Original Article

Primary mucinous carcinomas of the lung: Clinical characteristics and treatment outcomes

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ABSTRACT

Introduction: Invasive mucinous adenocarcinoma (IMA) of the lung is a distinct histologic variant of adenocarcinomas comprising about 2%–10% of lung adenocarcinomas. A large proportion of IMAs carry KRAS mutations and only rarely epidermal growth factor receptor (EGFR) mutations or ALK/ROS translocations; thus, most cases are not amenable for targeted therapy at present. This study was conducted to elicit the unique clinicopathological characteristics of IMA. **Materials and Methods:** Medical records of patients diagnosed with IMA by needle biopsy at Kidwai Cancer Institute, Bangalore, from 2013 to 2018, were retrieved and reviewed. Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). **Results:** Four hundred and ninety cases of needle biopsy of the lung were diagonosed at our institute between January 2013 and December 2018. Nine cases (1.8%) were diagnosed as IMA. The median age of presentation was 59 years. Six (66.7%) were current smokers with pack-year > 20. Three (33.3%) of the cases were initially misdiagnosed as pneumonia in view of computed tomography findings. The lung was the most common site of metastasis (77.8%). Serum Carcinoembryonic Antigen (CEA) was elevated in six cases (66.7%). None of the cases had any driver mutations in EGFR gene or ALK and ROS1 translocations. All cases were treated with pemetrexed–carboplatin doublet followed by pemetrexed maintenance till progression. The median progression-free survival (PFS) was 15 months (range: 5–18 months). Docetaxel was given as the second-line chemotherapy in all progressed patients. Best response noted was stable disease, seen in 4 (57.1%) cases. The median PFS for docetaxel was 6 months (range: 3–8 months). The median overall survival was 22 months (range: 9–27 months). Patients with initially raised CEA at progression had a serial rise in serum CEA. **Conclusions:** IMA is rarely diagnosed on needle biopsies due to insufficient tissue. They mimic pneumonia on imaging, thus delaying diagnosis. EGFR mutations, ALK, and ROS1 translocations are usually negative making them ineligible for tyrosine kinase inhibitors. Response to chemotherapy is modest.

KEY WORDS: Invasive mucinous carcinoma, mucinous adenocarcinoma, non-small cell lung cancer

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INTRODUCTION

Mucinous adenocarcinoma of the lung is an unusual histological variant of lung cancer. It was previously called bronchoalveolar carcinoma, and in 2015, the World Health Organization Classification of lung tumors categorized

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them as invasive mucinous adenocarcinomas.[1] It accounts for about 5% of cases in resected specimens.[2] However, their diagnosis is difficult on small biopsy specimens and may be missed. It is a distinct subtype of lung cancers with different clinical presentation and genetics. They mimic pneumonia on imaging leading to delay in diagnosis. They harbor k-RAS mutations and are usually epidermal growth factor receptor (EGFR) wild type, thus making them nonamenable for targeted treatment at present.[3]

This study is aimed at documenting the clinical characteristics of invasive mucinous adenocarcinoma (IMA) and their response to conventional chemotherapeutics.

MATERIALS AND METHODS

Medical records of patients diagnosed with IMA by needle biopsy at Kidwai Cancer Institute, Bangalore, from January 2013 to December 2018 were retrieved. Patient follow-up data were traced till July 2019. All patients' medical records were reviewed to investigate the clinical presentations, including age, gender, site of disease, treatment, and outcomes. The diagnosis was made based on the morphology – cancer cells were characterized by tall columnar cells with abundant cytoplasm that contain varying amounts of mucin. The following immunohistochemistry (IHC) markers were used to differentiate between primary and metastatic tumors: CK7, CK20, CDX2, WT1, PAX8, ER, CEA, TTF1, and Napsin. RECIST 1.1 was used for response evaluation. Overall survival (OS) was measured from diagnosis to death or the last follow-up. Progression-free survival (PFS) for first-line therapy was measured from diagnosis until the documentation of progression. PFS for first-line therapy was measured from progression with first-line therapy till disease progression with second-line therapy. Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patients and clinical characteristics
Four hundred and ninety cases of needle biopsy of lung were done at our institute between January 2013 and December 2018. Nine cases (1.8%) were diagnosed as IMA. The median age of presentation was 59 years (range: 49–76 years). The male-to-female ratio was 2:1. Six (66.7%) were current smokers with pack year >20. The median symptom duration before diagnosis was 3 months. Three (33.3%) cases were initially misdiagnosed as pneumonia in view of computed tomography (CT) findings of pneumonia-like multifocal consolidative appearance. Lung was the most common site of metastasis (77.8%). Serum CEA was elevated in six cases (66.7%). The clinical characteristics are summarized in Table 1.

Diagnosis and molecular pathology
The diagnosis was made by the characteristic appearance of mucin-secreting columnar cells with abundant cytoplasm.

