

Case Report

Bronchial Carcinoid Tumor in a Young Man with Neurofibromatosis. Case Report and Review of the Literature

Shaozeng Zhang, MD, PhD, Jiehao Zhou, MD, PhD, Ali Rizvi, MD, Frank Chen, MD, PhD

Abstract

Introduction: Neurofibromatosis 1 is a relatively common autosomal dominant disease characterized by the occurrence of distinctive skin pigmentation (café-au-lait spots and axillary/groin freckling) and multiple neuroectodermal and mesenchymal lesions (e.g. neurofibroma). Patients with NF1 also have a predilection for other types of tumors, such as carcinoid tumors in the duodenum, particularly in the periampullary region.

Case presentation: An 18-year-old man with neurofibromatosis 1 presented with obstructive pneumonia. Bronchoscopy showed an endobronchial tumor obstructing the superior segment of the left lower lobe. Pathologic studies showed a carcinoid tumor. Two weeks later, the patient underwent left lower lobe lobectomy with lymph node dissection. Metastatic carcinoid tumor was present in subaortic lymph node.

Conclusion: To our knowledge, this is the first reported case of endobronchial carcinoid tumor associated with NF1. A review of the literature and current insights regarding the pathogenesis of NF1-associated neoplasms are presented. [*NA J Med Sci.* 2009;2(1):17-20.]

Introduction

Neurofibromatosis 1 (NF1) is an autosomal dominant

Jiehao Zhou, MD, PhD, Frank Chen, MD, PhD

Department of Pathology, State University of New York at Buffalo, New York, USA

Shaozeng Zhang, MD, PhD, * (Corresponding author)

Ali Rizvi, MD

Department of Pathology and Laboratory Medicine, Roswell Park Cancer Institute, Buffalo, New York, USA

Email:

JZ: jzhao4@buffalo.edu

SZ: shaozeng.zhang@roswellpark.org

disorder whose hallmark feature is the occurrence of multiple cutaneous neurofibromas. Other diagnostic criteria for NF1 include café-au-lait spots, lisch nodules, optic glioma, skeletal dysplasia, skin-fold freckling and family history (affected first-degree relative). Individuals who fulfill 2 or more of these criteria can be diagnosed as having the disease. NF1 affects approximately 1 in 3000 to 4000 individuals worldwide, with both sexes and all races being equally affected. There is a significant increase in the occurrence of other types of tumors in NF1. Mixed neuroendocrine tumors are known to be associated with NF1, including pheochromocytoma, medullary thyroid carcinoma, and carcinoid tumors. Patients with NF1 also have a predilection for neurogenic tumors, such as malignant peripheral nerve sheath tumors, ganglioneuromas, schwannomas, and optic nerve gliomas.

Patients with neurofibromatosis (NF) are at risk for the development of hyperplasias and neoplasms of both neural crest and non-neural crest origin. Neuroendocrine tumors associated with NF have rarely been reported at non-intestinal sites.⁴ We present the occurrence of a bronchial carcinoid tumor of typical type histology, occurring in an 18 year old man with a known history of NF.

Case Presentation

An 18 year-old man with NF presented with a two-day history of cough, nausea, vomiting, and diarrhea. A temperature of 103° F was obtained in the emergency department and he was admitted to the hospital. A chest radiograph and computed tomographic scan showed haziness and opacification of the left lower lobe, consistent with pneumonia. The patient was given a course of intravenous antibiotics and was hospitalized for 5 days. His fever decreased, but his cough remained. When his chest radiograph showed no significant improvement, fiberoptic bronchoscopy was performed, revealing an endobronchial tumor obstructing the superior segment of the left lower lobe (**Figure 1**). There was associated post-obstructive pneumonia. Two bronchial biopsies showed carcinoid tumor of typical type histology. Two weeks later, the patient underwent left lower lobe lobectomy with mediastinal lymph node dissection.

The patient was diagnosed neurofibromatosis in infancy. The skin showed numerous café-au-lait spots. Only the father has documented NF, but the patient's mother and two sisters are without NF or other diseases. Two paternal uncles had small cell carcinoma of lung and carcinoid tumors of rectum, respectively. The father died of melanoma.

The bronchoscopic biopsies showed extensive granulation tissue and inflammation overlying a few small nests of tumor beneath the bronchial epithelium. The tumor cells were uniform, with round to oval nuclei, and moderate amounts of eosinophilic cytoplasm. No necrosis or mitotic figures were found in the biopsy sample. The tumor cells were immunoreactive with antibodies directed against cytokeratin (AE1/AE3), chromogranin A, and synaptophysin (**Figure 2**) using standard immune-histochemistry.

