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Case Report

A case report of Primary lung cancer and synchoronous breast cancer

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INTRODUCTION:

Cancer cells are a group of abnormal cells with uncontrolled growth (Yang, M. *et al.*, 2011). These particular cells do not perform the functions of a normal cell. Such as in case of primary cancer the abnormal set of cells do not form normal lung tissue. Continuous growth results in the benign or malignant tumour that interfere with the functioning of the different parts of body. All the cells contain the genetic material called deoxyribonucleic acid (DNA) (Zee, Y. K., & Soo, R. A. 2010). Replication of the cells duplicates the identical DNA. When an error occurs in the replication of DNA that results in a mutant form of cell. This could be result of ageing process or environmental factors, such as cigarette smoke, breathing in asbestos fibres, and to exposure to radon gas (King, H. W. *et al.*, 2012; & Chamberlain, M. C. *et al.*, 2017). Studies have demonstrated that it takes a series of mutation for primary lung cancer to occur (Zee, Y. K., & Soo, R. A. 2010; Ohno, S. I. *et al.*, 2013; & Mirrielees, J. A. *et al.*, 2014). Initially, there is a precancerous condition before sufficient mutations have occurred for the cancerous cells to develop (Pasikhova, Y. *et al.*, 2017). Every time the mutated cells replicate they add to the cancerous tissue. In later part of the disease, the cancerous cells develop the ability to travel away for the primary locations to other locations (Chaffer, C. L., & Weinberg, R. A. 2011). This type of process is known as metastasis.

Synchronous breast cancers are primary breast tumours which develop in either breast at the same time or simultaneously with other primary cancer whereas identifying another tumour after 6 months is termed as a metachronous tumour (Su, Z. *et al.*, 2015). The synchronous tumour is identified within 3 -6 months after first primary tumour is observed. studies have shown synchronous breast cancer accounts for 0.2-3% incidence of all newly diagnosed breast cancers (Scully, O. J. *et al.*, 2012). A similar study showed that 2.4% of the patient enrolled presented with Synchorornous breast cancer (Chaffer, C. L. *et al.*, 2011; & Jensen, J. D. e al 2012). It was observed that 36% of the second tumour is diagnosed by mammography (Schmid, S. M. *et al.*, 2011). The physicians recommend using MRI in treatment planning with a conservative approach to preserving the breast. This is most common way to rule out the presence of multifocality or multi-centricity especially in cases of bilateral cancers (Mirrielees, J. A. *et al.*, 2014).

Literature identified that 66 years of median age was estimated for the SBC to occur (Díaz, R. *et al.*, 2012). 39% of the people are observed to have a family history regarding the SBC (Schmid, S. M. *et al.*, 2011). Moreover, the literature suggested some predictive

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factor causing the occurrence of the SBC that includes BC familial history, BRCA gene mutations, HER-2/Neu positivity, overweight, lobular histology and presence of another tumour(11, 14). These SBC histological types are more aggressive and poorly differentiated as compared to the MBC; hence, poor survival chances are predicted for such patients (Jensen, J. D. *et al.,* 2012). Nevertheless, in unilateral cases the chances for survival increases. As it is observed that positive oestrogen receptors play role as an active risk factor in causing multiple breast cancer therefore, it is recommended in several cases to perform adjuvant hormonal therapies for the prevention of the relapse or new tumour occurrence (Rossi, S. *et al.,* 2015). A similar case of primary lung cancer and synchronous breast cancer was identified in our practice that has been discussed in detail.

CASE REPORT

A 39 years old Somalian women presented with shortness of breath and persistent cough in the emergency department. There was no significant past history and there was no family history of breast cancer.. She underwent an plain x ray chest in the ER deptt , which showed right-sided pleural effusion with a suspected lung mass. The patient underwent a series of investigations including C.E.C.T which revealed right side lung mass with contralateral lung nodules and right pleural effusion, the contralateral lung nodules were suspicion of metastatic origin. For pathological confirmation of the diagnosis, a biopsy was performed under a CT scan guidance. The histopathological result of the lung biopsy revealed adenocarcinoma, it was of lung origin, which was supported by Immunohistochemical markers. IHC markers CK7 and TTF1, both these markers were positive Pleural fluid aspiration was sent for cytological evidence of malignant cells, which came positive . Further work up and imaging of the patient revealed that there were presence of metastatic lesions in the brain.

The pt was planned for Palliative chemotherapy based on platinum (cisplatin) and pemetrexed, she received 2 cycles of chemotherapy The patient improved clinically with 2 cycles of chemotherapy and showed improvement in chest pain , headache , respiratory symptoms (shortness of breath and cough) . Her appetite also improved. She was planned to continue one more cycle of chemotherapy followed by referral for palliative radiotherapy to the whole Brain ,But after 2nd cycle of chemotherapy, the patient noticed a small painless, firm nodule on left breast , She immediately reported to us .She was examined and was found to have hard fixed small breast nodule with small axillary mobile lymphadenopathy The nodule was biopsied that proved to be invasive ductal carcinoma , hormone receptors ER +ve PR + , HER2 negative , Ki67 60%-75% **.** It was clinically stage II breast cancer . So she had a 2nd malignancy diagnosed with 4 months.

