CASE REPORT

SMARCA4/BRG1-deficient NSCLC: a case report and literature review

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Abstract

Patients with non-small cell lung cancer (NSCLC) deficient in SMARCA4 (SMARCA4-dNSCLC) are commonly diagnosed at advanced stages with a poor prognosis. Although immune checkpoint inhibitors (ICIs) combined with platinum-based chemotherapy regimens are widely used, their efficacy in SMARCA4-dNSCLC patients remains suboptimal. Herein, we present the case of a SMARCA4-dNSCLC patient treated at Yijishan Hospital on January 18, 2023. Following our comprehensive treatment, our patient's general condition and quality of life (QOL) have remained satisfactory, and there has been no disease progression to date.

Keywords: NSCLC, SMARCA4-deficient, Treatment, Prognosis.

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Introduction

SWI/SNF is a chromatin remodelling complex that relies on ATPase activity. It regulates cellular transcription, promotes cell differentiation, and is essential for DNA damage repair.[1] The oncogene SMARCA4 contributes to the formation of this complex's catalytic subunit by encoding the BRG1 protein.[2] Earlier studies indicate that about 10% of NSCLC exhibit susceptibility to deletions in SMARCA[4,3] which typically results in the development of advanced dedifferentiated tumours that in turn lead to distant metastasis.[4] In addition, roughly 83% of patients with SMARCA4-dNSCLC are diagnosed at stage IIIB-IV, with a median progression-free survival lasting merely 30 days.[5] Although ICIs combined with platinum-based chemotherapy regimens represent the most frequently utilized clinical approach, their effectiveness remains less than optimal. Thus, this article aimed to retrospectively outline the case of a SMARCA4-dNSCLC patient treated at the Department of Respiratory and Critical Care Medicine of Yijishan Hospital, detail the patient's clinical features, diagnosis, treatment course, as well as review previous literature to lay a theoretical reference for the diagnosis and treatment of SMARCA4-dNSCLC patients.

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Case Report

A 53-year-old male of Chinese Han nationality was treated at the department as mentioned above on January 4, 2023, following a "physical examination revealing a right lung lesion for over 10 days". He was physically fit, with no documented history of hypertension, diabetes, chronic diseases, and infectious diseases. Additionally, he had a smoking history of 20 pack-year and denied alcohol consumption. Upon admission, routine blood tests and biochemistry were performed, and the results were unremarkable. Common blood tumour markers were all within the normal range. Chest HRCT displayed right lower lung hilar occupancy, suggestive of lung cancer with lower lobe obstructive inflammation. Besides, localized thickening of the right pleura was observed (Figure 1A-B). Fiberoptic bronchoscopy revealed the presence of neoplastic organisms at the opening of the right lower lobe, which completely obstructed the lumen, and a biopsy was performed (Figure 1C). Pathological examination of the tracheoscopic samples displayed poorly differentiated carcinoma. Immunohistochemistry analysis indicated that the cancer cells were TTF-1 (-), p40 (-), CD56 (partially +), CK7 (-), SMARCA4(BRG1) (-), Ki-67 (60%+), with low expression levels of programmed cell death-ligand 1 (PD-L1). By immunohistochemical results, the case was diagnosed as SMARCA4-dNSCLC (Figure 1D-F). Meanwhile, next-generation sequencing (NGS) of the genome didn't detect mutations in common genes related to ROS1, ALK, and EGFR. PET-CT was conducted to evaluate systemic conditions, uncovering a high metabolic mass in the lower lobe of the right lung adjacent to the hilum with obstructive pneumonia and multiple small lymph nodes in the neck and mediastinum bilaterally, with no significant increase in Fludeoxyglucose (FDG) metabolism. Notably, no distant metastasis was noted. The diagnosis of a right lung SMARCA4-dNSCLC, stage IIB, T3N0M0, was made after a thorough evaluation. Afterward, the patient was initiated

