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肺浸润性腺癌伴纵隔淋巴结转移性NUT中线癌1例报告 及文献复习

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[摘要] **目的:** 分析1例肺浸润性腺癌伴纵隔淋巴结转移性睾丸核蛋白(NUT)中线癌患者的病理诊断过程, 为该病的临床诊断提供依据。**方法:** 收集1例肺浸润性腺癌伴纵隔淋巴结转移性NUT中线癌患者的临床资料, 术中送检肺肿物行冰冻快速病理诊断以判断病变性质, 术后另送纵隔肿瘤行慢病理检测, 肺及纵隔肿物均行常规病理检查和免疫组织化学染色, 结合相关文献分析该病的病理诊断过程, 并进行病理鉴别。**结果:** 患者, 男性, 59岁, 于外院行CT检查见前纵隔软组织密度影和右肺下叶磨玻璃样结节影, 均考虑肿瘤性病变。术中肺肿物快速病理诊断考虑肺浸润性腺癌, 术后经免疫组织化学染色证实为肺原发性浸润性腺癌。术后另送纵隔肿物, 经免疫组织化学染色、院外会诊及基因检测最终证实为淋巴结转移性NUT中线癌。**结论:** NUT中线癌是罕见的低分化鳞状细胞癌, 常发生于中线部位, 可伴发其他器官肿瘤并发生淋巴结转移, 其确诊需要结合组织学形态、影像学资料和基因检测结果。

[关键词] 肺浸润性腺癌; 胸腺肿瘤; 睾丸核蛋白中线癌; 免疫组织化学染色

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Invasive adenocarcinoma of lung complicated with metastatic NUT midline carcinoma of mediastinal lymph node: A case report and literature review

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ABSTRACT **Objective:** To discuss the pathological diagnostic process of one case of invasive adenocarcinoma of lung complicated with metastatic nuclear protein of testis (NUT) midline carcinoma of mediastinal lymph node, and to provide the basis for the clinical diagnosis of this disease. **Methods:** The clinical materials of one patient with invasive adenocarcinoma of lung complicated with metastatic NUT midline carcinoma of mediastinal lymph node were collected. Intraoperative frozen section pathological diagnosis of the lung tumor was performed to determine the nature of the lesion, and postoperative mediastinal tumor was sent for slow pathological examination. Both lung and mediastinal tumors underwent routine pathological examination and immunohistochemical staining, the pathological diagnostic process was

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analyzed combined with the relevant literatures, and the pathological differentiation was performed.

Results: The patient, a 59-year-old man, underwent a CT scan at an external hospital, which revealed a soft tissue density shadow in the anterior mediastinum and a ground-glass nodule in the lower lobe of the right lung, both were considered to be neoplastic lesions. The intraoperative rapid pathological diagnosis of the lung tumor suggested pulmonary invasive adenocarcinoma, and the postoperative immunohistochemical staining results confirmed it as primary pulmonary invasive adenocarcinoma. The postoperative mediastinal tumor was confirmed as lymph node metastatic NUT midline carcinoma through immunohistochemical staining, external consultation, and genetic testing. **Conclusion:** NUT midline carcinoma is a rare poorly differentiated squamous cell carcinoma that often occurs in the midline structures and may involve other organs and lymph node metastasis; its diagnosis requires a combination of histological morphology, imaging data, and genetic testing results.

KEYWORDS Invasive adenocarcinoma of lung; Thymoma; Nuclear protein of testis midline carcinoma; Immunohistochemistry staining

