To the Editor: Extranodal, nongestational choriocarcinomas are very rare neoplasms that mostly arise spontaneously in midline structures, such as the retroperitoneum, mediastinum, and vicinity of the pineal body, but they also have been reported in other visceral organs, such as the stomach, esophagus, small bowel, prostate, and urinary bladder.[1] In the last seven decades, there have been only 29 cases of male primary pulmonary choriocarcinoma (PPC) reported in the literature. Extranodal choriocarcinoma arising in the lung is thought to be unresponsive to treatment and is associated with a poor prognosis. We report a 71-year-old male patient with extranodal, nongestational choriocarcinoma apparently arising in the lung and review the characteristics of previously reported cases to explore the diagnosis and treatment of primary choriocarcinoma of the lung.

A 71-year-old man with a smoking history of 400 packs/year presented with cough and hemoptysis. A computed tomography (CT) scan revealed a 1.6-cm tumor with homogeneous density and smooth borders in the right medial lobe of the lung without swelling of the regional lymph nodes [Figure 1a–1c]. Both abdominal and brain CT scans showed abnormal findings. The results of routine laboratory examinations were all normal except for carcinoembryonic antigen (7.3 ng/ml) and D-dimer (0.79 mg/L) levels. Percutaneous lung puncture by CT localization was performed, which led to a pathological diagnosis of carcinoma without determinative findings to specify the histologic subtype of a frozen section [Figure 1d]. Therefore, right medial lobectomy followed by systemic lymph node dissection was performed. Pathological examination of permanent sections evidenced mononuclear cytotrophoblastic cells and syncytiotrophoblastic giant cells that were positive for immunostaining of beta-human chorionic gonadotrophin (β-HCG) [Figure 1e–1l]. No lymph node metastasis was observed. After the operation, serum and urine β-HCG levels were measured for the first time. The serum β-HCG level was 407.23 U/L (normal, 0–5 U/L), and the β-HCG level in the urine test was suspiciously positive. Systemic and brain CT scans showed abnormal findings. Nevertheless, the possibility of a metastasis from structures or in other visceral organs by CT scan or abdominal echography. The preoperative β-HCG level was absent, and tumor cells were poorly differentiated. The diagnosis of PPC was confirmed by histological features combined with immunohistochemical detection. In addition, the serum β-HCG level was confirmed to be significantly elevated postoperatively.

Since the lung is a frequent site of metastatic choriocarcinoma, the primary tumor should be diagnosed carefully. In this case, there were no lymph node metastasis and no apparent evidence of a primary genital tumor, and no lesions were found in midline structures or in other visceral organs by CT scan or abdominal echography. Nevertheless, the possibility of a metastasis from occult lesions in other locations could not be ruled out completely because the request for an autopsy was denied.

Currently, there is no established postoperative management for PPC because of its rarity. Male PPC is extremely rare, and 30 cases, including the current case, have been reported so far [Supplementary Table 1]. Patients with clinical data in publications

A Case of Male Primary Pulmonary Choriocarcinoma

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were aged from 4 months to 77 years.\(^1\) The median age of the patients was 53.1 years. Most patients had symptoms such as pleuritic pain, hemoptysis, dyspnea, cough, or precocious puberty, whereas 1 case was asymptomatic, and the tumor was discovered by chest roentgenogram. The fact that 8 cases have been diagnosed at autopsy reflects the aggressive nature of this tumor. Only 1 patient was diagnosed by a urine pregnancy test and bronchoscopic biopsy. One patient was diagnosed by CT-guided biopsy before the operation. Diagnosis is usually delayed until the patient is in the middle-late stage of the disease. Distant metastases are observed in many cases\(^1\) at the time of diagnosis, and overall prognosis is extremely poor. Treatment data were available for 22 patients: 8 patients were treated with surgery and chemotherapy; 1 was treated with surgery and radiotherapy; 3 were treated with surgery, chemotherapy, and radiotherapy; 4 were treated with chemotherapy alone; 3 were treated with surgery alone; and 3 patients did not receive treatment and died quickly. Only 5 patients survived for >1 year.

