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ORIGINAL ARTICLE

Clinicopathological characteristics of primary lung nuclear protein in testis carcinoma: A single-institute experience of 10 cases

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Abstract

Background: Nuclear protein in testis (NUT) carcinoma is a rare tumor associated with NUT rearrangement that can present as poorly differentiated to undifferentiated carcinoma, with or without abrupt squamous differentiation. It is often misdiagnosed as poorly differentiated carcinoma or undifferentiated carcinoma if NUT is not suspected. In this study, we retrospectively analyzed pulmonary NUT carcinoma cases diagnosed with NUT immunohistochemical staining and discuss the differential diagnosis to provide information for this rare and aggressive entity.

Methods: Cases, diagnosed as "NUT carcinoma" in lung pleura and "metastatic NUT carcinoma from the lung" in lymph nodes were diagnosed between 2017 and 2019 at the Samsung Medical Center (SMC). Clinical features such as age, sex, treatment and follow-up period, and pathological reports were obtained by reviewing patients' electronic medical records.

Results: A total of 10 NUT carcinoma cases were found in the SMC pathology database. Seven patients were men and six were non-smokers. Tumor cells showed various cellular features such as round, squamoid, and spindle. Some cases had initially been misdiagnosed as spindle cell neoplasm, round cell sarcoma, squamous cell carcinoma and small cell carcinoma. All cases showed diffuse strong nuclear expression of NUT immunohistochemical staining, and some were positive for p63 staining and negative for CD56 staining.

Conclusions: NUT carcinoma is often misdiagnosed because of its various morphologies. It is important to consider NUT as one of the differential diagnoses when encountering lung biopsy with undifferentiated morphology.

Key points

- Due to various morphological features, NUT carcinoma can be misdiagnosed
- It is important to consider NUT carcinoma when diagnosing a poorly differentiated or undifferentiated tumor

Introduction

Nuclear protein in testis (NUT) carcinoma is a rare tumor associated with *NUT* rearrangement.[1,2] It mostly arises in midline regions of the head, neck, and thorax but various organs, including the lung, bladder, pancreas, kidney, and salivary glands are affected with a diverse range reported in both age and sex of patients.[2–4] NUT carcinoma is a very aggressive disease, patients usually present at an advanced

stage, and it is refractory to conventional chemotherapy with an estimated 9% of patients with progression-free survival of only two years.[5–7]

Histologically, NUT carcinoma presents as poorly differentiated to undifferentiated carcinoma with or without abrupt squamous differentiation, which shows polygonal cells with eosinophilic cytoplasm and keratinization.[8–11] The tumor cells are usually composed of monomorphic and primitive-appearing tumor cells. The undifferentiated feature of NUT carcinoma leads to various differential diagnoses, including poorly differentiated non-small cell carcinoma, small cell lung carcinoma, round cell sarcoma, and high grade lymphoma.[7] As a result, it is often misdiagnosed as poorly differentiated carcinoma or undifferentiated carcinoma if NUT is not suspected.[5,7,12,13] A diagnosis of NUT carcinoma can be made using immunohistochemical staining for NUT protein, which shows 99% negative predictive value and a positive predictive value of 100%.[9,14] Previous studies have suggested a bromodomain inhibitor can be used as a target inhibitor of *BRD-NUT* fusion.[15,16] Approximately 70% of NUT carcinoma cases are associated with *BRD4-NUT* fusion and in the remaining 30%, *NUT* has been previously reported to fuse with *BRD3* or other unknown genes.[13,17]

In this study, we retrospectively analyzed patients with pulmonary NUT carcinoma diagnosed by NUT immunohistochemical staining and discuss the differential diagnosis to provide information for this rare and aggressive entity.

