

Adenoid cystic carcinoma of lung: An oncologic rarity treated with definitive chemo-radiation

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Received March 15, 2016; Revised August 09, 2016; Accepted August 15, 2016; Published Online September 18, 2016

Case Report

Abstract

Adenoid Cystic Carcinoma is a rare variant of adenocarcinoma originating mainly from salivary glands of the head and neck region distributed throughout the upper aerodigestive tract with a propensity for perineural invasion. Primary adenoid cystic carcinoma of lungs is exceedingly rare accounting for a mere 0.04 to 0.2 percent of all pulmonary neoplasms. The existing scant case reports about this lung malignancy mostly describe small lung lesions managed with upfront surgery followed by adjuvant radiotherapy. We hereby present this case of primary lung parenchymal pathology where the disease was treated with definitive chemo-radiation and to the best of our knowledge; this case is one of the rarest and earliest reports of upfront chemo-radiation in an inoperable primary lung parenchymal ACC. A 43-year-old woman presented with complaints of cough, severe dyspnea, right sided chest pain associated with occasional hemoptysis. Radiographic imaging of thorax showed a large mass lesion with smooth margins measuring 10.2 × 7.3 × 6.8 cm right lower lobe with invasion of adjacent vital structures. Image guided biopsy and immunohistochemical analysis confirmed the diagnosis. She was eventually treated with definitive radiotherapy with concurrent chemotherapy as she was deemed inoperable. Post therapy evaluation by imaging showed a partial response to chemo-radiation, however there was significant symptomatic relief. In view of CD 117 positivity, she has started on oral imatinib mesylate. Presently she is on follow up with a karnofsky performance status of 90%. A thorough review of literature also reveals that our case may be the largest adenoid cystic primary parenchymal pulmonary pathology ever reported.

Keywords: Adenoid cystic carcinoma, Lung, Radiotherapy, Chemotherapy

1. Introduction

Adenoid cystic carcinoma (ACC) is a rare, slow growing neoplasm of major and minor salivary glands accounting for 10% of all salivary gland tumors.¹ They originate from secretory glands found predominantly in head and neck region like lips, oral cavity, external auditory canal, nose, orolaryngopharynx, upper aerodigestive tract locations like esophagus, trachea and carina.² Primary lung ACCs are very rare and account for 0.04 to 0.2% of all lung tumors^{3,4} which can be central arising in trachea, main bronchus or segmental bronchi⁵ while peripheral lung parenchymal tumors are much rarer comprising of only 10% of all primary lung ACCs⁶ as in our case. Majority of case reports recommend surgery as the first line management of ACC lung with radiotherapy (RT) reserved for post-operative stage for local control of

disease. Upfront RT for unresectable ACC of trachea has shown satisfactory results⁷ while its definitive role in primary lung parenchymal ACC is still undefined. Since very less is known regarding the molecular pathways responsible for the pathogenesis of pulmonary ACC, chemotherapy has a very limited role⁸ apart from using imatinib mesylate in c-Kit positive cases^{9, 10} and concurrent carboplatin-paclitaxel with RT in unresectable tracheal ACCs.¹¹ Faced with this therapeutic challenge we used definitive RT with concurrent carboplatin and paclitaxel followed by oral imatinib.

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Cite this article as: Purkayastha A, Sharma N, Viswanath S, Sunita B. Adenoid cystic carcinoma of lung: An oncologic rarity treated with definitive chemo-radiation. *Int J Cancer Ther Oncol.* 2016; 4(3):4315. DOI: 10.14319/ijcto.43.15

2. Case presentation

A 43-year-old female with no known comorbidities or addictions presented with complaints of cough, progressive dyspnea, right sided chest pain with occasional hemoptysis of 8 months duration. Chest roentgenogram showed a homogenous opacity in the right lower zone merging with mediastinum (Figure 1). Computed tomography (CT) scan of chest showed a large well defined peripherally based heterogeneously enhancing mass lesion with smooth margins (Figure 2) in posterior basal segment of right lower lobe measuring $7.3 \times 6.0 \times 10$ cm extending upto right hilum encasing the right bronchus intermedius and abutting the right main pulmonary artery, the inferior vena cava with loss of fat planes with right hemi-diaphragm (Figure 3). Bronchoscopy was normal and broncho-alveolar lavage did not show any malignant cells.



