ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 8, Issue, 08, pp.37296-37300, August, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

SQUAMOUS CELL CARCINOMA LUNG WITH SKELETAL MUSCLE INVOLVEMENT, EIGHT YEAR STUDY OF A TERTIARY CARE HOSPITAL IN KASHMIR

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ARTICLE INFO

Article History:
Received 22nd May, 2016
Received in revised form
05th June, 2016
Accepted 04th July, 2016
Published online 31st August, 2016

Key words:

NSCLC- Non Small cell Lung Carcinoma, ISMM--Isolated Skeletal Muscle Metastasis, PTHrP --Parathyroid Hormone Related Peptide, CK—Cytokeratin, TTF-Thyroid Transcription Factor, SVC – Superior Vena Cava, PFS—Progression free Survival, OS—Overall Survival.

ABSTRACT

Aims: Lung cancer is the most common malignancy throughout the world. Non-small cell lung cancer (NSCLC) is most common type, and squamous cell type is most common in India. Mostly patients present with chest related symptoms and signs. Isolated skeletal muscle metastasis is rarely seen. Aim was to see muscle metastasis and its prognosis.

Methods: We are presenting our data of eight years about this common malignancy with relation to muscle metastasis, either alone or with other system metastasis.

Results: Muscle metastasis is seen 1.5% of patients, with M: F OF 8:1. Over all median survival was 15 months and progression free survival was 12 months.

Conclusion: One peculiarity seen was isolated skeletal muscle metastasis with no pulmonary system and severe paraneoplastic hypercalcemia. Local therapy may be having an impact on overall survival in metachronous muscle involvement.

Citation: Dr. Javvid Muzamil, Dr. T. Vishal, Dr. Naveed Mohsin, Dr. Firdousa Nabi and Dr. Gull Mohammad Bhat, 2016. "Squamous cell carcinoma lung with skeletal muscle involvement, eight year study of a tertiary care hospital in Kashmir", *International Journal of Current Research*, 8, (08), 37296-37300.

INTRODUCTION

Lung cancer is the most common malignancy throughout world, and non-small cell histology always out-numbers the small-cell type. Lung cancer has diverse clinical presentations, and chest complaints are the most common. Lung cancer metastaises to every organ with a rare involvement of isolated skeletal muscle. In one retrospective series, the prevalence of isolated skeletal muscle metastasis (ISMM) was seen in 0.16–6% (Tuoheti *et al*., 2004). In a study reported in literature, pain was the most frequent symptom (83%), mass was palpable in 78% of cases and the diagnosis was obtained by either fine needle/surgical biopsy or wide excision. The 5-year survival time was 11.5% with a median survival of 6 months (Pop and Nadeemy, 2009).

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METHODS AND MATERIALS

A study was conducted in our institute over a period of eight years. Clinical characteristics of lung cancer were noted down and types of lung cancer were segregated. Non- small cell lung cancer having muscle metastasis either singly or with multi system metastasis was taken for study. Patients who had no muscle metastasis were not enrolled for further study. Clinical

profile, laboratory and imaging profile was noted down and outcome with chemotherapy and other modalities of treatment was recorded. At the end overall survival was recorded.