Methods

Case selection

Cases diagnosed as "NUT carcinoma" in lung pleura and "metastatic NUT carcinoma from the lung" in lymph nodes between 2017 and 2019 were identified through the pathology database at the Samsung Medical Center, Seoul, Republic of Korea. Ultimately, 10 cases were included in the study. Also consecutive 10 cases of poorly differentiated squamous cell carcinoma (SCC), pleomorphic SCC and small cell carcinoma (SmCC) were reviewed for histological comparison. Clinical features such as age, sex, treatment and follow-up period, and pathological reports were obtained by review of patients; electronic medical records. Two independent pathologists (YAC and JHH) reviewed all hematoxylin and eosin (H&E)-stained slides for pathological features including histological morphology, keratinization, lymphovascular invasion, necrosis, and mitosis. Immunohistochemistry (IHC) slides and gross photographs were also reviewed. This study was approved by the Institutional Review Board of Samsung Medical Center (2020-04-124) and informed consent was waived.

Immunohistochemical staining, interpretation and fluorescence in situ hybridization assay

We used 5 μM formalin-fixed, paraffin-embedded tissue sections which were deparaffinized and rehydrated with a xylene and alcohol solution. Immunohistochemical staining was performed using the BOND-MAX autoimmunostainer (Leica Biosystems, Melbourne, Australia) according to the manufacturer's protocol. Sections underwent antigen retrieval with ER2 buffer (pH 8.0) for 20 minutes at 97°C. After treatment with endogenous peroxidase blocking for 10 minutes, sections were incubated with NUT antibody (C52B1, 1:50, Cell Signaling Technology, Danvers, Massachusetts) for 15 minutes, and Bond Polymer Refine Detection (DS9800, Leica Biosystems, Melbourne, Australia) as a secondary antibody for 10 minutes. IHC slides were interpreted by two independent pathologists (YAC and JHH) as previously described.[13] Antibody against anaplastic lymphoma kinase (ALK) (clone 5A4; 1:30, Novocastra, Newcastle upon Tyne, UK) was used and evaluation of ALK IHC expression was done as previously described.[18] PD-L1 expression was evaluated using PD-L1 IHC 22C3 pharmDx assay (Dako, Glostrup, Denmark) as previously described.[19] Two independent pathologists (YAC and JHH) evaluated tumor cells with membranous PD-L1 staining using tumor proportion scores with cutoff points as previously described.[20] The result of *NUT* gene (*NUTM1*) translocation, break-apart fluorescence in situ hybridization (FISH) was acquired as a generous gift from Dr Yoon Kyung Jeon (Seoul National University).

Results

Clinical characteristics

Clinical characteristics of the cases are summarized in Table 1. A total of seven male and three female patients were included in the study. The median age at diagnosis was 38 years (range, 18–49 years). Six patients were nonsmokers and the others were current or ex-smokers. All cases presented with lung nodules with or without pleural manifestation. Four patients were diagnosed following routine health examinations, two patients presented with cough, two patients presented with chest pain, one patient presented with right upper quadrant abdominal pain, and the other patient presented with flank pain. The radiological impression of the tumor was non-small cell lung cancer (nine cases) and malignant tumor (one case). The specimens were obtained from lung, lymph node, and pleural tissues. The majority of the patients were stage III and IV, except for one patient with stage IA (Table 1). With regard

