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Local Rib Invasion in Non-Small Cell Lung Cancer: A Bad Prognostic Factor that Owes a Characteristic Scintigraphic Appearance in Dual Phase Osseous Scintigraphy

SHEREEN WAGIEH, M.D.*; AHMED ZAHER, M.D.**; WALID OMAR, M.D.**; TAREK ABD EL-FATTAH, M.D.* and TAREK HASHIM, M.D.***

Nuclear Medicine Departments, Cairo University, Kasr El-Eini, National Cancer Institute** and Monofeya University***.*

ABSTRACT

Tumor invasion of the chest wall in non small cell lung cancer is one of the designation of T 3 resulting in upstaging of the tumor to stage III-A. This augurs a worse prognosis. Bone scan is a sensitive technique to detect remote metastases and local rib erosion.

Purpose: The rational beyond this study is that the presence of local rib destruction or involvement in the vicinity of a pulmonary shadow is virtually diagnostic of primary carcinoma of the lung associated with local rib erosion. *Aim of this study* is to detect characteristic scintigraphic appearance in dual phase osseous scintigraphy in diagnosis of local rib erosion in non small cell lung cancer.

Patients and Methods: Sixty patients with histopathologically proven bronchogenic carcinoma were included in the current study. Thirty had C.T. evidence of local rib erosion (Group I) and the remaining had no rib erosion (Group II). All were subjected to dual phase osseous scintigraphy. Images were interpreted for local rib erosion depending on specific criteria (presence of over-perfused mass in blood pool images/hyper-vascular overlying ribs in early images/abnormal tracer uptake pattern in the same ribs in late images). A scoring system was created for each patient according to presence or absence of these criteria.

Results: Twenty-eight patients in group I had hypervascular soft tissue mass in blood pool images versus 23 in group II. Over-perfused overlying ribs were seen in 28 patients in group I, in addition to rib involvement in late images in all patients in this group. Single involvement of one rib related to but remote from the hyper-vascular mass was seen in group II that proved to be distant metastatic deposit.

Conclusion: Dual phase osseous scintigraphy has characteristic scintigraphic criteria that can diagnose local rib erosion in non-small cell lung cancer with high sensitivity and specificity. These criteria are: Over-perfused soft tissue mass and overlying ribs in early blood pool images associated with abnormal tracer uptake in the same ribs in late images. Proper diagnosis of local rib erosion has a great impact on prognosis and subsequent patient management particularly in absence of remote osseous metastases.

Key Words: *Lung - Cancer - Prognosis - Bone scan.*

INTRODUCTION

Lung cancer is among the most commonly occurring malignant disease in the world. It is one of the malignancies that continues to show an increasing incidence (American Cancer Society, 2000) [1].

As tumor grows within lung parenchyma or within bronchial wall, it ultimately invades lymphatic and vascular channels, resulting in spread to regional draining lymph nodes and remote metastatic sites, respectively. It appears that lymphatic spread occurs earlier than distant metastases, involving broncho-pulmonary (N1), mediastinal (N2-N3) and supra-clavicular lymph nodes (N3). The primary tumor can also spread locally, invading contiguous structures including mediastinal pleura, pericardium, other mediastinal structures, the chest wall or the diaphragm. This local spread might indicate a worse prognosis and alters the stage of disease (Sorenson et al, 1989 [16], Mountain, 1986 [12]).

Rib destruction due to local invasion is sometimes visible on plain X-ray. Yet, C.T. scan is a more sensitive technique for detection of local rib erosion. It can define the whole extent of the tumor together with proper assessment of loco-regional and lymph nodal spread of the primary lesion.

The search for metastatic disease is the principal indication for bone scan in patients with bronchogenic carcinoma. It is also reported that Tc-99m MDP bone scan is a sensitive technique to assess local rib invasion. Bone scan is frequently positive when the plain film still shows no bony abnormality.

Rib involvement in bronchogenic carcinoma can be identified by more than one abnormal pattern in the bone scan. It usually appears as a linear elongated lesion involving the rib shaft which may affect one or more ribs. The ribs may also exhibit a homogenously active tracer uptake or irregular tracer accumulation pattern with photon deficient areas. Less commonly seen is the complete absence of tracer uptake in the involved rib when complete rib destruction occurs. The diagnosis of local rib erosion is clinically important particularly in absence of remote osseous deposits, as with local rib erosion only, the stage of the disease will be IIIA while with metastases it will be stage IV, with different therapeutic strategies between both conditions (Downey et al. [3]).