DISCUSSION

Studies have presented that in 55% of the cases lung cancer occurs as a primary while in 37% metastatic breast cancer occurs (von Minckwitz, G. *et al.,* 2013; Boughey, J. C. *et al.,* 2013; & Rashid, O. M., & Takabe, K. 2012). The main concern, in this case, is whether the breast cancer was already present and was triggered or it was a metastatic lesion. The extent of spread of either cancer is very important in addition to the metastatic location. Therefore, it is mandatory to perform biopsies of the different metastases and immunohistochemistry staining. Currently, the specimens are frozen; this could hamper the results. The intraoperative frozen section often provides false-positive diagnosis. this causes misunderstanding between identification of benign for malignant; however, there are 1.1% to 4.0% of false-negative diagnoses (Mirrielees, J. A. *et al.,* 2014; & Azim Jr, H. A. *et al.,* 2011). therefore, multiple biopsies were performed at the surgical time in different location for confirmation. Moreover, currently, liquid biopsies and circulating free DNA are utilised often in gaining evidence with statistical sensitivity and sensibility in a non-invasive and affordable procedure, with a more accurate molecular characterisation (Scully, O. J. *et al.,* 2012). Treatment of such cases depends upon the primary location of the tumour, tumours aggressiveness and staging genetic profile, comorbidities, performance status and toxicities of previous treatments performed (Scully, O. J. *et al.,* 2012).

Literature has presented with a current criterion for the diagnosis of multiple primary malignancies.
This follows as (Azim Jr, H. A. *et al.,* 2011):

First: the identified lesion will be malignant
Second: the lesion will be characterised distinctively according to pathologies
Third: exclusion of the metastases from the prior malignancies

Synchronous carcinomas are characterised as that cancer which is diagnosed either simultaneously or within an interval of six months after the identification of first diagnosis of primary tumour (Azim Jr, H. A. *et al.,* 2011). Breast cancers are among the most common types of cancer occurring in women; however, lung cancer has also been an increasing burden over a similar population. The increased incidence of multiple malignancies in a patient was first observed in1870 by Billroth (Kheirelseid, E. A. *et al.,* 2011). These breast cancers are often termed as metastatic tumours account for 0.4% to 1.3% of malignant cancer (Jensen, J. D. *et al.,* 2012). In such patient, the painless tumour grows rapidly with a firm, well circumcised and palpable mass. Elderly women aged 40 -44 are advised by the WHO for regular screening through mammography. This can be associated with several factors such as due to long life expectancy, progressive advances in

diagnostic techniques, regular follow-up and genetic predisposition to cancer (Yang, M. *et al.,* 2011).

Many cases are treated by the help of endocrine therapy, chemotherapy and radiotherapy adjuvant to surgeries (Nichol, A. M. *et al.,* 2011). This avoids the relapse of the tumour. Similarly, the same approach was invested in this patient in order to avoid tumour relapse in any part of body and metachronous breast tumours that will be followed by regular follow-ups. studies have shown that during the radiotherapy of the breast cancer there was an increased risk for lung cancer to occur (Scully, O. J. *et al.,* 2012; & Nichol, A. M. *et al.,* 2011). Nevertheless, in our patient who did not report any prior history of breast cancer reported an unexpected mass after 2 cycles of chemotherapy defining similar ideology. Chemotherapy at a time is beneficial against the cancerous cells but on the other hand, weakens the immunity and affects sensitive tissues causing them to undergo mutation leading to multiple cancers. To identify the pattern of the SBC it is necessary to have the knowledge of the mammographic pattern of index tumour (as mass/calcification) (Rossi, S. *et al.,* 2015). Nevertheless, the studies presented with numerous false-positive rates and limited availability of MRI guided biopsy creates obstacles for early diagnosis of these synchoronous cancers (Schmid, S. M. *et al.,* 2011).

Mammography is used in such instances to identify breast cancer. Mammography most commonly displays a multiple well-defined rounded firm mass that are well-circumscribed lesions with smooth margins. The mammary gland origin breast cancer present with the expression of ER, GCDFP-15 and MG. ER and GCDFP-15 that is expressed in 80% and 45% to 53% of breast tumour, respectively (Su, Z. *et al.,* 2015). Many studies revealed that ER expression in lung adenocarcinoma is low (7.6% to 14.1%) while GCDFP-15 is expressed in 5.2% to 15% of primary lung cancer. Further analysis of the breast presented in the studies MG was expressed in 48% to 72.1% however stained negatively in lung adenocarcinoma (Scully, O. J. *et al.,* 2012; & Schmid, S. M. *et al.,* 2011). Further detailed histological pointed out that lepidic growth pattern present with growth of neoplastic cells within the alveolar sacs displaying better survival rate compared to the poor survival rate in solid pattern displaying polygonal tumour cells in sheets with lack of characterisations. Other presentation includes acinar with round to oval-shaped with a central luminal space with tumour cells covering, papillary shows glandular cells growing along with central fibrovascular cores, and micropapillary: tumour cells presenting with papillary tufts growth with no fibrovascular cores.