The treatment strategies performed on patients included complete resection, chemotherapy, radiotherapy, supportive care, or a combination of the above treatments in published cases. At present, there is no evidence-based treatment recommendation, which makes it difficult to plan further therapy.

Next-generation sequencing is becoming more widely used as a valuable method for somatic mutation analysis in cancer. Comprehensive tumor mutation profiles can help identify biomarkers that are prognostic or predictive, relevant in clinical trials, or can be used for future development of novel therapies. We performed targeted capture sequencing covering 1021 cancer-related genes because little is known about the mutation profiles of choriocarcinomas.

Eight somatic mutations (STK11 c.291-1G>C, TP53 p.D281E, SMARCA4 p.E1542*, PCNT p.E1491D, INPP4B p.N228K, ALK p.S639R, DNMT3A p.Y395C, and INPP4B p.T671S) were detected in tumor-peripheral blood paired genetic testing.
STK11 c.291-1G>C is a conical splice site mutation. This variant has been reported as a somatic mutation in patients with lung cancer and as a germline mutation in patients with Peutz–Jeghers syndrome. In silico functional analysis predicted it to be a pathogenic loss of function mutation. It has been demonstrated that STK11 tumor suppressor negatively regulates mammalian target of rapamycin (mTOR) signaling; thus, loss of function mutation of STK11 may result in the activation of mTOR signaling.[4] Our finding was consistent with recent array comparative genomic hybridization (CGH) analysis of gestational and nongestational choriocarcinomas. In that study, in silico functional interaction analysis revealed involvement of the PI3K-Akt-mTOR signaling pathway in the pathobiology of choriocarcinomas.

The TP53 p.D281E mutation replaces a highly conserved aspartic acid (Asp, D) with glutamic acid (Glu, E) at codon 281 of the TP53 protein. This variant has been reported in ovary, lung, central nervous system, and hematopoietic cancers.[5] Experimental studies have shown that this missense change disrupts the transcriptional transactivation function of the TP53 protein. This finding suggests that the aspartic acid residue may be critical for TP53 protein function and that missense substitutions at this position may be pathogenic and may contribute to the development of choriocarcinoma. This finding was supported by a reported Japanese patient with gastric choriocarcinoma; mutational analysis of the TP53 gene in this patient revealed a point mutation in exon 5 (p.H179R). The authors concluded that mutation of the TP53 gene contributed to the oncogenesis of choriocarcinoma.

The SMARCA4 p.E1542* variant was a nonsense mutation that resulted in loss of function of SMARCA4. Although this mutation has not been reported in choriocarcinoma, loss of function mutation sensitized ovarian cancer cells to targeted therapy of vorinostat, a histone deacetylase inhibitor used in the management of cutaneous T-cell lymphoma. Other missense mutations were neither functionally tested nor reported in choriocarcinoma. Thus, those mutations might play a role as a “passenger mutation” in choriocarcinoma.