The rational beyond this study is that the addition of blood pool images of the chest to conventional routinely used delayed bone scan images will detect the hyper-vascular primary pulmonary lesion adjacent to the usually hyperperfused involved ribs. The latter also exhibit abnormal tracer uptake pattern in delayed images. This together with the fact that the presence of bone destruction or involvement in the vicinity of a pulmonary shadow is virtually diagnostic of primary carcinoma of the lung associated with local rib erosion. This makes the diagnosis of local rib erosion feasible using dual phase osseous scintigraphy which has further impact on decision making as regards therapeutic strategy.

The aim of this study is to evaluate the role of dual phase osseous scintigraphy in diagnosis of local rib erosion in non-small cell lung cancer and to try to establish a characteristic scintigraphic appearance using this technique at no additional cost or radiation exposure to the patient.

PATIENTS AND METHODS

The current study included 60 patients with histo-pathologically proven bronchogenic carcinoma. Patients included were divided into 2 main groups with the following criteria:

Group I: 30 patients with C.T. evidence of local rib erosion by the malignant growth.

Group II: 30 patients with no C.T. evidence of local rib erosion.

All patients were subjected to:

- Full clinical assessment (History taking and clinical examination).
- Reviewing the histo-pathological result.
- Dual phase osseous scintigraphy: without special patient preparation, each patient was injected with 740 MBq Tc-99m MDP. Blood pool images were taken (whole body in 40 patients and localized spot view of the chest in 20 patients) immediately following injection for 500 Kilocounts (KC) for the localized chest projection and 2-3 million counts for whole body images, using dual head gamma camera (ADAC vertex-plus (25 pts) and Siemens ECAM in 35 pts), in both anterior and posterior projections. Two hours later, whole body osseous phase was acquired using low-energy parallel hole high resolution collimator, with an overall count of 2-3 million counts.

Images were interpreted for:

1- Presence of hypervascular peripheral mass in blood pool images.

2- Presence of over perfused rib/ribs overlying the mass in early set of images.

3- Presence of involvement of 1 or more ribs overlying the hypervascular mass in late images (linear tracer uptake (homogenous, inhomogeneous) or complete absence of tracer uptake in 1 or more of these ribs).

Images were interpreted by 2 independent observers and a scoring system was employed as follows: For each of the above items, given 1 for its presence and 0 for absence of each scintigraphic criterion.

Also bone scan was interpreted for remote metastases or presence of associated scintigraphic evidence of pulmonary osteoarthropathy.

RESULTS

The sixty (57 males and 3 females) patients included in this study had an age range from 49-62, with a mean age of 55±6.6 years. No significant difference was found as regards sex or age between the two studied groups.

Clinically, ipsilateral chest pain was more common in group 1 (present in all patients) than in group II. On the other hand haemoptysis was more prevalent in the second group. No significant difference between the two groups as regards dyspnea and joint pains was found, Table (1).

Table (1): Clinical symptoms for the two groups included in the current study.

	Group I	Group II
Dyspnea	21 (70%)	26 (86.7%)
Haemoptysis*	3 (10%)	14 (46.6%)
Chest pain*	30 (100%)	11 (36.7%)
Joint pain	9 (30%)	7 (23.3%)

*p value < 0.005

As regards histopathological data, group I had more number of patients with adenocarcinoma compared to group II. While squamous cell carcinoma was more prevalent in group II patients (Table 2) compared to group I.

Table (2): Histopathological data of the 2 groups included in the current study.

Type	Group I	Group II
Adenocarcinoma	23 (76.7%)	11 (36.7)
Large cell carcinoma	3 (10%)	4(13.3%)
Undifferentiated carcinoma	4 (13.3%)	2(6.7%)
Squamous cell carcinoma	-(0%)	13 (43.3%)

In group I, all patients had a peripheral malignant growth, which was located posteriorly in 19 cases, (7 postero-medial and 12 postero-lateral location) and apically (superior sulcus syndrome) in 10 patients. Only one lesion was anteriorly situated with local erosion of related anterior rib (Fig. 1).

On the other hand for group II patients; 14 patients had central location and 13 peripherally situated (7 posteromedial & 6 posterolateral) (Fig. 3) and 3 had apical tumor (superior sulcus syndrome) (Table 3).

In group I patients, C.T. scan detected that the local invasion involved upper ribs in 10 cases, mid ribs in 13 cases, lower ribs in 6 cases and anterior rib in only 1 case. The involvement of single rib was seen in 4 patients, while involvement of more than 1 rib was found in the remaining 26 patients.

Table (3): Site of the primary lesions in both groups included in the current study.

