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Original Article

Well-differentiated fetal adenocarcinoma of the lung: clinicopathologic features of 45 cases in China

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Abstract: Objective: Well-differentiated fetal adenocarcinoma (WDFA) is a rare pulmonary carcinoma with low malignancy and favorable prognosis. All cases were collected, analyzed and summarized to better understand this disease. Methods: We used the keywords "fetal adenocarcinoma" and "epithelial pulmonary blastoma (EPB)" to search WANFANG MED ONLINE, CNKI and NCBI PUBMED for cases reported by Chinese authors from 1987 to July 2015. Results: A total of 64 cases reported in China were reviewed, and the details of the clinicopathological features of 45 cases were summarized. Among these 45 patients, 23 (23/45, 51.1%) patients were male and 22 (22/45, 48.9%) patients were female. The mean age at diagnosis was 35 ± 15 years old (range, 6-72 years old) with a bimodal peak in the second and third decades. Furthermore, 24 tumors (24/31, 77.4%) were found to have progressed past stage I, while only three (3/45, 6.7%) tumors had lymph nodes metastases. These tumor cells were 100% reactive for keratin, β-catenin, Napsin A and PDGFRα when stained by these antibodies. Better survival could be obtained if the metastatic tumor is removed in some patients with metastases. Four (4/31, 12.9%) patients died due to their tumors. Conclusions: WDFA is very different to conventional adenocarcinoma in clinicopathology. It prefers to occur in the second and third decades. Lymph node metastasis is infrequent. Beta-catenin may be a potential marker for disease. Surgery is the best therapy method if the technology is feasible.

Keywords: Lung cancer, well-differentiated fetal adenocarcinoma, pathologic diagnosis, treatment, prognosis

Introduction

In the Pulmonary and Mediastinal Pathology Department of the Armed Forces Institute of Pathology (AFIP), well-differentiated fetal adenocarcinoma (WDFA) has been recognized and diagnosed as a form of pulmonary blastoma (PB) since 1971. The classification by the World Health Organization (WHO) in 1999 removed WDFA from the PB category and classified it as a variant of adenocarcinoma. In 2004, the WHO classified WDFA as high-grade fetal adenocarcinoma (HGFA) and low-grade fetal adenocarcinoma (LGFA). These two kinds of tumors are microscopically similar, but with differences; that is, HGFA tumor cells show more prominent nuclear atypia, a lack of morule formation, a transition of conventional adenocarcinoma, and more necrosis [1].

WDFA, which was first described by Kradin [2] and Kodama [3], is a rare epithelial pulmonary malignancy, and its incidence rate has been reported to be at 0.5% in all cases of pulmonary adenocarcinoma [4, 5]. Few cases have been reported and very little research has been conducted on the molecular mechanism, treatment and prognosis of WDFA. Hence, a review of outstanding cases can help better understand WDFA. Therefore, cases reported by Chinese authors from 1987 to July 2015 were summarized and reviewed, including one case previously reported by the authors of the present study [6]. In this manner, we were able to accrue the present data on WDFA to better understand, diagnose and treat this disease.

Materials and methods

Retrieval condition

WANFANG MED ONLINE and CNKI were searched using keywords "fetal adenocarcinoma" and "epithelial pulmonary blastoma (EPB)",

