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Synchronous double primary lung cancer, small cell with non small cell histology: a therapeutic nightmare

KEYWORDS: Small cell, squamous cell, Synchronous, chemotherapy

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ABSTRACT *Lung cancer is the leading cause of death worldwide. Broadly it is classified into small cell and non small cell carcinoma. Non small cell carcinoma lung includes squamous, adeno and large cell variety. Smoking is a common risk factor for both small cell and non small cell histology. Bilateral involvement is common in lung cancer but synchronous involvement of both lungs, one with small cell and the other with non small cell type is extremely rare. Here we report such a case with small cell carcinoma in left lung and squamous cell carcinoma in right lung of a male smoker and the challenges we encountered during his treatment with systemic chemotherapy.*

INTRODUCTION

Lung cancer is one of the most dreaded cancers with very high mortality worldwide. It is strongly associated with smoking. More than 90% of lung cancers belong to two main groups, small cell carcinoma and non small cell carcinoma. The non small cell group comprises squamous cell carcinoma, adenocarcinoma and large cell carcinoma. The treatments of the two groups are different. In non small cell carcinoma, Surgery plays a major role along with chemotherapy and radiation. On the other hand, in small cell carcinoma, definitive surgery has no role. Simultaneous presence of both the histologies in the same patient is a therapeutic nightmare. These are of extremely rare occurrences, so no formal guidelines are available for management of such patients.

CASE REPORT

A 60 year old male smoker presented to our out patient's department (OPD) with complaints of hiccough, shortness of breath, cough and right sided chest pain for 3 months. On examination, tachypnoea, anemia, clubbing was seen, but there was no enlarged palpable lymph nodes. Chest auscultation revealed no abnormal sounds. Chest X-ray (CXR) showed a homogenous round opacity in left mid zone and an elongated opacity in right lower zone along the cardiac silhouette. Contrast enhanced computed tomography (CECT) scan (figure 1) revealed a large irregular heterogeneously enhancing soft tissue lesion (70mm X 62mm X 62mm)at left mid zone extending up to the left hilum and left lateral chest wall pleural surface and another heterogeneous soft tissue lesion (70mm X 61mm X 50mm) at right lower zone at Para-vertebral location with mediastinal lymphadenopathy and mild right sided pleural effusion. No space occupying lesions (SOL) could be seen in liver or adrenal gland. Fine needle aspiration cytology (FNAC) from the left lung SOL(figure 2) showed isolated or clusters of small to medium sized , pleomorphic malignant cells having irregular nuclear membrane, hyper-chromatic nuclei, nuclear molding and scanty rim of cytoplasm; a picture suggestive of small cell carcinoma of lung(SCLC). But FNAC from the right lung SOL (figure 3) showed clusters and discretely present pleomorphic malignant cells having large hyper-chromatic nuclei and variable amount of cytoplasm suggestive of poorly differentiated squamous cell carcinoma. The pleural fluid was negative for malignant cells. Other metastatic work ups including cranial magnetic resonance imaging (MRI) and bone marrow biopsy were negative. As this patient had an 'extensive stage' disease according to the Veterans' Administration Lung Study Group(VALSG) staging criteria for small cell carcinoma[1] we started chemotherapy with Cisplatin 100mg/m^2 intravenous(i.v) D_1 (with proper hydration and diuresis) and Etoposide 100mg/m^2 i.v D_1-D_3[2].

A repeat CECT scan of thorax (figure 4) after 3 cycles of chemotherapy revealed that the left lung SOL has retained its size (72mm X 59mm X 41mm) and the right lung SOL has just slightly decreased in size (56mm X 42mm X 32mm). There was persistent mediastinal lymphadenopathy but the pleural effusion had disappeared. We started second line chemotherapy regimen with Paclitaxel 200mg/m^2 i.v D_1 , Carboplatin (Area Under Curve {AUC} 6) and Tablet Etoposide 50mg per oral(PO) D_1, D_3, D_5, D_7, D_9 & Etoposide 100mg PO D_2, D_4, D_6, D_8, D_{10} [3]. The patient received 2 cycles of second line chemotherapy before he succumbed to his disease