Site	G I	G II
Apical	10	3
Posteromedial	7	7
Posterolateral	12	6
Ant.	1	-
Central	-	14

As regards dual phase osseous scintigraphy a hypervascular primary lesion in early blood pool images was seen in 28 patients in group I and in 23 patients in group II. In the former group two cases lacked significant overperfusion of the primary lesion in blood pool images, one had extensive central necrosis surrounded by faint overperfused rim and the other had ipsilateral massive effusion. While for the 7 cases who lacked overperfusion in blood pool images in group II, 5 cases had central small lesion by C.T.scan and 2 had massive ipsilateral effusion (Table 4).

Twenty eight patients in group I had variable degrees of overperfused ribs overlying the hypervascular mass (Fig. 2). Two cases with superior sulcus syndrome lacked any evidence of overperfused ribs overlying the mass. They exhibited absent tracer uptake in late images (complete rib erosion) (Fig. 4). While a single case with overperfused rib related to the mass was seen in group II (Table 4), (Fig. 5).

Table (4): Scintigraphic findings in blood pool images in both studied group.

	Over-perfused mass		Over-perfused ribs	
	+ve	-ve	+ve	-ve
G. I	28	2	28	2
G. II	23	7	1	29

As regards delayed conventional bone scan study, 27 cases showed evidence of linear enhancement of tracer uptake in an irregular pattern in one or more ribs overlying the overperfused mass seen in the early sets of images (Fig. 2). Out of them, 11 cases had central cold rib areas. The remaining three cases, 2 had superior sulcus syndrome with complete rib erosion (Fig. 4) (absent tracer uptake in the shaft of involved rib) and another one with absent uptake in anteriorly situated rib lesion that had active uptake at its lateral portion and looked hyper-perfused in early images (Fig. 1). While for group 2, single involvement of ribs adjacent to and remote from the hyperperfused mass was seen (Fig. 5), denoting remote metastases (Table 5).

As regards remote metastases, 3 patients in group I had remote osseous deposits, involving mainly the axial skeleton (2 patients) and both axial and appendicular skeleton in one single patient.

Table (5): Scintigraphic findings in late conventional bone scan in both studied groups.

	G I	G II
Local rib involvement overlying overperfused mass	30 (27: uneven uptake in rib/ribs) (2: complete absence of rib shaft) (1: absent uptake in anterior rib except for its lateral portion)	1 patient showed extensive remote metastases in the skeleton including several ribs
Remote metastasis	3	1
Osteoarthropathy	6	5

While for group II patients, remote deposits were seen in and appendicular two patients involving both axial skeleton (Table 5).

Pulmonary osteoarthrography was seen in both groups on delayed bone scan, in 6 & 5 patients in both groups respectively (Table 5).

Concerning quantitative data, 26 patients of group I had score 3, while 4 patients had score 2 (as they lacked overt hypervascularity in the primary lesion or the ribs (2 & 2, respectively). While for group II, 23 patients had score 1 and 6 patients had score 0, lacking scintigraphic features of local rib erosion, as the ribs are neither over-perfused in blood pool images nor involved in the late bone scan study in these 6 patients (Table 6). One single patient had score 3, showing over-perfused mass and overlying ribs, proved to be metastatic in late images.

Table (6): Quantitative data for criteria of local rib erosion.

	Score 0	Score 0	Score 0	Score 0
G. I	0	0	4	26
G. II	6	23	0	1

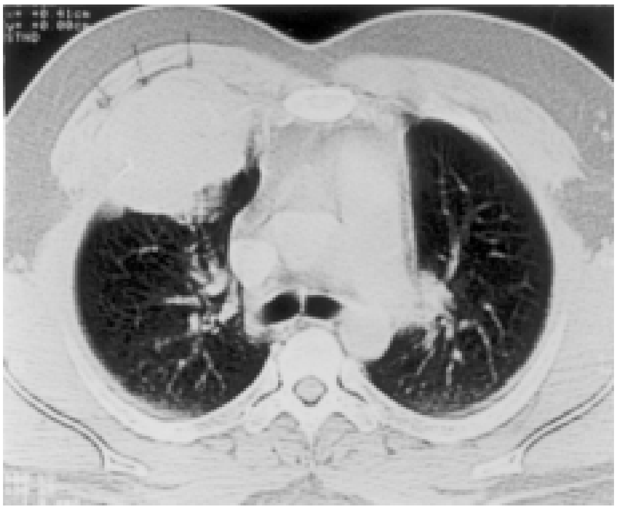

Fig. (1-A): Rt Ant. lung cancer with local rib erosion.