Table 1. Clinical data summary of 45 cases in Chinese

Num.	Age	Gender	Symptom	Smoke	Pathological Type	Max-diameter (cm)	Location	pTNM	Follow up (months)	Author
1	9	F	Chest pain, distress	ND	WDFA	4	L.U.L	pT2aN0M0	ND	Han JA [9]
2	6	M	Cough, sputum	ND	WDFA	5	L.U.L	pT2aN0M0	17/alive	Kou YL [10]
3	48	F	Hemoptysis, chest distress	ND	WDFA	6	R.L.L	pT2bN0M0	ND	Guo AT [11]
4	29	F	Cough, suptum	ND	WDFA	1.2	R.M.L	pT1aN0M0	2/alive	Tan MH [12]
5	26	M	Asymptomatic	Yes	WDFA	7	R.U.L	pT2bN0M0	86/alive	Zhang TM [6]
6	48	M	Chest pain, night sweat, fatigue	Yes	WDFA	3	L.U.L	pT2aN0M0	22/alive	Shi HQ [13]
7	27	F	Cough, blood-streak sputum	ND	WDFA	2.5	R.U.L	ND	ND	Fang GY [14]
8	23	M	Cough, blood-streak sputum	ND	WDFA	6.7	L.U.L	pT2bN2M0	14/alive	Fan JQ [15]
9	25	F	Cough, suptum	No	WDFA	9	R.M.L	pT3N0M0	1/alive	Zhang Y [16]
10	ND	F	Cough, suptum	ND	WDFA	3	R.U.L	pT1bN0M0	ND	Wang HY [17]
11	25	M	Chest pain, blood-streak sputum	No	WDFA	5.6	L.L.L	pT2bN0M0	36/alive	Luo CQ [18]
12	51	F	Cough, hemoptysis	ND	WDFA	3.6	L.U.L	pT2aN0M0	36/alive	Luo CQ [18]
13	58	F	Asymptomatic	No	WDFA	5.5	R.U.L	pT2bN0M0	ND	Li JZ [19]
14	41	M	Cough, suptum, chest pain	Yes	WDFA	4	L.U.L	pT2bN0M0	32/alive	Wang YF [20]
15	36	F	Asymptomatic	No	WDFA	3	L.L.L	pT1bN0M0	56/alive	Wang YF [20]
16	30	F	Cough, chest distress	Yes	WDFA	2.5	R.U.L	pT3N0M0	49/alive	Wang YF [20]
17	31	F	ND	No	EBP	12	L.U.L	pT3N0M0	131/alive	Liu ZF [21]
18	38	M	ND	Yes	WDFA	ND	Mul (right)	IIIb	72/alive	Liu ZF [21]
19	48	F	ND	No	EBP	6	R.L.L	pT2bN0M0	115/alive	Liu ZF [21]
20	72	M	ND	Yes	WDFA	5	R.L.L	pT2bN0M0	38/alive	Liu ZF [21]
21	59	M	Cough, bloody sputum, chest pain	Yes	WDFA	5	L.U.L	pT2bN0M0	101/death of CF	Xu T [22]
22	36	M	Cough, bloody sputum	Yes	EBP	6	L.U.L	ND	18/death of PD	Liu AJ [23]
23	27	F	Dry cough, chest pain	ND	WDFA	7.5	R.M.L.L	pT3N0M0	45/alive	Liu SH [24]
24	50	M	Cough, bloody sputum	Yes	EBP	10	L.U.L	pT3N0M0	36/death	Li QM [25]
25	38	M	Cough, bloody sputum, chest pain	Yes	EBP	7	L.U.L	pT3N0M0	ND	Qian B [26]
26	12	M	Hemoptysis, chest distress, weak	ND	EBP	6.5	R.L.L	ND	ND	Yin MX [27]
27	41	M	Dry cough, hemoptysis	ND	EBP	5	M.B (R)	ND	ND	Gao J [28]
28	34	F	Fever, cough	ND	EBP	2.0/1.5/0.8	Mul (left)	ND	ND	Gao J [28]
29	54	F	Asymptomatic	ND	EBP	0.6-2.1	Bilateral lung	pT4N0M1a	ND	Geng J [29]
30	33	M	Asymptomatic	ND	EBP	7	L.L.L	ND	ND	Zhang CL [30]
31	20	M	Asymptomatic	ND	EBP	5	R.L.L	ND	ND	Qin NS [31]
32	18	M	Asymptomatic	ND	EBP	6	R.U.L	pT2bN0M0	72/alive	Fan L [32]