Figure 1: Plain radiograph of chest showing a homogenous opacity in the right lower zone merging with mediastinum (yellow pointer).

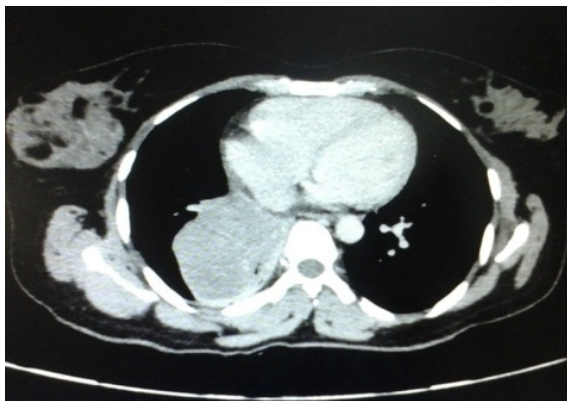


Figure 2: CT scan chest (axial view) showing a large well defined peripherally based heterogeneously enhancing mass lesion with smooth margins in right lower lobe of lung.

A CT guided biopsy of the lung mass showed cribriform pattern of tissue intermixed with scanty areas of normal respiratory epithelium. The tumor cells formed nests and tubular patterns along with mucin collection in some spaces (Figure 4). Immunohistochemistry (IHC) stained positive for CD 117 (Figure 5), smooth muscle actin (SMA), cytokeratin-7 (CK-7), epithelial membrane antigen (EMA) (Figure 6) and S-100 while negative for thyroid transcription factor-1 (TTF-1), CD-56, CD-99, neuron specific enolase (NSE), synaptophysin and chromogranin, suggesting the diagnosis of ACC lung. Positron emission tomography (PET) scan showed a localized disease and magnetic resonance imaging (MRI) of brain was normal. Patient denied any history of oral malignancy in past.



Figure 3: CT scan chest (coronal view) showing the mass in posterior basal segment of right lower lobe extending upto right hilum with loss of fat planes with right hemi-diaphragm.

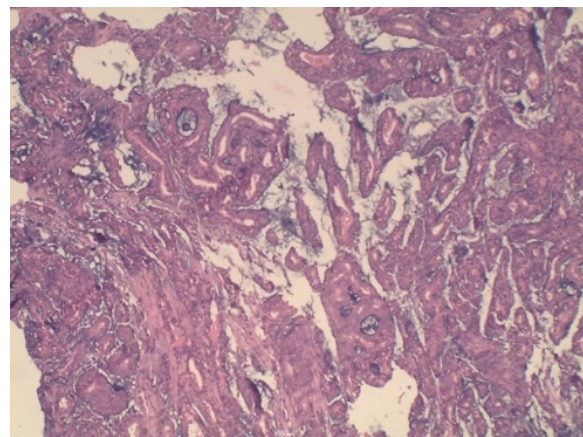


Figure 4: Biopsy of the lung mass showing cribriform pattern of tissue intermixed with scanty areas of normal respiratory epithelial lining forming nests and tubular patterns along with mucin collection in some spaces (H & E 100 X).

The patient was deemed inoperable due to involvement of adjacent vital structures where surgical resection could have led to high morbidity. Because of the high disease load and aggravated symptoms she was treated with definitive conformal radiation therapy to a dose of 60 Gray (Gy) in 30 fractions along with concurrent chemotherapy weekly Carboplatin (area under curve 2) and paclitaxel (50 mg/m²) for 6 weeks.