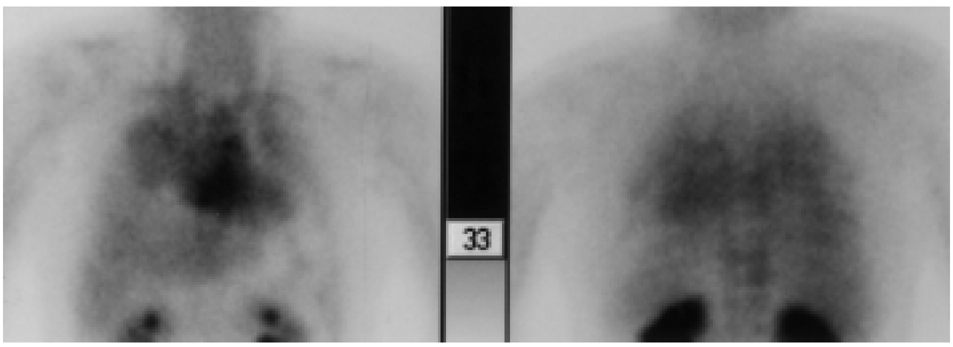

Fig. (1-B): Hyperperfused mass in Ant. upper Rt. Lung with overperfused overlaying ant. ribs.

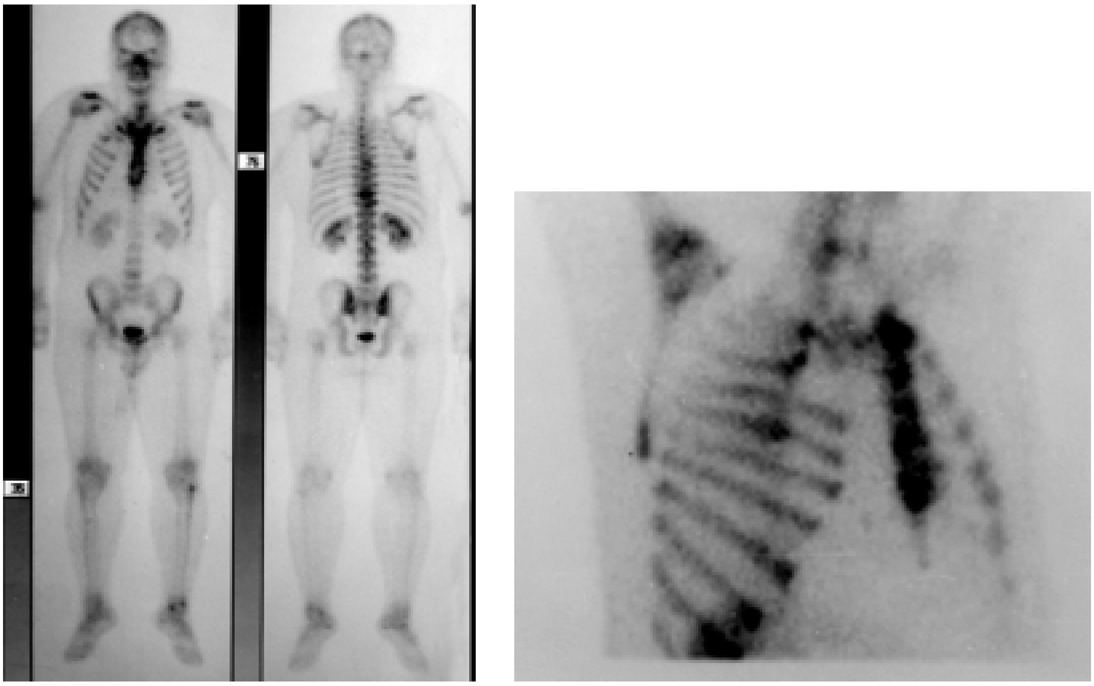

Fig. (1-C): Local rib erosion of Rt. Ant. third rib with active uptake at its lateral edge.