Table 1 Clinical characteristics of 10 nuclear protein in testis (NUT) cases

Case No.	Age	Sex	Specimen	Organ	Smoking history (PY)	Clinical symptoms	Stage	Tumor location	Treatment	Follow-up
1	34	M	Biopsy	Lung	Ex-smoker (7.5)	Right upper quadrant abdominal pain	IV	Peripheral	Genexol/carboplatin, radiation therapy, pembrolizumab	Transferred to another institute
2	45	M	Biopsy	Lymph node	Non-smoker	Incidental (routine check-up)	IIIA	Central	Alimta/carboplatin, pembrolizumab	Complete response
3	32	M	Biopsy	Liver	Ex-smoker (6)	Chest pain, cough	IV	Central	Refused further treatment	Increased liver function test, transferred to another institute
4	38	M	Biopsy	Lymph node	Non-smoker	Incidental (Routine check-up)	IIIA	Central	Palliative gemcitabine/ cisplatin, pneumonectomy, adjuvant navelbine/cisplatin	Complete response
5	49	M	Mass excision	Pleura	Non-smoker	Chest pain	IV	Peripheral	Palliative vincristine, doxorubicin, tripegfilgrastim and radiation	Disease progression, transferred to another institute
6	41	F	Biopsy	Pleura	Non-smoker	Flank pain	IV	Peripheral	s/p palliative gemcitabine/ cisplatin	Partial response
7	44	M	Resection	Lung	Ex-smoker (10)	Incidental (routine check-up)	IIIA	Peripheral	Lobectomy, adjuvant Paclitaxel/carboplatin	Gamma knife surgery for brain metastasis
8	48	F	Resection	Lung	Non-smoker	Cough (routine check-up)	IIIA	Central	Neoadjuvant carboplatin, genexol, pembrolizumab, lobectomy, adjuvant pembolizumab	Complete response
9	43	M	Biopsy	Lung	Current smoker (20)	Incidental	IA	Peripheral	Lobectomy with adjuvant paclitaxel/carboplatin	Complete response
10	18	F	Biopsy	Lung	Non-smoker	Chest pain	IV	Central	Palliative paclitaxel with carboplatin	Stable disease

PY, pack-year; s/p, status post.

to tumor location, they were centrally located in five cases and peripherally in the remainder.

Initial diagnoses of cases included spindle cell neoplasm, (metastatic) SCC, and undifferentiated round cell sarcoma. Except for one patient who refused further treatment and one patient who underwent surgery, the remaining eight patients underwent chemotherapy with different regimens. One patient who had multiple bone and lymph node metastases died one year after diagnosis. The remaining patients survived with four patients transferred to other institutes for further treatment.

Case presentation and pathological findings

Table 2 summarizes the pathological characteristics. Tumor cells showed round, squamoid, and spindle cellular features. Some patients showed overlapping morphological features of tumor cells and about 60% of cases showed squamoid morphology. However, no cases showed keratinization of tumor cells, even in those with predominant squamoid features. The cases showed poorly to undifferentiated features with scant cytoplasm and irregular nuclear contours. One case (10%) showed increased mitotic activity. In addition, three cases showed atypical features, mimicking round cell tumor and undifferentiated tumor features. Three cases (30%) showed fibrotic stroma with separated cell clusters. Coagulative necrosis was observed in four patients (40%). Inflammatory cell infiltration was identified in six patients (60%): two neutrophilic and four lymphocytic infiltration, respectively.

Detailed histopathological features of NUT carcinoma were as follows. Case 1 showed spindle cells that could be misdiagnosed as spindle cell neoplasm (Fig 1a,b). Squamous cell carcinoma had been previously diagnosed in three cases. Case 2 and 3 showed squamoid morphology with abundant clear to eosinophilic cytoplasm; however, no definite keratinization was found (Fig 1c,d). Lymphocytic infiltration with abrupt necrosis was found around the tumor cells. In Case 4, most of the cells showed epithelioid features separated by fibrous stroma (Fig 1e); however, abrupt changes to squamoid and dyskeratotic cells

