Case Report

Adenocarcinoma Lung Diagnosed as a 'Synchronous Primary Double Malignancy' in Treated Case of Carcinoma of Breast: Case Report

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Abstract

Double primary malignancies are rarely observed in breast malignancy, and frequently documented in hematological and gynecological malignancies due to genetic mutations. In present case report, 48-year female presented with left breast carcinoma undergone surgical treatment and received first chemotherapy cycle. Her general health deteriorated and present in our center due to worsened dyspnea. Her radiological workup shown possible metastatic lung process from on treatment carcinoma left breast as classically described 'bilateral cannon ball' opacities with middle lobe lung mass. Bronchoscopy was done in critical care unit with oxygen supplementation in sick health after clinical stability. Bronchoscopy workup documented Lung adenocarcinoma. Immunohistochemistry confirmed as Primary lung adenocarcinoma with EGFR positivity. Palliative care was offered due to poor performance status and EGFR targeted therapy was initiated. In this case report we have documented concurrent occurrence of carcinoma breast and adenocarcinoma lung as double primary malignancy.

Keywords: *Double primary malignancy, Carcinoma breast, Adenocarcinoma lung, Bronchoscopy, Targeted therapy*

Introduction

Double primary malignancies are occurrence malignant process in two different anatomically defined organ sites with different histology concurrently or sequentially. Double primary malignancies have been described since last century and more frequently documented in visceral, gynecological and endocrine malignancies. Rationale for more reporting of double primary malignancies would be increased survival of general population, increased awareness regarding cancer detection and advancement in cancer screening and diagnosis.[1] Depending on the time between tumor diagnoses, there are two categories of double primary malignancies.[2] Synchronous malignancies are those in which a secondary tumor develops at the same time as the primary tumor or within six months of it, whereas metachronous malignancies are those in which the secondary tumor develops more than six months after the primary tumor.[2]

Case summary

48-year-old female, farmer by occupation, no addiction history, normotensive, non-diabetic, referred to our center by family physician for-shortness of breath in recently diagnosed carcinoma of breast.

Clinical details documented as-

1. Cough-for 2 months dry, intermittent, with minimal white sputum production.
2. Shortness of breath on exertion in the last 2 months, initially grade 1 and progressed to grade IV and associated with drastically change in quality of life leading to inability to perform routine activities due to shortness of breath.
3. Loss of appetite and weight loss over period of 4months
4. Weakness and myalgia with fatigability for 4 months

Clinical Examination Documented as-
Restless, dry oral mucosa, cyanosis
Heart rate-130/min Respiratory rate: 46/bpm, BP-160/90 mmhg
PsO2: 71@ room air resting & 89-91% @ 14 litres/minute oxygen with reservoir bag
Respiratory system examination revealed-bilateral breath sounds normal, bilateral crepitation's heard on both lung fields
Nervous system examination- higher functions normal, no neurological abnormality

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Cardiovascular and gastrointestinal systems were normal

Her husband disclosed that she was diagnosed as case of infiltrating ductal carcinoma of left breast 6 months back. She undergone mastectomy left side with one follow up chemotherapy cycle. After first chemotherapy cycle, she developed loss of appetite, weakness and myalgia and they decided for prolongation of chemotherapy cycle to avoid further worsening of general health condition. Subsequently, she developed dry cough and breathlessness which was progressive and worsened over 2 months of initial symptoms to bedridden stage. She has consulted to local family physician and took chest x-rays. We have reassessed chest imaging and observed normal chest x-ray taken at one month **(Figure 1)** and two month **(Figure 2)** interval, and mammography reports showing micro lobulated irregular mass lesion in inner quadrant with left breast with rest of the parenchyma showing micro calcifications **(Figure 3)**. She was referred by family physician to our centre for worsening of dyspnoea. Her chest x-ray done by family physician shown right middle zone lobulated mass and left paracradiac nodular opacity **(Figure 4)**. As patients' general health is deteriorating and underestimation of bilateral lung pathology in previous hospital visits by general physicians, we have repeated chest X-ray and documented more advanced and predominant parenchymal abnormalities in bilateral middle and lower lung in bilateral lung in all zones **(Figure 5)**.

