Case Report

Primary thoracic extraskeletal osteosarcoma: a case report and literature review

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Abstract: Primary extraskeletal osteosarcoma (ESOS) presenting in thoracic locations is very rare and associated with a poor prognosis. The current study presents a case involving a large anterior mediastinal mass, which was histologically confirmed as a primary osteosarcoma. The literature concerning primary thoracic ESOS is reviewed. A total of 60 cases were identified. The median age was 60 years (range, 14–93 years) and males were more prevalent among the reported cases (65%). Survival analysis revealed that the overall 5-year survival was only 22.3%. The majority of cases of thoracic ESOS presented in the lung (n=24, 40%), with others presenting in the mediastinum, pleura, or chest wall. The benefit of surgery, chemotherapy and radiotherapy was confirmed by Cox regression survival analyses.

Keywords: Extraskeletal osteosarcoma; thoracic; literature review

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Introduction

Extraskeletal osteosarcoma (ESOS) is a malignant neoplasm producing osteoid in places other than bones or periosteum (1). Primary ESOS presenting in thoracic locations is very rare and associated with a poor prognosis. However, previously reported sporadic cases of primary thoracic ESOS did not provide a comprehensive profile of clinical manifestations. The optimal treatment of thoracic ESOS is largely unknown. Here we presented a case of primary ESOS located in the mediastinum. We discuss the clinico-characteristics with a review of the related literature.

Case presentation

A 55-year-old woman with a 3-month history of a palpable neck mass, progressive dyspnea and weight loss was admitted. She had a history of aluminum dust exposure and type 2 diabetes, but otherwise had no other major medical problems. Her general status was poor and a physical examination was unremarkable except for a palpable lymphadenopathy in the supraclavicular fossa. The blood biochemistry tests on admission showed largely normal results. A routine blood test, liver and kidney function tests, and levels of C-reactive protein, alkaline phosphatase and blood calcium were all normal. The tumor markers CEA, CYFRA21-1, SCC-Ag, NSE, and CA125 were within the normal range.

Contrast-enhanced computed tomography (CT) of the chest detected a 9.0 cm × 6.4 cm soft-tissue mass with irregular contours in the anterior mediastinum. The trachea was significantly compressed and the relationship between the mass and the adjacent vessels was unclear. A quasicircular calcification was visualized in the mass (regional SUV 63 HU). The enlarged mediastinal lymph nodes had merged with the mass (*Figure 1*).

Fine-needle aspiration cytology of the supraclavicular lymph node showed interstitial fibrosis with diffused malignant small round cell involvement. An immunohistochemistry analysis did not provide clues of where the tumor originated. A whole-body PET/CT did not suggest another primary site either.

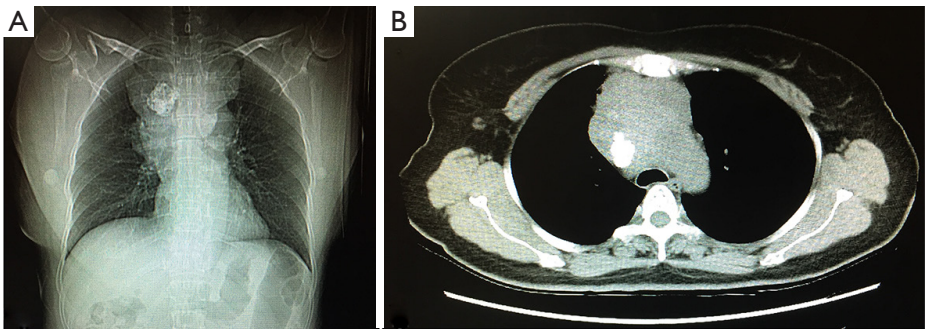

Figure 1 Computed tomogram of the lung showed an irregular mass (9.0 cm × 6.4 cm) with accompanying calcification or ossification in the anterior mediastinum.

The tumor was surgically resected through a median sternotomy. Intraoperative findings revealed that the tumor was hard and protruded into bilateral anonymous veins, the superior vena cava, diaphragm and vagus nerve. Prosthetic replacement of the superior vena cava was performed. The right upper lobe was involved and a wedge resection was performed.