The left lobectomy specimen demonstrated an endobronchial mass measuring 2.5 x 2.0 x 2.0 cm. in the superior segment bronchus. The tan, polypoid tumor extended beyond the bronchial wall into adjacent lung parenchyma, but did not extend to the visceral pleural surface. Microscopically, the resected tumor showed features of typical carcinoid tumor (**Figure 3A** and **3B**). Neither mitoses nor necrosis were seen. Metastatic carcinoid tumor was present in 1 of 2 subaortic lymph nodes (**Figure 4**). Nine additional lymph nodes (intra-lobar, parabronchial, periaortic and hilar) were free of tumor.

Discussion

To our knowledge, coexistence of endobronchial carcinoid tumor and NF1 has not been previously described. We now report the first occurrence of an endobronchial carcinoid tumor in a young man with strong paternal history of NF. Interestingly, both the patient and his father had a second tumor in addition to neurofibromatosis.

The association of NF1 with gastrointestinal carcinoid tumors, particularly duodenal carcinoid tumors, has been recognized for almost 3 decades.² In one large reported series of gastrointestinal carcinoid tumor in the setting of NF1, 27 of 29 cases were found in the duodenum and periampullary region (93%). The remaining 2 cases occurred in the stomach and ileum.³ Most NF1-associated duodenal carcinoid tumors are rich in somatostatin, so called D cell carcinoids or somatostatinomas,⁴ whereas similarly located tumors unrelated to NF1 are frequently multihormonal.⁵

In 1996, de Montpreville et al. reported 14 cases of thymic carcinoid tumor, one of which occurred in a patient with NF-1.⁶ More recently, Mathew et al. described a case of a mediastinal atypical carcinoid tumor occurring in an elderly woman with NF-1.⁷ The tumor was centered in the mediastinum, but the exact site of origin was difficult to determine because of the large tumor size.

Although the pathogenesis of NF1 is not currently well understood, some NF1-associated tumors, as seen in this family, may be due to the presence of heritable and

pathological mutations in the NF1 genes. The NF1 gene is large and located on chromosome 17. Neurofibromin, the gene product protein, is a negative regulator of *ras* gene, which is an oncogene very commonly detected in human cancers. Inactivation of the NF1 gene with loss of neurofibromin function has been shown to deregulate *ras* to induce tumorigenesis, suggesting that the NF1 gene may behave as a tumor suppressor gene by interacting with intracellular *ras* signaling.⁸ The neurofibromin-*ras* interaction is mediated by a GTPase-activating protein-related domain (GRD) of NF1 that is similar to the GTPase-activating protein (GAP) of *ras* proto-oncogenes. GAP-like protein of NF1 is known to be involved in the control of cell growth by interacting with *ras*-mediated signal transduction. NF1-GRD and *ras* gene mutations are frequently documented in the pathogenesis and progression of various tumors.⁹ Although a direct association between the NF1 gene product and *ras* gene mutations has not been documented in the carcinoid tumors, K-*ras* and N-*ras* mutations have been reported in carcinoid tumors, typical and atypical, of lung, pancreatic and extrahepatic bile ducts.^{10,11} In addition, Furukawa et al. reported 9 cases of small cell carcinoma of the lung, a much more aggressive tumor in the same neuroendocrine family of carcinoid, of which 3 showed mutations in the GRD of the NF1 gene.¹² Obviously, further studies are needed to identify neurofibromin mutations and possible interactions between the NF1 and *ras* gene products in the carcinoid tumors associated with NF.

In addition to the altered regulation of *ras* protein through mutagenized NF1-GRD, loss of heterozygosity (LOH) of the NF-1 allele has been demonstrated in malignancies. Kluwe et al. found a high rate of NF1 allele loss in NF1-associated astrocytomas, compared to sporadic pilocytic astrocytomas.¹³ Rasmussen et al. also found loss of heterozygosity of the NF1 gene in dermal and plexiform neurofibromas, as well as in malignant peripheral nerve sheath tumors.¹⁴ Knudson's two-hit hypothesis predicts that LOH events are the second step in the inactivation of both alleles of a tumor suppressor gene.¹⁵ It is possible that there may be various mutations in both copies of the NF1 gene. One of these mutations would be present in all cells of NF patients, whereas the other might only affect cells that eventually give rise to a specific tumor (second hit). This presents a possible mechanism explaining why NF patients frequently develop second tumors, as in the case of our patient.

Conclusion

To our knowledge, this is the first reported case of endobronchial carcinoid tumor associated with NF1. It is an addition to the archives to document the propensity of the NF patients to develop a second tumor.