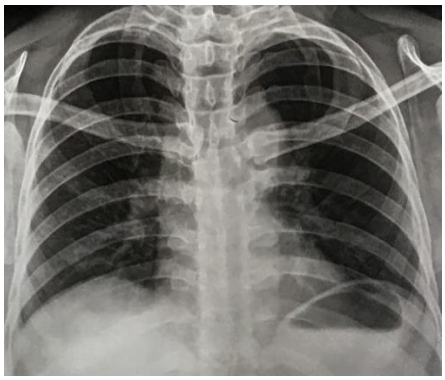


Figure 1. chest x-ray posteroanterior view showing normal lung parenchyma

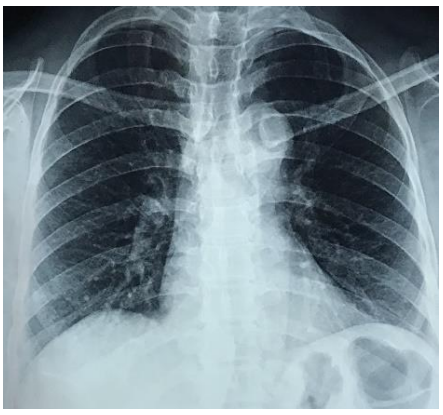


Figure 2. chest x-ray posteroanterior view showing normal lung parenchyma

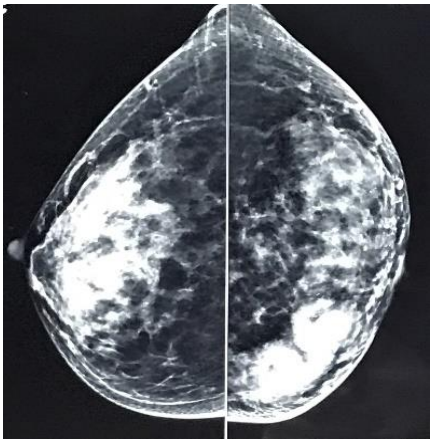


Figure 3. Mammography- microlobulated irregular mass lesion in inner quadrant with left breast with rest of the parenchyma showing microcalcifications (BIRADS-V)

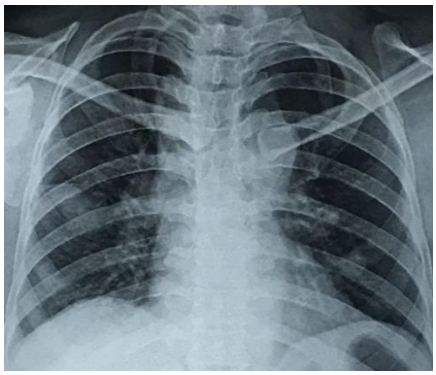


Figure 4. chest x-ray posteroanterior view showing right middle zone lobulated mass and left paracradiac nodular opacity

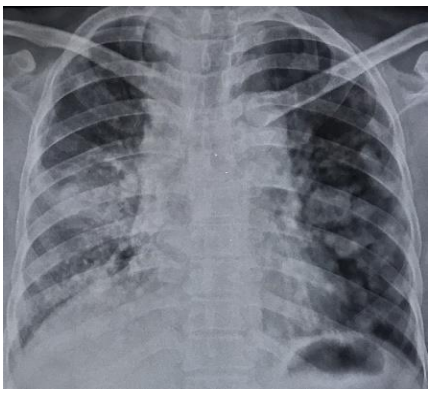


Figure 5. chest x-ray posteroanterior view showing predominant parenchymal abnormalities in bilateral middle and lower lung

Laboratory Examination Documented as-
Hemoglobin-10.3 gm% total white blood cells- 3000/mm^3 Polymorphs-70%, Platelet count-190000/uL
CRP- 45 mg/L (0-6 mg/L), random blood sugar level-144 mg% HbA1C-5.70 %
LDH-1080 IU/L (70-470 IU/L), Uric acid-3.4 mg (3.5-7.5 mg/dL)
Serum electrolytes: Sodium-131 meq/L (135-145 meq/L) Potassium-3.8 meq/L (3.5-5.5 meq/L) Ionic calcium-1.32 meq/L (1.09-1.36 meq/L)

D-dimer- 568 ng/ml (<500 ng/ml)
IL-6-4.75 pg/ml (0.00-7.00 pg/ml)
Thyroid functions-normal
Liver and kidney functions- normal
Induced Sputum examination for acid fast bacilli was negative and TB Gene Xpert MTB/RIF were negative for MTB genome.

As patient's tropical workup is negative and showing leucopoenia with raised CRP titre, we have started her on oxygen supplementation with target oxygen saturation above 90 % and intravenous methylprednisolone, Injection meropenem and moxifloxacin and supportive care with intravenous saline. Her general health improved on day 3 of hospitalization and we have done HRCT thorax to rule out opportunistic infection or pneumonia after chemotherapy.

