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Abstract

Malignant peripheral nerve sheath tumors (MPNSTs), also known as malignant schwannomas, rarely occur in the mediastinum. These tumors have a poor prognosis. A PubMed search was conducted from 1950 to September 2016, and 57 cases of mediastinal MPNSTs were identified in the English-language medical literature. The symptoms, imaging findings, diagnosis, therapy, and prognosis of these 57 cases were analyzed. A total of 44 patients underwent surgical resection. However, 9 of the 57 patients had no evidence of disease.

The patients had several symptoms including chest pain, back pain, coughing, dyspnea, and others derived from tumor oppression. However, MPNSTs occurring in the mediastinum seemed to be asymptomatic until the tumors had grown rather large.

The radiologic features of MPNSTs were an enlarging mass along a nerve or nerve root and the development of heterogeneous attenuation and high signal intensity in the preexisting nerve lesion. They usually exhibited variable signal intensity on T1- and T2-weighted magnetic resonance images. Although the imaging findings of MPNSTs were often nonspecific, fluorodeoxyglucose positron emission tomography–computed tomography appeared to play an important role in diagnosis.

Histologically, MPNSTs were usually hypercellular with spindle cell proliferation, nuclear atypia, mitotic activity, and areas of tumor necrosis. Nerve sheath differentiation was confirmed by immunohistochemical findings such as S-100 protein and SOX10 positivity for Schwann cells. However, expression of S-100 protein was often negative in MPNSTs.

This review revealed that the main therapy for MPNSTs is complete

surgical resection, but multimodal treatment including chemotherapy or radiotherapy plays an important role in improving survival.

Key words: Malignant peripheral nerve sheath tumor, mediastinum

1. Introduction

Malignant peripheral nerve sheath tumors (MPNSTs), also called malignant schwannomas or neurofibrosarcomas, are rare. They are defined as sarcomas that arise within peripheral nerves. MPNSTs comprise approximately 5% to 10% of all soft tissue sarcomas, and 50% to 60% of such tumors are associated with neurofibromatosis type 1 (NF-1), also termed von Recklinghausen disease [6, 16, 17, 26, 33]. MPNSTs are most often sporadic, but also develop in 2% to 16% of patients with NF-1 [25]. Patients with NF-1 are younger than those without NF-1 [6].

MPNSTs have an aggressive clinical course, with a high rate of local recurrence and a propensity to metastasize. Malignant triton tumor (MTT), subtype of MPNSTs, behaves more aggressively than conventional MPNSTs [20].

The expected overall 5-year survival rate of patients with MPNSTs ranges from 50% to 75% among those who have undergone complete surgical resection [26, 28].

MPNSTs commonly occur in the extremities but rarely in the mediastinum; their prognosis is poor. They cause various symptoms depending on their location and size.

In 2008, we reported the long-term survival of a patient with an MPNST that originated in the anterior mediastinum [27]. Since that report, new cases have been described.

We reviewed all case reports on MPNSTs that occurred in the mediastinum and herein summarize the symptoms, imaging findings, diagnosis, therapy, and prognosis.

2. Method

A PubMed search was conducted from 1950 to September 2016 using the terms “malignant peripheral nerve sheath tumor” and “mediastinum.” We identified 57 cases of MPNSTs occurring in the mediastinum that were described in detail in the English-language medical literature. We summarized these cases in terms of age, sex, location, symptoms, histological subtype, presence or absence of NF-1, tumor size, surgical or nonsurgical treatment, recurrence, metastasis, and outcome.

3. Results

We identified 57 reported cases of MPNSTs occurring in the mediastinum in the English-language medical literature. Fourteen patients had NF-1, and eight patients had the triton subtype of MPNST. Surgery was performed in 44 patients. Nine patients had no evidence of disease after surgery. The longest survival period with no evidence of disease was 277 months (Case 55). Twenty-six patients died of their MPNST (Table 1).