睾丸核蛋白(nuclear protein of testis, NUT)中线癌, 又称伴NUT基因重排的中线癌, 是一种组织起源不明的罕见低分化鳞状细胞癌^[1-2]; 其常发生于纵隔和头颈部等中线部位, 影像学和临床病理学诊断是最主要的诊断手段^[3-5]。纵隔区是常见的中线部位, 与肺毗邻, 纵隔区的主要器官为胸腺, 但也存在区域淋巴结。纵隔区既是胸腺肿瘤的易发生部位, 同时也可发生肿瘤的纵隔淋巴结转移^[6]。NUT中线癌多单发, 也可伴发其他器官肿瘤, 并发生转移, 其发病较为罕见, 但国内外也有少量报道^[7-11]。原发肺浸润性腺癌伴纵隔淋巴结转移性NUT中线癌目前尚未见相关报道。本研究报道1例肺浸润性腺癌伴纵隔淋巴结转移性NUT中线癌病例, 旨在通过形态学和分子检测方法鉴别胸腺瘤、胸腺癌及纵隔淋巴结转移癌, 以提高临床医生和病理医务人员对该疾病的认识。

1 临床资料

1.1 一般资料

患者, 男性, 59岁, 2023年2月16日于当地医院行胸部CT检查见前纵隔软组织密度影, 大小约13 mm×10 mm, 双肺纹理略增粗, 右肺下叶见磨玻璃样结节影, 大小约为23 mm×17 mm, 边缘模糊; 双肺见多个薄壁无肺纹理透光区。为进一步治疗, 于2023年2月21日在本院门诊收治住院。入院时患者间断咳少量白痰, 无咯血及痰中带血, 无胸闷胸痛, 偶有心悸, 无头痛头晕, 无明显腹痛、腹胀, 轻度乏力, 无盗汗。病程中患者饮食及睡眠尚可, 大小便正常, 体质量减轻约3.0 kg。查体显示: 胸廓对称, 呼吸平稳, 气管居中, 双侧肋

间隙无明显增宽或缩窄, 胸部无明显触痛及压痛, 听诊双肺呼吸音清晰, 未闻及明显干湿啰音, 无胸膜摩擦音, 双侧腋下未触及明显肿大淋巴结。临床实验室相关检查结果显示: 尿常规和血常规及肿瘤标记物均未见异常。家属同意手术切除肺肿物和纵隔肿物。

1.2 术中冰冻快速病理诊断

大体检查, 送检右肺下叶, 体积为16 cm×10 cm×2 cm, 支气管断端直径为2.1 cm, 肺叶脏胸膜大部分光滑, 距离支气管断端1.5 cm局灶胸膜表面见手术切口, 切口长为5.0 cm, 切口周围局灶系线, 线结处质地略韧, 可疑为肿物, 且距胸膜较远, 约为1.5 cm。支气管旁可探查2枚灰黑结节, 均为淋巴结。于线结处及周围取材, 行快速冰冻切片, HE染色, 显微镜下观察可见肺叶质韧区异型腺体, 考虑肺浸润性腺癌, 待慢病理及免疫组织化学染色检测结果进一步确诊。见图1。

1.3 术后慢病理检测

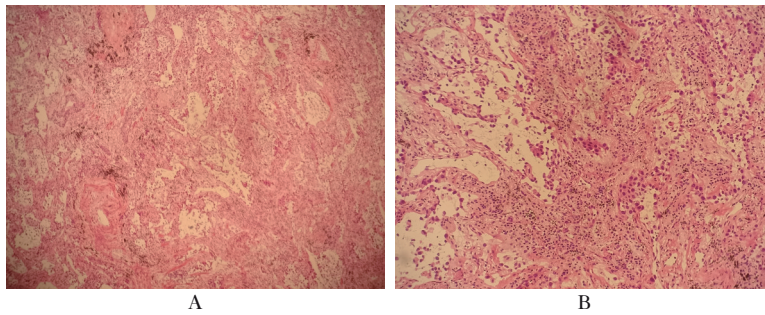
1.3.1 术后慢病理送检剩余肺组织和纵隔肿物

自支气管断端依次剪开各级支气管, 各级支气管黏膜尚光滑, 未见肿物累及。于支气管断端、血管断端、肿物带周围肺、支气管旁淋巴结和相对正常肺等部位行标准化取材。纵隔肿物(包括质韧区)全部取材, 质韧区体积为2.0 cm×1.5 cm×1.0 cm, 质韧区切面灰白实性。上述检材组织采用轮转切片机(型号: RM2245, 德国LEICA公司)行常规石蜡切片, HE染色和第二步法EnVision免疫组织化学染色, 显微镜(型号: BX50F4, 日本Olympus公司)下观察。