Abbreviations:

NF1: neurofibromatosis 1; NF: neurofibromatosis. LOH: loss of heterozygosity

Consent

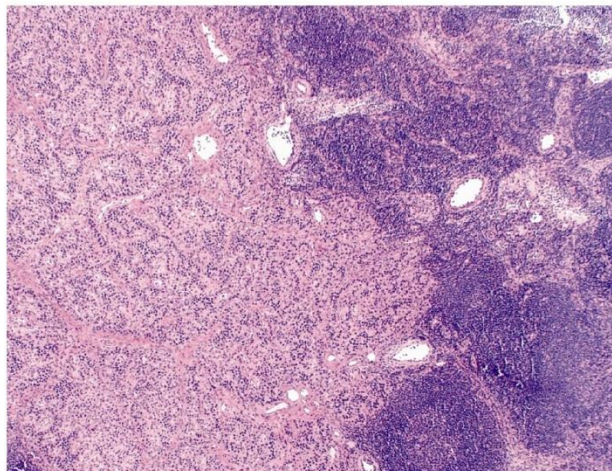
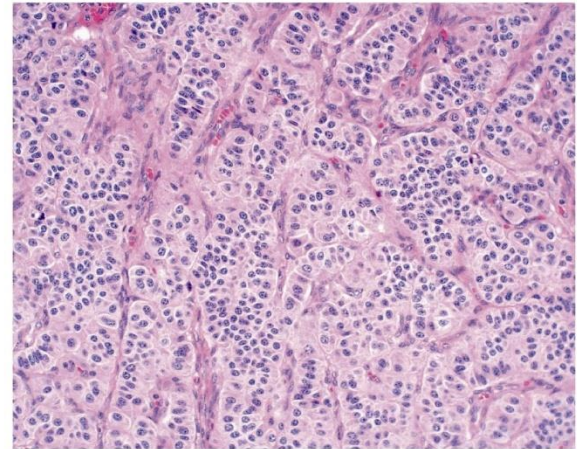
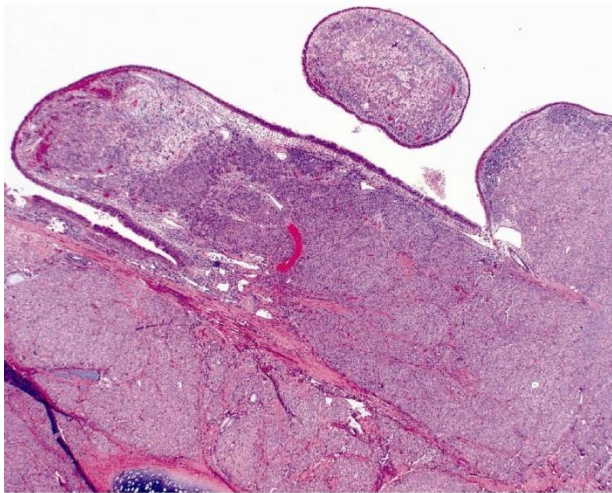
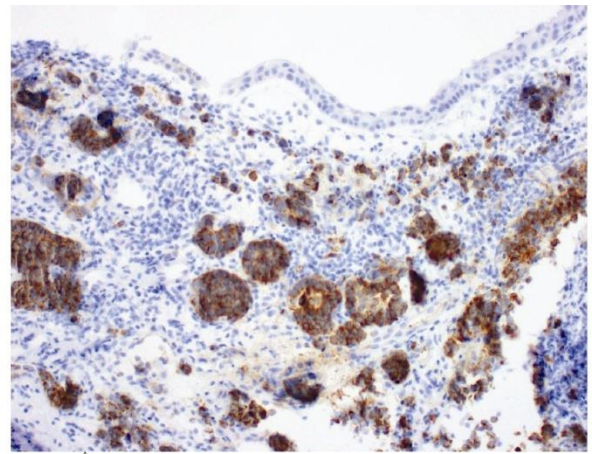
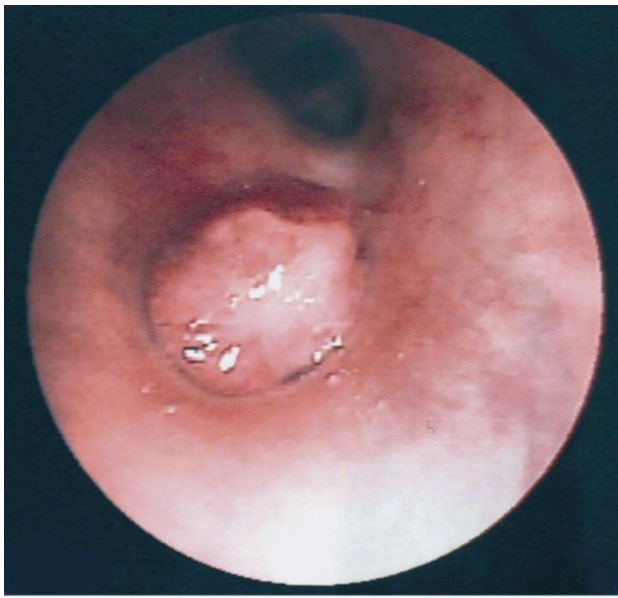
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no competing interests.