Case	Author	Ref	Age/Sex	Location	Symptom	subtype	NF1	Size	Surgery	Rec	Meta	Outcome
1	Ingels (1971)	10	21/F	PM					+		+	DOD 24months
2			39/M	PM					+			DOD 3days
3			39/M	PM			+		+		+	DOD 8months
4			52/M	MM					+			DOD 2months
5			13/F	PM					+	+		DOD 12months
6			-	M					+			DOD 5months
7			-	M					+		+	DOD 8months
8			-	M					+			
9			-	M					+			
10			30+/M	M					+		+	DOD 42months
11			30+/M	M					+			
12			30/M	M								
13			31/F	M								
14			51/F	M								
15			57/F	PM					+			
16			53/F	M					-			AWD 5months
17			65/M	PM					-		+	DOD
18			-	M								
19			48/M	MM	Acute shortness of breath			15×8×6cm	+		+	DOD 11months
20			8/M	MM	Chest pain, syncope			7cm	+		+	DOD 20months
21	Ducatman (1984)	5	31/F	AM			+		+	+		DOD 3months
22	Daimaru (1984)	7	29/M	PM		triton	+			+		DOD 6months
23	Brooks (1985)	4	70/F	M				3cm	+	+		AWD 53months
24	Wong (1991)	32	39/M	PM	Limb pain, chest pain	triton	-	8cm	+	+		DOD 15months
25	Fukai (1995)	7	27/M	M	Cough	epithelioid	-					DOD 8months
26	Otani (1996)	22	17/F	AM	Dyspnea	triton	+		+			
27	Kourea (1998)	16	20/M	RM			+	9cm	-		+	DOD 3months
28			17/M	PM			+	10.5cm	+	+	+	DOD 11months
29			41/M	M			+	5.0cm	+	-	+	DOD 27months
30			19/F	LM			+	4.5cm	+	-	-	NED 35months
31			26/M	LM			-	5cm<	+	+	+	DOD 27months
32			39/M	RM			-	10cm<	+	+	-	DOD 7months
33	Shijubo (2000)	26	51/M	M	Chest pain, dyspnea		-		-			DOD
34	Bose (2002)	3	35/M	MM	Cough, dyspnea	triton	+		+	-		Alive 18months
35	Lang-Lazdunski (2003)	18	22/M	PM	Asymptomatic	triton	-	5×2.5cm	+	+		Alive 108months
36	Asai (2004)	2	40/M	MM	Hoarseness		+	12cm	+	-	-	NED 12months
37	Shoji (2005)	28	46/F	LM	Hoarseness, Honer's syndrome		-	5.0cm	+	-	-	NED 24months
38	Zisis (2006)	33	30/M	AM	Chest discomfort	triton	-	5cm	+	-	-	NED 12months
39	Lai (2006)	17	50/F	PM	Back pain		-	7cm	+			AWD 5months
40	Shimoyama (2008)	27	75/M	AM	Asymptomatic		-	17×12×9cm	+		+	DOD 84months
41	Kawachi (2008)	14	56/M	PM	Dyspnea		+	21×19×9cm	+			DOD 6months
42	Kamran (2013)	13	38/F	MM	Arm pain		+	16cm				
43			31/M	PM	Back pain		-	14cm	+			
44			48/M	AM	Dyspnea		-	13.6cm				
45			18/F	MM	Dyspnea, Chest pain		+	8cm	+			
46			65/M	PM	Back pain		-	5.5cm	+			
47			33/F	AM	Asymptomatic		-	4cm	+			
48	Ren (2014)	24	42/M	AM	Cough, chest distress	triton	-	14.8cm	-			AWD
49	Koezuka (2014)	15	28/M	AM	Asymptomatic		-	10cm	+	-	-	NED 12months
50	Kalra (2014)	12	46/M	AM	Cough, dyspnea		-	18×16×10cm	+			NED
51	Thway (2015)	30	40/M	AM	Chest pain	triton	+	7cm	+		+	AWD 24months
52	Nakajima (2016)	21	17/M	PM	Back pain, cough			15.0cm	+	+	+	DOD 69months
53			65/M	SM				7.5cm	+			NED 170months
54			50/M	PM	Back pain			7.0cm	+			DOD 14months
55			45/F	MM	Chest oppression, cough			8.6cm	+			NED 277months
56			55/F	SM				11cm	+			NED 255months
57			72/M	PM	Back pain			12cm	+	+		DOD 18months

Table 1. List of mediastinul MPNSTs

Ref: Reference; M: male; F: female; M: Mediastinam; PM: posterior Mediastinum; MM: middle Mediastinum; AM: anterior Mediastinum; LM: left Mediastinum; RM right Mediastinum; SM: superior Mediastinum; Rec: Recrrence; Meta: Metastasis; DOD: Dead of disease; AWD: Alive with disease; NED: No evidence of disease

4. Symptoms

Patients with intrathoracic MPNSTs are often asymptomatic until the tumor causes local symptoms or features of metastasis. In particular, MPNSTs that occur in the mediastinum seem to be asymptomatic until the tumors grow rather large. The patients in the reported cases had several symptoms including chest pain, back pain, coughing, dyspnea, and others derived from tumor oppression, but some patients remained asymptomatic despite a larger tumor size (Cases 40 and 49).

5. Imaging

The radiologic features of MPNSTs are an enlarging mass along a nerve or nerve root and the development heterogeneous attenuation and high signal intensity in the preexisting nerve lesion. In patients with larger masses, however, it is sometimes difficult to differentiate the origin of the mass from the nerve.