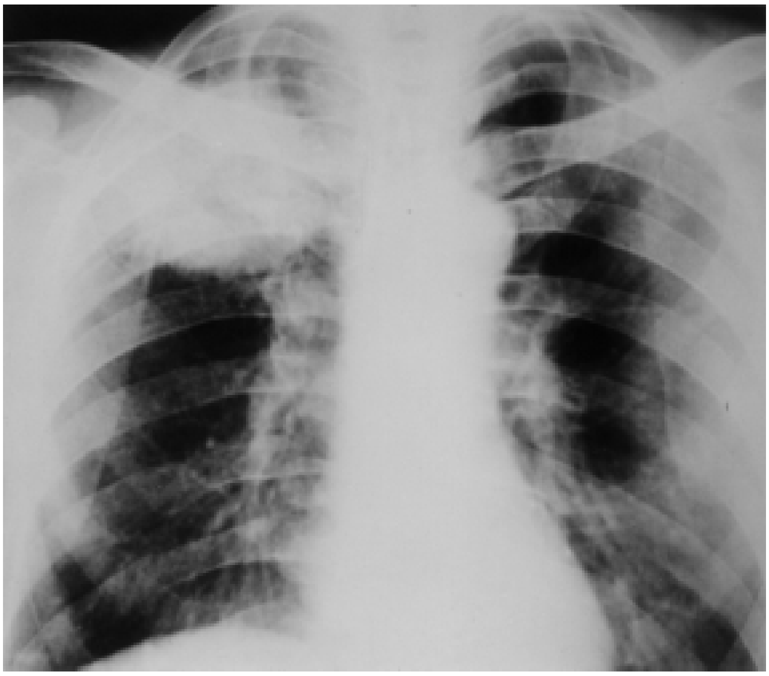

Fig. (2-A): Chest X-ray showing a big mass in the lower Rt. Lung.

Fig. (2-B): C.T. showing Rt. lung mass with local rib erosion.

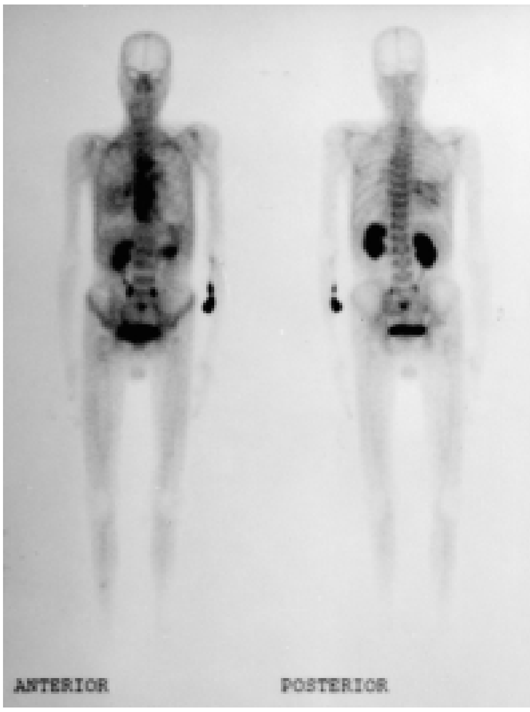

Fig. (2-C): Blood pool images showing hypervascular lung mass and hypervascular ribs overlying the mass.

Fig. (2-D): Delsyed bone scsn showing linear irregular uptake in the Rt, lower ribs and an osteolytic lesion in the Lt. sacroiliac region.

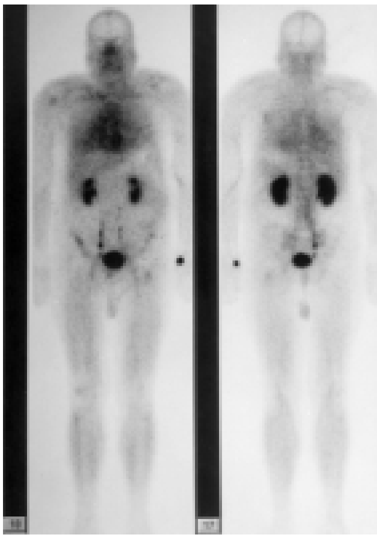

Fig. (3-A): Hyperperfused Rt. lower lung mass showing no overperfused ribs. Multiple hypervascular deposits.

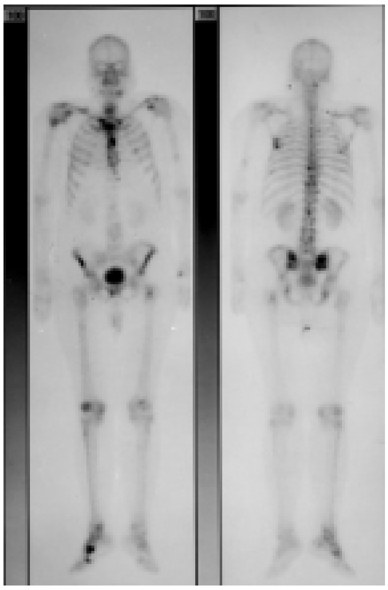

Fig. (3-B): Delayed bone scan. No rib erosion and multiple remote deposits.