Histologically, the tumor was 11 cm × 10 cm × 10 cm in size without a complete capsule. The cut surface was grayish yellow and necrosis was detected. A large amount of collagen and osteoid tissues had formed (*Figure 2*). Immunohistochemical studies showed positive staining for vimentin and were negative for S-100, CD56 and CD34. These pathologic findings are consistent with osteosarcoma. No evidence of an extra-thoracic primary tumor could be obtained through imaging studies. The tumor was therefore diagnosed as a primary osteosarcoma of the mediastinum.

The patient received best supportive care after the operation because of her poor performance status and died 2 months later.

Discussion

Epidemiology and clinical characteristics

ESOS is a malignant neoplasm producing osteoid in places other than bones or periosteum. It accounts for approximately 1–2% of all soft tissue sarcomas and 2–4% of all osteosarcomas (1). Individuals older than 30 years are the most commonly affected population for ESOS, which is quite different from patients with bone osteosarcoma. The prognosis of patients with ESOS remains poor, with reported 5-year survival rates varying from 25% to 66% (2-4).

Primary intrathoracic ESOS is extremely rare and a total of 60 ESOS cases have been reported in the international literature (*Table 1*). The majority of cases of thoracic ESOS have presented in the lung (n=24, 40%), with 9, 14 and 9 cases presenting in the mediastinum, pleura, or chest wall, respectively. Four additional chest ESOS cases did not document specific locations.

The patient characteristics are summarized in *Table 1*. The median age of the 60 patients was 60 years (range, 14–93 years). A majority of the cases involved males (65%, 39/60 cases), which is similar to previously reported case series (30). The tumors were usually large with a median size of 8.2 cm (range, 2.5–30 cm).

In the cases collected here, some patients had a previous history of radiation exposure, chemotherapy, asbestos exposure, pulmonary tuberculosis or traumatic hemothorax (2,7,10,11,35,41,47). The patient in the case study reported here was previously exposed to aluminum dust. It was speculated that pulmonary inflammation caused by the aforementioned factors might mediate tumorigenesis.

The most common manifestation is respiratory related symptoms caused by compression or invasion of surrounding structures such as cough, dyspnea or chest pain. Some patients were asymptomatic.

Diagnosis

The intrathoracic ESOS usually grows into a large tumor because initial symptoms are often non-specific. Ossification accompanied by malignant features on the chest CT scan is strongly suggestive of an osteosarcoma although a few exceptions were reported (38,40).

A definitive diagnosis was confirmed histopathologically. ESOS usually has a uniform sarcomatous pattern and produces osteoid. The criteria for the diagnosis of

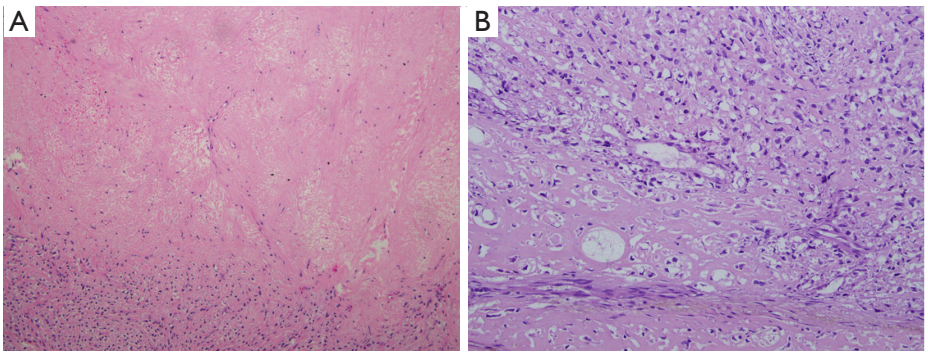

Figure 2 Microscopic findings show malignant cartilaginous foci. H&E staining. Magnification: (A) ×100; (B) ×200.

primary ESOS are as follows: the presence of a uniform morphological pattern of sarcomatous tissue that excludes the possibility of malignant mesenchymoma, the production of malignant osteoid or bone by the sarcoma and a primary osseous tumor is excluded (51).