33	30	F	Cough, chest pain, Dyspnea	No	EBP	5	R.U.L	PT3N3M0	9/death	Han LZ [33]
34	36	M	Cough, bloody sputum	ND	EBP	3.6/6	Mul (left)	ND	ND	Wei F [34]
35	ND	M	Cough	Yes	EPB	ND	R.U.L	PTxN0M0	24/alive	Huo Z [35]
36	12	F	Asymptomatic	No	EPB	10	R.M.L	pT3N0M0	5/death	Zhang GQ [36]
37	38	M	Asymptomatic	No	EPB	6.9	R.L.L	pT2bN0M0	32/relaps	Zhang GQ [36]
38	33	F	Asymptomatic	No	EPB	10.2	R.U.L	pT3N0M0	20/alive	Zhang GQ [36]
39	33	F	Asymptomatic	No	EPB	7	R.U.L	pT2bN0M0	15/alive	Zhang GQ [36]
40	55	F	Cough, bloody sputum	Yes	WDFA	6	R.U.L	pT2bN0M0	ND	Li SH [37]
41	ND	M	Cough, bloody sputum, chest pain	ND	WDFA	10	L.U.L	ND	12/alive	Yin Z [38]
42	ND	M	Cough, bloody sputum, chest pain	ND	WDFA	4	L.U.L	ND	12/alive	Yin Z [38]
43	ND	M	Cough, bloody sputum, chest pain	ND	WDFA	11	R.U.L	ND	12/alive	Yin Z [38]
44	ND	F	Cough, bloody sputum, chest pain	ND	WDFA	2.5	R.L.L	ND	12/alive	Yin Z [38]
45	23	F	Dry cough	ND	WDFA	4	R.U.L	ND	7/alive	Li XZ [39]

M: male; F: female; L.U.L: left upper lobe; R.L.L: right lower lobe; R.M.L: right middle lobe; R.U.L: right upper lobe; R.U.M.L: right upper and middle lobe; R.M.L.L: right middle and lower lobe; M.B: mainstem bronchus; L: left; R: right; Mul: multiple; ND: no description. CF: cardiac failure. PD: primary disease.

Table 2. Comparative clinical features of WDFA reported by Sato, Koss and this paper

Parameter	Chinese	Japan (Sato)	USA (Koss)
No. of cases	45	25	28
Mean age/range (years)	35/6-72	37/19-58	33/ND
Male/Female	23/22	10/15	13/15
Smoker (yes/no)	12/10	ND	19/4
Asymptomatic (%)	11/41 (26.8)	ND (76)	ND (57)
Solitary (%)	35/42 (83.3)	ND	ND (96)
Pleural effusion (yes/no)	1/40	ND	0/23
Metastasis at diagnosis/no metastasis	1/45	1/25	5/21
Tumor size (cm) mean/median/range	6/6/0.6-12	4.5/3.5/1.4-12	4.5/3.75/1-10
Location (right/left)	26/18	15/10	ND
Solitary/multiple	36/4	26/0	ND
Pathological stage	31	24	24
I	7	22	20
>I	24 (77.4%)	2 (8%)	4 (20%)
Lymph node metastasis	3 (0.9%)	2 (8%)	3 (14%)
N0/N1/N2	29/1/2	22/2/0	ND
No. follow-up	30	22	21
Median/mean follow up (months)	24/37.6	39/ND	95/97
No. died of tumor (%)	4 (13.3%)	2 (8.3%)	3 (14%)

ND: no description.

and 235 and 394 related articles retrieved, respectively. For NCBI PUBMED, the keyword "Well-differentiated fetal adenocarcinoma" was used for the search, and 180 related articles were retrieved. Life span: unlimited to July 2015. Retrieval mode: machine retrieval. Retrieval time: July 27, 2015. A total of 64 cases were reported by Chinese authors with WDFA and EPB. Among these cases, the clinicopathological characteristics of 45 cases were collected for the present study.

Case selection criteria

Fetal adenocarcinoma (FA) consists of complex glandular structures that comprise of glycogen-rich, non-ciliated cells resembling a developing epithelium in the pseudoglandular phase of the fetal lung. Low-grade (well-differentiated) FAs have been described with low nuclear atypia and morule formation. The neoplastic glands are typically enveloped by a loose fibromyxoid stroma [7].

Case inclusion criteria: cases with a pathological diagnosis for WDFA and epithelial type pulmonary blastoma in literature, and the performance of the tumor tissue under a microscope conform to the pathological diagnosis of WHO standards. All cases selected for this study were evaluated by one pathologist (Yiran Cai, Ph. D) and two oncologists (Tongmei Zhang, Assistant Chief Physician, and Baohua Lu, Attending Doctor).

TNM stage criteria

Referring to the 2009 International Union Against Cancer (UICC, Seventh Edition) TNM Staging of Lung Cancer, cases before 2009 were re-staged according to the new stage edition.

