Molecular features of giant-cell carcinoma of the lung: a case report and literature review

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Abstract: Giant-cell carcinoma of the lung (GCCL) is a rare histological form of poorly differentiated non-small-cell lung cancer, which is classified as a subtype of pulmonary sarcomatoid carcinomas. In this case report, we describe the case of a 50-year-old Chinese male who presented with a pulmonary nodule in the right upper lobe of his lung. After thoracoscopic lobectomy, a histopathologic diagnosis of GCCL was made. He did well postoperatively, showing no local recurrence or distal disease in a 7-year follow-up period. Furthermore, for this case, we also analyzed 295 tumor-related driver genes with high-throughput sequencing technology. We found that treatment using MEK inhibitor, CDK 4/6 inhibitor, and TP53 inhibitor may provide a new therapeutic direction for GCCL. Therefore, complete tumor excision is the best choice of treatment strategy at the early stage of GCCL and gene target therapy may be a new therapeutic option for this disease.

Keywords: giant-cell carcinoma of the lung, high-throughput sequencing, gene mutation

Introduction

According to the 2004 World Health Organization (WHO) classification of lung tumors, giant-cell carcinoma of the lung (GCCL) is classified as a subtype of pulmonary sarcomatoid carcinomas (PSCs).\(^1\) PSC accounts for 2%–3% of all lung cancers and is associated with smoking, which is more common in males. The mean age of onset is about 59 years, and generally, no specific signs or symptoms are observed.\(^2\)\(^-\)\(^4\) There are five subtypes of PSCs: polymorphic carcinoma, spindle cell carcinoma, giant-cell carcinoma, carcinosarcoma, and pulmonary blastoma.\(^1\) Herein, we report the case of a patient who presented with complaints of cough and bloody sputum, and received the diagnosis of GCCL followed by tumor resection in the right lung.

Case presentation

Seven years ago, a 50-year-old Chinese male with cough and expectoration (black phlegm) for about 2 weeks, sometimes accompanied with bloody sputum and breathlessness, was admitted to our hospital. These symptoms developed without apparent cause and in the absence of problems such as chest pain and/or distress, fever, nausea, or vomiting. A computed tomography (CT) scan of his chest showed a rough-edged shadow measuring nearly 32×22×10 mm in the right upper lobe of his lung, as shown in Figure 1 (A: before surgery; B: after surgery). The patient acknowledged several chronic disorders, including a 10-year history of bronchitis and emphysema, and was a smoker with a 30-pack-year history. The patient had no family history of lung cancer. There was no obvious abnormality noted in his system review. The results of a peripheral blood count, baseline serum chemistry screening, and urinalysis were normal on
admission, and tumor biomarker tests and a purified protein derivative test for tuberculosis were also negative. A rough-edged shadow of his right upper lobe was once again seen on an enhanced CT scan of his chest, although a CT scan of his abdomen, magnetic resonance imaging of his brain, and a bone scan were all normal. His right bronchial tree also appeared normal on bronchoscopic examination, with no indication of malignancy in the biopsy and washings procured.

A right-sided upper lobectomy and systematic mediastinal lymphadenectomy were performed. A tumor of his right upper lobe, roughly 3 cm in diameter, was evident at surgery, without puckering of visceral pleura. Microscopic sections showed the following findings: there were many large, multicore, and bizarre giant cells, without special arrangement; cytoplasm was moderate to abundant, dense, and eosinophilic; nucleus was pleomorphic and phylloid; and the tumor cells appeared to have lost adhesion, and to be separated and embedded in a fibrous myxoid stroma. Histopathologic examination revealed the tumor cells were positively reactive to cytokeratin (CK) and vimentin, while immunostaining for chromogranin A (CgA) and synaptophysin (Syn) was negative, as shown in Figure 2. Diagnostically, vimentin is the major cytoskeletal component of mesenchymal cells and is often used as a marker of mesenchymally derived cells or cells undergoing an epithelial-to-mesenchymal transition during metastatic progression. Here, it was used as a sarcoma tumor marker to identify mesenchyme. Syn is often combined with CgA as a specific marker to identify tumors arising from neural and neuroendocrine tissues, such as neuroblastoma, carcinoid, and small-cell carcinoma. Therefore, the above findings supported the diagnosis of a GCCL. The detection of bronchial stump and mediastinal lymph nodes was negative,