1.3.2 肺肿物术后慢病理检测 HE染色可见肺浸

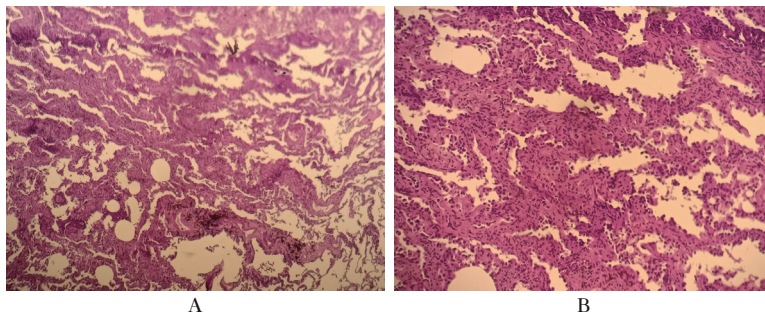
润性腺癌, 腺泡为主型, 伴少许贴壁型和乳头型。癌组织间质纤维化, 散在炎细胞, 周边肺局灶充血实变; 神经未见确切累及; 支气管旁淋巴结未见转移癌 (0/2); 支气管断端、肺门脉管和钉旁组织未见癌。见图2。肿瘤带周围肺组织切片免疫组织化学染色可见甲状腺转录因子1 (thyroid transcription

factor-1, TTF-1) (+)、胃酶样天氨酸蛋白酶A (gastric enzyme-like aspartic protease A, NapsinA) (+)、细胞角蛋白 (cytokeratin, CK) 7 (+)、P40 (-)、P53 (60%+) 和 Ki67 (10%+)。见图3。



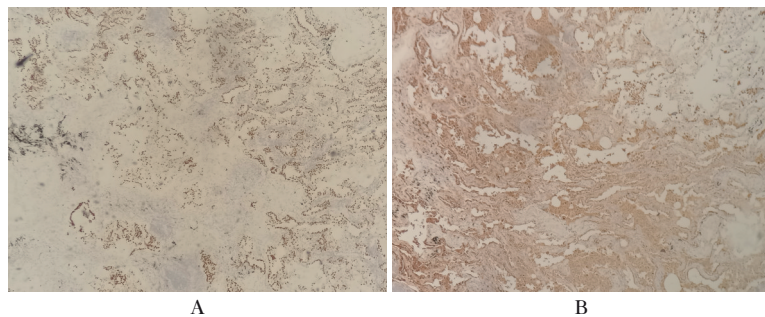
A: Atypic glands in pliable area of lung tissue (HE, ×4); B: Atypic glands in pliable area of lung tissue (HE, ×10).

图1 光学显微镜观察肺浸润性腺癌伴纵隔淋巴结转移性NUT中线癌患者术中送检肺组织质韧区形态表现
Fig. 1 Morphology of pliable area of lung tissue delivered intraoperatively in one patient with invasive adenocarcinoma of lung complicated with metastatic NUT midline carcinoma of mediastinal lymph node observed by light microscope



A: Lung invasive adenocarcinoma (HE, ×4); B: Lung invasive adenocarcinoma (HE, ×10).

