Human Pathology: Case Reports xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Human Pathology: Case Reports

journal homepage: http://www.humanpathologycasereports.com

Rare case of combined small cell lung cancer with adenocarcinoma and squamous cell carcinoma

Sameer AL Diffalha, MD [a], Saleh Hasan, BS [b], Maryam Tahmasbi, MD [a], Farah Khalil, MD [a,c]

[a] Department of Pathology and Surgical Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, United States
[b] Northeast Ohio Medical University, Rootstown, OH
[c] University of South Florida College of Medicine, Department of Pathology and Cell Biology, Tampa, FL, United States

ARTICLE INFO

Article history:
Received 8 February 2016
Received in revised form 5 May 2016
Accepted 18 May 2016
Available online xxxx

ABSTRACT

Combined small cell lung cancer (cSCLC) is relatively unusual. We report a case of cSCLC in a 78-year-old man with no prior medical history who presented for evaluation of right upper lobe (RUL) lung mass. A CT scan showed a 3.0 × 2.5 × 2.3 cm RUL lung mass with mildly prominent mediastinal and hilar lymphadenopathy. A right thoracotomy with right upper lobectomy and lymphadenectomy was performed. Histological examination and immunohistochemical stains confirmed the diagnosis of combined small cell lung carcinoma (SCLC) with adenocarcinoma (AC) and squamous cell carcinoma (SCC) components.

While there are available guidelines for treating SCLC, the optimal treatment for cSCLC which will improve prognosis has not been adequately determined. We report a very rare category of primary lung malignant neoplasm to represent our institution's experience in diagnosing and managing this type of rare case.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Combined small cell lung cancer (cSCLC) is rare and comprises about 2–14% of small cell lung cancer (SCLC) cases [1,2]. According to World Health Organization (WHO), cSCLC is considered as a lung cancer that has small cell lung carcinoma (SCLC) component admixed with one (or more) components of non-small cell lung carcinoma (NSCLC) [3]. The NSCLC component can be represented by AC, SCC, and large cell neuroendocrine carcinoma (LCNEC). Most of the cases are SCLC with either adenocarcinoma or SCC component; however there are also rare case reports of up to 3–4 different morphologic tumors which have been reported [4,5]. SCLC in general, is the most aggressive of major lung cancer types, with the worst long term prognosis and survival rates [6]. It is recommended that if a tumor is composed of more than one histological pattern and is found to contain any proportion of SCLC cells to be classified as cSCLC, regardless of component is predominantly seen in the mass [7].

The histogenesis of cSCLC appears to be complex. Wagner PL et al. suggested that the morphological deviation of the components happens when a SCLC-like cell is converted into a cell with the probability to develop NSCLC features. Daughter cells of this trans-differentiated SCLC-like cell then repeatedly divide and, under both internal and external cell environmental effects, they obtain some mutations [4]. However, the simultaneous appearance of both SCLC and other unrelated separate primary histological variants is controversial [8,9].

2. Case presentation

Our patient is a 78-year-old male who had smoked 2–3 packs of cigarettes per day for approximately 35 years. He was referred to Moffitt Cancer Center for evaluation of right upper lobe (RUL) lung mass. The patient first began to have productive cough in the summer but he denied hemoptysis. He attributed this change to increased amounts of dust at work and did not seek evaluation until August 2014. A CT scan was obtained which showed a 3.0 × 2.3 × 2.5 cm RUL lung mass with mildly prominent mediastinal and hilar lymphadenopathy (Fig. 1).

He had a follow-up CT scan of the chest, performed on October 2014 which did not show any changes. PET scan was performed on October 2014 which revealed a 2.7 cm RUL nodule that corresponded to the mass seen on CT scan.