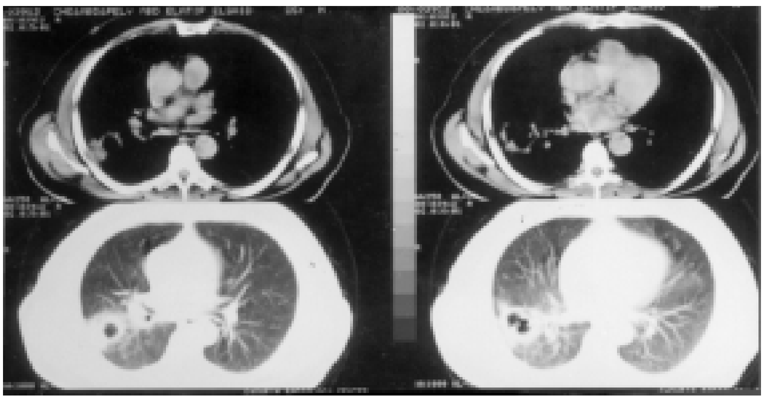

Fig. (3-C): C.T. showing cavitary lung cancer in lower Rt. Lung with no rib erosion.

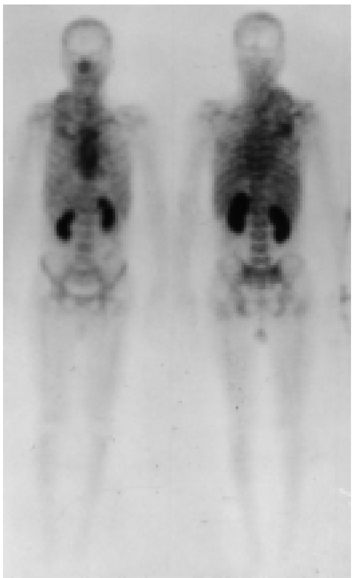

Fig. (4-A): Whole body blood pool showing large hypervascular Rt. apical lung cancer with central necrosis and no overperfused ribs.

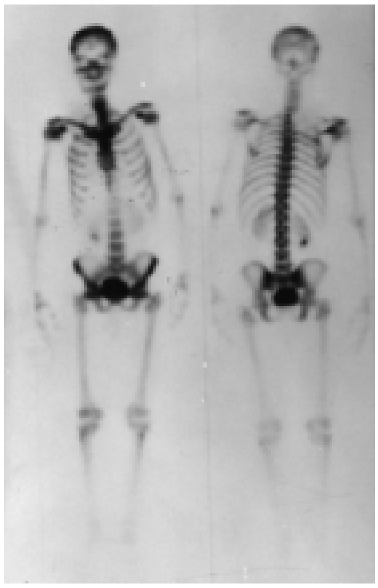

Fig. (4-B): Delayed bone scan showing complete destruction of upper Rt. Ribs due to local bone invasion.

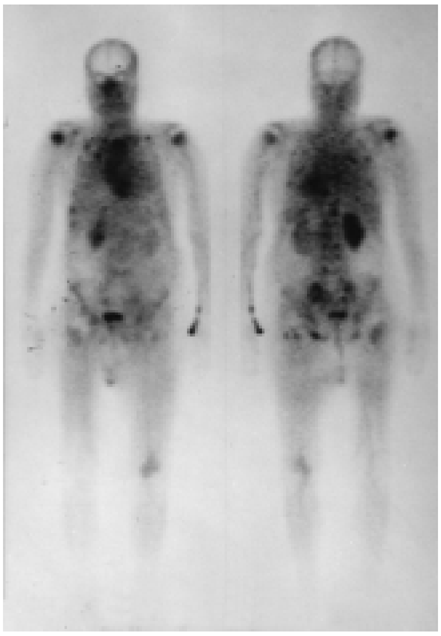

Fig. (5-A): W.B. blood pool showing multiple hypervascular bone deposits including ribs overlying but remote from hypervascular lung mass.

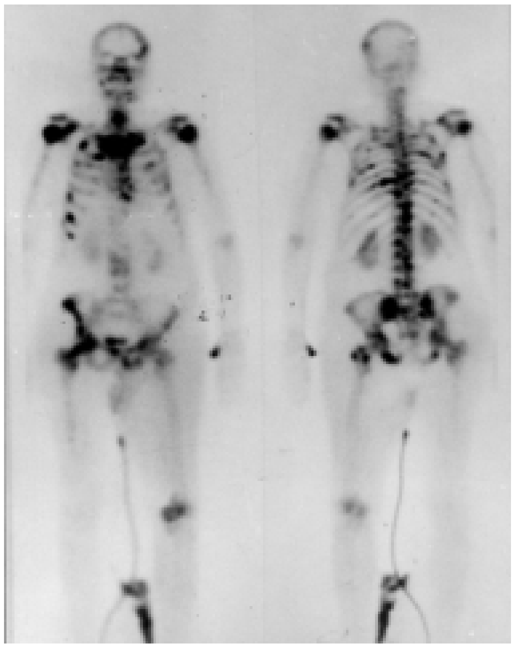

Fig. (5-B): Delayed bone scan showing multiple bone deposits in axial and appendicular skeleton with no local rib erosion.