图2 光学显微镜观察肺浸润性腺癌伴纵隔淋巴结转移性NUT中线癌患者慢病理肺组织质韧区形态表现
Fig. 2 Morphology of pliable area of lung tissue in slow pathology of one patient with invasive adenocarcinoma of lung complicated with metastatic NUT midline carcinoma of mediastinal lymph node observed by light microscope

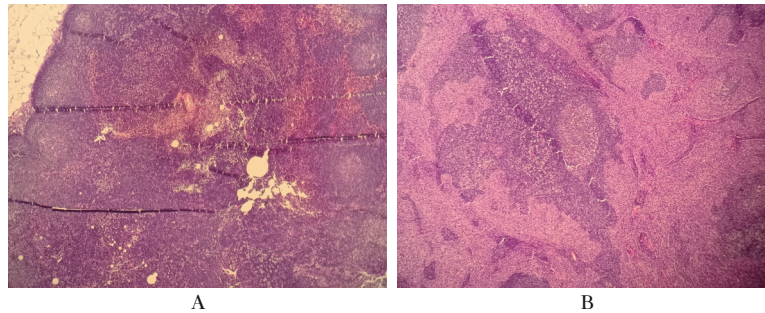


A: Antibody of TTF-1 (×4); B: Antibody of NapsinA (×4).

图3 免疫组织化学染色观察肺浸润性腺癌伴纵隔淋巴结转移性NUT中线癌患者慢病理肺组织质韧区形态表现
Fig. 3 Morphology of pliable area of lung tissue in slow pathology of one patient with invasive adenocarcinoma of lung complicated with metastatic NUT midline carcinoma of mediastinal lymph node observed by immunohistochemical staining

1.3.3 纵隔肿物术后慢病理检测 HE染色可见纵隔质韧区呈结节状,可见明显界膜,肿物内部分区明显,可见似淋巴结样皮质区(图4A),髓质区不明显,为异质性组织所替代(图4B),异质性组织高度考虑为癌。癌组织形态不同于肺肿物,倾向鳞状细胞癌,来源难定。查询影像学 and 临床资料高度怀疑纵隔肿物为胸腺瘤,隧行科内会诊。会诊结果共2种:其一倾向符合临床及影像学,即考虑胸腺瘤或胸腺癌;其二倾向淋巴结转移癌,会诊结果无

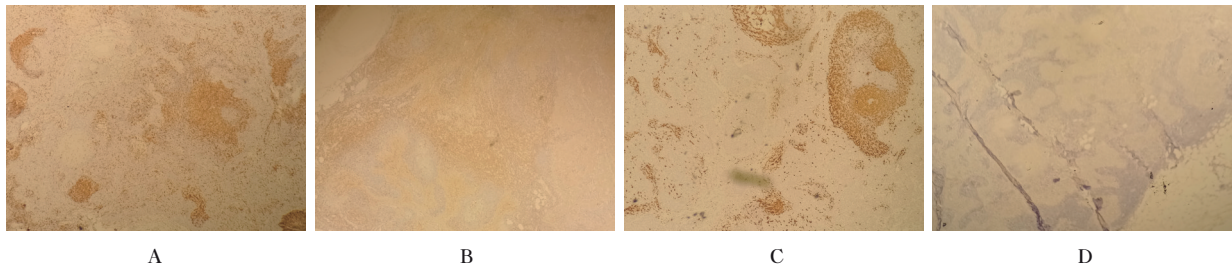
法统一。肿瘤带周围组织免疫组织化学染色可见CK(+),CK7(+),CK20(-),绒毛蛋白(Villin)(-),TTF-1(-),NapsinA(-),P40(+),突触素(synapsin, Syn)(部分+),CK19(+),Ki67(50%+),CD56(+),嗜铬蛋白颗粒A(chromogranin A, CGA)(-),P63(+),CK5/6(+),CD3(-),CD5(-),CD20(滤泡+)和CD1a(-)。见图5。



A: Mediastinum mass (HE, $\times 4$); B: Mediastinum mass (HE, $\times 10$).

图4 光学显微镜观察肺浸润性腺癌伴纵隔淋巴结转移性NUT中线癌患者慢病理纵隔肿物形态表现

Fig. 4 Morphology of mediastinal masses in slow pathology in one patient with invasive adenocarcinoma of lung complicated with metastatic NUT midline carcinoma of mediastinal lymph node observed by light microscope



A: CD3; B: CD5; C: CD20; D: CD1a.