His review of systems was within normal limits. His father died at age 89 from an unknown type of metastatic cancer. His brain MRI was negative for metastatic disease. All these findings had been discussed with the patient and he was given the option to proceed with lung biopsy to establish a diagnosis with the small chance of a non-diagnostic biopsy versus proceeding with right upper lobectomy and lymphadenectomy. Given the size and location of the hilar lymph node, robotic surgery was not advised due to the risk of injury to the pulmonary artery. The patient elected to proceed with right thoracotomy with right upper lobectomy, intercostal muscle flap, and lymphadenectomy.

http://dx.doi.org/10.1016/j.ehpc.2016.05.002
2214-3300/© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Please cite this article as: S. AL Diffalha, et al., Rare case of combined small cell lung cancer with adenocarcinoma and squamous cell carcinoma, Human Path Case Reports (2015), http://dx.doi.org/10.1016/j.ehpc.2016.05.002

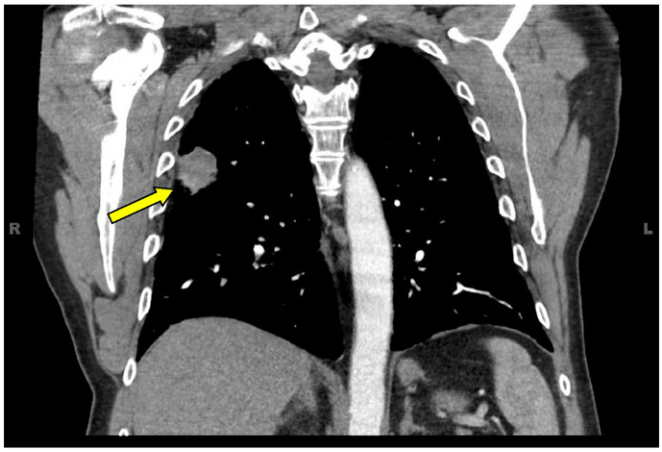

Fig. 1. Chest CT scan shows a 3.0 × 2.3 × 2.5 cm RUL lung mass.

The main surgical specimen consisted of upper lobe of right lung measuring 14.5 × 8.5 × 6 cm, weighing 245 g. The visceral pleura of the lobe was variegated, pink-tan to dusky red, and reveals an irregular, retracted area on the lateral posterior aspect of the lobe measuring 1.5 cm in greatest dimension (inked in black). The remaining visceral pleura was smooth and glistening. The posterior medial aspect of the lobe revealed an irregular, ill-defined, rubbery intraparenchymal tumor which measured 3.5 × 3.5 × 2.8 cm. The tumor did not appear to extend through the overlying visceral pleura. Neither bronchi nor blood vessels were grossly involved by the tumor. The cut surface of the tumor was variegated, tan-gray to pink, focally hemorrhagic and areas of necrosis occupied less than 20% of the tumor. The remainder of the pulmonary parenchyma was dark red, congested, and no satellite nodules were grossly appreciated.

The representative sections of the tumor showed approximately 90% adenosquamous carcinoma and 10% small cell carcinoma confined to the subpleural area. The lymph nodes show extensive involvement by small cell carcinoma, with a focus of adenocarcinoma involving level 11 lymph nodes.

A large panel of immunohistochemical stains was performed. The squamous cell carcinoma component was positive for AE1/AE3/CAM 5.2, CK7, CK5/6, and P40. The adenocarcinoma component was positive for AE1/AE3/CAM 5.2, CK7, TTF-1, Napsin A and focally positive for synaptophysin and chromogranin. The small cell component was positive for AE1/AE3/CAM 5.2, CK7, CD56 and weakly positive for synaptophysin. The tumor was negative for CK20 (Fig. 2). Manual morphometric analysis showed 99% of small cell carcinoma cells to be positive for Ki-67. Next Generation Sequencing (NGS) was performed; however, it did not identify any clinically relevant results.

3. Discussion

The case that we are presenting here has two challenges; first is the difficulty in establishing a preoperative diagnosis of these three components if the patient underwent FNA or core biopsy. We may encounter a diagnostic dilemma during evaluating cytology specimens which could be prepared from this tumor site. In our case there was no cytology or core biopsy performed before the surgery, but that will be an important diagnostic challenge and pitfall. The needle may be sampling only one component (SCC, AC or SCLC) or two components or all three of them together. Most often we classify the lung primary carcinoma as SCLC and NSCLC (SCC or AC). However we might not think that there are two or three components present, since it is rare. As we know that based on that diagnosis, the next step in managing the patient may be different. If the cytology is reporting only SCC or AC components, then the patient will undergo surgery with or without chemo and radiation therapy or neoadjuvant chemotherapy based on the updated American College of Clinical Pharmacology (ACCP) guidelines for treatment of clinical stages I and II NSCLC or no surgery for clinical stage III or IV. On the other hand, surgery will not be an option anymore if the diagnosis is SCLC on the cytology or the core biopsy. Unfortunately, literature has shown that cSCLC may often be resistant to chemotherapy because of the NSCLC component [4,10].