The histopathologic features of ESOS are the same as those originating from the skeletal system, including osteoblastic, fibroblastic, and chondroblastic subtypes. Small cell, giant cell, and telangiectatic subtypes occur less often. The immunophenotype of ESOS is also similar to osteosarcoma of the bone. CD99 is expressed in all types of osteosarcoma. ALP staining is positive and osteocalcin is the most specific antigen for ESOS. ESOSs are uniformly positive for vimentin, with some cases expressing smooth muscle actin, desmin, S-100 protein, EMA and keratin (52).

Treatment and prognosis

The outcome for patients with primary thoracic ESOS remains poor. The majority of patients died within months because of rapid disease progression. The overall 1-, 2- and 5-year survival was merely 41.8%, 31.3% and 22.3%, respectively (*Figure 3A*). The median follow-up time was 7 months (range, 1–100 months) and the median overall survival was 11 months (95% CI: 8.1–13.9).

The median overall survival for ESOS in the mediastinum, lung and other locations was 4.0 (1.3–6.7), 10.0 (5.3–14.7) and 24 (10.7–37.3) months, respectively. Comparing with ESOS located in the chest wall or pleura, ESOS in the mediastinum and lung had a significantly worse overall survival (log-rank P=0.0443; *Figure 3B*).

It is noteworthy that ESOS can be further classified into either low or high-grade. While the majority of published cases had high-grade histological features of marked cellular atypia, extensive areas of necrosis and atypical mitotic figures, Yu *et al.* reported a case of low-grade mediastinal ESOS characterized by mild cytological atypia. The low-grade ESOS had a slow progression and the patient demonstrated long-term survival after resection (12).

Little is known about the factors affecting the survival of ESOS patients (51). Complete surgical resection is the optimal treatment to improve survival (9). Chemotherapy is also advisable, especially for those without surgical indication (2). In ESOS of the pleura, tumor size was considered as a major predictor of survival (4). Among the 57 cases with documented treatment in this series, 53% (n=30) had surgery, 26% (n=15) received chemotherapy and 19% (n=11) received radiation therapy. The chemotherapy regimens included doxorubicin, cyclophosphamide, cisplatin, or methotrexate (10,12). Univariate and multivariate Cox regression analyses demonstrated that surgical treatment, chemotherapy and radiotherapy were three independent favorable prognostic factors for survival in ESOS patients (*Table 2*).

Despite complete resection, local recurrence occurred in 22% (2/9) of post-operative cases with well documented follow-up records. In addition, metastases occurred in 66% (6/9) of post-operative patients. The most common site of metastasis was the lung (55%, 5/9) and the kidney, brain or adrenal glands were other involved metastatic sites.

Conclusions

Primary thoracic ESOS is a rare but aggressive tumor associated with a very poor prognosis. Most ESOS cases are asymptomatic in the early stages and difficult to diagnose through small sample biopsies. Physicians should be aware of ESOS as a possibility, especially when