Observation and results

A cancer registry is maintained in our institute for last fifteen years and oncological setup is present over last three decades. We registered 26,660 cancer patients in last eight years. Out of this data, 4800 (18%) patients were cancer of esophagus and stomach, 3068 (11.5%) patients had lung cancer. In our registry upper gastrointestinal tract cancer was rank one tumor followed by lung cancer. Lung cancer was further segregated into common two types as small cell and non- small cell variant. Small cell carcinoma lung comprised 460 (15%), and non- small cell lung carcinoma comprised 2608 (85%). On morphological and immunohistochemistry, Squamous cell carcinoma comprised 1227 (40%), Adenocarcinoma of lung comprised 920 (30%), Large cell carcinoma 150 (5%) and Non- small cell carcinoma lung not otherwise specified 306 (10%). Further study was concentrated on squamous cell carcinoma patients having skeletal muscle metastasis either singly or with multi system metastasis. All other patients either resectable disease or non- muscle metastatic disease were excluded. All patients underwent imaging of chest and referable sites, along with bone scan, laboratory parameters, and muscle biopsy of involved muscle site. Out of 1227 patients, 18 (1.5 %) patients had muscle metastasis. Out of this 10 patients had multiple site metastases along with muscle metastasis and 8 patients had only muscle metastasis. Males were 16 and females 2, with M:F of 8:1. All patients were smokers and all were rural dwellers. The clinical features of these patients are depicted in Table 1 and 2. Median age of presentation was 48.5 years, with youngest patient of 35 years and oldest patient of 85 years. Among this cohort, most common symptom was isolated muscle pain followed by cough. Most common sign was pallor followed by SVC syndrome features. In Lab parameters, anemia was peculiar, renal failure was seen in three patients, which was because of hypercalcemia (Table 3). Severe hypercalcemia was seen in one patient who required immediate hemodialysis and this was associated with high PTHrP level in serum.

Table 1. Symptomatology of presentation

Symptom	Percentage of patients having symptom
Cough	55
Shortness of breath	33
Hemoptysis	33
Chest pain	16.5
Anorexia	11
Weight loss	11
Seizures	11
Headache	11
Fever	16.5
Localized muscle pain	88
Bone pain	5.5
No chest complaints	44

Further evaluation was carried out with imaging of chest and abdomen, along with imaging of referable sites. CECT chest and abdomen was carried out in all patients, revealing right hilar mass in 66% of patients, left hilar mass in 22 % of patients and 12% had right peripheral lung mass. Superior vena cava (SVC) partial or complete occlusion was seen in 33 %, right sided plural effusion, ascites and liver metastasis was seen in 11% each (Image 1& 2).

Table 2. Clinical signs of patients

Signs	Percentage of patients
Performance status(ECOG)	
II	66
III	22
IV	11
Pallor	55
Pedal Edema	22
Consolidation	33
SVC features	33
Pleural effusion	11
Ascites	11
Hepatomegaly	11

Table 3. Laboratory parameters

Laboratory parameter	Minimum value	Median value	Maximum value
HB(Gm/dl)	6.4	9.5	14.0
TLC($\times 10^3/\mu l$)	4.0	8.0	14.0
PLT ($\times 10^3/\mu l$)	50.0	80.0	150.0
Urea(mg/dl)	20	30	112
Cr(mg/dl)	1.0	1.2	2.87
Calcium (mg/dl)	8.0	9.5	18.87
Albumin (mg/dl)	2.5	3.5	4.5
LDH(IU/L)	150	250	650
ALP (IU/L)	130	160	270
PTHrp (pmol/L)	5	10	15

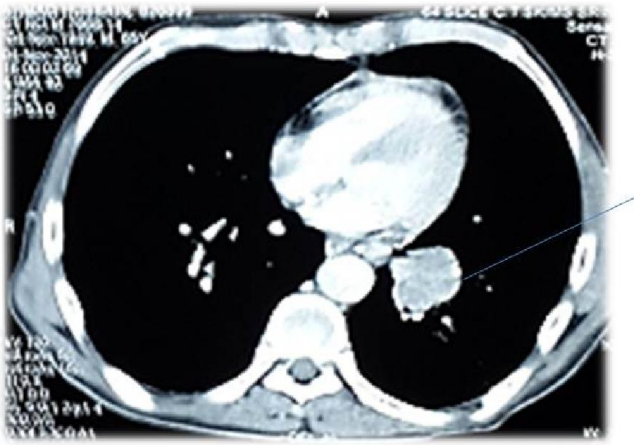
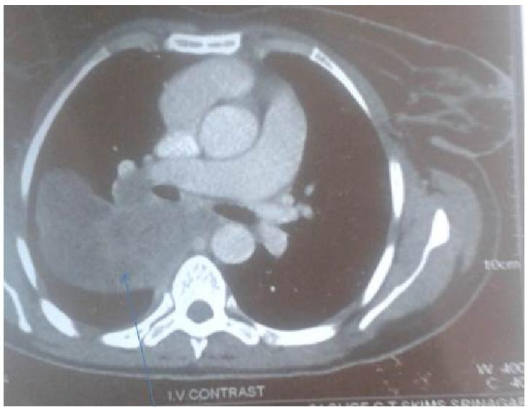
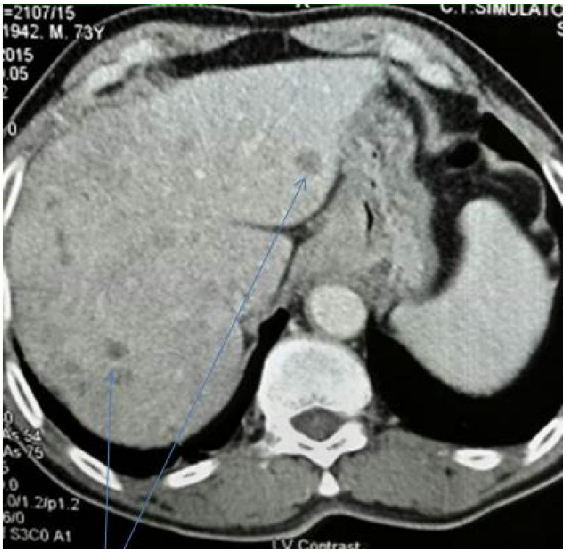