Figure 1 Computed tomography (CT) scans of the chest. (A) CT scan before surgery: tumor-like mass in the right upper lobe with blurred contour and irregular margin shown in the lung and mediastinal windows. (B) The 7-year follow-up CT scan after surgery.

Figure 2 Pathological characteristics demonstrated by H&E staining and immunohistochemistry. CK and vimentin immunostaining was positive, while CgA and Syn immunostaining was negative. Abbreviations: CgA, chromogranin A; CK, cytokeratin; H&E, hematoxylin and eosin; Syn, synaptophysin.
and it indicated that there was no lymph node metastasis in this patient.

Since 2 months after surgery, the patient was treated with combined chemotherapy using gemcitabine (1,000 mg/m² on days 1 and 8) and cisplatin (75 mg/m² on day 1) every 3 weeks for four cycles, and then whole-body radiography examinations were carried out every year in a local hospital. He was still alive 7 years after surgery, free from disease progression. Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Follow-up and outcomes

Until now, the therapeutic result of this case is satisfactory. With the development of high-throughput sequencing technology, more and more genomes have been successfully sequenced. Recently, in order to explore the molecular structure of this tumor, mutations of 295 tumor-related driver genes were detected by a high-throughput sequencing test (Burning Rock Biotechnology Inc., Guangzhou, People’s Republic of China). All the 295 genes are listed in Table S1. We analyzed normal and tumor tissues of this patient, after ruling out genetic variations; nine tumor-related somatic mutations were confirmed, of which six were missense variants and three were synonymous variants. The high-throughput screening results of the patient are shown in Table S2. The six missense mutations included KRAS, KMT2D, TP53, SETD2, TET2, and MAP3K. As a hotspot mutation, KRAS gene mutation on chromosome 12, exon 2 p.G12D, with a mutant abundance of about 26.7%, indicated the tumor may be sensitive to MEK inhibitor and CDK 4/6 inhibitor like trametinib and abemaciclib. TP53 gene mutation on chromosome 17, exon 7 p.R249K, with a mutant abundance of about 8.30%, indicated the tumor cell may be sensitive to some novel compound that can reverse the TP53 mutation like APR-246. For the other four somatic mutations, including KMT2D, SETD2, TET2, and MAP3K, there was no sufficient evidence to show their correlation with target drugs known so far in clinical use.

Discussion and review of the literature

GCCL is a rare malignant form of large-cell lung carcinoma, a subtype of PSCs. Nash and Stout first described this tumor in 1958. For the past 25 years, the WHO has been under constant pressure to change the classification of sarcomatoid tumors of the lung, and this has been driven by our evolving understanding of their histogenetic origins. In the second revision (1981) of the WHO classification, GCCL was considered as a subtype of large-cell carcinomas. In the third revision (1999) of the WHO classification, it was placed within a subtype called “carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements”, along with pleomorphic carcinoma, spindle cell carcinoma, carcinosarcoma, and pulmonary blastoma, which are related variants. The rules for classifying PSC under WHO classification in 2004 were identified as more improved than in the past, for now accurate classification of a pulmonary carcinoma as a GCCL requires that the entire tumor consists only of malignant giant cells. Therefore, complete sampling of the entire tumor obtained via a surgical resection is absolutely necessary for a precise diagnosis of GCCL to be made.

