in genes participating in cellular apoptosis and cellular proliferation have been described for patients with both IPF and cancer [23]. Abnormal methylation of DNA has been seen in both lung cancer and IPF (although to a lesser extent in IPF). [24] Finally, mutations in surfactant protein A genes have been associated with both lung cancer and IPF in two families with familial IPF [25].

Prognosis

Whether lung cancer behaves differently in patients with IPF is unknown. Many practitioners suspect that the development of this complication worsens the prognosis of the patient. However, data to support or refute this conclusion are lacking. Two studies have sought to examine the effect of diagnosis of lung cancer on the outcome of IPF. The first was the study by Ozawa et al. of 21 incident cases of lung cancer in a cohort of 103 IPF patients [10]. They found no difference between median survival of those who developed lung cancer and those who did not (median survival 139.5 months for those with lung cancer versus 108.4 for those without). They believed there was little difference because the lung cancer was usually a late complication (median time to diagnosis was 102 months after diagnosis of IPF). However, median survival after the cancer was diagnosed was only 13.1 months. A second study by Araki et al. followed a cohort of elderly patients with IPF and, again, found that survival of those with and without lung cancer was similar, and that lung cancer was typically a late development [26].

Treatment

As noted above, it is unknown whether lung cancer behaves differently in patients with IPF and, thus, if having IPF should alter the therapeutic approach from a cancer biology basis. However, it is clear that having IPF does affect treatment choices, because it affects the patient's ability to tolerate therapy. As described in our case vignette, there are many case reports and now surgical case series describing acute exacerbation after surgical resection of lung cancer in patients with IPF. In the Mayo series 22 of their 24 patients with IPF and lung cancer underwent surgery [15]. Nearly 40 % had a surgical complication and 3 (14 %) died within 30 days of surgery. Watanabe et al. reviewed their institution's experience of surgical resection of lung cancer [27]. They performed 870 resections for lung cancer. Fifty-six of these had IPF in addition to their cancer. They found surgical mortality was higher for those with IPF (7.1 % versus 1.9 %). Seven percent of their IPF patients had acute exacerbation after surgery. They noted five-year survival for stage I cancer in their cohort was 83 % for those without IPF and 62 % for those with IPF. Interestingly, this was not solely because of the mortality of IPF itself—the incidence of recurrence at five years was increased among those with IPF compared with those without (56 % versus 83 %). Another review of an institution's experience with resection of lung cancer in IPF obtained similar results. Of 711 patients overall, 53 had IPF. Their post operative mortality for those with IPF was 8 %, with 26 % post operative morbidity, versus 0.8 % and 9 % respectively for those without IPF. Again, five year survival was less in the IPF group (43 % versus 64 %) and they noted that 35 % of the deaths in the IPF group were unrelated to cancer versus 18 % in the non-IPF group.

The frequency of acute exacerbation varies from study to study, from 7 % to as high as 27 % [28]. Unfortunately, studies have been inconsistent in the risk factors identified. Potential risk factors include reduced FVC (<80 % predicted) [28, 29], elevated pre-operative LDH [29], and a higher smoking index [30].

Given the risks of surgery, even for early-stage cancer, other therapeutic approaches, for example chemotherapy and radiation, may seem more appropriate. Unfortunately, there are case reports of acute exacerbation after these interventions also [30, 31]. Although preliminary data suggest stereotactic body radiation therapy may be effective against early-stage cancer for people with COPD who are not candidates for surgery [32], there are no data for IPF about either efficacy or risk of worsening fibrosis. Studies are needed to help determine which therapy may be most appropriate for patients with IPF.

Conclusion

The prevalence of lung cancer is likely elevated among patients with IPF. The risk is likely to be 4–10 times higher than that for

a person without IPF. Independent risk factors for development of lung cancer include male gender, increasing age, and greater smoking history. There is a probably an increased incidence of squamous cell cancer. In addition, cancers are more often at the lung periphery and near the patients' fibrosis, but these findings are not universal. There is some circumstantial evidence that increased cell turnover and DNA damage in areas of fibrosis may progress to lung cancer. There also seem to be genetic abnormalities that predispose to both conditions. The overall effect of the development of lung cancer on prognosis of IPF is unclear, but survival from the time of the dual diagnosis is likely to be poor. Therapeutic options are complicated by the high incidence of acute exacerbation and difficulty in potential interventions. Optimum treatment strategies are unknown.

Compliance with Ethics Guidelines

Conflict of Interest Maryl Kreider declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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