Original Research Article

Sarcomatoid carcinoma of lung- rare but dangerous histology - A case series

A Preethi[1*], K Kalaichelvi[2], S Suresh Kumar[3], G Raja[4]

[1]Final year DM Post-graduate, [2]Professor & HOD, [3,4]Assistant Professor, Department of Medical Oncology, Madras Medical College and RGGGH, Chennai, INDIA.
Email: pritams.2004@gmail.com

Abstract

Sarcomatoid carcinoma of lung, a rare variant of poorly differentiated non-small cell carcinoma of lung, is found to have an aggressive clinical course thus projecting very poor prognosis. Recent advances in pathology including immunohistochemical studies have improved the chance of diagnosis of these variants. The case series has been reported due to the rarity of the disease and inadequate treatment recommendations. Four cases presented in our department diagnosed with this tumor during the period January 2015 to December 2018 with varied clinical and diagnostic features. The first patient presented with inoperable disease staged IIIC which later further progressed with rib metastasis despite chemotherapy showing increased aggressiveness. The second patient also diagnosed with metastatic disease showed ALK positivity hence was treated with crizotinib, showing partial response to treatment with close monitoring. The third and fourth patients were operable hence treated with surgery followed by cisplatin based chemotherapy and radiation. The third patient succumbed to the disease and the fourth patient is on regular follow up for 4 months. All the patients were male and above 40 years of age predominantly presenting with advanced stages, three of them being chronic smokers. All patients had a pathological diagnosis of sarcomatoid carcinoma with a supporting immunohistochemistry of vimentin and CK positivity. The rarity, rapid progression and short survival with heterogenous pathological qualities of this disease have made it difficult to formulate proper treatment recommendations. Further prospective studies are required to further define the role and efficacy of chemotherapy and targeted agents in this disease.
Key Word: sarcomatoid carcinoma, lung, aggressive variant, rapid progression, vimentin

[*]**Address for Correspondence:**
Dr. A Preethi, Final year DM Post-graduate, Department of Medical Oncology, Madras Medical College and RGGGH, Chennai, INDIA.
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INTRODUCTION

Sarcomatoid carcinoma of lung, sometimes referred to as pleomorphic carcinoma including both spindle and giant cell components, is a rare histologic subtypeof poorly differentiated non-small cell carcinoma accounting for 0.1-0.4%[1,2,3] of all pulmonary malignancies and considered to have a poor prognosis. Due to recent pathological advances including immunohistochemistry, these variants are being identified accurately. Here we present a series of four cases diagnosed and treated in our department during the time period of January 2015-Dec2018.

CASE 1: A 50 year old male, a chronic smoker for 15 years, a farmer by occupation, belonging to lower middle class, had presented with complaints of breathlessness on exertion for 3 months. On examination, he had the performance status of ECOG-2, comfortable at rest and not dyspnoeic. The breath sounds were absent on auscultation of the right interscapular and suprascapular regions. He was evaluated with a chest X-ray which showed opacity in the upper lobe of right lung. CT Chest showed an iso to hypodense lesion of size 13x12.2x14.4cm in the right upper lobe lung and mediastinum in right paratracheal and hilar regions, which extends posteromedially in the subcarinal region displacing the trachea and esophagus.(Figure 1). Fibre-optic bronchoscopy showed no endobronchial lesion. CT guided biopsy was done along with

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immunohistochemistry showing vimentin and CK positivity thus concluding it to be Sarcomatoid carcinoma of lung. The tumor belonged to stage IIIC and was deemed inoperable. Hence the patient was put on a palliative chemotherapy regimen consisting of cisplatin, adriamycin and cyclophosphamide. After 5 cycles, the disease was found to be static. Hence the patient was subjected to palliative radiotherapy 30 Gy(300cGy/10#). Partial response of 40% reduction in size was observed. Patient was then put on metronomic chemotherapy consisting of oral cyclophosphamide. But after 6 months, the disease progressed with development of liver lobe metastasis and rib bone metastasis and there was deterioration in the general condition of the patient. The patient was put on supportive care and finally succumbed to the disease.