Due to the lack of accurate data from a large sample, the incidence and mortality of GCCL is generally unclear until now. It is known to be a very rare tumor variant of all races. Travis et al described in their study of a database of more than 60,000 patients in the US that GCCL comprised about 0.3%–0.4% of primary lung cancers, with an incidence of about three new cases per million persons per year. However, the GCCL incidence was much lower than other four PSC subtypes, in a series of 4,212 lung cancer cases, in which only one (0.024%) case was confirmed to be a pure giant-cell component after complete sectioning of all tumor samples. Like other non-small-cell lung cancers (NSCLCs), GCCL can invade in any lung lobes, but it is observed much more frequently in the upper lobes and always at periphery. Usually, patients with GCCL complain of no specific signs or symptoms, but experience cough or hemoptysis, or may be asymptomatic just like other NSCLC patients. GCCL is a poorly differentiated tumor with early metastasis through lymph and blood circulation to the brain, bone, adrenal gland, and liver, similar to other NSCLCs, but uncommon metastasis to the gastrointestinal tract, kidney, and heart is reported constantly.

GCCL is essentially undifferentiated and usually appears as a bulky necrotic mass, having no distinct architectural pattern. Under microscope, the background of GCCL contains plenty of neutrophils and lymphocytes. The tumor cells are big, multi-core, and bizarre, and the size of the tumor cells varies by more than fivefold. The tumor cells have an abundant, thick, and well-demarcated cytoplasm. The nucleus is oval or irregular and centrifugal. Multinucleated giant cells are observed more often than uninuclear cells. The size of nucleus is more than five times that of normal lymphocytes. The nuclear membrane is thin, and nuclear chromatin is coarsely granular, while the nucleolus is single and round. In cytological preparations, giant cells typically appear as single cells or in flat loose clusters, and occasionally...
in fascicles. Another specific feature known about this malignancy is the presence of a phenomenon called emperipolesis: collections of polymorphonuclear leukocytes within the giant cells, apparently phagocytosing cytoplasmic contents. However, the etiology of emperipolesis in GCCL is unclear. Some exocrine features of GCCL are also analyzed under electron microscope. The immunohistochemical features of GCCL are also nondistinct. In Rossi et al’s study, CK7 was positive in two of three (67%) GCCL samples, thyroid transcription factor-1 was negative in one of three (33%) GCCL samples, and CK20 was negative in all three samples (100%).

GCCL does not have specific radiologic characteristics. Only Park et al described in their paper that on positron emission tomography scanning, GCCL was found to have exceedingly high standardized uptake values for radioactive glucose, values that were statistically significantly higher than other histological variants of lung cancer, and so it was difficult to diagnose with only radiologic imaging such as CT and magnetic resonance imaging.

For limited-stage GCCL, surgical resection is an effective treatment and provides adequate local control. However, most cases of GCCL are quite advanced at the time of diagnosis (50% of patients present with metastasis situation), and even after surgery, most patients experience tumor recurrence or death within 16–18 months. Platinum-based chemotherapy has been used to treat GCCL by most clinicians, but plenty of studies demonstrate the poor response of GCCL to chemotherapy in general. There is no study in the literature showing the efficacy of radiotherapy in the treatment of GCCL until now.