A sudden increase in size or the development of internal necrosis and hemorrhage on computed tomography suggest malignancy. MPNSTs usually exhibit variable signal intensity on T1- and T2-weighted magnetic resonance images. The development of heterogeneous signal intensity on T2-weighted images with loss of the peripheral hyperintensity and central hypointensity (target sign) that is characteristic of neurofibromas indicates malignant transformation [8].

Kamran et al. [13] assessed the clinical and imaging characteristics of primary intrathoracic MPNST. They summarized the masses as hypoattenuating on computed tomography, hyperintense on T2-weighted images, often heterogeneous, and intensely fluorodeoxyglucose-avid. An MPNST should be considered as a differential diagnosis when a large, elongated intrathoracic mass is found [13]. Patients with malignant triton tumors (MTTs) tended to have larger tumors at diagnosis than did patients with conventional MPNSTs [20]. MTTs also had a higher maximum standard uptake value than conventional MPNSTs.

Although the imaging findings of MPNSTs are often nonspecific, fluorodeoxyglucose positron emission tomography–computed tomography may play an important role.

6. Diagnosis

In the present review, the two criteria for a diagnosis of MPNST were as follows: the tumor originated from a nerve, demonstrated either at surgery or by gross or microscopic examination, and the tumor was associated with a contiguous neurofibroma [6].

Grossly, MPNSTs appear similar to benign peripheral nerve sheath tumors such as schwannomas and neurofibromas. The definitive diagnosis is based on histological and immunohistochemical findings, but diagnosis is often difficult because of the uncharacteristic features of this tumor.

Histologically, MPNSTs are usually hypercellular with spindle cell proliferation, nuclear atypia, mitotic activity, and areas of tumor necrosis. The most frequent pattern closely resembled a fibrosarcoma, and several tumors reportedly exhibited a storiform pattern of cell orientation [6, 17]. The differential diagnoses of MPNST include fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, monophasic synovial sarcoma, and rhabdomyosarcoma [6]. MPNSTs with rhabdomyoblast differentiation are called MTTs. MTTs account for <10% of MPNSTs. Eight patients with MTTs were identified among the reported cases (Cases 22, 24, 26, 34, 35, 38, 48, and 51).

The antibodies commonly used in diagnosis of MPNST are S-100 protein, desmin, alpha-smooth muscle actin, HHF35, cytokeratin (CAM5.2), and the proliferation marker MIB-1 [9]. Nerve sheath differentiation is confirmed by immunohistochemical findings such as S-100 protein and SOX10 positivity for Schwann cells. However, expression of S-100 protein is often negative in MPNSTs [26]. Pekmezci et al. [23] reported that S-100 and SOX10 expression was focally positive in all cellular schwannomas but in only a fraction of MPNSTs.

7. Therapy

Surgical resection is the main therapy for MPNSTs; adjuvant chemotherapy or radiotherapy appears to provide little additional benefit [6, 9, 17, 28, 31]. Therefore, complete surgical removal of the tumor is the optimal goal and should be the first-choice treatment whenever possible.

MPNSTs within the thoracic cavity are usually asymptomatic until the grow to be rather large in size and invade the surrounding organs, making complete surgical resection difficult. Among the 57 reported cases, 44 patients underwent surgical resection.

Combination chemotherapy is recommended for unresectable tumors. Adjuvant radiation therapy should be delivered to improve local control; it may also be beneficial for survival [1].

Chemotherapy is typically reserved for aggressive tumors and when tumor rupture, positive margins, or metastasis is present; however, improvement in survival has not been demonstrated [29]. Like most soft tissue sarcomas, MPNSTs are insensitive to chemotherapy. However, some drugs have been shown to be effective. Shoji et al. [28] reported that contingent chemoradiotherapy (cisplatin and tegafur– uracil plus radiotherapy for a tumor misdiagnosed as non-small cell lung cancer) was partially effective (Case 37). Masui et al. [19] reported a case of an MPNST in the S1 nerve root. They administered adjuvant chemotherapy in which high-dose ifosfamide, vincristine, doxorubicin, and cyclophosphamide resulted in a complete response. Therefore, the use of chemotherapy remains controversial.