In summary, our comprehensive genetic profiling of choriocarcinoma showed that multiple somatic mutations occur in PPC. Abnormal TP53 and mTOR signaling might play a central role in PPC.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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| Authors                  | Year | Age, year | Symptoms                      | Diagnostic method                  | Therapy                                      | Follow-up                                      |
|-------------------------|------|-----------|--------------------------------|-------------------------------------|----------------------------------------------|-----------------------------------------------|
| Guichard et al.         | 1953 | NA        | NA                             | NA                                  | NA                                           | NA                                            |
| Starichkov et al.       | 1962 | NA        | NA                             | NA                                  | NA                                           | NA                                            |
| Cacciamani              | 1971 | 19        | Cough                          | Autopsy                             | CT                                           | Died 5 months after diagnosis                |
| Hayakawa et al.         | 1977 | 45        | Gynecomastia                   | Biopsy postoperatively              | IR + RT                                      | Died 4 months after initial symptoms          |
| Hayakawa et al.         | 1977 | 57        | Cough, gynecomastia            | Autopsy                             | None                                         | Died 2 months after initial symptoms          |
| Kalla et al.            | 1980 | 27        | Pleuritic pain                 | Biopsy postoperatively              | CR + CT                                      | Still alive after 2 years                     |
| Zapatero et al.         | 1982 | 67        | Hemoptysis                     | Biopsy postoperatively              | CR                                           | Still alive after 3 years                     |
| Uspenskiĭ et al.        | 1982 | NA        | NA                             | NA                                  | NA                                           | NA                                            |
| Kuang                   | 1984 | NA        | NA                             | NA                                  | NA                                           | NA                                            |
| Endou et al.            | 1988 | NA        | NA                             | NA                                  | NA                                           | NA                                            |
| Sullivan                | 1989 | 51        | Cough, weight loss             | Autopsy                             | None                                         | Died 1 week after admission                  |
| Sridhar et al.          | 1989 | 37        | Cough, chest pain              | Biopsy postoperatively              | Neoadjuvant CT, CR, resection of brain metastasis, palliative CT | Died 15 months after diagnosis                |
| Adachi et al.           | 1989 | 71        | Hemoptysis, dyspnea, chest pain| Biopsy postoperatively              | Resection + RT, palliative CT               | Died 6 months after initial symptoms          |
| Dura                    | 1991 | NA        | NA                             | Two case by autopsy and one case by | NA                                           | NA                                            |
| Durieu et al.           | 1994 | 61        | Hemoptysis, chest pain         | Biopsy postoperatively              | CR + RT + palliative CT                      | Died 11 days after starting chemotherapy      |
| Otosuka et al.          | 1994 | 0.33      | Precocious puberty             | Biopsy postoperatively              | Resection, CT, skull RT                      | Died 5 months after surgery                   |
| Toda et al.             | 1995 | 69        | Hemoptysis                     | Autopsy                             | CT                                           | Died 1.5 months after admission              |
| Canver and Voytovich    | 1996 | 69        | Shoulder pain                  | Biopsy postoperatively              | CR + CT                                      | Still alive 6 months after surgery           |
| Uwatoko and Kajita      | 1997 | 66        | Asthenia                       | Biopsy postoperatively              | CR + CT                                      | Died 5 months after surgery                   |
| Ikura et al.            | 2000 | 60        | Incidental finding (preoperative chest X-ray) | Autopsy                             | CT                                           | Died 5 months after the tumor detected       |
| Chen et al.             | 2001 | 61        | Hemoptysis                     | Biopsy postoperatively              | CR + CT, best supportive care               | Still alive after 6 months                   |
| Tsai et al.             | 2002 | 23        | Hemoptysis and progressive dyspnea | Urine pregnancy test and bronchoscopic biopsy | Aggressive CT + management in the ICUs       | Died 8 days after admission                  |
| Vaideswar et al.        | 2004 | 60        | Cough, dyspnea, hemoptysis     | Autopsy                             | NA                                           | NA                                            |
| Yamamoto et al.         | 2006 | 77        | Rapid progressive respiratory dysfunction | Autopsy                             | None                                         | Died 6 days after admission                  |
| Hadgu et al.            | 2010 | 48        | Shortness of breath, cough, drenching night sweats | CT-guided biopsy of right lung lesion | CR+CT                                        | Died 5 days after surgery                     |
| Jiang et al.            | 2014 | 45        | Fainting                      | Biopsy postoperatively              | IR+CT                                        | Died 10 months after diagnosis               |
| Kamata et al.           | 2016 | 70        | Cough                         | Biopsy postoperatively              | CR                                           | Still alive after 2 years                    |
| Zhu et al.              | 2016 | 67        | Asymptomatic                  | Biopsy postoperatively              | CR+CT                                        | Alive >13 months after the tumor detected    |
| Our case                | 2017 | 71        | Cough, hemoptysis              | Biopsy postoperatively              | CR                                           | Died 3 months after surgery                  |

CR: Complete resection; CT: Chemotherapy; IR: Incomplete resection; NA: Not available; RT: Radiotherapy; PPC: Primary pulmonary choriocarcinoma; ICU: Intensive care unit.