When multiple tumors were present in one patient, the tumor's maximum diameter was calculated based on the largest tumor.

Follow-up time was calculated according to the reported literature, which varied between patients.

Statistical methods

All statistical analyses were executed using SPSS 18.0 software. The level of significance was defined as $P<0.05$. Fisher's exact test was performed to explore associations between survival and factors including age, gender, asymptomatic, smoke, tumor size, lymph nodes metastases and pathologic stage.

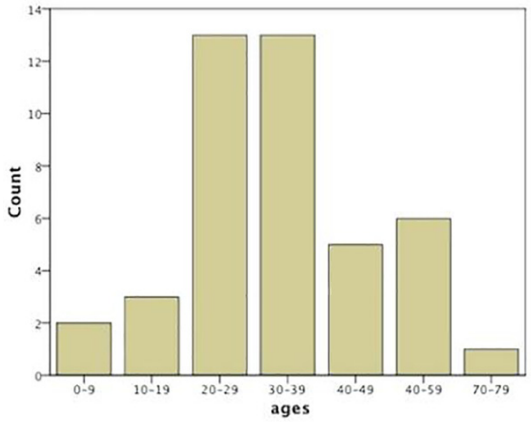

Figure 1. The number of cases in different decades, with a bimodal peak in the second and third decades, are mainly in 20-39 ages, cases that younger than 10 ages or older than 60 ages are very rare.

Table 3. The X-ray characteristics in WDFA cases

X-ray characteristics	Cases (%)
Tumor location	
Left lung	18/45 (40.0)
Right lung	26/45 (57.8)
Bilateral lung	1/45 (2.2)
Upper lobe	26/45 (57.8)
Lower lobe	11/45 (24.4)
Central	13/43 (30.2)
Peripheral	30/43 (69.8)
Tumor number	
Single lesion	40/45 (88.9)
Double/multiple	5/45 (11.1)
Tumor shape	
Single Solitary mass/nodules	34/42 (81.0)
Mass with liquefaction	1/42 (2.4)
Multiple nodules	5/42 (11.9)
Lobe consolidation	1/42 (2.4)
Patch shadow	1/42 (2.4)
Tumor size	
<5 cm	13/43 (30.2)
≥5 cm	30/43 (69.8)

Results

There were 24 WDFA and 21 EPB cases reported by Chinese authors (**Table 1**) [6, 9-39]. These Chinese cases were also compared with cases reported in Japan (Sato [8]) and USA (Koss [4]) (**Table 2**).

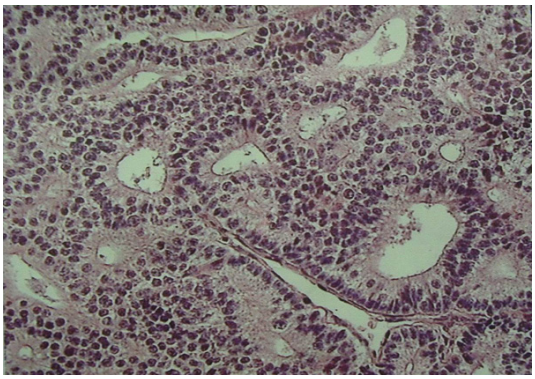

Figure 2. Pathological changes from microscope, cancer cells are made of tubular or adenoid structure. The tumor have well-ordered neoplastic glands and moruls. The glands consisted of branching tubules lined by stratified columnar cells with a clear cytoplasm and relatively little nuclear hyperchromasia or pleomorphism.

Epidemiology

Among the 45 patients in this review, 23 (23/45, 51.1%) patients were male and 22 (22/45, 48.9%) patients were female. The mean age at diagnosis for all patients was 34.69 ± 14.71 years old (range, 6-72 years old) with a bimodal peak in the second and third decades. The age distribution is presented in **Figure 1**. Furthermore, 12 patients (12/22, 54.5%) were smokers and 10 (10/22, 45.5%) patients were nonsmokers (**Table 2**).