Table 1 Patient characteristics

Location	Case No.	Age	Sex	Symptom	Size (cm)	Reference	Treatment	Survival (months)
Mediastinum (n=9)	1	19	M	Swelling	–	Wilson [1941] (5)	–	DOD 2 months after onset
	2	22	M	Chest pain, mild dyspnea	13	Ikeda [1974] (6)	Surgery, RT	CDF 60+ months postop
	3	30	M	Dyspnea on exertion, fatigue	–	Catanese [1988] (7)		DOD 1 m after onset
	4	69	F	–	8.5	Greenwood [1989] (8)	Surgery	–
	5	68	M	–	10	Burt [1995] (9)	Surgery	CDF 38+ months postop
	6	21	M	Dyspnea	7	Ulusakarya [1999] (10)	Surgery, CT	DOD 4 months postop
	7	77	F	Shortness of breath	16	Hishida [2009] (11)	Surgery	DOD 4 months postop
	8	38	F	Cough	5.5	Yu [2015] (12)	Surgery, CT	CDF 28+ months postop
	9	56	F	Neck mass	11	Our case	Surgery	DOD 2 months postop
Lung (n=24)	10	35	F	Chills, fever	7	Greenspan [1933] (13)	–	DOD 11 months after onset
	11	74	F	Progressive athmatic symptoms	–	Yamashita [1964] (14)	–	DOD 6 months after onset
	12	66	M	Dyspnea, chest pain, hemoptysis	>10	Nosanchuk [1969] (15)	–	DOD 4 months after onset
	13	62	M	Pneumonia	6	Reingold [1971] (16)	CT	DOD 7 months after onset
	14	56	F	Chills, fever, chest pain	7	Reingold [1971] (16)	Surgery	CDF 14 months after onset
	15	49	F	–	–	Bagarić [1982] (17)	–	DOD
	16	77	F	Asymptomatic	4	Nascimento [1982] (18)	Surgery	DUC 6 months postop
	17	72	M	Asymptomatic	5.5	Nascimento [1982] (18)	Surgery	DUC 10 months postop
	18	81	M	Dyspnea	>10	Colby [1989] (19)	Surgery	DOC several months later
	19	51	M	Cough	>10	Colby [1989] (19)	Surgery	CDF 6 months after surgery
	20	77	F	Pneumonia	<5	Colby [1989] (19)	Surgery	DOC 6 months postop
	21	54	M	Chest pain, paresthesia at upper extremity	10	Loose [1990] (20)	Surgery, CT, RT	CDF 7 months postop
	22	45	F	Chest pain	5.5	Loose [1990] (20)	Surgery, CT	CDF 2 months postop
	23	70	M	Asymptomatic	6	Petersen [1990] (21)	Surgery, RT	CDF 6 months after onset
	24	59	M	Influenza–like	11	Stark [1990] (22)	Surgery	–
	25	58	M	Fever, cough	18	Bhalla [1992] (23)	–	DOD 1 months after onset
	26	72	M	–	–	Miller (1993) (24)	CT, RT	DOD 12 months after onset
	27	56	M	Tingling in left fingertips	4	Sievert [2000] (25)	Surgery	CDF 12 months postop
	28	33	F	Cough, chest pain	5.5	Chapman [2001] (26)	Surgery, CT	CDF 42 months postop
	29	74	F	Asymptomatic	5.7	Magishi [2004] (27)	Surgery	DOD 11 months postop
	30	72	M	Dyspnea	9	Kadowaki [2005] (28)	–	DOD 5 months after onset
	31	77	M	Back pain, limb edema, hemosputum	11	Kadowaki [2005] (28)	–	DOD 3 months after onset
	32	72	M	Dyspnea	30	Miimi [2008] (29)	–	DOD 7 months after onset
	33	58	F	Asymptomatic	2.5	Karfis [2010] (30)	Surgery, CT, RT	CDF 6 months postop

Table 1 *(continued)*

Table 1 *(continued)*

Location	Case No.	Age	Sex	Symptom	Size (cm)	Reference	Treatment	Survival (months)
Pleural (n=14)	34	61	M	Chest pain, cough, hemoptysis, weight loss		Cohn [1968] (31)	Surgery	DOD shortly postop
	35	66	M	–	–	Pearson [1969] (32)	Surgery	DOD 5 months after onset
	36	73	F	–	–	Pearson [1969] (32)	Surgery	DOD 6 months postop
	37	93	M	Asymptomatic	4	Connolly [1991] (33)	–	DOD 24 months
	38	72	M	–	–	Meeus [1994] (34)	–	–
	39	73	M	Chest pain, hemoptysis	4.5	Sabloff [2003] (35)	Surgery	–
	40	76	M	Breathlessness	–	Chandak [2007] (36)	Biopsy	–
	41	74	M	Cough, breathless	11.3	Matono [2008] (37)	–	–
	42	64	M	cough	13.1	Kasagi [2009] (38)	Surgery, RT	–
	43	47	M	Dyspnea	10.9	Wang [2010] (39)	–	–
	44	77	M	Asymptomatic	4	Tokue [2011] (40)	Surgery	DOD 24 months postop
	45	67	M	Dyspnea on exertion, cough	12	Shiota [2013] (41)	Surgery, CT	DOD 24 months postop
	46	37	F	Flank pain, dyspnea	8	Lee [2014] (42)	Surgery, CT	CDF 14 months postop
	47	75	F	Chest pain, hemoptysis	8.2	Rapicetta [2017] (43)	–	–
Chest wall (n=9)	48	14	F	Back pain, cough, dyspnea	–	Stauss [1951] (44)	–	DOD 7 months
	49	59	M	–	–	Hoffmann [1966] (45)	Surgery	–
	50	53	F	–	–	Das Gupta [1968] (46)	Surgery	DOD 46 months postop
	51	41	F	Lump	3	Alpert [1973] (47)	Excisional biopsy	CDF 12 months after onset
	52	57	F	–	9	Lee [1995] (3)	RT	CDF 100 months
	53	40	M	Vision blurring	–	Kelkar [2010] (48)	RT	CDF 6 months
	54	30	M	Shoulder immobilisation	30	Sabatier [2010] (49)	CT	DOD 60 months after onset; 12 months after diagnosis
	55	76	M	–	–	Nystrom [2016] (50)	Surgery	DOD 9 months
	56	58	M	–	17	Nystrom [2016] (50)	CT, RT	DOD 12 months
Chest (not specified) (n=4)	57	47	M	–	–	Torigoe [2007] (2)	CT	DOD 28 months
	58	25	M	–	–	Torigoe [2007] (2)	CT	CDF 70 months
	59	39	M	–	–	Torigoe [2007] (2)	CT, RT	CDF 68 months
	60	76	M	–	–	Torigoe [2007] (2)	RT	DOD 6 months

