Cancer Treatment Communications 7 (2016) 8–10

Contents lists available at ScienceDirect

Cancer Treatment Communications

journal homepage: www.elsevier.com/locate/ctrc

Radiation-induced *KRAS* G12V mutant lung adenocarcinoma in a never smoker

Maeghan P. Gibson [a], Joseph Sailors [b], Dwight H. Oliver [b], Hak Choy [c,d], David E. Gerber [a,d,*]

[a] Department of Internal Medicine, United States
[b] Department of Pathology, United States
[c] Department of Radiation Oncology, United States
[d] Division of Hematology–Oncology, Harold C. Simmons Comprehensive Cancer Center, 5323 Harry Hines Blvd, Dallas, TX 75390, United States

ARTICLE INFO

Article history:
Received 19 October 2015
Received in revised form
12 January 2016
Accepted 12 February 2016

Keywords:
Genomic alteration
Molecular profiling
Thoracic
Toxicity
Secondary cancer
Oncogene addiction

ABSTRACT

The molecular profile of radiation-induced cancers remains poorly understood. This case report describes a 59-year-old male never smoker with a distant history of Hodgkin's lymphoma treated with mantle radiation who decades later develops primary lung adenocarcinoma within the prior radiation portal. Genomic profiling of the cancer demonstrated a *KRAS* G12V mutation. We briefly review the clinical entity of radiation-induced second malignancies and *KRAS* mutant lung adenocarcinoma. Although to date there is no standard molecularly targeted therapy available for *KRAS* mutant lung cancer, prior reports of activating *EGFR* mutations in a proportion of radiation-induced lung cancers suggest that a variety of genomic alterations may occur in these secondary malignancies. Given the potential to identify other molecularly defined subsets of lung cancer for which specific therapies exist, routine molecular profiling of these cases seems reasonable.

1. Introduction

Radiation-induced secondary cancers represent a major clinical concern. Given the prolonged interval between treatment and cancer development, risks are most apparent among individuals cured from their initial cancer. Hodgkin's lymphoma is the paradigm of this clinical scenario. Hodgkin's survivors treated with thoracic radiation face a lung cancer relative risk of 2.6–7.0 compared to the general population [1]. Risk is particularly heightened for individuals treated prior to the widespread use of involved-field radiotherapy, which has substantially reduced the likelihood of secondary malignancies. In some models, the use of involved-field in contrast to extended-field (mantle field) radiation therapy may reduce excess relative risk of lung cancer by more than 50% [2]. Radiation-induced secondary cancers have been noted as early as 1–4 years after treatment, and the excess risk from radiation is thought to last up to 20–25 years [3].

Relatively little is known about the molecular phenotype of radiation-induced lung cancers. In a recent report of seven lung adenocarcinomas attributed to prior radiation therapy in Hodgkin's survivors for which mutational analyses were performed, two cases had *EGFR* mutations [4]. In an earlier series of 19 secondary primary lung cancer cases after Hodgkin's radiation therapy, *TP53* mutations were identified in 11 (58%) and *KRAS* mutations were detected in two (11%) [5]. The identified *KRAS* mutations (G12C and G13D) occurred in current or former smokers. Herein we report a case of radiation-induced lung cancer in a never smoker harboring a characteristically smoking-associated *KRAS* G12V mutation. The identification of such a case highlights the potential of radiation therapy to induce a variety of molecular alterations and the importance of evaluating radiation-induced lung cancers for driver mutations.

2. Case report

A 59 year-old Caucasian male never smoker presented with cough and dyspnea. He had a history of Hodgkin's lymphoma in his 20s treated with chemotherapy and mantle radiation, and a subsequent history of abdominal non-Hodgkin's lymphoma in his 40 s treated with combination chemotherapy and abdominal radiation therapy. Chest computed tomography demonstrated regions of subpleural consolidation with well-demarcated lateral borders in all three lobes of the right lung (Fig. 1), consistent with a prior radiation port. Bronchoscopic biopsy of the mass demonstrated mucinous adenocarcinoma (Fig. 2). Tumor genomic analysis revealed a *KRAS* G12V mutation (Fig. 3) but no *EGFR* mutation or *ALK* rearrangement.