Clinical characteristics

The main symptoms at the time of diagnosis were coughing, sputum, blood-streak sputum or hemoptysis, chest distress, chest pain and other respiratory symptoms. In 30 patients (30/41, 73.2%), only three patients (3/41, 7.3%) had systemic symptoms at the same time, such as fever, fatigue and night sweat. Eleven patients (11/41, 26.8%) were asymptomatic, and lesions were only occasionally found upon physical examination. The X-ray characteristics of WDFA are detailed in **Table 3**. All patients underwent operations that allowed for a definite diagnosis. Minimally invasive biopsy specimens such as those obtained through computed tomography (CT)-guided lung biopsy and tracheostomy with bronchoscopic biopsy failed to confirm the diagnosis before surgery, and only six cases were diagnosed as malignant before surgery.

Table 4. Immunochemical staining of WDFA in 45 cases

Antibody	Positive (No. cases positive/No. stained)	Percent (%)
Keratin, CK, AE1/AE3	8/8, 20/22, 4/4	100.0/90.9/100.0
CEA	4/10	40.0
Vimentin	2/6	33.3
Actin	0/3	0
S-100	3/11	27.3
NSE	6/9	66.7
AFP	2/8	25.0
CgA	17/26	65.4
Syn	11/15	73.3
PAS	5/10	50.0
β-catenin	10/10	100.0
EMA	4/5	80.0
P53	4/7	57.1
PDGFRα	2/2	100.0
EGFR	1/3	33.3
AAT	3/5	60.0
Her2	0/2	0
ER	0/8	0
PR	0/8	0
TTF-1	11/13	84.6
CD56	3/9	33.3
NapsinA	4/4	100.0
Ki-67	2/2	100.0
CK7	7/8	87.5
CK20	0/2	0
CDX-2	0/5	0
CA125	0/1	0
CD117	1/1	100.0

CEA: carcinoembryonic antigen; NSE: nero-specific enolase; AFP: alpha-fetoprotein; CgA: chromogranin A; Syn: synaptophysin; PAS: periodic acid Schiff; EMA: epithelial membrane antigen; PDGFR: platelet-derived growth factor receptor; EGFR: epidermal growth factor receptor; AAT: α1 antitrypsin; Her2: human epidermal growth factor receptor; ER: estrogen receptor; PR: progesterone receptor; TTF-1: thyroid transcription factor-1; CD: neural cell adhesion molecules; CK: cytokeratins; CA125: cancer antigen 125.

The progression in 31 patients was quantified by the authors *via* the TNM stage. Among these patients, 7, 20, 1, 2 and 1 patients were at stage I, II, IIIa, IIIb and IV, respectively. Merely three patients had N1 and/or N2 lymph nodes (**Table 1**)

Pathological characteristics and gene mutation

Gross pathological characteristics were described in only a few of the cases. The color of the tumors was typically variegated, with mixtures of white, tan, or gray. Four (4/45, 8.9%) lesions had foci of little necrosis, which was often central in location. Through a microscope, the tumor appeared to have well-ordered neoplastic glands, and moruls could often been observed. Some tumors displayed a scanty, mature spindle cell mesenchyme. The glands consisted of branching tubules lined by stratified columnar cells with a clear cytoplasm and relatively little nuclear hyperchromasia or pleomorphism (**Figure 2**). A total of 34 tumors were reported by the authors in the present study based on immunochemistry staining results, but the immunohistochemical antibodies were greatly differed among the 31 patients (**Table 4**).

The mutation status of epidermal growth factor receptor (EGFR) and KRAS genes were tested in only six patients, none of these patients revealed a mutation. The echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) gene was investigated in three patients, and no mutations detected; while the P53 gene was assayed in one patient, and no mutations were observed.

Treatment and prognosis

All patients underwent surgery to remove these tumors, while 10 (10/45, 22.2%) patients also received radiotherapy and/or chemotherapy. The chemotherapy regimens presented in these studies had 2-3 drug combinations, and were usually platinum-based regimens. Terminal cases and cases that received radiotherapy and/or chemotherapy were also reviewed in other studies with available clinical data (**Tables 5** and **6**) [4, 8, 15, 21-25, 33, 35, 36, 40-46].