Image 1. CECT chest showing left hilar mass



Lung mass with necrosis



Multiple liver metastasis in lung carcinoma

Image 2. CECT chest showing huge right hilar mass and multiple liver metastasis

Bronchoscopy revealed intra-bronchial pathology and clinched the diagnosis in 88% of patients, rest of patients needed CT guided biopsy of lung for getting histological diagnosis. Lung biopsy was positive for Napsin, CK 5/6 and negative for synaptophysin and TTF 1 (Image 3). Bone scan was positive in two patients with one uptake in ileac bone and other in Tibia (image 4 of X-ray tibia). CECT of muscle metastasis sites were done and biopsy was carried out in each patient (image 5). Distribution of metastasis was unique, 66% patients had pelvic skeletal muscle involvement, 22% had thigh muscle and 11% had lower para-spinal muscle metastasis.

Finally diagnosis of squamous cell carcinoma lung with muscle metastases was established. In our research, 44 % patients had no symptoms referable to chest; they presented with pain in the region of muscle metastases. Most of our patients had contralateral lung metastases; with 16.5% patients had distant metastases to liver, bone and brain.

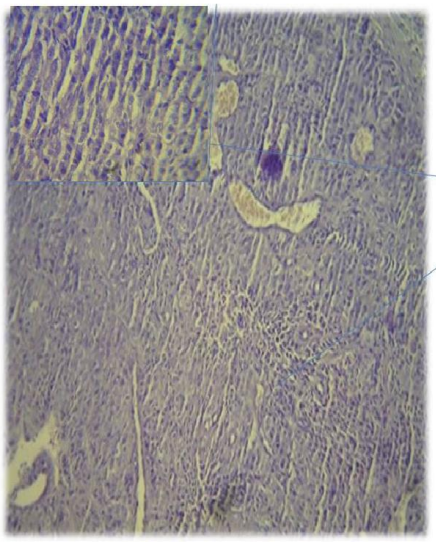


image 3- HPE of lung biosy with low and high power view: squamous cell carcinoma

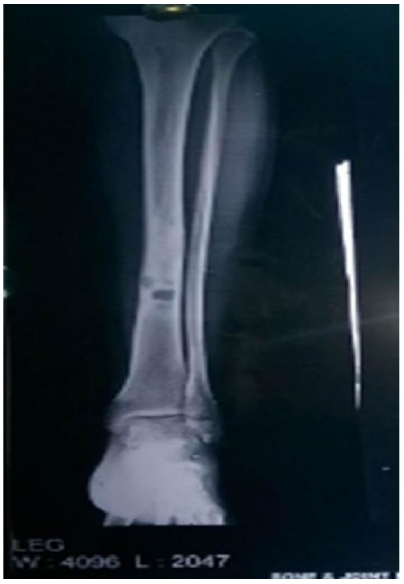


Image 4: Lytic lesion with sclerosis in tibia in a patient of carcinoma lung

Hypercalcemia was seen in 16.5% patients, all such patients had no bone metastases and was associated with rise of PTHrP (Para thyroid hormone related peptide), a paraneoplastic manifestation. Finally patients received palliative chemotherapy with supportive treatment, either hemodialysis, bisphosphonates, brain irradiation, blood transfusions and paracentesis.