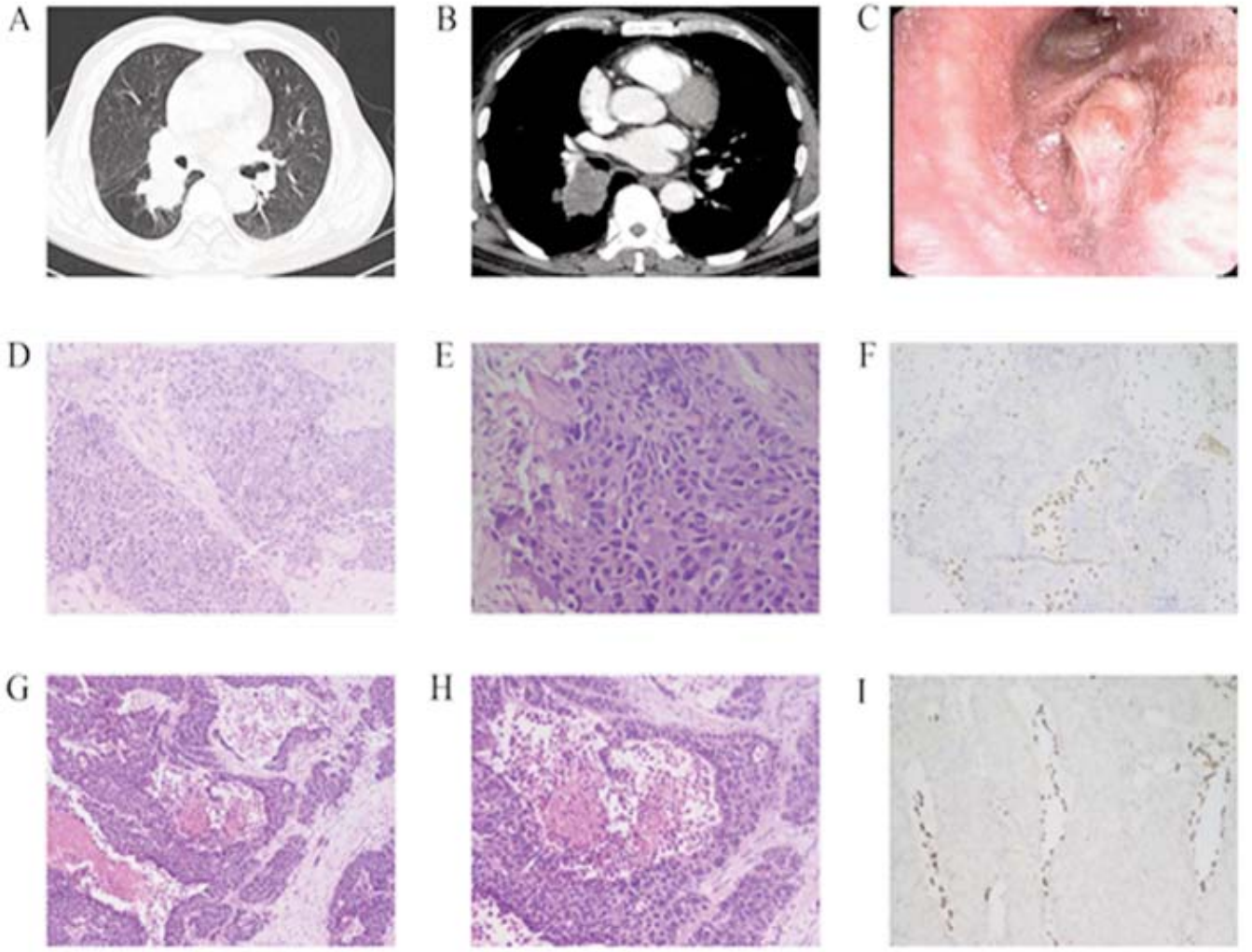

Figure-1: A-B Chest HRCT displaying right lower hilar occupancy (lung window) and mediastinal thickening (mediastinal window); C Fiberoptic bronchoscopy illustrating complete luminal occlusion by neoplasm at the opening of the right lower lobe; D-E Fiberoptic bronchoscopic pathology (HE staining, D × 200, E × 400); F Fiberoptic bronchoscopic pathology with immunohistochemical staining demonstrating SMARCA4 (BRG1) deletion (× 200); G-H Postoperative pathological examination (HE staining, G × 100, H × 200); I Postoperative pathology with immunohistochemical staining showing SMARCA4 (BRG1) deletion (× 200).