DISCUSSIONS

According to the World Health Organization International Agency for Research on cancer, about 1.8 million new cases of lung cancer were reported in 2012[4]. Lung cancer has a high mortality rate mostly because by the time it is diagnosed, it usually has passed on to an advanced stage and the treatment options are limited [5]. The best strategy to control lung cancer is its prevention. There are a multiple etiological factors associated with lung cancer but the most important one is undoubtedly smoking [6]. More than 50 carcinogens have been identified in tobacco smoke including nitrosamines and polycyclic aromatic hydrocarbons [7]. With constant effort via social and political forums, some success has been achieved regarding tobacco control. And as a result the incidence rate of lung cancer in males appears to be falling or at least stabilizing in developed countries [8].

Lung carcinomas are classified into four major histological categories; small cell, squamous cell, adeno and large cell [9]. The later three are grouped under non small cell carcinoma. Rarely two lung malignancies of different histology may be diagnosed in the same patient. This is called

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double primary lung cancer (DPLC). The diagnosis of DPLC was primarily based on the guidelines by the American College of Chest Physicians on lung cancer published in 2003, which suggested such a diagnosis when lesions of different histological types or molecular genetic characteristics are found at the same time but originating from different carcinoma in situ or lesions of the same histological type observed in different lobes, and neither N2-3 lymph node metastasis nor systemic metastasis detected [10]. According to the chronological order of occurrence, DPLC can be classified as synchronous or metachronous[10]. Synchronous primary lung cancer (SPLC) occurs in up to 0.5% of patients with lung cancer [11]. Among SPLC cases, coexistence of small cell carcinoma (SCLC) and non-small cell carcinoma has been reported in a very small fraction [11]. SPLC is often misdiagnosed as metastasis owing to the lack of knowledge and shortcomings of the diagnostic methods [10]. Even in this case we first mistook the right lung lesion to be metastatic. But FNAC from the lesion showed it to be a second primary lung malignancy of a different histology. The lesion in left lung was small cell variety. And that in the right lung was squamous cell variety. While designing the treatment in this patient we had to keep in mind that we are dealing with two different malignancies in the same patient. We had to come up with a single solution for two different problems.

The VALSG staging criteria[1] divides SCLC into a limited stage and an extensive stage. In the later, the lesion cannot be treated by a single radiation field with acceptable toxicity. Our case was clearly an extensive stage disease. So we started chemotherapy. The current standard chemotherapy for extensive small-cell lung cancer is a regimen of etoposide and cisplatin or this combination alternating with a combination of cyclophosphamide, doxorubicin, and vincristine. Both these regimens yield a median survival of 8 to 10 months and a 2-year survival rate of 10% [12]. Platinum based doublet including the Cisplatin plus Etoposide combination was considered standard chemotherapy in non small cell histology as well [13]. As surgery is not an option in SCLC [14], we did not seek surgical consultation. After three cycles of chemotherapy we evaluated the patient and found stable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST)[15]. Both SCLC and squamous cell carcinoma are chemo-sensitive[14]. It was quite a surprise that none of the lung lesion were affected by chemotherapy. We started second line treatment with Paclitaxel, Carboplatin and Etoposide [3]. We could only administer two cycles of this regimen as the patient expired after that.

The patient did not have any metastasis; both the lung lesions were primary. But still we could not offer any definitive therapy in the form of surgery or radiotherapy. If only small cell lesion was there we could have offered concurrent chemo-radiation with curative intent. If only squamous cell lesion existed we would have managed it with definitive surgery. But coexistence of both of these histology meant none of the curative options were feasible. We had to resort to chemotherapy which would affect both histologies. Hence we could offer only palliative therapy in a non metastatic case. Also there is no established chemotherapy regimen for such a situation. More data are needed to be collected from various reports in order to ascertain a specific management approach.

Legends of figure 1-- CECT scan of thorax reveals a large irregular heterogeneously enhancing soft tissue lesion (70mm X 62mm X 62mm)at left mid-zone extending up to the left hilum and left lateral chest wall pleural surface and another heterogeneous soft tissue lesion (70mm X 61mm X 50mm)at right lower zone at para-vertebral location with mediastinal lymphadenopathy and mild right sided pleural effusion.