* Corresponding author at: Division of Hematology–Oncology, Harold C. Simmons Comprehensive Cancer Center, 5323 Harry Hines Blvd, Dallas, TX 75390, United States.
E-mail address: david.gerber@utsouthwestern.edu (D.E. Gerber).

http://dx.doi.org/10.1016/j.ctrc.2016.02.001
2213-0896/

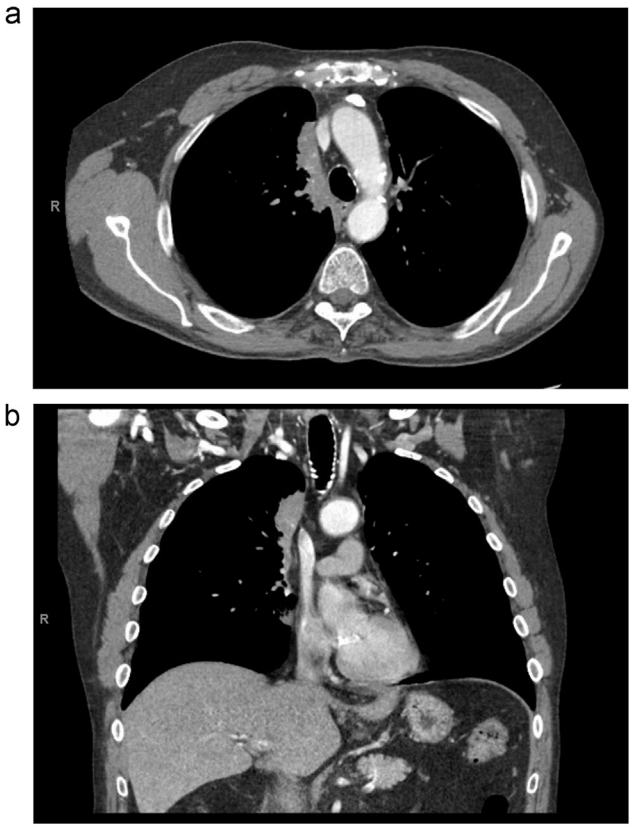

Fig. 1. Axial (a) and coronal (b) computed tomography images demonstrate regions of subpleural consolidation with well-demarcated lateral borders in all three lobes of the right lung, consistent with distribution of a prior radiation port.

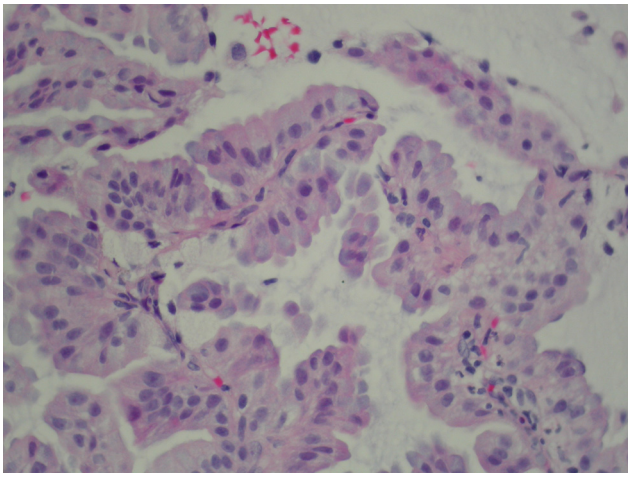

Fig. 2. Biopsy of the right lower lobe of the lung demonstrates papillary adenocarcinoma. Mucin is present in the cytoplasm as well as in surrounding space. Hematoxylin and eosin, 400 ×.

The patient completed chemoradiation with 6 cycles of weekly carboplatin–paclitaxel concurrent with thoracic radiation, followed by two cycles of consolidation carboplatin–paclitaxel. Treatment was complicated by radiation esophagitis and pneumonitis, neutropenic fever, and peripheral neuropathy. Imaging performed six, nine, and 12 months after completing treatment demonstrated ongoing good response to treatment with no evidence of disease progression.

3. Discussion

To our knowledge, this is the first reported case of a radiation-induced lung cancer harboring a *KRAS* G12V mutation. Along with prior reports of activating *EGFR* mutations, other *KRAS* mutations, and *P53* mutations in radiation-induced lung cancer [4,5], this finding suggests that a variety of genomic alterations may be identified in these secondary malignancies.

