A rare site of metastasis in lung cancer: Silent or loquacious?

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ABSTRACT

Lung cancer is the most common cause of cancer-related deaths worldwide. Most of the lung cancer patients present at an advanced or metastatic stage (84%). Common sites of lung cancer metastasis are the liver, bone, brain, and adrenals. In our index case, we describe a rare site of metastasis in a 59-year-old gentleman that presented to us with cough and easy fatigability. On examination, he was pale and had crepitation's in the left infrascapular region. The chest radiograph revealed a right hilar mass, which was confirmed on computed tomography. Bronchoscopy-guided biopsy revealed squamous cell lung cancer. Among significant baseline investigations, his hemoglobin was low (6.2 g/dl) with an elevated leukocyte and platelet count. Serum iron profile revealed a picture suggestive of anemia of chronic disease. Bone marrow examination was done, which revealed the presence of bone marrow metastasis with squamous cells. A diagnosis of Stage IVB squamous cell lung cancer with bone marrow metastasis was made and the patient was started on chemotherapy (carboplatin and paclitaxel). After the fourth cycle of chemotherapy, it was seen that the overall tumor was showing partial remission, and hemoglobin had also increased which was suggestive of bone marrow recovery. This demonstrates that bone marrow metastasis, though rare, needs not be silent overall.

Key words: *Anemia, Bone marrow, Lung cancer, Metastasis*

Lung cancer is the most common cause of cancer-related deaths worldwide with a yearly prevalence of 74,000 in India [1,2]. Most (≥80%) of the lung cancer patients present at an advanced stage (Stage IIIB or higher). This is further confounded by multiple comorbidities present among the patients of lung cancer [3]. These factors in addition to advanced age contribute toward high mortality in lung cancer. The advanced stage is depicted by metastasis to distant sites both intrathoracic and extrathoracic. Within the histological subtypes of lung cancer, the tendency to metastasize is highest with small cell lung cancer followed by adenocarcinoma, whereas squamous cell lung cancer has a predilection to locally invade the surrounding structures such as the chest wall and mediastinum [4]. The mechanism of metastasis can be hematogenous or lymphatic. The most common sites of extrathoracic metastasis for lung cancer are the brain, bone, liver, and adrenals [5]. In addition, anemia is a frequent companion of lung cancer. Etiology of anemia may be related to nutrition, bleeding, and chronic disease related. This is in addition to the iatrogenic causes like chemotherapy-induced anemia [6].

Here, we describe a case of lung cancer in which anemia was coexistent with an unusual site of metastasis which led to a rare peripheral blood finding. This case adds to the knowledge of causes of such hematological alterations. Along with this, we also encountered an irreconcilable reaction to chemotherapy where anemia was actually improving, whether it was related to the site of metastasis or not, remains an *enigma*.

CASE REPORT

A 59-year-old gentleman presented with complaints of dry cough, easy fatigability, and loss of weight for four months. He was a former heavy smoker (smoking index 600) and had no known comorbidities. Examination of his vitals (heart rate 86/min, respiratory rate 18 per min, blood pressure 134/88 mmHg, and saturation at room air was 94%) and general physical examination were largely unremarkable except for the presence of pallor and clubbing. Respiratory system examination revealed crepitations in the left infrascapular region. Cardiovascular, central nervous system, and per abdomen examination did not reveal any significant abnormality.

Routine blood evaluation revealed anemia, leukocytosis, and thrombocytosis (Table 1). The liver function tests, renal function tests, and coagulation profile were within the normal limits (Table 1). The chest radiograph showed a right hilar prominence with fine reticular shadows in bilateral lower zones. Contrast-enhanced computed tomography of the thorax revealed ill-defined lobulated heterogeneously enhancing mass lesion in the right hilar region measuring (3.3 cm × 4 cm) and interlobular septal thickening with ground glass opacities in dependent regions

of the lower lobes, more so on the left side (Fig. 1). Multiple variable-sized subpleural and parenchymal nodules in the bilateral lung parenchyma, predominantly in lower lobes, were also present.

The patient underwent flexible bronchoscopy under conscious sedation. An endobronchial growth was detected in the right bronchus intermedius at the opening of the right middle lobe bronchus. Endobronchial biopsy taken from the growth showed feature suggestive of squamous cell carcinoma on histopathological examination with immunohistochemistry showing p63 positivity (Fig. 2).

On evaluation for anemia, a peripheral blood film examination was done which showed a microcytic and hypochromic picture. The iron profile revealed low serum iron, low iron-binding capacity, normal transferrin saturation, and high serum ferritin which were suggestive of anemia of chronic disease (AOCD) (Table 1). For the same, packed red blood cells were transfused multiple times.

In view of disproportionately affected bone marrow (low hemoglobin and high leukocyte and platelet count), the patient underwent bone marrow aspiration and biopsy from the right superior iliac crest. Histopathology examination findings revealed that normal hematopoietic elements were totally replaced with clusters of numerous tumor cells with squamous differentiation (Fig. 3). This led us to believe that the causation of anemia could be multifactorial (AOCD along with the invasion of bone marrow with tumor cells).