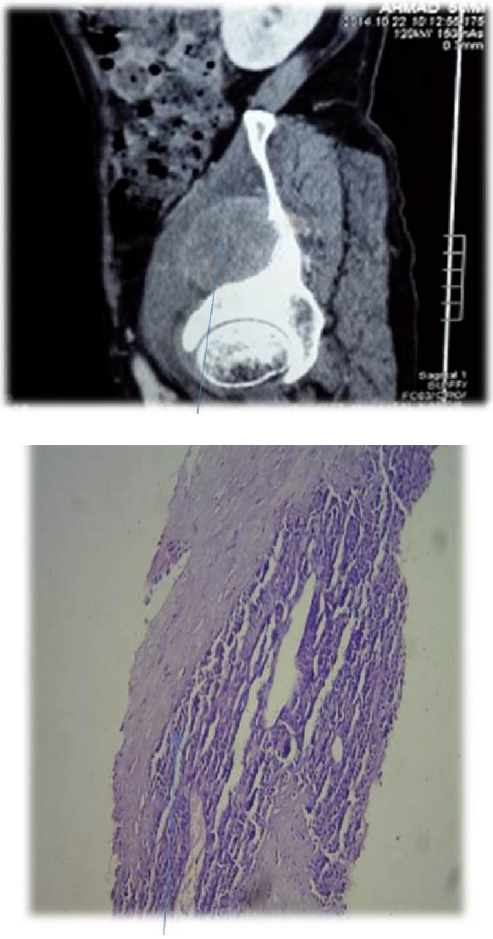


Image 5. CECT hip showing ileacus muscie involvement and biopsy of same revealing metastatic squamous cell carcinoma

Patients were divided into two groups, 50% received Gemcitabine 1 gm/m^2 on day 1 & 8 with Carboplatin AUC 5 as three weekly schedule and other group received Paclitaxel 175mg/m^2 with Cisplatin 80 mg/m^2 as three weekly schedule. On progression of disease both groups received second line chemotherapy as Docetaxel 75mg/m^2 with growth factor support. Patients who had PS III/IV received supportive care only. In both groups, median number of courses received was 6, with 33% of patients received less than six cycles. Progression was seen in all patients with either increase in number of metastases in contralateral lung or more distant metastases. For second line chemotherapy, only 66% of patients were available, median number of courses received was 6 and minimum of 3. First Progression free survival was six months in both arms. Maximum progression free survival (PFS) was 15 months in Gemcitabine arm and 13 months in Paclitaxel arm. Second median PFS was six months, with minimum of four months. Overall median PFS was 12 months; with maximum PFS of 21 months. Median overall survival was 15 months, with minimum OS of 4months and Maximum OS of 26 months. We have observed that median OS in our patients was 15 months with median PFS as 12 months. Our all patients succumbed to chemo toxicity and disease progression. There was some peculiarity of having paraneoplastic hypercalcemia with muscle metastasis in patients having no pulmonary symptoms. Is there some correlation or it was co-incidental finding, only research will reveal that.

DISCUSSION

Skeletal muscles are an uncommon site of hematogenous metastases from epithelial neoplasms. Intramuscular metastases in cancer patients are rare (Di Giorgio *et al*., 2004). This in itself is quite peculiar because muscular mass accounts for approximately 50% of total body weight. It is thought that muscular contractile actions, local pH environment, and accumulation of lactic acid and other metabolites contribute to the rare occurrence of this phenomenon (Tuoheti *et al*., 2004). The true incidence of muscular metastasis remains unknown, but an autopsy series suggests that its incidence could be as low as 0.8% (Kaira *et al*., 2009). Lung carcinoma seems to be the underlying primary cancer in most of these cases. Many other tumors, such as kidney, stomach, pancreas, thyroid gland, breast, and ovary, prostate, and bladder cancers have also been sporadically described in association with intramuscular secondaries (McKeown *et al*., 1996; Heyer *et al*., 2005; Belhabis *et al*., 2001; Menard *et al*., 1990; Cheong *et al*., 1989).