References

1. Hochberg FH, Dasilva AB, Galdabini J, Richardson EP Jr. Gastrointestinal involvement in von Recklinghausen's neurofibromatosis. *Neurology*. 1974; 24:1144-1151.
2. Dawson BV, Kazama R, Paplanus SH. Association of carcinoid with neurofibromatosis. *South Med J*. 1984;77(4):511-513.
3. Arnesjo B, Idvall I, Ihse I, Telenius M, Tylen U. Concomitant occurrence of neurofibromatosis and carcinoid of the intestine. *Scand J Gastroenterol*. 1973;8(7):637-643.
4. Ohtsuki Y, Sonobe H, Mizobuchi T, et al. Duodenal carcinoid (somatostatinoma) combined with Von Recklinghausen's disease. *Acta Pathol Jpn*. 1989;39(2):141-146.
5. Dayal Y, Tallberg KA, Nunnemacher G, DeLellis RA, Wolfe HJ. Duodenal carcinoids in patients with and without neurofibromatosis. *Am J surg Pathol*. 1986;10(5):348-357.
6. de Montpreville VT, Macchiaroni P, Dulmet E. Thymic neuroendocrine carcinoma (carcinoid): a clinicopathologic study of fourteen cases. *J Thorac Cardiovasc Surg*. 1996;111(1):134-141.
7. Mathew P, Roberts JA, Zwischenberger J, Haque AK. Mediastinal atypical carcinoid and neurofibromatosis type 1. *Arch Pathol Lab Med*. 2000;124(2):319-321.
8. Viskochil D. Genetics of neurofibromatosis 1 and the NF1 gene. *J Child Neurol*. 2002;7(8):562-570.
9. Yunoue S, Tokuo H, Fukunaga K, et al. Neurofibromatosis type 1 tumor suppressor neurofibromin regulates neuronal differentiation via its GTPase-activating protein function toward Ras. *J Biol Chem*. 2003;278(29):26958-69.
10. Couce ME, Bautista D, Costa J, Carter D. Analysis of K-ras, N-ras, H-ras, and p53 in lung neuroendocrine neoplasms. *Diagn Mol Pathol*. 1999;8(2):71-9.
11. Maitra A, Krueger JE, Tascilar M, et al. Carcinoid tumors of the extrahepatic bile ducts: a study of seven cases. *Am J Surg Pathol*. 2000;24(11):1501-1510.
12. Furukawa K, Yanai N, Fujita M, Harada Y. Novel mutations of neurofibromatosis type 1 gene in small cell lung cancers. *Surg Today*. 2003;33(5):323-7.
13. Kluwe L, Friedrich R, Mautner VF. Loss of NF1 allele in Schwann cells but not in fibroblasts derived from an NF1-associated neurofibroma. *Genes Chrom Cancer*. 1999;24:283-285.
14. Rasmussen SA, Overman J, Thomson SA, et al. Chromosome 17 loss-of-heterozygosity studies in benign and malignant tumors in neurofibromatosis type 1. *Genes Chrom Cancer*. 2000;28:425-431.
15. Knudson AG. Hereditary cancer: two hits revisited. *J Cancer Res Clin Oncol*. 1996;122(3):135-140.



1	2
3A	3B
4	

Figure 1. Bronchoscopic image showed an endobronchial tumor obstructing the lumen of a bronchial segment of left lower lobe of lung.

Figure 2. An immunohistochemical stain for synaptophysin was strongly immunoreactive in the tumor cells (Immunohistochemical anti-synaptophysin monoclonal antibody SY 38, hematoxylin counterstain, x100).

Figure 3. A, Carcinoid tumor in resected left lower lobe of lung. The tumor bulged into the bronchial lumen and was present beneath respiratory mucosa (hematoxylin and eosin, x 20). **B,** Tumor cells were monotonous and arranged in solid nests typical of carcinoid tumor (hematoxylin and eosin, x400).

Figure 4. Metastatic carcinoid tumor was present in one of two subaortic lymph nodes (hematoxylin and eosin, x40).