Because of the higher rate of resistance to conventional chemotherapy than other NSCLCs, we need more treatment options like molecular targeted therapy for patients with GCCL. However, molecular structure features of GCCL are still mysterious. A clinical trial involving 42 pleomorphic carcinomas was conducted to investigate the somatic mutations of EGFR and TP53. EGFR mutations were detected in carcinomas, including mixed components (giant cells, spindle cells, and/or adenocarcinoma cells). EGFR mutation was found in one pleomorphic carcinoma sample with more than 10% adenocarcinoma components, which indicated that point mutation may occur in adenocarcinoma area. However, EML4-ALK gene fusion was discovered in one sample comprising entirely spindle cells and giant cells, and no KRAS gene mutation was found in any sample. In this case, the tumor comprised pure giant cells, and missense mutation of the KRAS, TP53, KMT2D, SETD2, TET2, and MAP3K was detected. This result was similar to the finding of Terra et al. They reported 10 of 33 PSCs harbored KRAS mutations, and 19 cases had TP53 mutations. There are no relevant target drugs or clinical trials on KMT2D, SETD2, TET2, and MAP3K mutations until now. A selective allos-teric inhibitor of MEK1/MEK2, trametinib, showed similar progression-free survival and response rates as docetaxel in patients with previously treated KRAS-mutation-positive NSCLC in clinical trial GSK1120212. The JUNIPER study (NCT02152631) with abemaciclib, an inhibitor of CDK4 and CDK6, showed a safety profile allowing continuous dosing to achieve sustained target inhibition. The first-in-human experience demonstrates single-agent activity for patients with advanced breast cancer, NSCLC, and other solid tumors. The TP53 molecule is a nuclear protein with a tumor suppressor function related to sequence-specific DNA binding and repair of damaged DNA. Generally, mutant TP53-carrying tumors reveal poorer sensitivity to conventional chemotherapy and have worse prognosis than wild-type tumors. This is a possible reason for chemotherapy resistance of GCCL. The high incidence of TP53 mutation in human tumors made it a potential target for new-concept cancer therapy. APR-246 is an effective compound which can reverse the TP53 mutation in tumor cells by synergizing with many DNA-damaging cytotoxic drugs and has little toxicity on normal cells. However, the effect of APR-246 on GCCL needs more experimental confirmation.
**Conclusion**

GCCL is a poorly differentiated non-small-cell lung cancer. Throughout the decades, the classification and concepts pertaining to the histogenesis have been controversial before the five subtypes of PSCs were established by the WHO. GCCL has exceptionally aggressive characteristics, and its prognosis is much poorer than other NSCLCs. Although complete tumor excision and chemotherapy are often adopted in clinical use, the tumor seems to have a poor response to any currently known treatment modality, including platinum-based chemotherapy and radiotherapy. More studies are needed to deeply understand the molecular structure of GCCL, and target therapy using MEK inhibitor, CDK 4/6 inhibitor, and TP53 mutation reversal drugs may be a potent treatment option for this disease in future.

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**Author contributions**

Xin Li and Jun Chen wrote the manuscript and analyzed all of the data. Xin Li, Zihe Zhang, Jinghao Liu, and Sen Wei provided medical care for the patients and collected the data. Dan Wang assisted in the pathological analysis. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

**Disclosure**

The authors report no conflicts of interest in this work.