Table 2 Pathological characteristics of 10 nuclear protein in testis (NUT) cases

Case No.	Initial diagnosis	Final diagnosis	Morphology	Necrosis	Fibrotic stroma	Keratini-zation	Inflamm-atory cells	Other IHC results	PD-L1 IHC TPS (%)	ALK IHC	ROS-1 IHC	EGFR status
1	Spindle cell neoplasm	Atypical cell proliferation, suggestive of NUT carcinoma	Spindle	N	N	N	N	NUT, p63, TTF-1, CD34, STAT6: +	80	—	—	Wild type
2	Metastatic NUT-midline carcinoma	Metastatic NUT-midline carcinoma	Round, squamoid	Y	N	N	Y (neutrophil)	NUT, CK (AE1/AE3), p63: + TTF-1, CD56, chromogranin, CD99, CD45: –	70	—	—	N/A
3	Squamous cell carcinoma	Poorly differentiated carcinoma, favor NUT carcinoma	Squamoid	Y	N	N	Y (neutrophil)	NUT, p63:+ TTF-1: –	1	—	—	Wild type
4	Metastatic squamous cell carcinoma from lung	NUT carcinoma, squamous cell type with pseudoglandular pattern	Squamoid	Y	Y	N	N	NUT, p63:+ TTF-1: –	0	—	—	Wild type
5	Undifferentiated round cell sarcoma, FNCLCC grade 3/3	NUT carcinoma	Round	N	Y	N	N	NUT, p53: + Bcl-2: Focal + CK (AE1/AE3): Weak + p63, CD56, Desmin,Pan TRK, S-100, Actin (Smooth muscle): –	0	—	—	Wild type
6	Metastatic Squamous cell carcinoma	Suggestive of NUT carcinoma	Squamoid	Y (focal)	Y	N	Y (lymphocyte)	NUT: +	0	—	—	Wild type
7	Poorly differentiated, non-small cell carcinoma, consistent with NUT carcinoma	Poorly differentiated, non-small cell carcinoma, consistent with NUT carcinoma	Round	Y	Y	N	Y (lymphocyte)	NUT:+ p63, CD56:–	0	—	—	Wild type
8	Metastatic squamous cell carcinoma	NUT carcinoma, squamous cell type	Squamoid	N	N	N	Y (lymphocyte)	NUT, p63:+ CD56:–	0	—	—	Wild type
9	Consistent with NUT carcinoma	Consistent with NUT carcinoma	Spindle, squamoid	N	N	N	Y (lymphocyte)	NUT, p63:+	0	—	—	N/A
10	NUT carcinoma, undifferentiated carcinoma component	NUT carcinoma, undifferentiated carcinoma component	Spindle, round	N	N	N	N	NUT, p63:+ TTF-1, CD56:–	0	—	—	N/A

–, negative staining; +, positive staining; ALK, anaplastic lymphoma kinase; CK, cytokeratin; EGFR, epidermal growth factor receptor; FNCLCC, Fédération Nationale des Centres de Lutte le Cancer; N, Absent; N/A, not available; TPS, tumor proportion score; Y, present.