IHC panel was done which showed variable expression of CK7, CK20, CDX2, TTF1, and Napsin [Table 2]. CEA was positive in all specimens. ER, WT1, and PAX8 were done only in female patients and were negative in all of them. Patients with CDX2 did not have any lesions in the gastrointestinal tract that suggested the lung to be metastatic; thus, these tumors were also considered to be lung primaries. Figure 1 shows the IHC results of one of the patients.[3] All the cases were negative for EGFR mutations, ALK, and ROS1 translocations.

Treatment and outcomes
All cases were treated with pemetrexed–carboplatin doublet followed by pemetrexed maintenance till progression. Five (55.6%) patients had stable disease, 3 (33.3%) had partial response, and 1 (11.1%) had progressive disease. The median PFS was 15 months (range: 5–18 months).

Docetaxel was given as second-line chemotherapy in all progressed patients. The best response noted was a stable disease, seen in 4 (57.1%) cases. The median PFS for docetaxel was 6 months (range: 3–8 months).

The median OS was 22 months (range 9–27 months). Figure 2 shows the Kaplan–Meier curves. Patients with

Table 1: Clinical characteristics of patients

Clinical characteristics	*N* (%)
Median age (years)	59 (49-7)
Gender (%)	
Male	6 (66.6)
Female	3 (33.3)
Smoking status	
Smoker	6 (66.6)
Nonsmoker	3 (33.3)
Site of metastasis	
Lung	7 (77.8)
Nonregional lymph nodes	4 (44.4)
Bone	2 (22.2)
Serum CEA	
CEA raised	6 (66.6)
CEA normal	3 (33.3)

CEA: Carcinoembryonic Antigen
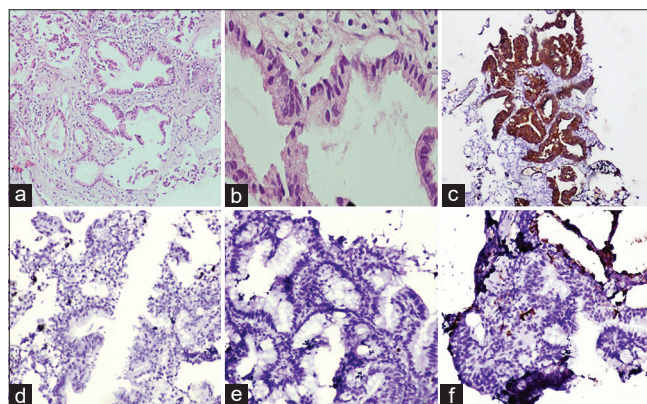
Figure 1: IHC panel done in one of the cases. (a) H/E Low power. (b) H/E High Power – Tumour showing gland formation. (c) CK7+. (d) CK20–. (e) TTF–. (f) Napsin –
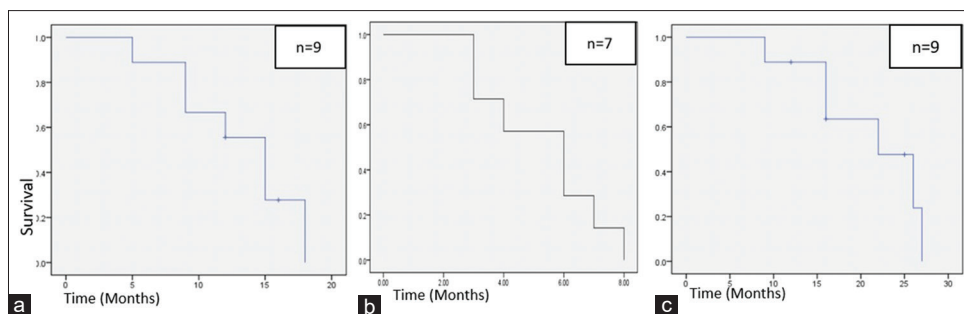
Figure 2: Kaplan–Meier curves showing. (a) Progression-free survival with first-line chemotherapy. (b) Progression-free survival with second-line chemotherapy. (c) Overall survival

Table 2: Immunohistochemistry findings, progression-free survival with first-line therapy and overall survival

Patient ID	IHC	PFS with first-line chemotherapy (months)	OS (months)	Status at last follow-up
1	CK7+, CK20-, TTF1+, CDX2-, and Napsin-	9	16	Dead
2	CK7+, CK20-, TTF1+, CDX2-, and Napsin+	12	12	Alive
3	CK7-, CK20+, TTF1-, CDX2+, and Napsin+	15	25	Alive
4	CK7+, CK20-, TTF1-, CDX2-, and Napsin-	9	16	Dead
5	CK7-, CK20-, TTF1-, CDX2-, and Napsin-	12	27	Dead
6	CK7-, CK20-, TTF1-, CDX2+, and Napsin+	16	16	Alive
7	CK7-, CK20-, TTF1-, CDX2-, and Napsin+	18	26	Dead
8	CK7-, CK20+, TTF1+, CDX2+, and Napsin-	15	22	Dead
9	CK7+, CK20-, TTF1+, CDX2-, and Napsin-	5	9	Dead