Legends of figure 2-- FNAC from the left lung SOL showing isolated or clusters of small to medium sized, pleomorphic malignant cells having irregular nuclear membrane, hyper-chromatic nuclei, nuclear molding and scanty rim of cytoplasm; a picture suggestive of small cell carcinoma.

Legends of figure 3-- FNAC from the right lung SOL showing clusters and discretely present pleomorphic malignant cells having large hyper-chromatic nuclei and variable amount of cytoplasm suggestive of poorly differentiated squamous cell carcinoma

Legends of figure 4-- CECT scan of thorax after three cycles of chemotherapy reveals that the left lung SOL has retained its size (72mm X 59mm X 41mm) and the right lung SOL has just slightly decreased in size(56mm X 42mm X 32mm). There is persistent mediastinal lymphadenopathy but the pleural effusion has disappeared

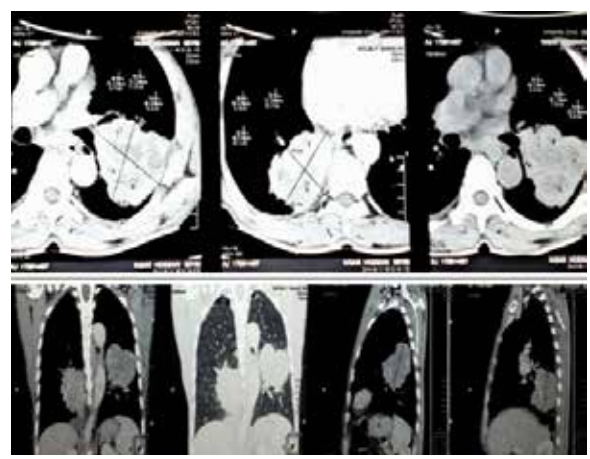

Figure 1

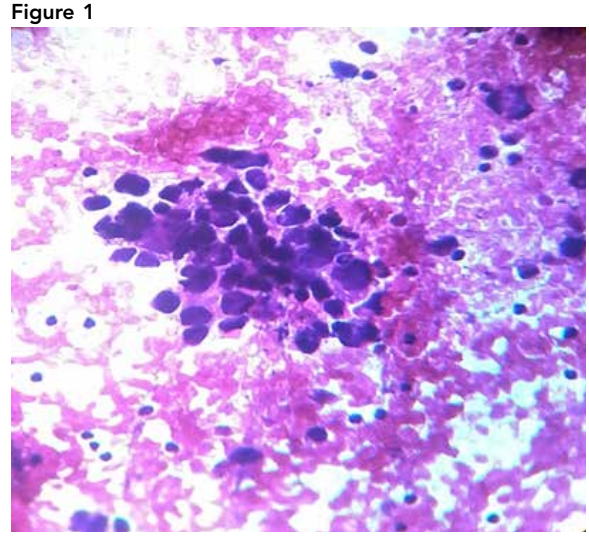

Figure 2

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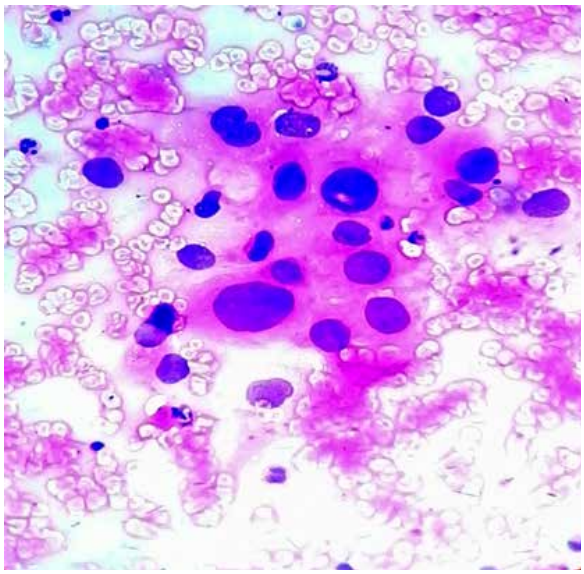