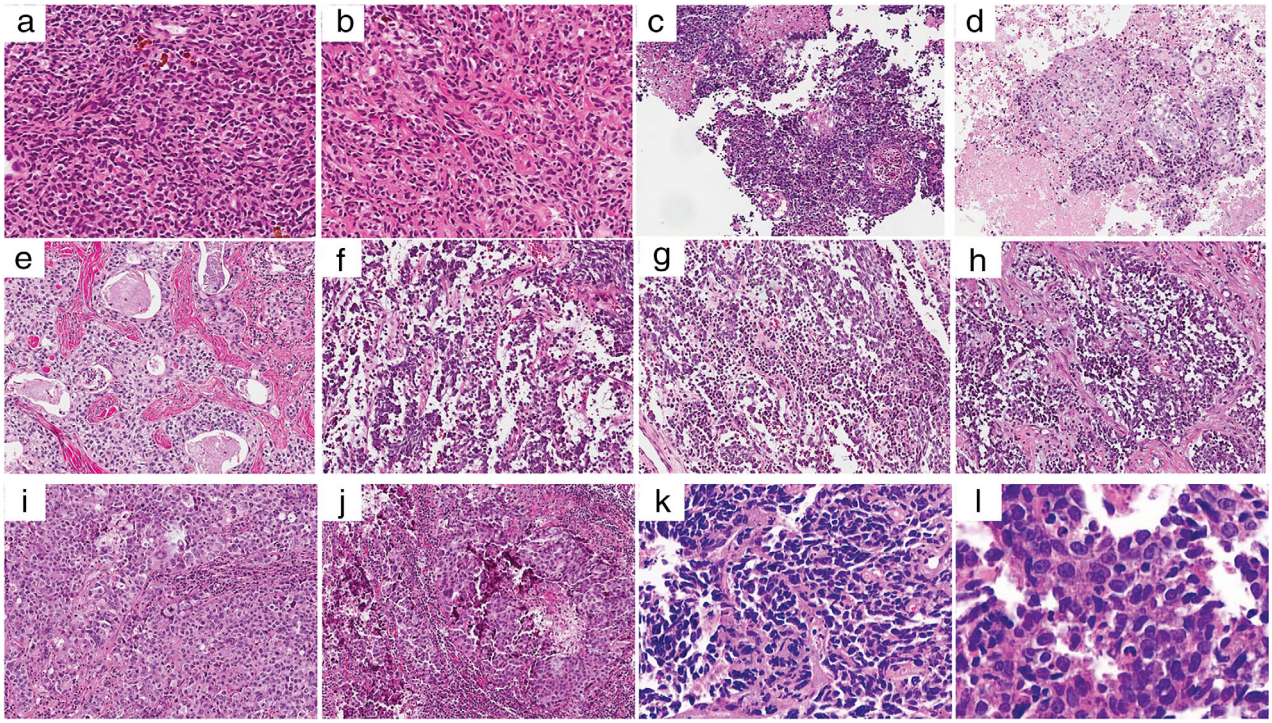

Figure 1 Histological features of representative nuclear protein in testis (NUT) carcinoma. (**a**, **b**) NUT carcinoma consists of spindle cells that can be misdiagnosed as spindle cell neoplasm (Case 1). (**c**) The tumor shows abrupt transition to a squamoid component intermingled with undifferentiated features (Case 2); and (**d**) may show necrosis (Case 3). (**e**) Tumors might be separated with fibrous stroma (Case 4). (**f**–**h**) The undifferentiated round cells without cytoplasm can mimic round cell sarcoma (Case 5). (**i**, **j**) There might be mitotic and pleomorphic features (Case 7); and (**k**, **l**) small round tumors with suspicious nuclear molding and inconspicuous nucleoli for neuroendocrine tumors (Case 10).

with clear cytoplasm were identified. Necrosis was also easily found. Case 8 showed a lobulated growth pattern divided with fibrous stroma. The tumor cells consisted of polygonal cells with scant cytoplasm and inconspicuous nucleoli. Neither necrosis, keratinization, nor abrupt change of dyskeratotic cells were identified. Similar to NUT carcinoma, poorly differentiated SCCs consisted of epithelioid cells, without mature keratinization and were separated by fibrous stroma. Case 5 was initially diagnosed as undifferentiated round cell sarcoma, Fédération Nationale des Centres de Lutte le Cancer (FNCLCC) grade 3/3. Radiological findings suggested pleural malignancy such as sarcoma and mesothelioma due to diffuse pleural infiltration with fluid collection in the right hemithorax and pleural seeding. The tumor showed undifferentiated features with scant cytoplasm, high nuclear to cytoplasmic ratio, and round and spindle morphology (Fig 1f–h). Case 7 showed pleomorphic features (Fig 1i,j). Cells were separated by fibrous stroma and three mitotic figures were found. Pleomorphic features were also found in some SCCs. Similar to NUT carcinomas, there was lymphocytic and neutrophilic infiltration with fibrous stroma. Case 10 showed undifferentiated features with high nuclear to cytoplasmic ratio, inconspicuous nucleoli, and severe crushing artifacts without definite necrosis and mitotic figures (Fig 1k,l). SmCCs also showed similar histological features, such as severe crushing artifacts and scant cytoplasm.