DISCUSSION

Lung cancer is the leading cause of cancer death in men and it surpassed breast cancer as the leading cause of death in women in late 1980's. The incidence of lung cancer is now 70 per 100.000. As we enter the 21st century, it is expected that the altered smoking habits during the last two decades together with decreased tar content of cigarettes will result in decreasing the incidence of lung cancer (Parkin et al. [14]).

In addition to lymphatic and haematogenous spread, the primary malignant lung tumor can spread locally, ultimately invading contiguous structures including mediastinal pleura or organs, the chest wall or the diaphragm, with a worse prognosis as this upgrades the stage of disease to stage IIIA. Loco-regional spread occurs more frequently in adenocarcinoma, representing 40% of all lung cancer, as most of these tumors are peripheral in origin, arising from alveolar surface epithelium or bronchial mucosal glands. Other than T1N0 tumors, it appears that this tumor has a somewhat worse prognosis than squamous cell carcinoma of the same stage (Sorerson et al., 1989) [16]. In the current study, there is agreement with Sorenson's data as regards the commonest histopathological type with local rib erosion which is adenocarcinoma representing 76.7% of the first group with rib erosion in our study and only accounts for 36.7% in the second group without rib erosion ($p < 0.05$).

Ginsberg et al., 2001 [4], stated that radicular chest pain develops in association with rib erosion, it is also associated with pleuritic chest pain and shortness of breath due to pleural invasion. In our study all patients with rib invasion had chest pain confined to the ipsilateral hemithorax, while dyspnea was present in 70% of cases. On the other hand dyspnea and haemoptysis were more prevalent in those with no rib erosion (86.7%, 46.7% respectively). In the latter group of patients (group II), chest pain was present in the ipsilateral hemithorax in 11 cases (36.7%). This is mostly attributed to the fact that non-specific and vague chest pain generally referred to the ipsilateral hemithorax is of frequent occurrence in patients suffering from lung cancer. These pains are of visceral origin and unrelated to local chest wall invasion (Ginsberg et al., 2001 [4], Robert et al. [15]).

The classic superior sulcus syndrome (Pancoast tumor) includes lower brachial plexopathy, Horner's syndrome and shoulder pain.It usually manifests with local chest pain due to local invasion of ribs. The latter is seen in approximately one third of patients. This incidence is higher in our study where 13 patients in both groups had superior sulcus tumor out of them 10 patients (77%) had rib erosion. This is attributed to different patient population, selection criteria and smaller number of patients in our study.

Proper diagnosis of rib involvement should have an influence on decision making as regards therapeutic strategy and surgical approach in order to achieve better prognosis in these patients with this bad prognostic factor that upgrades the primary lesion to stage IIIA.

C.T. scan is a sensitive tool for diagnosis of local rib erosion; it gives an idea about the exact extent of the lesion as well as presence of nodal involvement. The addition of blood pool images to conventional delayed bone scan can be helpful in diagnosis of local rib erosion in addition to the original value of bone scan in diagnosis of remote metastases (Saha and Boyd, 1979 [17]).

The movement of the tracer can be followed clinically by triple phase bone scan imaging, during radio-nuclide angiography the tracer is largely intravascular, during early static images of the blood pool at 1-2 min. post injection (phase 2), the tracer is both intra- and extravascular. In delayed or metabolic imaging (phase 3) the tracer is largely associated with bone (Subramania et al., 1974 [19], Krishnamurthy et al., 1976 [9]).

Conventional delayed bone scan has gained wide acceptance in bronchogenic carcinoma in searching for metastatic disease. It is highly sensitive for detection of bone metastases by surveying the entire skeleton. Ten to 40% of skeletal metastases have normal radiographs with positive bone scans. The incidence of bone metastases at autopsy in patients with primary lung cancer ranges from 30-50%. Actually the presence of bone metastases gravely affects the prognosis (stage IV disease) (Gravenstein et al., 1979 [5], Kelly et al., 1979 [8]).

The chief unresolved question is the role of bone scintigraphy in asymptomatic patients with stage I and II non-small cell lung cancer. True bone scan positive results in this group of patients were less than 4%. There is a general agreement that bone scintigraphy at initial staging is essential when the histology is small-cell type, the patient has bony pains, elevated serum alkaline phosphatase or extensive primary lesion regardless of the symptoms. Also follow-up bone scan is performed yearly in absence of clinical symptoms suggesting disease worsening (Kelly et al., 1979 [8]; Donato et al., 1979[2]; McNeil, 1984 [10]).