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**Supplementary materials**

**Table S1** Cancer-related 295-gene panel

| Gene     | Reference | Amino acid change | Impact | Mutant abundance |
|----------|-----------|------------------|--------|-----------------|
| ABL1     | BRAF      | KRA5             | Missense_variant | Moderate         |
| AKT1     | BRC1A     | KMT2D            | Missense_variant | Moderate         |
| AKT2     | CIC       | TP53             | Missense_variant | Moderate         |
| AKT3     | CRBN      | EWSR1            | Synonymous_variant | Low |
| ALK      | CREBBP    | E2F2             | Synonymous_variant | Low |
| ALOX12B  | CRKL      | FAM123B          | Synonymous_variant | Low |
| APC      | C110R30    | FAM6C            | Synonymous_variant | Low |
| APCDD1   | C170R39    | GATA1            | Synonymous_variant | Low |
| AR       | C14DD1    | TCF3             | Synonymous_variant | Low |
| ARAF     | CASP8     | GNA1I            | Synonymous_variant | Low |
| ARFRIP1  | CBFB      | GNAQ             | Synonymous_variant | Low |
| ARID1A   | CBL       | GNAS             | Synonymous_variant | Low |
| ARID1D   | CUL4B     | GPR124           | Synonymous_variant | Low |
| ASXL1    | CCND2     | GRIN2A           | Synonymous_variant | Low |
| ATM      | CCNE1     | HGF              | Synonymous_variant | Low |
| ATR      | CD79A     | HLA-A            | Synonymous_variant | Low |
| AURKA    | CD79B     | FBXW7            | Synonymous_variant | Low |
| AURKB    | CDC73     | IDHI             | Synonymous_variant | Low |
| AXL      | CDH1      | IDH2             | Synonymous_variant | Low |
| BACH1    | CDK12     | IGF1             | Synonymous_variant | Low |
| BAPI     | CDK4      | IGFI             | Synonymous_variant | Low |
| BARD1    | CDK6      | IGFR             | Synonymous_variant | Low |
| BCL2     | CDK8      | IKBK             | Synonymous_variant | Low |
| BCL2L2   | CDKN1B    | IFP3             | Synonymous_variant | Low |
| BCL6     | CDKN2A    | IL7R             | Synonymous_variant | Low |
| BCOR     | CDKN2B    | INHBA            | Synonymous_variant | Low |
| BCORL1   | CDKN2C    | IFR4             | Synonymous_variant | Low |
| BCR      | CEBPA     | IRS2             | Synonymous_variant | Low |
| BLM      | CHEK1     | PTEN             | Synonymous_variant | Low |
| FOXL2    | CREBBP    | E2F2             | Synonymous_variant | Low |
| IDH1     | DDI1      | JAK1             | Synonymous_variant | Low |
| MDM4     | FOXL2     | JAK3             | Synonymous_variant | Low |
| MDM2     | FOXL2     | JAK3             | Synonymous_variant | Low |
| MDM4     | FOXL2     | JAK3             | Synonymous_variant | Low |
| MPM1     | FOXL2     | JAK3             | Synonymous_variant | Low |
| NPM1     | FOXL2     | JAK3             | Synonymous_variant | Low |
| NIP1     | FOXL2     | JAK3             | Synonymous_variant | Low |
| NIP1     | FOXL2     | JAK3             | Synonymous_variant | Low |
| NIP1     | FOXL2     | JAK3             | Synonymous_variant | Low |
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| NIP1     | FOXL2     | JAK3             | Synonymous_variant | Low |
| NIP1     | FOXL2     | JAK3             | Synonymous_variant | Low |
| NIP1     | FOXL2     | JAK3             | Synonymous_variant | Low |
| NIP1     | FOXL2     | JAK3             | Synonymous variant | Low |
| NIP1     | FOXL2     | JAK3             | Synonymous variant | Low |

**Table S2** High-throughput sequencing results of the patient

| chr:posi | ref>alt | Type | Gene name | Amino acid change | Effect | Impact | Mutant abundance |
|----------|--------|------|-----------|------------------|--------|--------|-----------------|
| 12:253982849 | C>T | SNP | KRAS | p.G12D | Missense_variant | Moderate | 26.7% |
| 12:34920858 | C>T | SNP | KMT2D | p.R4964H | Missense_variant | Moderate | 34.0% |
| 17:7577535 | C>T | SNP | SETD2 | p.E1222K | Missense_variant | Moderate | 8.30% |
| 3:47147512 | T>C | SNP | SETD2 | p.Y1605C | Missense_variant | Moderate | 16.60% |
| 4:106164796 | G>A | SNP | TET2 | p.L2345 | Missense_variant | Moderate | 48.50% |
| 5:56177065 | A>T | SNP | MAP3K1 | p.T779S | Missense_variant | Moderate | 41.40% |
| 12:19434520 | A>G | SNP | KMT2D | p.D828 | Synonymous_variant | Low | 6.40% |
| 17:8882693 | C>T | SNP | RPTOR | p.D828 | Synonymous_variant | Low | 42.60% |

**Abbreviations:** alt, gene alteration; chr, chromosome; posi, position; ref, reference genome; SNP, single-nucleotide polymorphism.