KRAS mutant lung adenocarcinoma remains a major unmet clinical need. This subset comprises up to 25% of lung adenocarcinoma cases, predicts resistance to existing molecularly targeted therapies, and currently lacks clinically available direct inhibitors. *KRAS* mutations are strongly associated with smoking but are also encountered in approximately 5% of lifetime never smokers with lung cancer [6]. In lung cancer, almost 90% of *KRAS* mutations occur at codon 12. Among codon 12 mutations, approximately 80% are guanine-to-thymidine (G > T) (purine for pyrimidine) nucleotide transversions (including the G12V mutation seen in this case). Transversions are considered the characteristic mutation related to tobacco smoke exposure. *KRAS* mutations in lung tumors from never smokers are typically G > A (purine to purine) transitions [6].

Despite the widespread recognition of radiation-induced lung cancers, to date relatively few studies have examined the molecular phenotype of such cases. In the largest series to date we identified, incidence of *KRAS* and *TP53* mutations, allelic loss, and microsatellite alterations occurred at similar rates to spontaneous lung cancer cases [5]. All analyzed cases had developed in smokers. Although no firm conclusions can be drawn from a single case, the present report is notable for a number of reasons. First, to our knowledge, radiation-induced *KRAS* G12V mutations have not been previously described. Second, the unusual development of a characteristically smoking-associated mutation in a never smoker raises the possibility that the spectrum of molecular alterations in radiation-induced lung malignancies may differ in ways from that seen in non-radiation-related cases. Third, the interval between radiation therapy and development of lung cancer in this case of a never-smoker (at least 30 years) exceeds that of all cases (range 2.3–24.6 years) reported in the earlier series of smokers [5]. This observation may suggest that, in addition to increasing the risk of radiation-induced lung cancers substantially [7,8], smoking may also have an effect on the time-course of these events.

The *KRAS* mutant lung adenocarcinoma described in this case meets the longstanding, general criteria that have been suggested to render a diagnosis of radiation-induced second malignancy [9–11]: (1) a history of prior radiation; (2) new cancer arising within previously irradiated field; (3) second cancer histologically different from the first; (4) a relatively long latent period between the two cancers. Clinical and treatment factors that have been associated with heightened risk of radiation-induced cancers include large fraction dose, large field size, lower age, DNA repair mechanism defects (e.g., ataxia telangiectasia heterozygotes), active smoking at the time of treatment, and administration of concomitant chemotherapy [12–14].

Proposed mechanisms of radiation-induced secondary malignancies center around the concept of radiation-induced genomic instability and include direct DNA damage, intracellular signaling, cytokine production, and free-radical generation [15]. In an animal model of radiation-induced lung tumors, *KRAS* codon 12 mutations were identified as rare and late events [16].

Although there are no published randomized studies comparing outcomes for treatment-induced lung cancers and for spontaneous tumors, the existing indirect evidence suggests that these cases may have particularly poor outcomes. In a single-center series of 14 patients with inoperable disease, median survival was

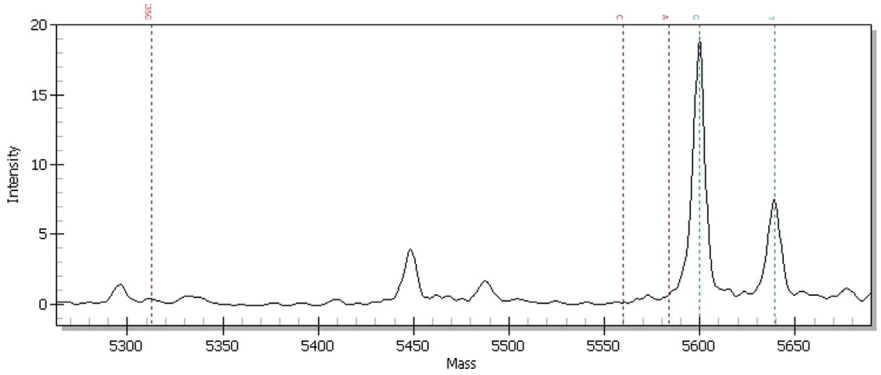

Fig. 3. *KRAS* G12V mutation. Mass spectrometry analysis shows two PCR product peaks, with masses corresponding to a wild type "G" and mutant "T" nucleotide at position 35 (c.35G > T).