In the present study, 31 cases were followed-up for 1-131 months, with a mean follow-up duration of 37.6 months. Among these 31 patients, five patients died within the follow-up period, one patient died of cardiac failure 101

Table 5. The data of patients received radiotherapy or/and chemotherapy in this paper and literatures

Author	Age	Sex	Smoke	Size (cm)	Stage pTNM	Surgery	CT Regimen	RT	Therapy Effect	Recurrent sites	Follow-up (months)
Fan JQ [15]	23	M	ND	6.0	IIIa (T2bN2M0)	Lobe	DP*	No	SD	Brain M	14/alive
Liu ZF [21]	31	F	No	12.0	IIb	ND	NP#	No	SD	No	131/alive
	48	F	No	6.0	IIa	ND	NI#	No	SD	No	115/alvie
	72	M	Yes	5.0	IIb	ND	IPV#	No	SD	No	38/alive
Liu SH [24]	27	F	ND	7.5	ND	ND	TP#	No	SD	No	45/alive
Huo Z [35]	ND	M	Yes	ND	ND	Lobe	ND	Yes	SD	No	24/alive
Zhang GQ [36]	12	F	No	10.0	IIb (T3N0M0)	ND	CVK#	Yes	SD	Multiple M	5/death
	38	M	No	6.9	IIa (T2bN0M0)	ND	IVE#	No	SD	No	32/relaps
	33	F	No	10.2	IIb (T3N0M0	ND	NP#	No	SD	No	20/alive
	33	F	No	7.0	IIa (T2bN0M0	ND	NP#	No	SD	No	15/alive
Lkhoyaali S [40]	29	M	Yes	12.5	IIb (T3N0M0)	Lobe	EP*	No	SD	No	24/alive
Zaidi A [41]	27	F	Yes	9.0	IIIb (T4N0M0)	Lobe	MIP*	No	SD	No	29/alive
	44	M	Yes	9.0	IIIb (T4N0M0)	Pneu	No	Yes	SD	Brain M	55/alive
Kyung C [42]	48	M	Yes	7.7	ND	No	D	Yes	PR	No	7/alive
Van Loo [43]	44	M	ND	9.0	IIIa (T4N0M0)	Pneu	No	Yes	ND	No	55/alive
	27	F	ND	9.0	IIIa (T4N0M0)	pneu	MIP	No	ND	No	29/alive
Junping W [44]	39	M	ND	1.0	IIb (T3N0M0)	Pneu	TC#	No	ND	No	30/alive
Patnayak R [45]	50	M	Yes	10.0	IIb (T3N0M0)	Lobe	TC#	No	SD	No	18/alive
Chao SC [46]	56	M	Yes	ND	IV	No	GEM	Yes	ND	Cutaneuos, brain	12/death

CT: chemotherapy; M: male; F: female; pneu: pneumonectomy; lobe: lobectomy; RT: radiotherapy; M: metastases; ND: no description; #: adjuvant chemotherapy; *: neoadjuvant chemotherapy; SD: stable disease; PR: partial response; DP: docetaxel-cisplatin; NP: navelbine-cisplatin; NI: navelbine-ifosfamide; IPV: ifosfamide-cisplatin-etoposide; TP: paclitaxel-cisplatin; CVK: cyclophosphamide-vincristine-actinomycin; IVE: ifosfamide-vincristine-etoposide; EP: etoposide-cisplatin; ND: no description; D: docetaxel; MIP: mitomycin-C-ifosfamide-cisplatin; TC: paclitaxel-carboplatin; GEM: gemcitabine.

Table 6. The clinical characteristics of dead WDFA patients in this paper and literature

Author	Age	Gender	Smoke	Size (cm)	pTNM	Therapy	Recurrent Sites	Survival Time (months)	Death Reason
Xu T [22]	59	M	Yes	5.0	pT2bN0M0	Surgery	ND	101	CF
Liu AJ [23]	36	M	Yes	6.0	pT3N0M0	Surgery	ND	18	PD
Li QM [25]	50	M	Yes	10.0	pT3N0M0	Surgery	ND	36	PD
Han LZ [33]	72	M	Yes	5.0	pT3N3M0	Surgery	ND	9	PD
Zhang GQ [36]	12	F	No	10.0	pT3N0M0	S+C	Multiple	5	PD
Koss MN [4]	ND	ND	ND	ND	ND	Surgery	Brain	2	PD
	ND	ND	ND	ND	ND	S+C	Lung	34	PD
	ND	ND	ND	ND	ND	S+C	Lymph nodes	34	PD
Sato S [8]	52	M	ND	6.0	pT1N0M0	Surgery	Yes	28	PD
Caho SC [46]	55	F	ND	5.0	pT2N1M1	ND	ND	24	PD
	56	M	Yes	ND	IV	C	Brain, cutaneous	12	PD