Case 2: A 41 year old male, non-smoker, a welder by occupation, belonging to upper middle classhad presented with complaints of cough and breathlessness for 6 months along with loss of appetite and weight. On physical examination, patient belonged to performance status ECOG-2 and not dyspnoeic at rest. On auscultation, decreased breath sounds were heard in the right interscapular region. He was evaluated in a private setup with a PET-CT scan showing right lung mass of size 6x9x6cm in the superior segment with multiple lymph node enlargement including peribronchial, hilar, precarinal, subcarinal, mediastinal and bilateral supraclavicular nodes along with multiple lung nodules in both lungs and metastatic lesions in the pancreas, kidney, abdominal lymph nodes. (Figure 2, Figure 3). Thus the tumor was staged as stage IV. Biopsy from the lesion had shown sarcomatoid carcinoma showing vimentin, CK and ALK-D5F3 positivity. Patient was started on Tablet Crizotinib 250mg on BD dosage. Repeat PET-CT scan after 2 months of crizotinib had shown partial response. The patient at present is on close observation, being continued on crizotinib after assessing blood counts along with liver and renal function.

Case 3: A 60 year old male, chronic smoker and alcoholic, a known case of hypertension and diabetes mellitus, belonging to upper middle class, had presented with complaints of hemoptysis, 3-4 episodes 2 months back and breathlessness on exertion for 2 months. On examination, patient belonged to the performance status ECOG-3, with decreased breath sounds on the left side on auscultation with no added sounds. Chest X ray had shown a heterogeneous opacity involving most of left lung field.CT chest showed enhancing soft tissue mass of size 4x4x3cm involving the left hilum causing cut off of left main bronchus with involvement of carina and hence showing passive collapse of left distal lung. (Figure 4, Figure 5). There is tracheal shift to left with mild pleural thickening with enlargement of left hilar necrotic node and few subcentrimetricprevascular, lower and upper paratracheal nodes. Fibre-optic bronchoscopy showed mass in the left lung main stem bronchus. Tumorwas staged as cT4N1M0 (III A). The patient was taken up for Left pneumonectomy. Per operative findings included a mass in left main bronchus infiltrating the bronchial wall, periaortic tissue, extending to carina and involvement of adventitia. Gross pathology showed grey, white hilar mass of size 4.5x4x2.5 cm with resected hilar margin infiltrated by growth. Microscopically, the tumor had features of sarcomatoid carcinoma with one positive lymph node and positive margin. Immunohistochemistry showed CK, p63 and vimentin positivity. Pathologically, the tumor was staged as pT4N1M0. Post operatively, patient was started on concurrent chemoradiation. Chemotherapy included cisplatin, adriamycin and cyclophosphamide. A radiation dose of 60Gy(200cGy/30#) was delivered to the tumor volume with appropriate margins. The patient progressed during treatment developing recurrence and finally succumbed to the disease 6 months later.

Case 4: A 56 year old male, chronic smoker and a known hypertensive and history of tuberculosis 3 years back, belonging to the upper middle class, had presented with complaints of cough with expectoration and right chest pain for 3 months duration and 2 episodes of hemoptysis. On examination, patient was found to be of performance status ECOG-2, with muffled breath sounds on the right side on auscultation and no other added sounds. Chest x rayhad shown a homogenous opacity in the upper lobe of right lung. Contrast enhanced CT scan showed a thick walled irregular cavity of size 8.1x7cm in the apical segment of upper lobe with tiny aorto-pulmonary nodes. Fibre-optic bronchoscopy showed no evidence of mass. Bronchial wash showed inflammatory cytology. CT guided biopsy from mass was inconclusive. Patient was taken up for right upper lobectomy with wedge resection of 6th segment of right lower lobe. Per op findings included a 10x8cm cavitating mass lesion in posterior and apical segment of right upper lobe with involvement of right lower lobe. Histopathological examination showed a tumor mass of size 5x4x2.5cm with spindle shaped tumor cells with desmoplasia. Immuno-histochemistry showed strong positivity for p63 and vimentin with scattered positivity for TTF suggestive of sarcomatoid carcinoma. Post op chemotherapy consisting of cisplatin, adriamycin and cyclophosphamide was given with concurrent radiation (60Gy/200cGy/30#), indications being inadequate nodal dissection and unknown margins. Patient completed chemotherapy and is on regular follow up for 4 months.