Immunohistochemical and fluorescence in situ hybridization findings

All cases showed diffuse strong nuclear expression of NUT. Five cases showed positive p63 IHC staining, with three cases (Cases 3, 4, and 8) showing squamoid features. One case showed TTF-1 positivity and remaining cases showed negative staining. All cases showed negative staining for CD56. Additional immunostaining was performed in cases with unusual morphology. Case 1, which showed spindle cell morphology, showed positivity for CD34, p63, STAT6, and TTF-1, with negativity for CK (AE1/AE3). Case 5 showed negativity for desmin, panTrk, CD34, S-100, CD56, and smooth muscle actin staining and weak positivity for CK(AE1/AE3) staining. Case 10, which presented with spindle to round cell morphology with fine

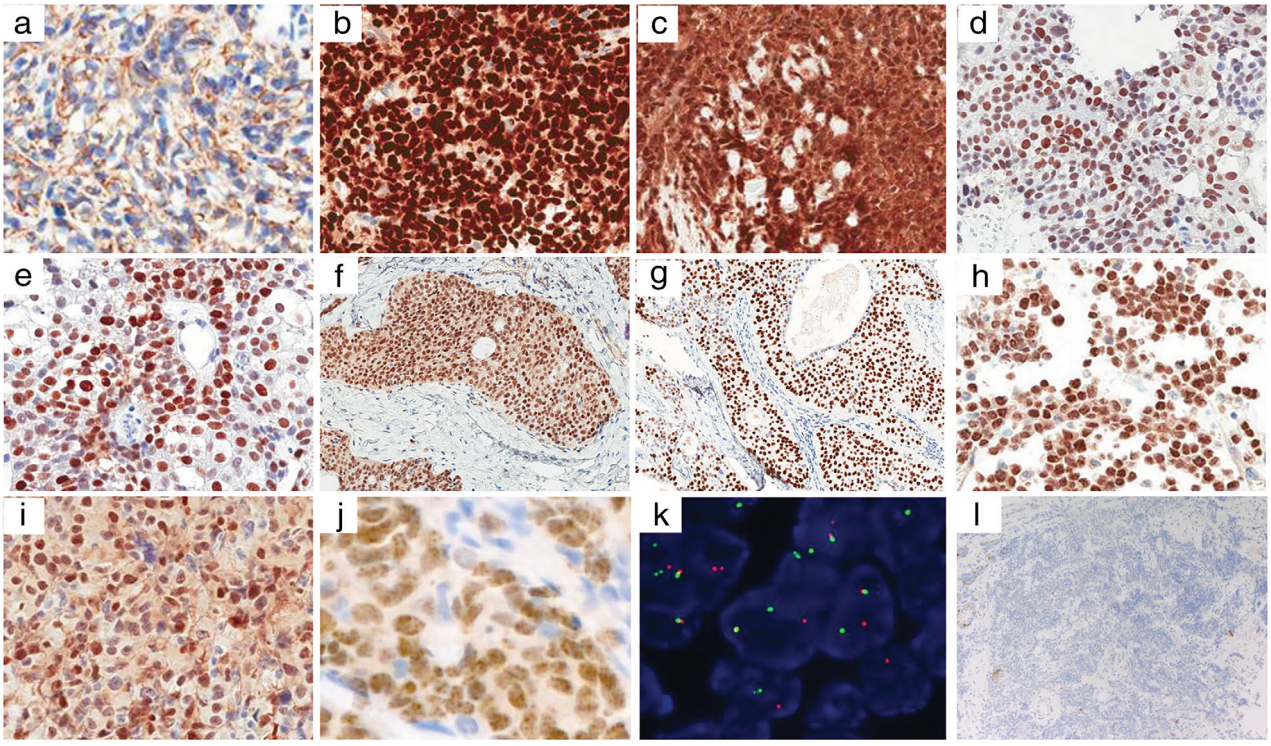

Figure 2 Immunohistochemical staining of representative nuclear protein in testis (NUT) carcinoma. Case 1 shows positive staining for (**a**) cytokeratin (AE1/AE3): (**b**) NUT: and (**c**) STAT6. Case 3 shows positive staining for (**d**) NUT; and (**e**) p63. (**f**) NUT; and (**g**) p63 can be positive, as in Case 4. Diffuse NUT staining is shown for (**h**) Case 5; and (**i**) Case 7. (**k**) Case 5 and Case 7 showed *NUT* translocation confirmed by fluorescence in situ hybridization. Case 10 showed positive (**j**) NUT; and negative staining for (**l**) CD56.

chromatin, was suspicious for neuroendocrine features and diffuse growth patterns. The tumor showed no necrosis and fibrotic stroma. This case showed positivity for p63 and negativity for CD56 staining. The representative immunostaining results are shown in Figure 2. Two cases, showing p63 IHC negativity also showed *NUT* translocation by fluorescence in situ (FISH) assay (Fig 2). All cases diagnosed as poorly differentiated SCCs, pleomorphic SCCs and SmCCs showed negative staining for NUT IHC.