图5 免疫组织化学染色观察肺浸润性腺癌伴纵隔淋巴结转移性NUT中线癌患者纵隔肿物形态表现($\times 10$)

Fig. 5 Morphology of mediastinal masses in one patient with invasive adenocarcinoma of lung complicated with metastatic NUT midline carcinoma of mediastinal lymph node observed by immunohistochemical staining($\times 10$)

1.4 初步诊断

肺肿物初步诊断为肺浸润性腺癌,而纵隔肿物科内诊断意见无法统一。由于异质性组织表达鳞状细胞癌标记及神经内分泌标记,且发生于纵隔内,可为鳞状细胞癌,也可倾向为NUT中线癌。纵隔肿物的组织学表现与淋巴结相似,因此本文作者倾向为淋巴结转移癌,最终报告肺肿物为肺浸润性腺癌,腺泡型为主,伴少许贴壁型和乳头型;纵隔肿物:淋巴结转移癌(1/2),癌组织来源难定,结合免疫标记结果倾向NUT中线癌。

1.5 院外会诊及分子检测

与患者家属沟通后,家属同意送院外会诊。1周后,院外会诊结果回报:肺肿物为肺浸润性腺癌,纵隔肿物为胸腺原发性鳞状细胞癌。本文作者基本同意纵隔肿物倾向为鳞状细胞癌,但对于纵隔肿物为胸腺原发或淋巴结转移,且纵隔肿物表达鳞状细胞癌标记和表达神经内分泌标记是否仅为单纯性的鳞状细胞癌方面存在歧义。再次与患者家属沟通,家属同意行基因检测,2周后基因检测结果回报:纵隔肿物NUT相关基因突变,为致病因素。

根据初步诊断、院外会诊和基因检测结果并结合影像学及临床表现, 最终确诊本例患者为肺原发性浸润性肺腺癌伴纵隔淋巴结转移性NUT中线癌。

2 讨论

胸腺是前纵隔内的主要器官, 前纵隔内的常见肿瘤通常源于胸腺, 即胸腺瘤和胸腺癌, 但前纵隔内不仅是胸腺存在部位, 还是区域淋巴结的主要聚集处及肺和头颈部肿瘤的常见转移位置^[6]。胸腺的原发性恶性肿瘤主要包括胸腺瘤和胸腺癌, 通常可见残存的胸腺结构, 如皮质和髓质内的胸腺小体。胸腺瘤主要分为A、B1、B2、B3和AB型^[7], 胸腺癌多为鳞状细胞癌, 其中B1型和B2型胸腺瘤主要以淋巴细胞为主, 上皮性哺育细胞较少; A型和B3型胸腺瘤主要为上皮性哺育细胞, 淋巴细胞相对较少。淋巴细胞为幼稚T淋巴细胞, 常表达末端脱氧核苷酸转移酶 (terminaldeoxynucleotidyl transferase, TdT)、CD3和CD5等, 不表达B淋巴细胞标记物, 如CD20等, 且不形成淋巴结内淋巴滤泡样结构; 上皮性哺育细胞常表达CD1a和P63等; 淋巴细胞和上皮性哺育细胞均不表达神经内分泌标记物, 如Syn、CgA和CD56等^[12]。

NUT中线癌常发生于中线部位, 是罕见的低分化鳞状细胞癌, 多为单发, 也可伴发其他器官肿瘤并转移^[13-15]。NUT中线癌表达鳞状细胞癌的相关标记物, 如P40、P63和CK5/6, 同时可不同程度表达神经内分泌标记物^[7, 11, 16-18]。基因检测常有溴结构域蛋白 (bromodomain-containing protein, BRD) 4-NUT基因重排及BRD3-NUT或NUT-varinant融合^[19-27]。