on four cycles of neoadjuvant therapy by karelizumab combined with albumin paclitaxel and nedaplatin on January 18, 2023. After excluding relevant contraindications, open thoracic exploration combined with right middle and lower lobectomy and mediastinal lymph node dissection was performed on May 27, 2023, under general anaesthesia. The surgical procedure proceeded smoothly, and subsequent postoperative pathological examination displayed evidence of non-small cell carcinoma in the right middle and lower lungs. The carcinoma measured roughly 5.5 cm × 5.0 cm × 4.0 cm. Cancerous emboli were detected in the vasculature, with no evidence of nerve invasion and cancerous involvement of the pleura and bronchial stumps. Furthermore, examination of five peribronchial lymph nodes revealed no cancerous metastasis. Likewise, no metastatic lesions were observed in 13 lymph nodes of groups 2-4, 17 lymph nodes of group 7, 1 lymph node of group 9, 3 lymph nodes of group 10, and 2 lymph nodes of group 11. Immunohistochemistry results exposed that the cancer cells were TTF-1 (-), CK7 (-), p40 (-), SMARCA4(BRG1) (-), with about 1% of PD-L1 positive tumour cells, the cancer was diagnosed as SMARCA4-dNSCLC (Figure 1G-I). Post-surgery, the patient continued to receive two cycles adjuvant chemotherapy with albumin paclitaxel and nedaplatin. As anticipated, in regular follow-up checks since the surgery until now, no evidence of distant metastasis or recurrence was observed, and the patient's general condition and QOL are satisfactory too.

Discussion

SMARCA4-dNSCLC was first reported by Wong et al. in 2000, who pointed out that tumour-suppressing properties are possible for BRG1.[6] Previous studies have concluded that SMARCA4-dNSCLC is prevalent among male smokers, with an average age of over 60 years.[7] In addition, due to the high aggressiveness of the tumours, a poor prognosis is generally associated with patients.[5,7] Noteworthy, the clinical features of our patient were consistent with those described in previous reports. However, given that the patient was at stage IIB at the time of diagnosis and had no distant metastases, the patient underwent immunotherapy combined with chemotherapy, followed by sequential surgical resection and adjuvant chemotherapy postoperatively. Overall, the patient's prognosis was favourable.

Noteworthily, the immunohistochemical characteristics of previously reported SMARCA4-dNSCLC cases included CK7 (+), HepPar-1 (+), claudin-4 (+), p40/p63 (-), TTF-1 (-), Napsin A (-), and CK5/6 (-), as well as neuroendocrine markers.[7] These features are largely consistent with our patient and may assist in differentiating SMARCA4-dNSCLC from others.

SMARCA4-dNSCLC is generally associated with mutations in SMARCA4, KRAS, TP53, STK11, KEAP1, and LRP1B, but less frequently linked to ALK, ROS1, or EGFR mutations.[5,7] SMARCA4 mutations result in the down-regulation of BRG1 protein, and the mutation testing is not necessary if immunohistochemistry analysis of BRG1 protein expression is negative.7 Herein, our patient was unveiled SMARCA4 deletion and negative BRG1 protein expression.

At present, the treatment of SMARCA4-dNSCLC is challenging due to a lack of standardized protocols. Available therapeutic options include drugs targetting oxidative phosphorylation and inhibitors of SMARCA2, EZH2, etc. molecules.[8] Luo et al. documented that SMARCA4-dNSCLC, except for stage I, has a high risk of postoperative recurrence but is responsive to immunotherapy.[9] Liang et al. found out: The median overall survival of advanced SMARCA4-dNSCLC patients who received immunotherapy in combination with chemotherapy was significantly longer compared to those who received chemotherapy alone. However, overall survival did not differ significantly between immunotherapy-only patients and non-immunotherapy patients.[7] Meanwhile, AURKA, which is highly implicated in assembling cellular mitotic spindles, and a treatment of SMARCA4-dNSCLC with its inhibitor is being investigated.[10] Therefore, the outcome of immunotherapy in treating SMARCA4-dNSCLC remains to be elucidated and may be influenced by the tumour immune microenvironment, driver gene mutations, etc. In this case, the patient was negative for common driver mutations and had low PD-L1 expression, and the combination of immunotherapy with chemotherapy was effective.

Conclusion

SMARCA4-dNSCLC is characterised by high aggressiveness and poor prognosis. Following diagnosis on January 17, 2023, an individualised treatment plan was formulated for the patient. After four cycles of immunotherapy combined with chemotherapy, surgical resection was promptly performed. Then, the patient underwent two additional cycles of the initial chemotherapy regimen. At 16 months post-surgery, thoracic and abdomen CT, cranial MRI, and a whole-body bone scan with Emission Computed Tomography (ECT) revealed the absence of SMARCA4-dNSCLC. Collectively, these findings highlight the importance of timely surgical resection when surgical indications are met and indicate that the combination of immunotherapy and chemotherapy represents a novel potential strategy for the management of SMARCA4-dNSCLC.

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