PFS: Progression-free survival, OS: Overall survival, IHC: Immunohistochemistry

Table 3: Comparison of our data with other studies

	This study	Cha *et al*., 2016[3]
Total patients	9	36
Duration of study	January 2013-December 2018	March 2000-February 2015
Study site	Bangalore, India	Seoul, South Korea
Response with chemotherapy, *n* (%)	9 (100)	
Partial response	5 (55.5)	5
Stable disease	3 (33.3)	9
Progressive disease	1 (11.1)	20
EGFR mutation or ALK/ROS1 rearrangement	0	0
K-RAS mutations (%)	Not done	15/25 (60)

EGFR: Epidermal growth factor receptor, ALK/ROS1: Anaplastic Lymphoma Kinase/ c-ROS oncogene, K-RAS: Kirsten Rat Saecoma viral oncogene

initially raised serum CEA at progression had a serial rise in serum CEA.

DISCUSSION

Invasive mucinous adenocarcinoma is an unusual histological variant of lung cancer. It constitutes about 2%–10% of adenocarcinomas in various series. Diagnosis is mainly made on resected specimens and difficult to make on small biopsies. Mucus production is a typical feature which may be discharged as sputum, but if excessive mucin is produced, it may obstruct airways and cause obstructive pneumonia.[4] A characteristic feature of IMA is spread through airspace. It is a concept defined as the spread of tumor cells within the air spaces in lung parenchyma beyond the edge of the main tumor.[5] The abundant alveolar mucin production in IMA allows tumor cells for intrabronchial and intra-alveolar spread.[6]

It has a distinctive clinical course. It is usually misdiagnosed as pneumonia on imaging which leads to diagnostic delay. In our series, one-third of the patients were initially treated as pneumonia before a diagnosis of carcinoma was made. Cha *et al*. reviewed 36 cases of IMA and reported that they were predominantly located in lower lobes (75%), frequently presented with lung-to-lung metastasis and multifocal consolidation.[3] In our series, 3 patients (33.3%) had features suggestive of consolidation on CT and the lung was predominant site of metastasis (77.8%).

Shim *et al*. extensively studied the molecular makeup of IMAs. They found that most cases were associated with KRAS mutations, followed by NRG1 fusions. The mutational burden was lower in mucinous tumors compared to nonmucinous tumors. EGFR was rarely mutated in these tumors.[7,8] In our series too, all the cases were EGFR wild type.

Cha *et al*. analyzed the survival of IMAs compared to other invasive adenocarcinomas of the lung and stated that when treated with chemotherapy, OS was similar in both the groups. With regard to tumor response, IMA had lower rates of partial response to chemotherapy compared to other adenocarcinomas. The overall duration of response was also significantly better in non-IMA group. The objective response rate with platin combination was 4.2% and with pemetrexed (or pemetrexed-based combination)

was 36.4%. The disease control rate was 25% and 72.7%, respectively, among IMAs.[3] In our series, all patients were treated with pemetrexed–carboplatin combination and partial response was seen in only 33.3% of the cases. However, OS was 16 months with chemotherapy alone. This suggests that IMAs are less responsive to treatment with chemotherapy, but this does not translate into a poorer outcome. Serum CEA was elevated in two-third of the cases and could be used as a tumor marker to monitor progression in these cases. Table 3 compares our data with that of Cha *et al.* In our series, many cases of IMA may have been missed due to the small size of the biopsy and limited tissue for definitive diagnosis.[9] Furthermore, since IMAs are a relatively rare entity, metastasis from common mucinous tumors of the gastrointestinal tract has to be kept in mind. IHC markers like CDX-2 help in differentiating primaries of the lung. In our series, three patients had CDX2 positivity; however, no lesion in the gastrointestinal tract was found on imaging, colonoscopy, or endoscopy in any of them to suggest a different primary. Mucinous tumors of the ovary and breast also metastasize to the lung and need to be excluded. IMAs of the lung may be negative for both Napsin and TTF1, as seen in two of our patients [Table 2]. These are similar to previously reported IHC features of IMAs.[6]

Newer modalities of therapy are required in IMA to improve survival. The benefit of immunotherapy needs to be explored. IMAs have lower mutational burden than other tumors and response to immunotherapy may be limited. Guo *et al.* tried to identify a mutational signature for IMA. They reported that PDL1 is expressed only in <10% of the cases. A different immune checkpoint VTCN1 (also known as B7-H4) is expressed in 64% of the cases. Thus, the current immunotherapy regimens that focus on either PD1-PDL1 or CD28-CTLA-4 axis may not be beneficial.[10] Nakaoku *et al.* identified NRG1 fusion proteins in up to 18% of IMA without k-ras mutations. Thus, NRG1 fusion protein inhibitors may be a suitable target for these tumors.[11]

CONCLUSIONS

IMAs have clinically and genetically distinct characteristics. Diagnosis may be missed on small biopsies. Response to conventional chemotherapeutics is poor. Serum CEA may be used as a tumor marker for response assessment. EGFR and other common driver mutation/translocation pathways with drug targets are usually absent in IMA. NRG1 fusion may be a possible target for drug development.

Conflicts of interest
There are no conflicts of interest.

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