该例患者于当地医院行CT检查同时发现肺占位及纵隔占位, 影像学检查结果考虑肺占位为肺恶性肿瘤, 纵隔占位为胸腺肿瘤, 但不能除外纵隔淋巴结转移。在本院行手术切除肺肿物和纵隔肿物, 术中送检肺肿物, 术中病理和术后慢病理均诊断为肺浸润性腺癌。术后送检纵隔肿物, 其镜下组织形态表现与淋巴结相似, 具有残存的皮质、髓质和被异质性组织占据的淋巴窦。异质性组织的形态表现不同于肺肿物, 其可表达鳞状细胞标记物和神经内分泌标记物^[11, 16, 21]。根据送检部位、影像学 and 免疫标记检测结果, 本文作者倾向于淋巴结转移性鳞状细胞癌或NUT中线癌, 遂建议患者家属行院外会诊及基因检测, 并确诊为胸腺鳞状细胞癌。但关于肿瘤是否为单一的鳞状细胞癌以及是否为胸腺

原发或淋巴结转移方面仍存在歧义。基因检测结果证实NUT相关基因突变为致病因素, 确认纵隔肿物的癌属性为NUT中线癌。纵隔肿物内可能存在胸腺和淋巴结。该例患者术后送检纵隔肿物, 镜下边界清晰, 可见明显的皮质、髓质和淋巴窦。如纵隔肿物内为胸腺, 则应为不完整的分叶状, 且内部不会出现明显的淋巴滤泡。免疫标记检测结果显示: 胸腺标记物CD1a呈阴性, 且CD20清晰, 可见淋巴滤泡的形态表现。通过查阅文献和相关书籍, 本文作者认为该例患者为淋巴结转移性NUT中线癌。

综上所述, 肺浸润性腺癌伴纵隔淋巴结转移性NUT中线癌患者诊断较为困难, 病理诊断不可单纯依靠个人经验, 需结合形态学和临床表现, 同时还需结合前沿诊疗手段。

利益冲突声明:

所有作者声明不存在利益冲突。

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[参考文献]

- [1] 何雪颖, 刘兆会, 张倩. 鼻腔鼻窦睾丸核蛋白中线癌影像学分析一例[J]. 中国医学科学院学报, 2020, 42(2): 279-282.
- [2] ELKHATIB S K, NEILSEN B K, SLEIGHTHOLM R L, et al. A 47-year-old woman with nuclear protein in testis midline carcinoma masquerading as a sinus infection: a case report and review of the literature[J]. J Med Case Rep, 2019, 13(1): 57.
- [3] 孙诗响, 丁莹莹. 鼻窦中线癌一例[J]. 放射学实践, 2019, 34(6): 709-710.
- [4] 张思情, 赵德育. 儿童肺NUT中线癌1例报道[J]. 南京医科大学学报(自然科学版), 2020, 40(7): 1078-1080.
- [5] SHOLL L M, NISHINO M, POKHAREL S, et al. Primary pulmonary NUT midline carcinoma: clinical, radiographic, and pathologic characterizations [J]. J Thorac Oncol, 2015, 10(6): 951-959.
- [6] 邹仲之. 组织学与胚胎学[M]. 5版. 北京: 人民卫生出版社, 2001: 126-128.
- [7] MARX A, STRÖBEL P, BADVE S S, et al. ITMIG consensus statement on the use of the WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting [J]. J Thorac Oncol, 2014, 9(5): 596-611.
- [8] SIROHI D, GARG K, SIMKO J P, et al. Renal NUT