Discussion

Due to various histological features, NUT carcinoma can be misdiagnosed as other tumors when NUT is not suspected.[5,7,12,13] NUT carcinoma can present as entirely undifferentiated carcinoma or present with abrupt transition to squamous differentiation.[8–11] In this study, four cases were initially diagnosed as squamous cell carcinoma due to evident squamoid morphology; however, in all cases, there was no definite mature keratinization. In previous studies, keratinization is often focal, which can cause sampling bias.[1,16] When abrupt keratinization in undifferentiated carcinoma is observed, NUT carcinoma may be suspected.

In the present study, six out of 10 cases showed neutrophilic or lymphocytic inflammatory cell infiltration. Inflammatory cell infiltration has also been reported in a previous study.[21] The presence of poorly or undifferentiated tumors in a background of neutrophilic infiltration might suggest the possibility of NUT carcinoma.

One case in our study showed spindle cell morphology, with an initial diagnosis of spindle cell neoplasm. In a previous study, various IHC was performed in a patient with NUT carcinoma with spindle cell morphology to rule out spindle cell carcinoma, high grade neuroendocrine tumor, and sarcoma.[22] In our case, CD34 and STAT6 staining was positive, which was suspicious of a solitary fibrous tumor, but the patient presented with a lung mass with aggressive biological behavior. Intraparenchymal solitary fibrous tumors are very rare and usually benign,[23] and not compatible with our case. However, NUT IHC was performed and the patient was finally diagnosed with NUT carcinoma. Further studies are needed to explore whether aberrant expression of CD34 and STAT6 expression in NUT

carcinoma is clinically significant. In addition, in the clinical setting of intrapulmonary mass with extensive spindle cells, NUT carcinoma should be also included in the differential diagnosis together with spindle cell carcinoma, pleomorphic carcinoma, and sarcoma.

NUT carcinoma can mimic undifferentiated round cell sarcoma,[8] since the tumor may consist of small cells with round nuclei and scant cytoplasm.[24] In four of our cases scant cytoplasm, with round morphology was evident. Although one of the cases mimicked mesothelioma and round cell sarcoma, the immunostaining profile was not indicative of mesothelioma or round cell sarcoma. After intradepartmental discussion, NUT IHC was performed to make a final diagnosis. In addition, round cell morphology with inconspicuous nucleoli and scant cytoplasm might be reminiscent of neuroendocrine tumors, as in Cases 2, 7, 8 and 10; however, CD 56 staining was negative.

NUT carcinoma in our study showed poorly to undifferentiated morphology with or without necrosis, and this can mimic various diagnoses. All our cases showed diffuse strong positive staining for NUT immunostaining. In various studies, NUT immunostaining showed 99% negative predictive value and positive predictive value of 100%,[9,14] thus immunostaining is useful in daily practice even in patients with various morphologies.

Clinically, age of patients ranged from 18 to 49 years old, which is in accordance with previous studies.[1,6,9,12] Patient symptoms included cough, chest pain, and flank pain, which are nonspecific. Four cases diagnosed incidentally on routine health check-up showed no evidence of disease after operation and adjuvant chemotherapy; however, the remaining patients showed disease progression or no response to chemotherapy and radiation therapy.

In conclusion, NUT carcinoma can be a diagnostic challenge due to the various morphologies of the tumor and rarity of the disease. Thus, it is important to consider NUT carcinoma as a differential diagnosis when encountering lung biopsy with undifferentiated morphology.

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Disclosure

The authors have no conflicts of interest to declare.

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