A final diagnosis of metastatic squamous cell lung carcinoma ($T_4N_2M_{1C}$ – IVB as per 8th TNM staging) [7] was made and he was started on chemotherapy (carboplatin with paclitaxel, once every 3 weeks) with supportive care of blood transfusions. We did not use any erythropoiesis-stimulating agent due to financial constraints. Before every chemotherapy cycle, he required transfusion of packed red blood cells (two to three). His blood counts were investigated before every cycle of chemotherapy apart from the renal and liver function tests. By the time, the fourth cycle was due; his hemoglobin had increased to 10.9 g/dl without transfusions. Meanwhile, there was normalization of leukocyte and platelet count (Fig. 4). Ferritin was still very high (3204 ng/ml). Post fourth cycle of chemotherapy imaging was repeated and the response as per RECIST version 1.1[8] was a partial response. At present, the patient is on follow-up and is having sustained partial remission and is doing well post four cycles of chemotherapy.

Table 1: Hemogram, serum iron profile, kidney and liver function tests, and coagulation profile of the patient

Parameters	Values
Hemoglobin	6.2 g/dl#
Total leukocyte count	32,500/µl*
Platelets	585 thousand/µl*
Serum iron	16 µg/dl#
Total iron-binding capacity	143 µg/dl#
Ferritin	3878.4 ng/ml*
Transferrin saturation	26.2%
Urea/creatinine	21.9/1.2 mg/dl
Uric acid	8.5 mg/dl*
Bilirubin (total/direct/indirect)	0.7/0.4/0.3 mg/dl
SGOT/SGPT	40.0/37.8 U/L
Serum alkaline phosphatase	358.2 IU/L*
Total protein/albumin	4.8/2.5 g/dl#
PT/INR	18.2/0.91

***More than the normal range, #less than the normal range, SGOT: Stands for serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, PT: Prothrombin time, INR: International normalized ratio**

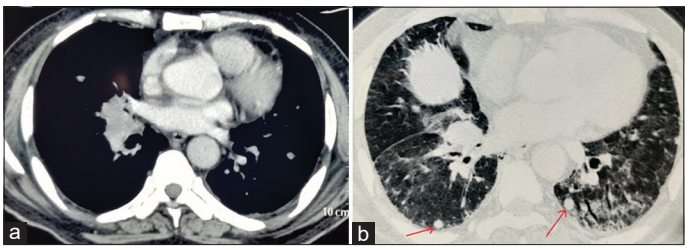

Figure 1: (a) Contrast-enhanced computed tomography (CECT) of thorax (mediastinal window) showing right hilar mass lesion. (b) CECT thorax lung window showing multiple subpleural nodules present in bilateral lower lobes (arrow). Inter- and intra-lobular septal thickening is present in the left lower lobe

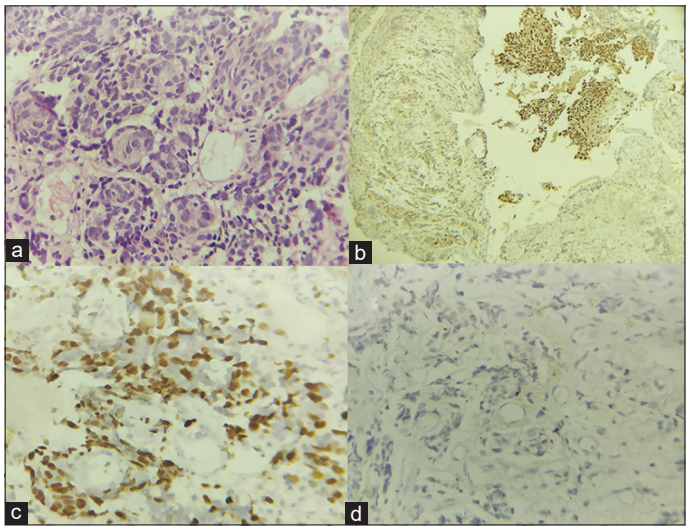

Figure 2: (a) Hematoxylin and eosin stained slides of endobronchial biopsy showing cells with hyperchromatic nuclei and scanty cytoplasm forming foci of pseudostratified epithelium and keratin pearls. (b) Immunohistochemistry (IHC) slides of p63 staining showing strong positivity. (c) Ki-67 staining showing expression greater than 30%. (d) Negative expression of TTF-1 using IHC