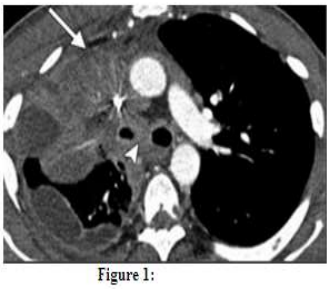
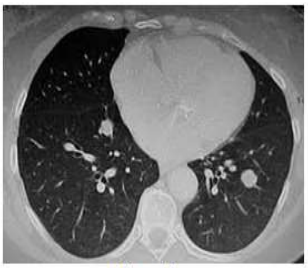


Figure 1:



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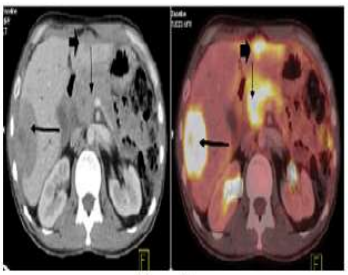

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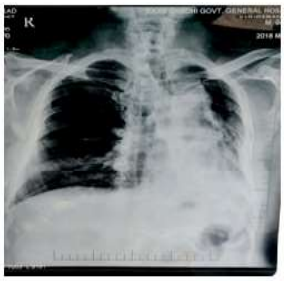

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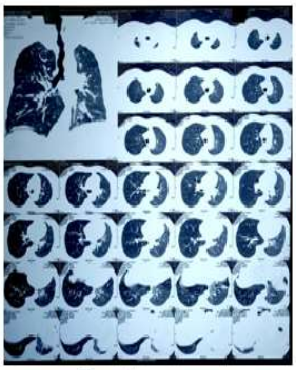

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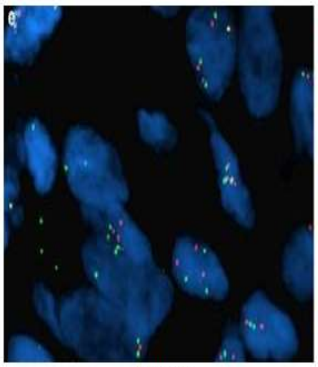

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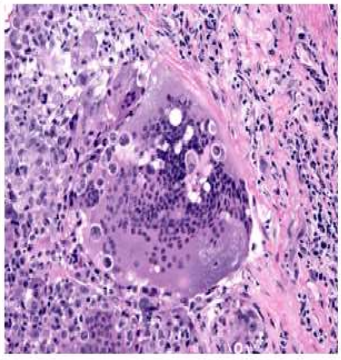

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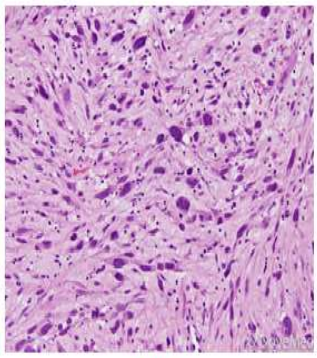

Figure 8:

DISCUSSION

Sarcomatoid carcinomas are a rare malignancy. According to WHO 2004 classification, five subtypes were demonstrated: pleomorphic carcinoma, spindle call carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma[2,4]. It commonly occurs in chronic smokers[5] and diagnosed at a mean age of 65 years[17]. There is a male preponderance with a male: female ratio of 1.5:1[17,18]. The exception is pulmonary blastoma which has equal sex ratio and occurs most commonly around 35 years of age[20]. The most common symptoms include cough, hemoptysis and chest pain[21]. The other risk factors include exposure to asbestos and electrical insulation[26]. It can occur in multiple other organs too like skin, bone, thyroid, liver, breast, pancreas and urinary tract.[6] This malignancy has an aggressive clinical course, rapid growth invasion, recurrence and metastases, the mean or median survival ranging from 5 months to 35 months[22,23] and overall 5 year survival being 20%[1].Sarcomatoid carcinomas have a predilection for upper lobe involvement and can arise centrally, infiltrating and obstructing the bronchus or peripherally, often invading the chest wall, the latter being more common similar to other smoking related non small cell carcinoma lung[7]. The most important prognostic factor is stage of the disease at presentation[1]. The origin of sarcomatoid carcinoma is based on four hypothesis – collision hypothesis, embryonic rest hypothesis, stromal induction/metaplasia hypothesis and totipotential hypothesis[24]. Macroscopically, the tumor is described as soft and fleshy to firm, hard or even rubbery. Cut surfaces may vary from whitish-grey to tan-yellow, frequently showing areas of hemorrhage and necrosis and occasionally demonstrating cavitation[20,23]. Pleomorphic carcinoma is defined as a poorly differentiated non small cell cancer of lung admixed with giant cells (Figure 7) and spindle cells (Figure 8) and vascular invasion is more common in this subtype. Spindle cell carcinoma and giant cell carcinoma consists of spindle shaped cells and anaplastic giant tumor cells respectively. Carcinosarcoma is a mixture of non small cell carcinoma and true sarcoma. Carcinoma component is most commonly being squamous cell carcinoma and the corresponding sarcoma component being rhabdomyosarcoma followed by osteosarcoma mixed with chondrosarcoma or osteosarcoma alone. Metastasis to hilar and mediastinal lymph nodes is common if parenchyma is involved. Pulmonary blastoma is a biphasic tumor consisting of a primitive epithelial and mesenchymal component. Due to heterogeneity of these tumors, small biopsies may be under/ over represented. Hence extensive tumor sampling is recommended[2,8]. Additive immunohistochemical staining including cytokeratin and differentiation associated markers such as TTF-1, Napsin A, P40, Vimentin, Desmin, Myogenin, Epithelial membrane antigen, CEA, CD31, CD34, Melan A, S100, Ber-Ep4, WT1 and D2-40 also help in identifying the diverse cell types and pointing towards potential differential