- carcinoma: a case report[J]. *Histopathology*, 2018, 72(3): 528-530.
- [9] AGAIMY A, FONSECA I, MARTINS C, et al. NUT carcinoma of the salivary glands: clinicopathologic and molecular analysis of 3 cases and a survey of NUT expression in salivary gland carcinomas[J]. *Am J Surg Pathol*, 2018, 42(7): 877-884.
- [10] CHAU N G, HURWITZ S, MITCHELL C M, et al. Intensive treatment and survival outcomes in NUT midline carcinoma of the head and neck [J]. *Cancer*, 2016, 122(23): 3632-3640.
- [11] 王 龙, 王 薇, 辛 毅, 等. 老年NUT中线癌合并多发转移1例[J]. *中国肿瘤临床*, 2016, 43(23): 1067.
- [12] 孙晨蕊, 肖 琼, 付 昱, 等. 基于免疫基因的直肠癌预后模型的建立及验证研究[J]. *中国实用内科杂志*, 2023, 43(1): 45-51.
- [13] ENGLESON J, SOLLER M, PANAGOPOULOS I, et al. Midline carcinoma with t(15;19) and BRD4-NUT fusion oncogene in a 30-year-old female with response to docetaxel and radiotherapy [J]. *BMC Cancer*, 2006, 6: 69.
- [14] LEE A C, KWONG Y I, FU K H, et al. Disseminated mediastinal carcinoma with chromosomal translocation (15; 19). A distinctive clinicopathologic syndrome [J]. *Cancer*, 1993, 72(7): 2273-2276.
- [15] KO L N, WENG Q Y, SONG J S, et al. A 48-year-old male with cutaneous metastases of NUT midline carcinoma misdiagnosed as herpes zoster [J]. *Case Rep Oncol*, 2017, 10(3): 987-991.
- [16] 杨永强, 周鹏程, 潘媛媛, 等. 鼻前颅底NUT中线癌1例[J]. *中国肿瘤临床*, 2022, 49(1): 53-54.
- [17] GUPTA R, MUMAW D, ANTONIOS B, et al. NUT midline lung cancer: a rare case report with literature review[J]. *AME Case Rep*, 2022, 6: 2.
- [18] 曾 雷. NUT中线癌中BRD4-NUT和p300结合在染色质上异常调控基因转录的结构机制[A]// 2022生物物理大会摘要集[C]. 北京:中国生物物理学会, 2022, 1.
- [19] FRENCH C A, MIYOSHI I, KUBONISHI I, et al. BRD4-NUT fusion oncogene: a novel mechanism in aggressive carcinoma[J]. *Cancer Res*, 2003, 63(2): 304-307.
- [20] FRENCH C A, KUTOK J L, FAQUIN W C, et al. Midline carcinoma of children and young adults with NUT rearrangement[J]. *J Clin Oncol*, 2004, 22(20): 4135-4139.
- [21] BAUER D E, MITCHELL C M, STRAIT K M, et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma[J]. *Clin Cancer Res*, 2012, 18(20): 5773-5779.
- [22] CLAUDIA G, ALEXANDRA G. Challenging diagnosis in NUT carcinoma [J]. *Int J Surg Pathol*, 2021, 29(7): 722-725.
- [23] HAEFLIGER S, TZANKOV A, FRANK S, et al. NUT midline carcinomas and their differentials by a single molecular profiling method: a new promising diagnostic strategy illustrated by a case report [J]. *Virchows Arch*, 2021, 478(5): 1007-1012.
- [24] DEVAIAH B N, LEWIS B A, CHERMAN N, et al. BRD4 is an atypical kinase that phosphorylates serine2 of the RNA polymerase II carboxy-terminal domain [J]. *Proc Natl Acad Sci U S A*, 2012, 109(18): 6927-6932.
- [25] KUBONISHI I, TAKEHARA N, IWATA J, et al. Novel t(15;19)(q15;p13) chromosome abnormality in a thymic carcinoma[J]. *Cancer Res*, 1991, 51(12): 3327-3328.
- [26] 张国梁, 王利顺, 李伟伟, 等. 超声、磁共振及染色体基因检测联合诊断胎儿颅脑异常的临床价值[J]. *中国医学物理学杂志*, 2023, 40(8): 985-987.
- [27] OLIVEIRA L J C, GONGORA A B L, LATANCIA M T, et al. The first report of molecular characterized BRD4-NUT carcinoma in Brazil: a case report [J]. *J Med Case Rep*, 2019, 13(1): 279.