CT, chemotherapy; RT, radiotherapy; DOD, dead of disease; CDF, continuous disease-free; DOC, dead of other causes; DUC, dead of unknown causes.

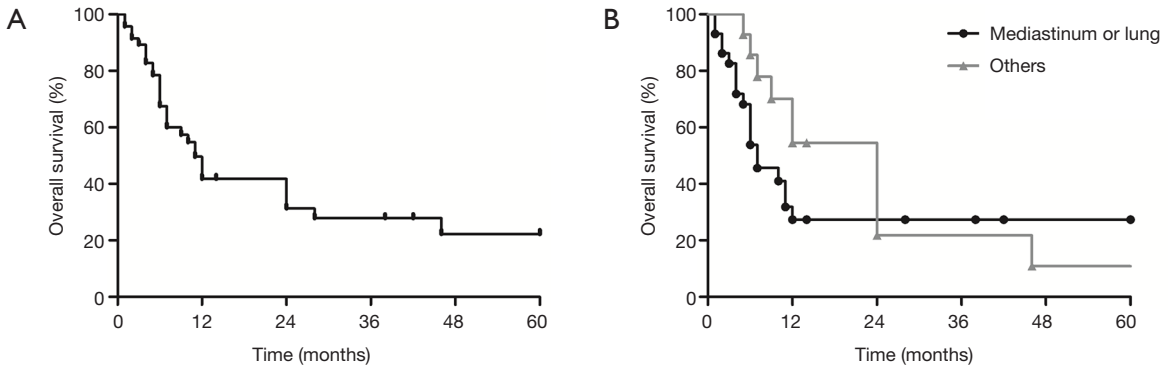

Figure 3 (A) Overall survival of all 60 cases of intrathoracic ESOS; (B) survival curves of ESOS patients with different originating sites. The median overall survival for patients with intrathoracic ESOS was 11 months (95% CI: 8.1–13.9) and the 5-year overall survival was 22.3%. ESOS in the mediastinum and lung had a significantly worse overall survival compared with that located in the chest wall or pleural (log-rank P=0.0443).

Table 2 Univariate and multivariate analysis of prognostic factors of survival

Characteristic	Univariate analysis P	Multivariate analysis		
		HR	95% CI	P value
Sex	0.523	–	–	–
Age (years)	0.036	1.027	0.989–1.027	0.423
Site	0.275	–	–	–
Tumor size	0.112	–	–	–
Surgery	0.107	0.297	0.137–0.660	0.003
Chemotherapy	0.050	0.297	0.120–0.732	0.008
Radiotherapy	0.055	0.236	0.069–0.811	0.022

Indicators with P value less than 0.2 by univariate analysis were included in the multivariate analysis.

calcification is present in CT images. Histologically, osteoid and bone production is a typical characteristic of ESOS and immunohistochemistry serves as a diagnostic aid. If considered as a primary tumor, surgical resection is the primary choice and chemotherapy and radiotherapy are considered as effective.

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None.

Footnotes

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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