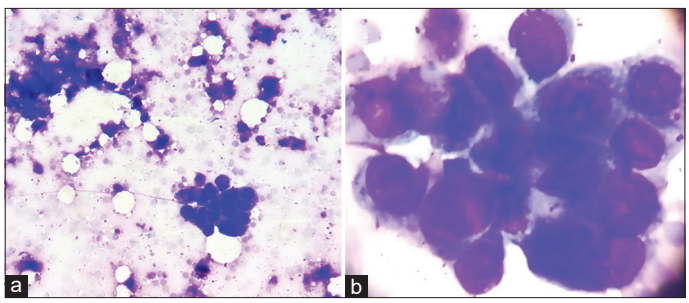

Figure 3: (a) Leishman stained slides of bone marrow aspirate showing clusters of tumor cells (×40). (b) Leishman stained slides of bone marrow aspirate showing clusters of epithelial tumor cells with nigh nuclear to cytoplasm ratio, hyperchromatic nucleus, and well-defined moderate to scanty cytoplasm (×100)

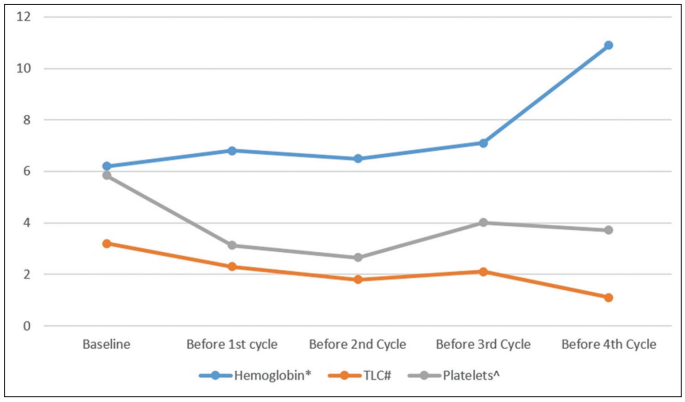

Figure 4: Line diagram of hemogram showing all the three blood cell lines, checked before every chemotherapy cycle. A rise in hemoglobin with normalization of other two cell lines can be appreciated

DISCUSSION

Lung cancer is one of the most commonly diagnosed cancers and is the primary cause of cancer-related deaths worldwide [9]. The metastasis descriptor in the 8th edition of the TNM staging system is considered to be representative of the last stage of tumor progression. Distant metastases are commonly diagnosed in the brain, followed by bone, liver, and adrenal gland. In spite of the recent developments in lung cancer screening like low-dose computed tomography [10], most of the patients of lung cancer either present at a locally advanced or a metastatic stage [5].

Similarly, the index case presented to us at an advanced stage. In addition, our case at presentation had severe anemia. On further evaluation, the patient was also found to have bone marrow metastasis. Now, anemia is a common coexisting hematological alteration among patients of lung cancer. Nutritional deficiencies, AOCD, and chemotherapy-induced anemia are the major culprits [6]. Although AOCD was already labeled in the index case and bone marrow examination was not indicated but given the inconsistencies of peripheral blood findings with respect to other cell lines, we decided to go ahead. This was to our surprise that we found metastasis in bone marrow evolution.

Bone marrow metastasis is rare with lung carcinoma. Most bone marrow metastases are known to be silent given the huge reserve of progenitor cell lines. In a previous retrospective analysis of solid tumor patients, only five cases of lung cancer were found to have bone marrow metastasis [11]. Similarly, in a study done on 124 patients of different types of solid tumors; of which, 19 were lung cancers and only four were found to have bone marrow metastasis [12]. The bone marrow metastasis has the potential to affect the normal hemopoiesis, leading to anemia and other cytopenias, albeit rare [13].

Our case was peculiar in two aspects. First, in spite of having bone marrow involvement, there was a paradoxical increase in leukocyte and platelet count. This could have been explained by the local immune reaction against the tumor cells. Second, the manner in which there was a rise in hemoglobin after the third cycle of chemotherapy. Although not confirmatory but at the same time, it suggests an active role of tumor cells in the causation of anemia. After four cycles of chemotherapy, the tumor in the body was showing a favorable response by demonstrating partial emission as per RECIST 1.1 criteria [8]. Extrapolating this knowledge to the territory of bone marrow as well, it is likely that tumor cell burden in bone marrow was also in decreasing trend and thereby contributing to the recovery of erythropoiesis. Previously, authors have described the presence of hypercellular bone marrow in patients with lung cancer with evidence of micrometastasis [14]. Successful treatment of bone marrow metastasis has also been described in a case with anaplastic lymphoma kinase fusion positive [15].

Among the few shortcomings of our cases, we could not get PDL-1 stands for programmed death ligand-1 levels done on the tissue sample, and hence, we could not use immunotherapy on this patient. Immunotherapy in India is still in its infancy and most of these drugs are economically exhausting for the patients. We as a routine are not able to prescribe these drugs, given their high cost. Response to immunotherapy could have been an interesting aspect of our index case.

Few points that the index case taught us were – bone marrow metastasis can be a contributing factor in the pathogenesis of anemia among lung cancer patients and chemotherapeutic response to tumor cells is in parallel to bone marrow recovery in patients who have a known metastasis.

CONCLUSION

Anemia in lung cancer patients can be multifactorial, and albeit rarely, bone marrow metastasis can be one important contributor toward the same. Bone marrow examination in suspected cases can be diagnostic and should be included in the evaluation of anemia.

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