Primary adenocarcinoma of the lung in a case of von Recklinghausen neurofibromatosis

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Von Recklinghausen disease (neurofibromatosis, NF-1) is the most common inherited syndrome predisposing to neoplasia, particularly neural crest-derived tumors. However, occurrence of primary lung adenocarcinoma in association with NF-1 is not common. We present a 42-year old man with NF-1 and primary adenocarcinoma of the lung to discuss the linkage between these two entities. [Turk J Cancer 2002;32(1):32-36]

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Von Recklinghausen neurofibromatosis is an autosomal dominant disease which features hyperplasia and neoplasia of neuroectodermal tissues largely derived from the neural crest (1,2). The classic or peripheral form of the disease, described by von Recklinghausen in 1882, is also known as neurofibromatosis type 1 (NF-1) and accounts for 85% of all cases. Its cardinal features are café-au-lait macules and multiple neurofibromas. The presence of at least six café-au-lait spots of more than 1.5 cm in diameter is diagnostic of NF-1. Other features include hamartomas of the iris (Lisch nodules), axillary freckling and pseudoarthrosis of the tibia (3).

Mutation of NF-1 gene causes von Recklinghausen’s disease. The NF-1 gene on chromosome 17 encodes a protein, neurofibromin, which is a GTPase that modulates signal transduction through the ras pathway. NF-1 is a tumor-suppressor gene. Patients with NF-1 are at increased risk of developing nervous system neoplasms (4). Even though it is known as the most common inherited syndrome in man predisposing to neoplasia, occurrence of malignant tumors other than neurogenic tumors is not common (4-7). Therefore, we present this case to discuss the risk factors for the development of lung carcinoma in a patient with NF-1.

Case Report

A 42-year old male was admitted to our hospital with a history of left-sided chest pain and progressive dyspnea on exertion for 1 month. He was a life-time nonsmoker, and he had no previous diagnosis for a specific disease. There
were no remarkable data in his medical and family histories, and he denied any environmental or occupational asbestos exposure. Physical examination revealed a number of cafe-au-lait spots, and multiple cutaneous neurofibromas suggesting a diagnosis of NF-1. His chest X-ray revealed pleural effusion on the left side. Computed tomography of the chest showed bilateral multiple bullae predominantly in the upper zones (Figure 1) and a minimal left sided pleural effusion associated with obstruction of the left lower lobe bronchi by a surrounding mass, sized 4x5 cm (Figure 2).

Repeated biochemical and cytological examinations of the pleural fluid yielded an exudate without malignant cells. Biochemical and cellular features of the pleural fluid were as follows; hematocrit, 23%; white blood cells, 0.92x10³/µL (differentiation of 70% lymphocytes); protein, 5.2 gr/dL; lactic dehydrogenase, 740 IU/L (normal range, 240-480 IU/L); glucose, 85 mg/dL. Pleural biopsy by Abrams’ needle yielded chronic inflammation. Fiberoptic bronchoscopic examination confirmed obstruction of the left lower lobe bronchi by a tumoral lesion, and bronchial biopsies revealed adenocarcinoma. A metastatic survey including CT scan of the abdomen, cranium and total body bone scan revealed no evidence of metastatic disease. He underwent left lower lobectomy along with the partial resection of the diaphragm which was invaded by tumor, and regional lymph nodes were resected. Histopathologically, the tumor was staged as T3,N0,M0 (Stage IIIa). The pleural effusion was completely disappeared on the chest X-ray obtained 3 months after the surgery. No evidence for recurrence of the tumor or pleurisy was observed during the nine months of follow up.
Discussion

Pulmonary involvement in NF-1 occurs in up to 20% of the cases, and fibrosis and thin-walled bullae formation, predominantly in upper zones are the most common pulmonary manifestations (2,3).

It has been suggested that the genetic abnormality responsible for NF-1 increases a patient’s risk of various kinds of malignancies, and therefore, individuals with NF-1 have a significantly higher incidence of malignant schwannoma, neurofibrosarcoma, intracranial glioma, and pheochromacytoma (8). However, association of primary lung carcinoma with NF-1 is not common (7). A Japanese review reported only 11 cases of NF-1 with primary lung carcinoma until 1992 (6). Adenocarcinoma was the most frequent histologic diagnosis (72.9%) in this report as well as in most of the recent surveys of lung cancer in Japanese population (9). We found a few more cases in the medical literature presenting this association, and interestingly, those were also from Japanese researchers (5,6,10-13). The questions raising from these reports are; whether that occurrence of primary lung adenocarcinoma in these patients with NF-1 is coincidental, or there is an increased risk for the development of lung adenocarcinoma in patients with NF-1. Since NF-1 is not a very rare disease and adenocarcinoma is the most frequent histologic type among reported primary lung carcinomas, coincidental association of lung adenocarcinoma with NF-1 might be possible. On the other hand, the hypothesis of the increased risk for primary lung adenocarcinoma in NF-1 can be explained by two different mechanisms: 1) most of these reports addressed
the possibility that adenocarcinoma might be originating from previous scar tissue or bullae wall because the tumor was usually in the upper lobes where bullae and scar tissues were predominant in NF-1 (13-15); 2) NF-1 is the most common inherited syndrome predisposing to neoplasia, and individuals with NF-1 have a significantly higher incidence of neural crest derived-tumors, particularly benign neurofibromas, malignant schwannoma, neurofibrosarcoma, intracranial glioma, and pheochromocytoma, so there might be also an increased risk for the development of primary lung carcinoma in NF-1 (8). Latter has been investigated in some genetic based studies which were not able to show a strong relation but some evidences to support this hypothesis. NF-1 gene has been mapped to a small region of chromosome 17q (4). Therefore, many surveys were conducted to show any genetic linkage between the abnormalities on chromosome 17 and the malignant transformation in NF-1 (5,6,16). In a study by Menon et al (16) deletions of chromosome 17 in NF-1-derived tumor specimens were searched. While no loss of markers on chromosome 17 was observed in any of the benign tumors from NF-1 patients, 17p but not 17q deletions were observed in neurofibrosarcomas. This region is known to contain a candidate gene, P53, which has been implicated in the progression of a broad spectrum of human cancers including lung carcinomas (5). Most recently, a highly significant association between P53 mutations and deletions on 17p was found in the pathogenesis of non-small cell lung carcinomas (17). In accordance with these findings, a loss of heterozygosity on chromosome arm 17p, but not 17q, in small cell lung carcinoma from a patient with NF-1 was detected in a subsequent study by Shimuzi et al (5). And it was suggested that inactivation of tumor suppressor gene on chromosome 17p, most likely P53, might be responsible for the development of small cell lung carcinoma in their patient with NF-1.

On the basis of these findings, one can speculate that the risk for the development of primary lung carcinoma in NF-1 might be increased at least in some patients due to increased prevalence of deletions on chromosome arm 17p.

In our case, the tumor was originated from the left lower lobe bronchi and there was no association with scar tissue or bullae formation excluding the possibility of a scar carcinoma. Since, our patient was a non-smoker young man and there was no family history of a previous cancer, whether this was a coincidental association, or development of the lung adenocarcinoma was associated with the increased genetic susceptibility of NF-1 is not certain.

We specifically presented this case because of the rare association of NF-1 and primary adenocarcinoma of the lung. We suggest that the lung adenocarcinoma in our case was not originated from a scar tissue, and the linkage between these two entities should be further investigated in genetic based studies.

References