F: female; M: male; ND: no description; CF: cardiac failure; PD: primary disease; S+C: surgery and chemotherapy; C: chemotherapy.

months following surgery to remove the tumor, and four (4/31, 12.9%) of the 31 patients died due to their tumors, with a mean survival time of 17 months (range, 5-36 months) in terminally ill patients. One patient had tumor recurrence after initial surgery, and was treated with three chemotherapeutic drugs. This patient was still alive after a follow-up at 32 months later (case 37). The remaining cases all survived without tumor recurrence during the follow-up.

The clinical, radiologic and pathologic indicators were also reviewed to determine whether these were correlated to the prognosis. A cor-

relation could not be found in terms of age, gender, asymptomatic, smoker, tumor size, lymph node metastasis and pathologic stage.

Discussion

Before 1999, FA was diagnosed as EPB, a subtype of pulmonary blastoma. In 1998, Nakatani Y [1] first distinguished HGFA from WDFA through the presence of disorganized glands, prominent nucleoli, pronounced anisonucleosis, the absence of morules, extensive necrosis and transition to conventional adenocarcinoma. In 1999, the WHO classified WDFA as a variant of invasive adenocarcinoma, according to its predominant component, malignant glandular structures. With the increasing number of cases reviewed, WDFA has been found to differ from conventional adenocarcinoma and HGFA in clinicopathology and biology [47, 48]. Hence, collecting cases reported in literature is very significant to better study this disease. This is the first study that conducted a review of Chinese WDFA patients and included the largest number of patients with the most detailed data. However, regrettably, we could not further study these specimens in terms of its molecular and genetic characteristics, because these cases were collected from literatures, which belong to various hospitals.

In the 45 cases included in existing Chinese literatures, no gender predominance was observed, although some groups [43, 49] reported a male or female predominance of WDFA. Although the mean age at diagnosis was the same with the other reported cases, the bimodal age peak was at the second and third decades in Chinese patients, which was different to the cases reported by Koss [4] and Larsen [49]. No smoking tendency is observed, because only 22 patients had a history of smoking in the present study.

The common symptoms were not specific, and it was difficult to distinguish WDFA from other respiratory diseases with just their symptoms. Furthermore, only 11 patients (26.8%) were asymptomatic. This was lower than that reported by Koss [4], and it may be because 77.4% of tumors were higher than stage I and 69.8% of tumors had a maximum diameter >5 cm in the present study.

These tumors were preferentially located in the right lung, upper lobe and peripheral field in X-ray. Most of the tumors were a single, solitary mass in CT scans. Few patients revealed multiple nodules, lobe-consolidation, pleural effusion and patchy shadows. Furthermore, there were few incidences of lymph node metastases in WDFA patients the present study, as well as in other reviews [4, 8, 45].

In the present study, a N2 patient received neoadjuvant chemotherapy, and the tumor did not respond; but lymph node metastasis was significantly reduced. Then, the patient underwent resection of the cerebral metastatic tumor at nine months after the initial surgery, and was still alive without tumor recurrence at five months after cerebral tumor resection (case 8). Another 12-year-old girl at stage II, who received adjuvant chemoradiotherapy, was found with wide metastasis and died due to its progression at five months after initial surgery (case 36). Lkhoyaali [40] reported a case that received neoadjuvant chemotherapy, and revealed a 12% reduction in tumor mass. Zaidi [41] reported a case, wherein the treatment of neoadjuvant CMT with mitomycin, ifosfamide and cisplatin for a stage T4 N0 M0 patient successfully downstaged the tumor before surgical resection. In addition, Kyung [42] reported a patient with a locally advanced stage, who was treated with concurrent chemoradiotherapy with docetaxel, and achieved partial tumor response. In the reviewed literature, 19 patients received chemotherapy and/or radiotherapy; and 10 of these patients received adjuvant chemotherapy (**Table 5**). To date, there is no evidence for the effectiveness of chemotherapy and radiotherapy in WDFA patients, and there also no standard or recommended chemotherapy regimen. Surgery is preferred when technically possible, since surgery increases the survival of patients, even for patients with recurrence [4, 15, 36].