Certain studies have presented a notable difference between genders presenting with primary lung malignancies (Rossi, S. *et al.,* 2015). In the presences of the synchronous secondary malignancy of breast and lung, there is always a hidden risk for bone or adrenal metastasis. Literature states that the secondary form of breast cancer often presents as a painless, palpable lump with skin tethering(in some cases) (Jensen, J. D. *et al.,* 2012; & Kheirelseid, E. A. *et al.,* 2011). Cases such as current one present with poor prognosis. Studies have shown secondary form of breast cancer occurring as a result of primary lung cancer in 80% of people survive up to 1 year (Bear, H. D. *et al.,* 2012).

In the present case, the patient initially did not show any signs of breast metastasis; however, this became evident after the chemotherapy sessions (Bear, H. D. *et al.,* 2012). Studies have shown that chemotherapy plays a double edge sword role that is it a be beneficial and harmful at the same time (Bear, H. D. *et al.,* 2012). Sometimes it is noted that the chemotherapy fails to counteract the cancer cell thereby allowing them to adapt intrinsic or extrinsic change. Intrinsic change allows them to invade and migrate whereas extrinsic cause host to aid them in migrating to other sites. Studies shave presented that during the cancer treatment the chemo induces increase amount of TAMS in the primary tumour especially in breast cancer (von Minckwitz, G. *et al.,* 2013) These tumour associated macrophage (TAMS) act as a cancer progression tool(18). The body mechanism holds inhibitors against such factors that allow chemo efficiently to act. It is suggestive that primary tumour cells from the lung cancer metastasised to different area such as brain and breast (Bear, H. D. *et al.,* 2012). When the chemotherapy was employed in our case it acted as pro activator and cancelled out its own efficiency leading to breast cancer (Boughey, J. C. *et al.,* 2013).

Theory presented for such metastasis follows production of the soluble factors and exosomes from the primary tumour that changes the microenvironment (Teillant, A. *et al.,* 2015). This makes the environment more favourable for the approaching cancer cells in distant sites. After settling in the cancer cells takes the area more favourable for them to survive known as the metastatic niche (Teillant, A. *et al.,* 2015). Following same principles, some of the in vitro experiments presented that chemotherapy acts as the soluble factors that create pathway for the migration of the cancer cells in the distant sites (Teillant, A. *et al.,* 2015). A study conducted using paclitaxel showed breast cancer cells to metastasise in the mice having Af3 gene (Wu, C. P. *et al.,* 2011). This gene was observed as a key factor in promoting cancer progression. This gene is responsive towards stress signals leading to destructive act within cells such as DNA damage. Therefore, during the stress, it deregulates the immune system. some authors claim that during the transformation of the cancerous cells these Af3 factors are induced in mammary tissue (Wu, C. P. *et al.,* 2011). For the Atf3 to express, it imitates a reactive mass in a microenvironment and dysregulated immune function (Wu, C. P. *et al.,* 2011). Therefore,

this indicates the importance of promoting metastasis through Af3 activation.

Although majority of the studies pointed out that family history is an important factor contributing to the SBC. However, our case did not report any particular family history. Histology is an important factor in identifying the SBC. Lobular histology was assumed to be a risk factor observed in the found in one of 60 tumours (Dieci, M. V. *et al.*, 2014). A similar study in India investigated on similar 2 cases both demonstrated no lobular carcinoma (Dieci, M. V. *et al.*, 2014). Certain factors are important in histological diagnosis such as Differing tumour types, different degree of differentiation and presence of in-situ component. This suggests the second primary compared to intra-breast metastasis. one of the studies showed histological and grade concordance in 70 5 of the tumour (Schmid, S. M. *et al.*, 2011). In addition, the SBC present with more estrogen receptor. Reports have stated that diagnosing the synchronous as well as metachronous within five years of occurrence serves as a poor prognosis (Gruber, I. V. *et al.*, 2013). Another commonly identified gene involvement is Her2 overexpression. 71% Her2 overexpression of bilateral cancer was observed compared to 35% unilateral cases (Jensen, J. D. *et al.*, 2012). Therefore, indicates increase incidence of mortality in SBC cases. In such cases, the patient is provided with bilateral mastectomy treatment. Although the synchronous cancers are noted at an early stage compared to the index cancer they still possess risk of further spread.

It is recommended to conduct a clinical trial to identify the potential synchronous breast cancer with other primary malignancies in order to improve and devise better diagnostic tools and management strategies.

CONCLUSION:

Synchronous breast cancer in accordance with primary malignancies accounts for about 2% of primary diagnosed breast cancers. The Somalian women case illustrates the difficulties and challenges in the diagnosis and characterisation of primary tumour and metastatic lesions, in addition, the difficulty in identifying and managing synchronous secondary malignancies, where either one of them is metastatic and the other one is primary that was potentially curable.

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