Figure 3

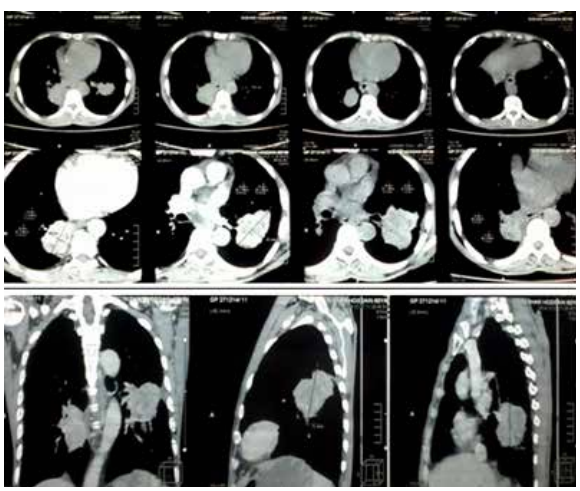

Figure 4

REFERENCE

1. Micke P1, Faldum A, Metz T, Beeh KM, Bittinger F, Hengstler JG, Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? Lung Cancer. 2002 Sep;37(3):271-6 | 2. Ihde, D. C., Mulshine, J. L., Kramer, B. S., Steinberg, S. M., Linnoila, R. I., Gazdar, A. F., ... & Phares, J. C. (1994). Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. Journal of clinical oncology, 12(10), 2022-2034. | 3. Hainsworth, J. D., Gray, J. R., Stroup, S. L., Kalman, L. A., Patten, J. E., Hopkins, L. G., ... & Greco, F. A. (1997). Paclitaxel, carboplatin, and extended-schedule etoposide in the treatment of small-cell lung cancer: comparison of sequential phase II trials using different dose-intensities. Journal of clinical oncology, 15(12), 3464-3470. | 4. Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., ... & Bray, F. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer,136(5), E359-E386. | 5. Youlden, D. R., Cramb, S. M., & Baade, P. D. (2008). The international epidemiology of lung cancer: geographical distribution and secular trends.Journal of Thoracic Oncology, 3(8), 819-831. | 6. Watson, W. L., & Conte, A. J. (1954). Smoking and lung cancer. Cancer, 7(2), 245-249. | 7. Hecht, S. S. (1999). Tobacco smoke carcinogens and lung cancer. Journal of the national cancer institute, 91(14), 1194-1210. | 8. Horm, J., & Kessler, L. (1986). Falling rates of lung cancer in men in the United States. The Lancet, 327(8478), 425-426. | 9. Travis, W. D. (2011, July). Classification of lung cancer. In Seminars in roentgenology (Vol. 46, No. 3, pp. 178-186). WB Saunders. | 10. Liu, X.-D., Qu, Y., & Lu, S.-S. (2014). Synchronous double primary lung cancer: a report of three cases. Chinese Journal of Cancer Research, 26(1), E17–E21. doi:10.3978/j.issn.1000-9604.2014.01.03 | 11. Hiraki, A., Ueoka, H., Yoshino, T., Chikamori, K., Onishi, K., Kiura, K., ... & Harada, M. (1999). Synchronous primary lung cancer presenting with small cell carcinoma and non-small cell carcinoma: diagnosis and treatment. Oncology reports, 6(1), 75-155. | 12. Noda, K., Nishiwaki, Y., Kawahara, M., Negoro, S., Sugiura, T., Yokoyama, A., ... & Saijo, N. (2002). Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. New England Journal of Medicine, 346(2), 85-91. | 13. Belani, C. P., Lee, J. S., Socinski, M. A., Robert, F., Waterhouse, D., Rowland, K., ... & Natale, R. B. (2005). Randomized phase III trial comparing cisplatin–etoposide to carboplatin–paclitaxel in advanced or metastatic non-small cell lung cancer. Annals of oncology, 16(7), 1069-1075. | 14. Koul, P. A. (2012). Surgery in limited-disease small-cell lung cancer. Lung India : Official Organ of Indian Chest Society, 29(1), 2–3. doi:10.4103/0970-2113.92345 | 15. Eisenhauer, E., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., ... & Verweij, J. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer, 45(2), 228-247. |