HRCT Thorax suggestive of

1. bilateral, peripheral and central multifocal nodular masses and cannon ball opacities
2. central right lung mass with narrowing of right main stem bronchus
3. right middle lobe mass with narrowing of intermediate bronchus
4. right lower lobe parenchymal mass with collapse of bronchial luminal opening
5. left hilar mass

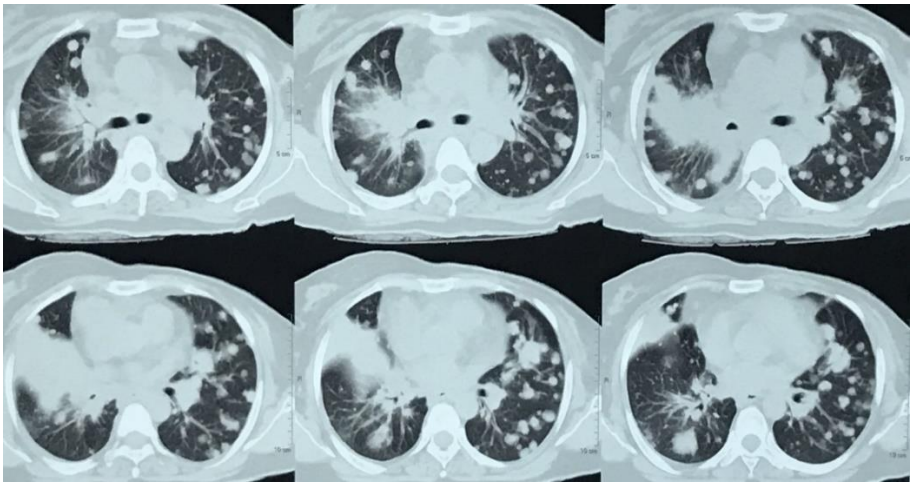
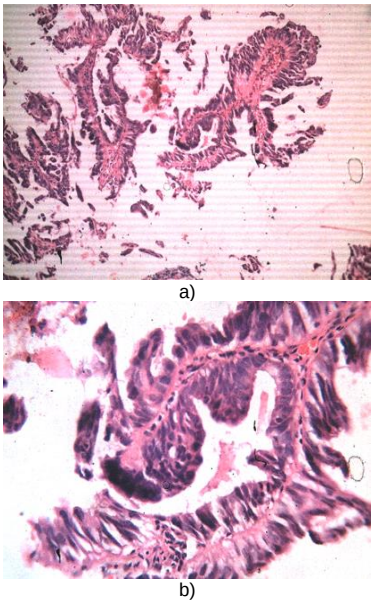


Figure 6. HRCT thorax showing bilateral cannon ball opacities with central parenchymal opacities suggestive of metastatic lung disease

As HRCT thorax was showing possible malignant lesions in lung, we have performed portable bronchoscopy in intensive care unit with oxygen supplementation and documented growth in intermediate bronchus. Bronchoscope could not negotiate distal to mucosal narrowing and fragile nature of growth. We have taken four bronchial biopsy specimens and sent for histopathology. Local minor bleeding documented after biopsy and vital parameters were normal after bronchoscopy.

We have sent 40 ml of bronchial aspirate collected after instillation of 60 ml saline during procedure and biopsy specimens to onomatologist.

BAL AFB-Negative, Gene Xpert MTB/RIF- Negative
BAL Bacterial culture- no growth,
Bronchial aspirate was showing malignant cells positive with possible adenocarcinoma type. Histopathology of bronchial biopsy were showing papillary adenocarcinoma **(Figure 7)**.



a)

b)

Figure 7. Histology revealed papillary adenocarcinoma

Initially we thought as this may be metastatic malignant lung process secondary to breast carcinoma and our suspiciousness for double malignancy increase after histopathology

documented Adenocarcinoma lung. We have sent for biopsy block for immunohistochemistry analysis to screen primary lung versus metastatic lung disease.

Immunohistochemistry analysis documented

TTF-1= Positive (clone 8G7G3/1)
CK7 = Positive (clone EP16)
PAX8= Negative (clone EP331)
EGFR= positive
ALK=Negative
ROS= Negative

Oncology opinion suggested palliative care with targeted therapy for double malignancy. We have started letrozole and Erlotinib for breast and lung cancer respectively. She was discharged with targeted therapy Erlotinib and home oxygen supplementation and supportive care for conservative care after discussion with care givers and our team of pulmonologist and oncologist and advised to follow up in oncology and department for further oncology care and hospitalization in intensive care unit if any parameters deteriorated.