Koss [4] reported 28 WDFA cases, in which only six (29%) patients had recurrent tumors. Among these patients, three patients were treated surgically, and were tumor free after a follow-up duration of 33, 101 and 153 months. Furthermore, only three (14%) of the 21 patients died due to their disease, and two of them received postoperative chemotherapy.

Larsen [49] reported 23 WDFA cases, in which 57% were male and 43% were female. These tumors from these cases were stained with 38 different antibodies and more than 90% positive reactions were demonstrated with NSE and CEA. Furthermore, only two WDFA patients received chemotherapy, while no objective response was observed. In the present study, the positive reactions of NSE and CEA were only 66.7% and 40%, respectively; which were lower than that reported by Larsen.

Although some studies [50-54] reported that using aspiration cytomorphology or a bronchial brush would allow for a diagnosis before the operation, none of the diagnosis of patients in this study were confirmed before the operation; and it is difficult to determine a diagnosis based on a small biopsy, such as that reported by Van Loo [43]. With the research of more molecular biomarkers and the elevated awareness of WDFA, cytodiagnosis would be an easy and popular approach for this.

The mutation of EGFR, KRAS and ALK genes was not found in the present study. Some studies [19, 54, 55] reported the aberrant nuclear localization and gene mutation of β-catenin in WDFA, and noted that the upregulation of the Wnt signaling pathway may be a common denominator for the development of tumors. This review also revealed that these tumors had a 100% positive reaction to β-catenin, PDGFRα, and NapsinA staining after staining with the antibodies. Beta-catenin is a potential diagnostic marker for WDFA [19, 52, 53]. However, further research on its molecular mechanism is needed, such as the β-catenin, PDGFRα, NapsinA and Wnt signaling pathway.

Sato [8] reported a case of WDFA, and reviewed 25 cases reported in Japan. There were two cases with N1 lymph node metastasis of resection, and one of these cases had a distant metastasis to an eye at the time of diagnosis. There were no N2-postive cases, and almost all of these cases were N0 (22 cases, 88%). The follow-up period was 36 months (range, 5-120 months), and two (8%) of these patients died due to their tumors. Mortality was lower than that in this study (12.9%) and that reported by Koss [4] (14%).

Difurio [56] reviewed eight pediatric patients with WDFA. However, only four patients had detailed data and the maximum diameter of the tumor was 1.5-5.5 cm. Three tumors presented in the upper lobe, while one tumor presented in the lingual lobe. Furthermore, only three patients were followed for 39, 28 and 24 months, respectively. This review included five pediatric patients, in which two patients were younger than 10 years old. One 12-year-old girl died of the tumor even though she received surgery and chemotherapy. To our knowledge, there were very few WDFA cases younger than 10 years old and cases older than 60 years old.

The mortality due to WDFA in the literature is presented in **Table 6**. Except for one case where a patient died of cardiac failure, the 10 cases reported died due to tumor progression. The mean age was 47.6 years old (range, 12-72 years old), and the mean survival time was 20.2 months (range, 2-36 months). The TNM stage was noted for each patient who died. We could not observe the correlation between survival and the clinicopathological indexes in this study. This may be attributed to fewer terminal patients during the follow-up periods and the great variations in the follow-up time for each patient (1-131 months).

WDFA is an infrequent and slowly developing tumor, and its 5-years survival rate is more than 80% [4]. Chemotherapy or radiotherapy is seldom effective, and complete surgical resection is essential for long-term survival. WDFA has favorable prognosis in existing data, but the outcome remains worse in some cases (case 8, 13, 22, 24, 33, 36 and 37). Due to the small specimen used to diagnose WDFA, and the frequency of heterogeneity in tumors, it is possible to diagnose HGFA as WDFA. This is because HGFA is similar to WDFA in pathological changes, and has a worse prognosis. Pathologists play an increasingly important role in personalized medicine for patients with lung cancer, including WDFA; and a correct pathological diagnosis is very important to provide an effective therapy. There is still a need to gather more information and detailed cases to further determine the pathological and molecular mechanism of WFDA.

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Disclosure of conflict of interest

None.

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