Patient tolerated treatment well and experienced significant reduction in her dyspneic episodes and cough with improvement in exercise tolerance. Response assessment with CT scan chest 12 weeks post combined therapy showed a partial response (PR) and to maintain the PR status of the patient she was started on oral imatinib mesylate (400 mg per day), a c-KIT tyrosine kinase inhibitor. Presently on regular follow up maintaining a Karnofsky Performance Status (KPS) of 90%.

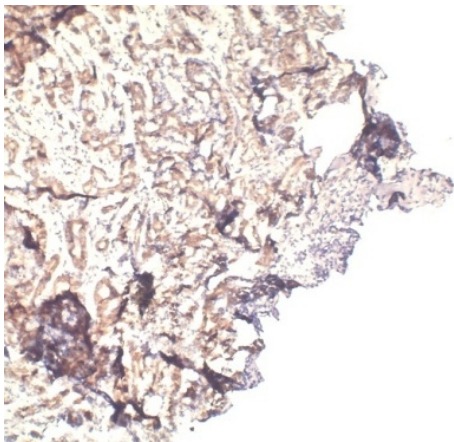


Figure 5: IHC showing CD 117/ c-Kit positivity (100 X).

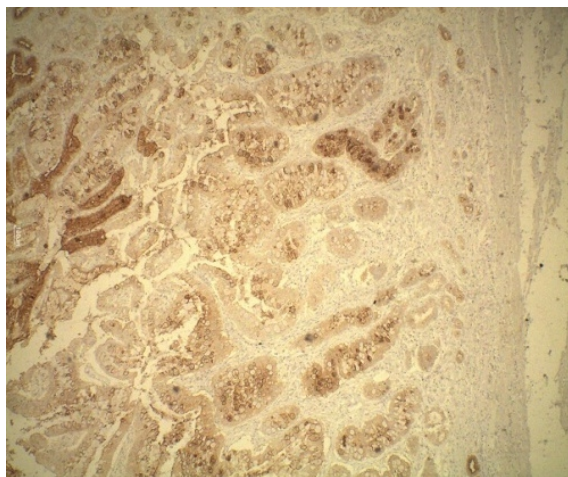


Figure 6: IHC showing EMA positivity (100 X).

3. Discussion

Adenoid cystic carcinoma (ACC) is a rare malignancy belonging to the adenocarcinoma group denoting a

glandular origin arising from both minor and major salivary glands of head and neck, comprising 10% of salivary gland malignancies.¹ The involved sites are lips, oral cavity, hard palate, nasopharynx, external auditory canal, oropharynx, larynx, parotids, submandibular, sublingual glands and the aerodigestive structures like esophagus, trachea, carina, main bronchus and segmental bronchi² while lung parenchymal tumors are much rarer.⁶ ACC are also known to arise in lacrimal glands, skin, breast, cervix and bone. ACC is known for its indolent clinical course with a propensity for perineural invasion resulting in high incidence of local recurrence and distant metastasis to lungs followed by liver.¹²

Primary pulmonary ACC are extremely rare and comprise 0.04 to 0.2% of all lung malignancies.^{3,4} These can arise from tracheobronchial glands of central pulmonary structures like trachea, main bronchus, both extra-pulmonary and intra-pulmonary bronchi⁵ accounting for 0.2%¹³ of all lung primaries while peripheral lung parenchymal ACCs are exceedingly rare constituting just 10% of all pulmonary ACCs.⁶ The risk factors associated with lung ACC are not known and smoking, alcohol consumption, environmental carcinogen exposure, infection or any family history are not commonly associated as compared to squamous cell lung carcinomas. It is an equal opportunistic disease affecting young and middle aged individuals both males and females with a slight tilt towards the male sex in their fourth to sixth decade of life, a decade younger than other lung carcinomas.²

Most common presentations of lung ACCs are cough, chest pain, dyspnoea, hemoptysis, wheeze and stridor in tracheal involvement. The clinical course may be slow and meandering with symptoms appearing months before a patient reports to a physician for any troublesome complaints. Initial Imaging with chest roentgenogram, CT scans, magnetic resonance imaging (MRI) generally show intrapulmonary heterogeneously enhancing mass lesions often invading surrounding structures and vital organs but do not possess the specific features to differentiate the mass from other lung neoplasms while PET scans and bone scans often form the part of a metastatic workup. In our case the mass lesion on CT scan showed a smooth margin as compared to irregular margins of squamous cell histology.