Results and Discussion

Billroth first described multiple primary malignancies in a single patient in 1879.[3] The neoplasms may only affect one organ or, as in our case, they may affect several anatomically distinct organs. Because of an increase in the number of elderly cancer survivors, greater awareness, and improved diagnostic modalities, metachronous primary malignancies are becoming more prevalent. Comparatively, synchronous tumours are rare, and the breast is the most frequent location for synchronously coexisting multiple tumours.

Warren and Gates Criteria for Diagnosis of Double Primary Malignancies.[3]

1. Malignancy in the primary and secondary tumours has been confirmed by histology.
2. Between each tumour, there should be at least 2 cm of healthy mucosa. If the tumours are in the same place, they should be at least five years apart in time.
3. One must rule out the possibility that the other is a metastasis of the former.

Multiple primary tumours are divided into two categories by the North American Association of Central Cancer Registries (NAACCR): (1) Synchronous, in which the cancers develop simultaneously (the Surveillance Epidemiology and End Results Program (SEER) definition is within two months), and (2) Metachronous, in which the cancers develop sequentially, that is, more than two months apart.[4] The SEER Program database has shown that the prevalence of multiple primaries varies from 1% (initial liver primary) to as high as 16% (initial bladder primary).[5]

It has been hypothesized that the pathophysiology underlying the occurrence of multiple primary malignancies is a combination of genetic predisposition to neoplasia and common-carcinogen-induced multiple cancers on an exposed epithelial surface, known as "field-cancerization" and seen in head-neck tumours.[4] Other potential causes include ongoing environmental carcinogen exposure; advancing ozone depletion and the effects of ionizing radiation; an increase in organ transplantation; and an increase in the use of more modern therapeutic approaches like hormonal manipulation, target therapies, genetic manipulation, and immunomodulators.[4]

We found synchronous multiple primary malignancies (MPM-Multiple primary malignancies & SPM-synchronous primary malignancies) in the breast and lung in our case. Although breast and lung cancer have been documented in the literature, adenocarcinoma of the lung has never been reported. Sas-Korczyska *et al*. reported in a retrospective review of synchronous MPMs (SPMs) in breast cancer patients that SPMs were observed in only 112 (0.009%) of the 118,952 patients treated between 1965 and 2014. Contralateral breast cancer was the most prevalent synchronous primary malignancy (63.4%), and female genital malignancies (36.6%) were the most prevalent synchronous secondary malignancies.[6] Reports of MPMs related to breast cancer and hematologic malignancies have also been recognized; moreover, breast cancer has been reported to be the most frequently diagnosed cancer after radiation therapy for Hodgkin lymphoma. On the contrary, the development of non-Hodgkin lymphoma (NHL) after breast cancer treatment is very rare.[7]

Conclusion

In our case, we thought initially as it was primary breast cancer presented with lung metastasis. After complete workup we came to conclusion as double primary malignancy by documenting primary lung adenocarcinoma by histopathology and immunohistochemistry.

Key learning points from this case report are

1. Double primary malignancy is frequently reported due to advancement in cancer diagnostics and survival of patients.
2. The possibility of multiple primary malignancies existence should always be considered during pre-treatment evaluation. Screening procedures were especially useful for the early detection of associated tumours, preferably before clinical manifestations occurrence.
3. Concurrent or synchronous type of double primary malignancy is frequently reported with breast malignancy. Advanced investigation modality has crucial role in timely diagnosis of double primary malignancy
4. Although breast and lung cancers are the two most frequent cancers detected in women, double primary

cancer involving the concurrent two organs has been reported rarely.

5. Most common diagnosis at first site in our case would be primary breast carcinoma with lung metastasis from primary breast which was ruled out by bronchoscopy.
6. Bronchoscopy trainings in intensive care unit with expertise in biopsy procedure is the crucial step in work up of advanced cases with poor performance status in suspected lung cancer cases.
7. Cancer sample cytology facility at bed side i.e. rapid on site evaluation (ROSE) is need of hour in centres dealing with lung cancers and histopathology expertise with immunohistochemistry plays a vital step in defining primary origin of tumour.
8. Advancement in treatments and availability of targeted therapy had played important role in prolonging survival with negligible side effects.
9. Targeted therapy can be started at any stage including advanced stage with poor performance status and limited survival. Importantly, these agents are universally available and cost effective.
10. We especially mention 'rare things rare to happen' and high index of suspicion is must for diagnosis of double primary malignancy.

Acknowledgments
None.

Conflict of interest
None.

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None.

Ethics statement
Ethical committee approval taken as our institutional policy and written informed consent from patient and her husband regarding necessary interventions required during complete evaluation process.

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