3 months [17]. In another report that did not include breakdown of tumor stage, median survival was 1 year for 22 patients [14].

4. Conclusion

Recognizing the limitations of a case report, this case suggests that delayed radiation effects may be associated with G > T nucleotide transversions, resulting in *KRAS* G12V mutant lung adenocarcinoma. Although to date there is no standard molecularly targeted therapy available for *KRAS* mutant lung cancer, prior reports of activating *EGFR* mutations in a substantial proportion of radiation-induced lung cancers suggest that a variety of genomic alterations may occur in these secondary malignancies. Given the potential to identify other molecularly defined subsets of lung cancer for which specific therapies exist (including *EGFR* and potentially others), routine molecular profiling of these cases seems reasonable. This information may be particularly valuable in cases of radiation-induced lung cancer, as these cases may have inferior outcomes compared to de-novo malignancies.

Funding support

None.

Disclosures

The authors report no relevant conflicts of interest.

References

[1] P. Lorigan, J. Radford, A. Howell, N. Thatcher, Lung cancer after treatment for Hodgkin's lymphoma: a systematic review, Lancet Oncol. 6 (2005) 773–779.
[2] E.S. Koh, T.H. Tran, M. Heydarian, et al., A comparison of mantle versus involved-field radiotherapy for Hodgkin's lymphoma: reduction in normal tissue dose and second cancer risk, Radiat. Oncol. 2 (2007) 13.
[3] L.B. Travis, M. Gospodarowicz, R.E. Curtis, et al., Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease, J. Natl. Cancer Inst. 94 (2002) 182–192.
[4] D.A. Bond, N. Dunavin, G.A. Otterson, Mutational profiling of second primary lung cancers in patients who have received radiation for the treatment of Hodgkin's disease, Cancer Invest. 33 (2015) 86–88.
[5] C. Behrens, L.B. Travis, I.I. Wistuba, et al., Molecular changes in second primary lung and breast cancers after therapy for Hodgkin's disease, Cancer Epidemiol. Biomark. Prev. 9 (2000) 1027–1035.
[6] G.J. Riely, M.G. Kris, D. Rosenbaum, et al., Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma, Clin. Cancer Res. 14 (2008) 5731–5734.
[7] F.E. van Leeuwen, W.J. Klokman, M. Stovall, et al., Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease, J. Natl. Cancer Inst. 87 (1995) 1530–1537.
[8] S.H. Moolgavkar, E.G. Luebeck, D. Krewski, J.M. Zielinski, Radon, cigarette smoke, and lung cancer: a re-analysis of the Colorado Plateau uranium miners' data, Epidemiology 4 (1993) 204–217.
[9] B. Chudecki, Radiation cancer of the thoracic oesophagus, Br. J. Radiol. 45 (1972) 303–304.
[10] W.G. Cahan, H.Q. Woodard, et al., Sarcoma arising in irradiated bone; report of 11 cases, Cancer 1 (1948) 3–29.
[11] S. Warren, O. Gates, Multiple primary malignant tumors: a survey of the literature and a statistical study, Am. J. Cancer 1932 (1932) 1358–1414.
[12] A. Walton, A.L. Broadbent, Radiation-induced second malignancies, J. Palliat. Med. 11 (2008) 1345–1352.
[13] L.B. Travis, R.E. Curtis, W.P. Bennett, B.F. Hankey, W.D. Travis, J.D. Boice, Lung cancer after Hodgkin's disease, J. Natl. Cancer Inst. 87 (1995) 1324–1327.
[14] A.K. Ng, M.V. Bernardo, E. Weller, et al., Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors, Blood 100 (2002) 1989–1996.
[15] S.A. Lorimore, P.J. Coates, E.G. Wright, Radiation-induced genomic instability and bystander effects: inter-related nontargeted effects of exposure to ionizing radiation, Oncogene 22 (2003) 7058–7069.
[16] S.A. Belinsky, S.K. Middleton, S.M. Picksley, F.F. Hahn, K.J. Nikula, Analysis of the K-ras and p53 pathways in X-ray-induced lung tumors in the rat, Radiat. Res. 145 (1996) 449–456.
[17] S.A. Laurie, M.G. Kris, C.S. Portlock, et al., The clinical course of nonsmall cell lung carcinoma in survivors of Hodgkin disease, Cancer 95 (2002) 119–126.