Although, our case did not show any molecular signature by next generation sequencing, it is considered a good practice to reach the exact classification of lung cancer in view of the fact that different types of lung malignancies have different biological and clinical properties and response to treatment [11,12]. It is recommended to perform genetic testing (*EGFR* and *ALK*) on all NSCLC for the purpose of selecting the targeted therapy according to the Association of Molecular pathology (AMP), College of American College (CAP) and the International Association for the Study of Lung Cancer (IASLC). As it is known that EGFR and ALK are by far have the most published and data based evidence in determining the treatment. For example if the patient with NSCLC has an *EGFR* mutation generally responds to erlotinib, however, crizotinib can be used if ALK mutation is present. It is important to mention that while *EGFR* mutations are very rare in SCLC, they are quiet common (about 15–20%) in cSCLC, usually in nonsmoking females who have AC component. KRAS also has important therapeutic input in which is excluding therapy.

It has been reported that cSCLC shows reactivity to estrogen receptor and/or progesterone receptor using immunohistochemical stains in a about 50–67% of cases, despite that there is no available data yet if that plays any rule in the prognosis and patient treatment [13]. In general, patients with cSCLC have poor prognosis similar to patients with SCLC [14].

We know that there are available guidelines for treating SCLC as a single tumor [15], but in our case we are facing unusual SCLC with additional AC and SCC components. The optimal treatment for cSCLC which will improve prognosis has not been adequately determined.

A few studies in the literature suggest surgical resection for the very early stage cSCLC which might improve the patient's outcome [16]. Another approach is to start chemotherapy (CT) and/or radiation therapy (RT), followed by surgical intervention for the residual NSCLC components [17]. The long term prognosis of cSCLC patients is determined by the SCLC component; it may be even show worse prognosis than that of pure SCLC because it is more resistant to therapy [2,18].

Our patient was referred to the thoracic clinic for further treatment recommendations. Since no molecular abnormalities were identified by next generation sequencing, he received 3 cycles of cisplatin/etoposide every 3 weeks, with thoracic radiation over 35 fractions, completed in April 2015. His treatment course was complicated by admission for neutropenic fever with sepsis, after which he was discharged home in a stable condition. His last visit was in December 2015, when he complained of productive cough associated with low-grade fevers, dyspnea and dysphagia. His prior chest CT-scans, as well as his most recent one showed changes consistent with prior radiation effects on the right side and focal consolidation which given his dysphasia history was concerning for aspiration. In addition, there were changes suggestive of pulmonary fibrosis seen on his scan from May 2015. These changes had progressed on his most recent scan but there was no discrete evidence of disease recurrence or progression on all his CT scans.

4. Conclusion

Combined tumors in any organ site raise interesting biologic questions about the pathogenesis and relationship of the individual components. Moreover, an accurate understanding of cSCLCs is of great practical importance because treatment strategies are significantly different for NSCLC and SCLC.

Please cite this article as: S. AL Diffalha, et al., Rare case of combined small cell lung cancer with adenocarcinoma and squamous cell carcinoma, Human Path Case Reports (2015), http://dx.doi.org/10.1016/j.ehpc.2016.05.002