Primary lung ACC can be often be misdiagnosed with a metastatic lung lesion, mucinous adenocarcinoma or primitive neuroectodermal tumors (PNETs) and therefore a thorough history of tumors in other sites of body especially in oral cavity is of utmost importance. IHC is crucial for the exact diagnosis, however there are very few case defining the IHC characteristics of ACC lung.^{14,15} Hu *et al.*¹⁴ and Moran *et al.*¹⁵ reported immunopositivity for p63, S-100, SMA and EMA while

immunonegative for TTF-1, CD 56, CK-20. Our case stained positive for CK-7 which favored a lung origin. TTF-1 is found predominantly in pulmonary adenocarcinomas and thyroid, CD 56 is expressed in any neuroendocrine tumors or PNET group of tumors while CK-20 denotes any gastro-intestinal origin which was negative in our case thus ruling out other lung lesions and establishing the diagnosis of primary ACC lung. Our case stained positive for CD 117, a stem cell growth factor receptor (SCGFR) also known as proto-oncogene c-Kit or tyrosine protein kinase Kit expressed on surface of stem cells, mainly associated with gastrointestinal stromal tumors (GISTs), seminomas, melanomas and leukemias and ACC is also known to express high levels of CD 117 or c-Kit.¹⁶

Regarding management of ACC lung, surgical resection remains the optimal treatment approach wherever feasible.¹⁴ Hu *et al.*¹⁴ reported no overall survival benefit for patients with R0 and R1 resection, however rate of local recurrence was high in R1 individuals for which adjuvant RT was reserved for margin positive cases to reduce the rate of local recurrence and eventual distant metastasis. Definitive RT for primary lung parenchymal ACC has not been described in literature, however, unresectable tracheal entities have shown satisfactory results as were demonstrated by Fields *et al.*⁷ The role of chemotherapy in definitive or adjuvant setting is not proven, however, concurrent administration with RT in treating tracheal ACCs was described by Sasiya *et al.*¹⁷, Videtic *et al.*¹⁸ and Aaron *et al.*¹¹ using carboplatin and paclitaxel chemo-regime in management of tracheal ACCs with good result.^{11,17,18} Based on these facts we used upfront RT to a dose of 60 Gy with concurrent carboplatin-paclitaxel regime to which our case responded well, though with a radiological PR but with excellent symptomatic response. Imatinib mesylate, a c-Kit tyrosine kinase inhibitor (TKI) is used against ACC of salivary glands^{9, 10} but not for lung pathology. Since our patient was positive for c-kit, we used oral imatinib to maintain the PR status with significant response. The use of Sorafenib, a novel TKI has shown good response in metastatic ACC to lungs.¹⁹

4. Conclusion

By reporting this case, we recommend that the diagnosis of ACC lung should always be considered in patients presenting with cough and dyspnoea showing a pulmonary parenchymal mass on imaging. Presently there are no definite therapeutic guidelines for this disease entity as most information is based on solitary case reports and small case series. Apart from 3-DCRT, highly conformal techniques like intensity modulated radiotherapy (IMRT) and proton therapy can be used to prescribe higher radiation dosage without normal tissue toxicity. We also emphasize the need for clinical trials and better understanding of the molecular and biologic pathways involved in its pathogenesis with development

of novel chemotherapeutic drugs acting against this pulmonary pathology to improve the disease free and overall survival.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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