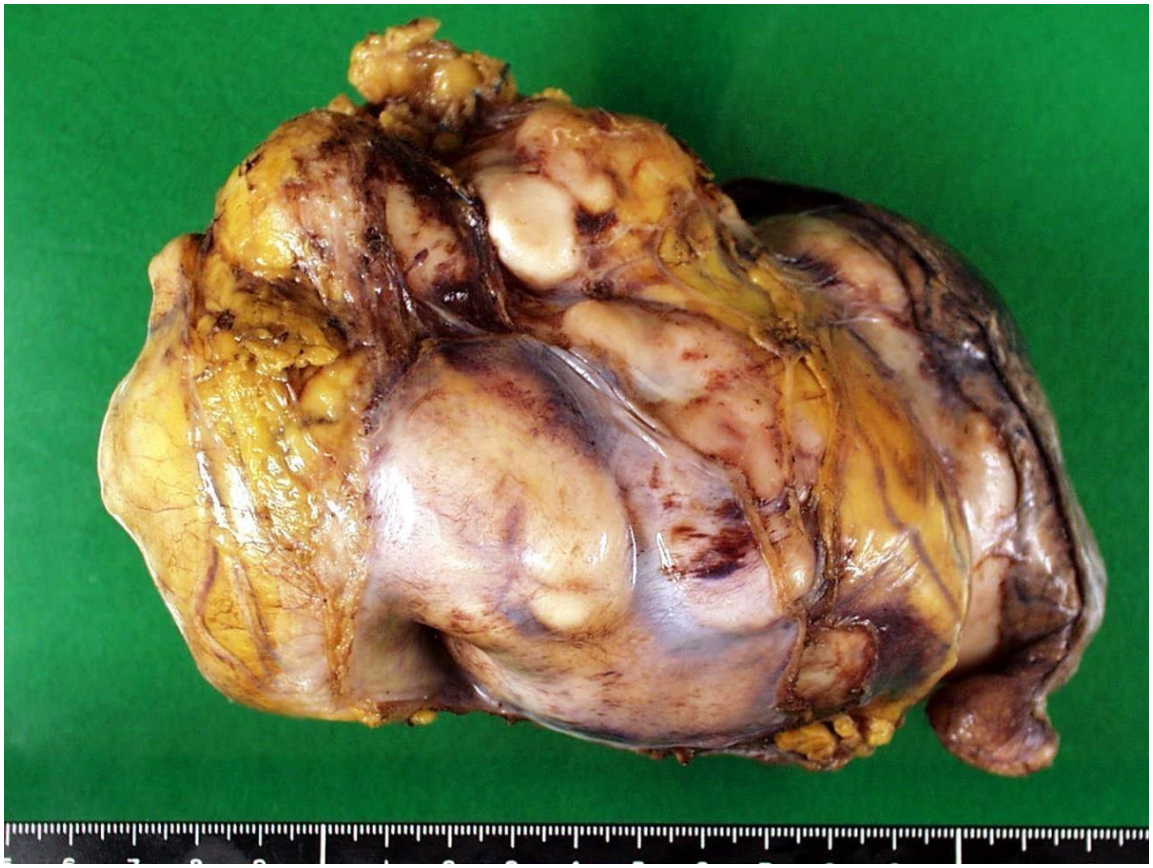

Figure 1. Gross photograph of Case 40. The tumor was completely resected. It was a well-defined hard mass without invasion of the partially resected lung and pericardium.

A novel trial therapy has also been described. Inoue et al. [11] reported that boron neutron capture therapy was effective for a recurrent MPNST in the mediastinum. They suggested that this therapy might be a treatment option for subcutaneous mediastinal tumors, which are resistant to conventional irradiation.

8. Prognosis

The prognosis of MPNSTs is poor. The largest studies of MPNSTs performed by Ducatman et al. [6], Wanebo et al. [31], and Stucky et al. [29] reported 5-year survival rates of 34.0%, 43.7%, and 60.0%, respectively. The local recurrence rate ranges from 42% to 65%, and the distant metastasis rate ranges from 28% to 68% [6, 16, 17].

The risk factors for a poorer prognosis include an age at onset of ≤30 years, a tumor size of >5 cm, a high tumor grade, occurrence inside the trunk, the presence of NF-1, the presence of an MTT, incomplete resection, and local recurrence [6, 16, 17, 29, 31]. The tumor location plays a role in the outcome; tumors in the trunk are associated with a poorer prognosis, which is likely attributable to difficulty in achieving negative surgical margins and consequent local or regional recurrence [29, 31].

MTTs, which account for <10% of MPNSTs, are biologically more aggressive and associated with an even worse prognosis than conventional MPNSTs [13, 20, 30]. McConnell and Giacomantonio [20] reported that the overall survival at 5 years was 14%, which is significantly worse than the 34% to 52% survival rate reported for other MPNSTs.

Nakajima et al. [21] recently reported several cases of very long-term survival. They suggested that MPNSTs localized within the membrane, which can be completely excised, are associated with a good long-term prognosis (Cases 53, 55, and 56).

9. Conclusion

MPNSTs in the mediastinum are rare, but the numbers of such case reports are increasing. Most such patients die relatively soon after surgery, although the outcomes seem to have improved recently. The main therapy for MPNSTs is complete surgical resection, but multimodal treatment including chemotherapy or radiotherapy plays an important role in improving survival. Further progression in establishing an optimal treatment strategy for MPNSTs is expected.

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