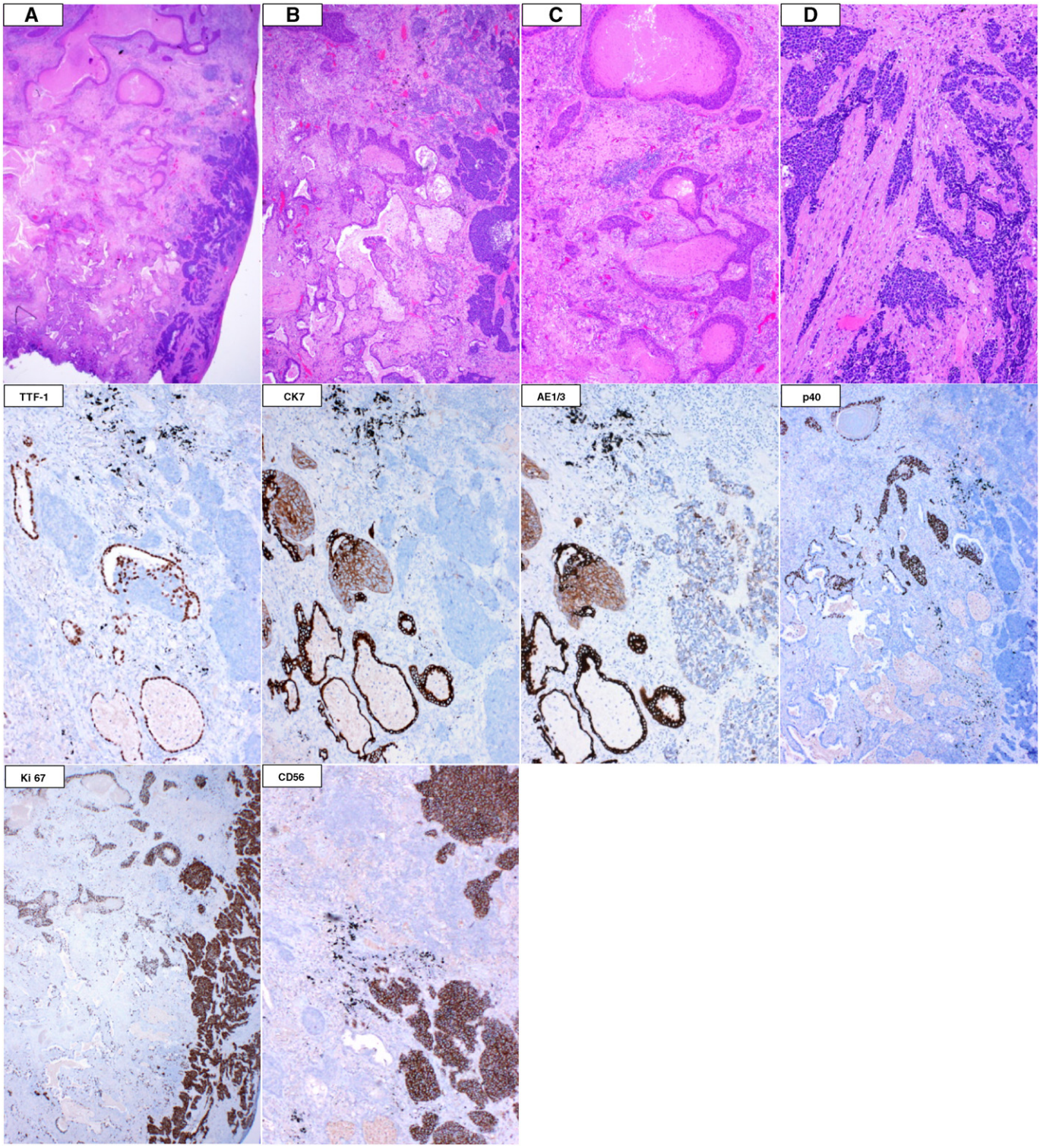

Fig. 2. The H&E sections of the tumor shows approximately 90% adenosquamous carcinoma and 10% small cell carcinoma, confined to the subpleural area (A–D). The squamous component is positive for AE1/AE3/CAM 5.2, CK7, CK5/6, and P40. The adenocarcinoma component is positive for AE1/AE3/CAM 5.2, CK7, TTF-1, and Napsin A and focally positive for synaptophysin and chromogranin. The small cell component is positive for AE1/AE3/CAM 5.2 and CD56. The tumor is negative for CK20. Manual morphometric analysis shows 99% small cell carcinoma cells positive for Ki-67.

References

[1] M.D. Mangum, F.A. Greco, J.D. Hainsworth, K.R. Hande, D.H. Johnson, Combined small-cell and non-small-cell lung cancer, J. Clin. Oncol. 7 (5) (May 1989) 607–612.

[2] M. Sehested, F.R. Hirsch, K. Osterlind, J.E. Olsen, Morphologic variations of small cell lung cancer. A histopathologic study of pretreatment and posttreatment specimens in 104 patients, Cancer 57 (4) (Feb. 1986) 804–807.

[3] M. Gotoh, Y. Yamamoto, C.L. Huang, H. Yokomise, A combined small cell carcinoma of the lung containing three components: small cell, spindle cell and squamous cell carcinoma, Eur. J. Cardiothorac. Surg. 26 (5) (Nov. 2004) 1047–1049.