diagnosis[2,8]. Squamous cell carcinoma markers are CK5/6 and p63 and the markers of adenocarcinoma include SP-A and TTF-1. CK7 and CK20 help to differentiate between primary and secondary lung lesions. Pan cytokeratin (CAM 5.2 and LP 34) is reported to be present in sarcomatoid carcinoma of lung[27]. According to Huang *et al*[1], tumor size is an independent prognostic factor. The proportion of sarcomatoid component varies with tumor size. Smaller tumors may not have enough sarcomatoid elements to have a negative impact on survival. Differential diagnosis consists of carcinoma consisting of desmoplastic stroma, malignant mesothelioma and primary or metastatic sarcoma. Malignant mesothelioma presents with diffuse pleural involvement. Metastatic lesions are most commonly multiple but solitary metastatic lung lesions may occur too in extrathoracic sarcoma[25]. Surgery is the mainstay of treatment. In completely resected stage IIa-IIIa NSCLC, cisplatin based adjuvant chemotherapy has shown to improve survival in several trials. In N2 and T4 tumors,neoadjuvant chemotherapy with or without radiotherapy shows survival benefit[9]. Two studies including Vieira *et al*[10] and Yendamuri *et al*[28] showed pleomorphic sarcoma to have resistance to conventional chemotherapy. Alternatively, Huang *et al*[1] showed a positive benefit of post operative chemotherapy in such patients. Due to the rarity of this disease, the treatment options and prognosis are still elusive. Several chemotherapy regimens have been used to treat these tumors including drugs like cisplatin, docetaxel, gemcitabine, cyclophoshamide, doxorubicin, vincrsitine, ifosfamide and several others.[1,10,11] The overall 1-,3-,5-year survival probabilities of surgically operated cases in our series were 57.7%, 35.8%, 28.7% respectively, which is inferior to that of NSCLC patientswhich have overall survival of 75-80% in stage IA and 55-60% in IB. For stages IIA and IIB, it is 45-55% and 35-45% respectively.[12,13] Prognosis of sarcomatoid carcinoma is poor when compared to non small cell carcinoma of lung. Chemotherapy may be of survival benefit in advanced diseases but not in early stages. Surgery remains the cornerstone treatment in case of early stage diseases showing good overall survival benefit. EGFR inhibitors have been used as an alternative to chemotherapy due to similar prevalence of EGFR mutation in 0-28% as in lung adenocarcinoma[3,11,14,15]. ALK translocation (Figure 6) and MET amplifications have also been observed.Crizotinib targeting both the above mentioned mutations may play an important role in the treatment of pulmonary sarcomatoid carcinoma[16]. Monoclonal antibodies targeting PD-1/PD-L1 system have improved overall survival when compared to chemotherapy in disease progression due to high prevalence of these receptors in sarcomatoid carcinoma than in other non small cell lung cancer of the lung[17,18].

CONCLUSION

From the above case series, we can conclude that the sarcomatoid carcinoma of lung is a rare entity showing increased aggressiveness and rapid progression. Early stages may be adequately treated with surgery. But advanced stages may require adjuvant or palliative chemotherapy to achieve some benefit. Chemotherapy has not shown significant benefit in overall survival according to the several studies except may be as adjuvant treatment. The rarity, rapid progression and short survival with heterogenous pathological qualities of this disease has made it difficult to formulate proper treatment recommendations. Further prospective studies are required to further define the role and efficacy of chemotherapy in this disease. Studies involving targeted agents may also be of significance for accurate treatment of sarcomatoid carcinoma of lung.

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