In the current study bone metastases were seen in two cases in group II, involving axial and appendicular skeleton, representing 6.6% of cases, which agrees with the low incidence of osseous deposits in these early stages of the disease (I & II). Actually routine radionuclide bone scanning to rule out asymptomatic unsuspected metastases in early stages of disease has never been shown to be cost effective but is still advocated by many practitioners (Ginsberg et al., 2001 [4]). On the other hand with more advanced stage (IIIA), in group I of our patients, 3 (10%) patients showed remote osseous metastases, 2 in axial skeleton and 1 involving both axial and appendicular skeleton. So in clinical stage III disease before curative therapy is considered, bone scan is definitely cost effective and is certainly of value when bony pains are present (Michel et al., 1991 [11]).

The high prevalence of involvement of the axial skeleton, seen in all 4 patients with metastases in our study, is due to the fact that bone metastases spread haematogenously and the distribution of red marrow is about 90% in axial skeleton and 10% is found in the appendicular skeleton.

Hypertrophic osteoarthropathy is found in as many as 10% of patients with lung cancer, presenting as symmetrical enhancement of tracer uptake in long bones and around joints, mainly the knees. Those patients may complain of joint pain. In our patients this scintigraphic feature was seen in 11 patients representing 18.3 % of patients in both groups, all patients complained of pain around the knees.

In conventional delayed bone scan, malignant rib involvement usually presents as elongated lesions in one or more ribs, showing irregular enhancement of tracer uptake with possible photopenic areas. This should be differentiated from post-traumatic rib uptake, which presents as small active spots arranged along the same axis if involving more than one rib. This abnormal rib uptake exhibits decrease in tracer uptake intensity overtime (Harbute, 1982 [6]; O'mara, 1988 [13]; Holder, 1990 [7]).

Additionally, local erosion by underling malignant growth may present with complete absence of tracer uptake in the whole shaft of the involved rib/ribs. The ability of blood pool images to detect hypervascular soft tissue mass together with detection of rib involvement by scintigraphy in the vicinity of a pulmonary shadow is virtually diagnostic of primary pulmonary growth associated with local rib erosion, making the addition of blood pool images of great value in this particular issue.

These facts represent the basis for the rational beyond this study. The following criteria being diagnostic and characteristic of local rib erosion:

(1) hyper-vascular soft tissue mass in blood pool images at the same site close to involved ribs (2) over-perfused overlying rib or ribs in blood pool study (3) Linear irregular enhancement of tracer uptake in the involved rib or ribs overlying the hyper-vascular mass in late images or complete absence of tracer uptake in the rib shaft in delayed images.

Applying these criteria to group I of our patients; the 3 criteria were seen in 26 patients (86.7%) (Score 3), only 2 patients lacked the over-perfused rib pattern due to significant rib erosion with absent uptake in late images (both had superior sulcus tumor). Also 2 patients lacked the over-perfused mass in blood pool images due to massive effusion and extensive necrosis (the latter 4 patients had score 2).

In-group II patients, with no rib erosion, the mass appeared over-perfused in blood pool images in 22 patients (score 1) with no related or overlying rib over-perfusion or tracer uptake. In the remaining 7 patients, even the over-perfused mass was not detected (2 massive effusions, 5 small central primary lesions) (score 0). Only one patient who had score 3 abnormal uptake, with over-perfused mass and related overlying ribs, proved to be metastatic in late images. So, the presence of the 2 or 3 criteria (Score 2 or 3) is diagnostic of local rib erosion with a sensitivity of 96.8%. On the other hand , the latter two criteria (over-perfused ribs overlying the mass in blood pool image as well as abnormal tracer uptake pattern in late images) had sensitivity, specificity, PPV and NPV of 100%, 96.6%, 96.5% and 100% respectively for diagnosis of local rib invasion. So, the absence of rib over-perfusion in blood pool image and/ or normal tracer uptake in late study is exclusive of local rib erosion.

Finally, it is concluded that in addition to the established value of bone scan to search for metastatic deposits in cases of bronchogenic carcinoma, the addition of early blood pool chest images can help in diagnosis of local rib erosion by the underlying malignant growth.

The criteria of erosion include hyper-vascular soft tissue mass and over-perfused overlying rib/ribs in blood pool images associated with irregular linear enhancement of tracer uptake or complete absence of uptake in rib shafts of the same overlying rib/ribs.

The presence of more than one of these criteria is 96.8% sensitive for detection of local rib erosion. The C.T. has the advantage of detecting nodal involvement in addition to confirmation of scintigraphic findings of local rib erosion while bone scan has the advantage of exclusion of other remote metastases. If local rib erosion is the only osseous involvement in bone scan without bone metastases , this would be of great influence in decision making as regards therapeutic strategy and major en bloc surgery may be attempted.

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