[4] P.L. Wagner, N. Kitabayashi, Y.T. Chen, A. Saqi, Combined small cell lung carcinomas: genotypic and immunophenotypic analysis of the separate morphologic components, Am. J. Clin. Pathol. 131 (3) (Mar. 2009) 376–382.

Please cite this article as: S. AL Diffalha, et al., Rare case of combined small cell lung cancer with adenocarcinoma and squamous cell carcinoma, Human Path Case Reports (2015), http://dx.doi.org/10.1016/j.ehpc.2016.05.002

ARTICLE IN PRESS

[5] D.J. Adelstein, J.F. Tomashefski, N.J. Snow, T.P. Horrigan, J.D. Hines, Mixed small cell and non-small cell lung cancer, Chest 89 (5) (May 1986) 699–704.
[6] W.D. Travis, L.B. Travis, S.S. Devesa, Lung cancer, Cancer 75 (1 Suppl.) (Jan. 1995) 191–202.
[7] W.D. Travis, E. Brambilla, H. Muller, H. Kea, Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart, IARC Press, Lyon, 2004 (ed, http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb10/. ISBN 9283224183: World Health Organization Classification of Tumours.; 2010).
[8] T. Murase, H. Takino, S. Shimizu, et al., Clonality analysis of different histological components in combined small cell and non-small cell carcinoma of the lung, Hum. Pathol. 34 (11) (Nov. 2003) 1178–1184.
[9] S. Dacic, S.D. Finkelstein, E. Sasatomi, P.A. Swalsky, S.A. Yousem, Molecular pathogenesis of pulmonary carcinosarcoma as determined by microdissection-based allelotyping, Am. J. Surg. Pathol. 26 (4) (Apr. 2002) 510–516.
[10] B.S. Kasimis, R.B. Wuerker, J.D. Hunt, C.A. Kaneshiro, J.L. Williams, Relationship between changes in the histologic subtype of small cell carcinoma of the lung and the response to chemotherapy, Am. J. Clin. Oncol. 9 (4) (Aug. 1986) 318–324.
[11] M.D. Vincent, Optimizing the management of advanced non-small-cell lung cancer: a personal view, Curr. Oncol. 16 (4) (Aug. 2009) 9–21.
[12] G. Rossi, A. Marchioni, G. Sartori1, L. Longo, S. Piccinini, A. Cavazza, Histotype in nonsmall cell lung cancer therapy and staging: the emerging role of an old and underrated factor, Curr. Respir. Med. Rev. 3 (2007) 69–77.
[13] G. Sica, P.L. Wagner, N. Altorki, et al., Immunohistochemical expression of estrogen and progesterone receptors in primary pulmonary neuroendocrine tumors, Arch. Pathol. Lab. Med. 132 (12) (Dec. 2008) 1889–1895.
[14] S.A. Nicholson, M.B. Beasley, E. Brambilla, et al., Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens, Am. J. Surg. Pathol. 26 (9) (Sep. 2002) 1184–1197.
[15] E. Ruffini, O. Rena, A. Oliaro, et al., Lung tumors with mixed histologic pattern. Clinico-pathologic characteristics and prognostic significance, Eur. J. Cardiothorac. Surg. 22 (5) (Nov. 2002) 701–707.
[16] R. Hage, J.R. Elbers, A. Brutel de la Rivière, J.M. van den Bosch, Surgery for combined type small cell lung carcinoma, Thorax 53 (6) (Jun. 1998) 450–453.
[17] F.A. Shepherd, R. Ginsberg, G.A. Patterson, et al., Is there ever a role for salvage operations in limited small-cell lung cancer? J. Thorac. Cardiovasc. Surg. 101 (2) (Feb. 1991) 196–200.
[18] F.R. Hirsch, K. Osterlind, H.H. Hansen, The prognostic significance of histopathologic subtyping of small cell carcinoma of the lung according to the classification of the World Health Organization. A study of 375 consecutive patients, Cancer 52 (11) (Dec. 1983) 2144–2150.

Please cite this article as: S. AL Diffalha, et al., Rare case of combined small cell lung cancer with adenocarcinoma and squamous cell carcinoma, Human Path Case Reports (2015), http://dx.doi.org/10.1016/j.ehpc.2016.05.002