Solitary muscle metastasis has been reported in lung cancer by Giorgio *et al*. who reported study of 3000 patients treated for lung cancer, described only three cases showing skeletal muscle metastasis (Di Giorgio *et al*., 2004). Tuohetietal. found that only 4 (0.16%) out of 2557 patients with lung cancer developed metastasis to the skeletal muscle (Tuoheti *et al*., 2004). In our study we also documented prevalence of skeletal muscle involvement in 1.5% of patients. Males out number females, because lung cancer is common in males in our part of the world. Most frequent muscle involvement is seen in the thigh, iliopsoas, and paraspinous muscle (Kaira *et al*., 2009). In our patient cohort, distribution of metastasis was unique, 66% patients had pelvic skeletal muscle involvement, 22% had thigh muscle and 11% had lower para-spinal muscle metastasis. A unique thing observed was paraneoplastic hypercalcemia in isolated muscle metastases, even though it was seen in only 16.5% of patients. In our study, the most common symptom was involved site muscle pain (88%) which is consistent with the study conducted by Pop *et al*. (2009). According to Prior (Prior, 1953), the first description of muscle metastasis was reported by Wittich in 1854, and Willis was the first to report a muscle metastasis of lung origin. Despite being highly vascular, the exact incidence is not much known. Subclinical metastasis may indeed be more common than generally thought. One large autopsy study of 5298 people found that 6% involved skeletal muscle metastasis (SMM) of the chest or abdominal wall (Picken, 1976). Nowadays, an autopsy on all cancer-related deaths is not performed routinely. An important help is the 18 fluoro-deoxi-glucose positron emission tomoscintigraphy-scan mostly for detecting subclinical metastasis (Heffernan *et al*., 2006; Liu *et al*., 2006). Since this imaging procedure was introduced into practice in 2004, single SMM has rarely been seen. Certainly, there are several limitations to muscle enhancement in positron emission tomography scan, so in this study only the patients with CT-scan confirmation and a histologic sample of one metastatic deposit was taken as an absolute metastatic deposit. Almost 1/3 of metastases in this study were discovered before the lung cancer. The most common appearance (83%) of the lesions on contrast-enhanced helical CT is that of a rim-enhancing mass with central hypo attenuation (Sridhar *et al*., 1987). There are several theories to explain muscle resistance of metastatic disease. The most important hypotheses are mechanical (muscle contraction, high tissue pressure (Toussirot *et al*., 1993), and extremely variable blood flow (Weiss, 1989), metabolic (pH, lactic acid production (Seely, 1980), and toxic-free radical oxygen (Sridhar *et al*., 1987) or immunologic (cellular and humoral immunity and hypersensitivity reaction (Stein-Weiblowski, 1974). None of them in isolation can explain the full mechanism, but a combination of them could.

In our study median OS was 15 months and PFS was 12 months, with one lived up to 26 months. Since all these patients had synchronous metastatic disease, no patient survived for five years. Our OS was better in isolated muscle metastasis than in multiple site metastasis. As per the study conducted by Pop *et al*. (2000) the 5-year survival time was 11.5% with a median survival of 6 months.Almost all types of non-small cell lung carcinoma (NSCLC) can metastasize in the muscle with no particular preferences. The presence of SMM suggests an aggressive disease. Selection of patients for a local treatment is an important factor that determines survival, which is possible in metachronous setting or synchronous single site muscle metastases.

Conclusion

Carcinoma lung is always an aggressive disease to handle, when in metastatic stage, curative treatment is not possible. Involvement of muscle is very rarely seen, and if present, tells about aggressive disease. If there is isolated muscle involvement in metachronous setting, one can look for longer survivals with good local treatment. There is also scope for research, as why there are high paraneoplastic manifestations in isolated muscle involvements in lung cancer?

Conflict of interest: nil

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