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Original Article

Mediastinal myelolipoma/extramedullary hematopoiesis presenting as a mass: rare differential diagnosis among mediastinal tumors

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Abstract: Objectives: Mediastinal myelolipoma/extramedullary hematopoiesis presenting as a mass is infrequent and can lead to misdiagnosis. Here we describe a large series aiming to illustrate the clinicopathologic features. Methods: We retrospectively searched mediastinal tumors and myelolipoma diagnosed at the Department of Pathology, West China Hospital from 2010 to 2015 and collected 14 mediastinal myelolipoma/extramedullary hematopoiesis cases presenting as an encapsulated mass among 1324 mediastinal mass diseases and 252 myelolipomas. Results: There were 8 females and 6 males aged from 35 to 67 years old, most of whom were diagnosed incidentally. Cross-sectional imaging revealed encapsulated masses located in the posterior mediastinum with fat and soft tissue density showing heterogeneous enhancement. Radiologic diagnosis was neurogenic tumor for most cases. All but one patient underwent surgery and postoperative pathologic findings showed fat and hematologic elements. Considering the accompanying hematologic disorders, 5 patients were diagnosed as extramedullary hematopoiesis and the remaining 9 as myelolipoma. The average hematopoietic tissue percentage in extramedullary hematopoiesis was 70%, significantly higher than it was in myelolipoma. Patients showed no sign of recurrence or metastasis apart from the patient with hepatocellular carcinoma. Conclusions: Mediastinal myelolipoma/extramedullary hematopoiesis is a rare entity of solid tumors in the posterior mediastinum, affecting patients from their third decades, with no sex predilection and lacking unique clinical symptoms, and may be misdiagnosed as a malignant tumor on cross-sectional imaging. The final diagnosis relies on pathologic findings, and the precise classification of myelolipoma or extramedullary hematopoiesis relies on percentage of hematopoietic tissue and accompanying clinical symptoms. Surgery is the recommended treatment.

Keywords: Mediastinum, myelolipoma, extramedullary hematopoiesis

Introduction

Myelolipoma (ML) was first described in 1905 [1] and named 'myelolipoma' in 1929 [2]. It is characterized by an encapsulated mass composed of yellow adipose tissue and red-brown tissue corresponding to hematopoietic tissue or hemorrhages. It is commonly found in the adrenal gland [3-5] and accounts for 2%-4% of all adrenal tumors [6], but may also occur in extra-adrenal locations [7, 8], including retroperitoneum [8, 9], liver [10], spleen [11], stomach [12], and mediastinum [13]. Mediastinal MLs are rare and most of the cases are case reports.

Extramedullary hematopoiesis (EMH) is defined as the production of blood components (hematopoiesis) outside the bone marrow [14]. Pathologic EMH mostly occurs in chronic hematologic conditions, such as anemia and myelodysplastic syndromes. EMH shows evidence of hematopoietic stimuli or bone marrow hyperplasia and most often occurs in the spleen, liver, and occasionally in the lymph nodes, lungs, gastrointestinal tract, breast, brain, kidneys, and adrenal glands. Mediastinal EMH is common and sometimes causes life-threatening hemorrhage, but mass-forming EMH occurring in the mediastinum is rare and almost indistinguishable from other tumors.

Pathologically, there is no clear difference between ML and EMH presenting as a mass [15, 16]; some believe that the accompanying hematopoietic conditions is the main way to distinguish these two: EMH are accompanied by chronic hematopoietic disorders while ML is not. According to this definition, some cases reported in the literature as mediastinal MLs with accompanying chronic anemia or myelodysplastic syndrome should be EMH instead of ML.

Here we describe 14 MLs/EMHs of the mediastinum diagnosed in a single institute, illustrating the clinicopathologic features of this rare disease.

Materials and methods

We searched mediastinal mass and myelolipoma from the archived database in the Department of Pathology, West China Hospital, Sichuan University from January 1st 2010 to December 31th 2015 to identify mediastinal ML/EMH, and collected the patients' clinical symptoms, laboratory tests, radiological scans, treatment and prognostic information. The specimens were fixed in 10% formalin solution and embedded in paraffin. Sections were cut and stained with hematoxylin and eosin (HE) for microscopy. All available histologic materials were reviewed. For cases suspected to be hematopoietic disease, we performed immunohistochemical (IHC) staining with a 2-step Envision procedure using a DAKO Autostainer (Dakopatts, Copenhagen, Denmark). Local ethical guidelines were followed for the use of archival tissues for research with the approval of the ethics committees of the institution. The disease was described as ML in this article until the accompanying hematologic conditions were reviewed.

Results

We identified 1324 mediastinal mass diseases in the selected time periods, 299 of which were non-neoplasms, including 218 cystic diseases, 47 thymic hyperplasia, 28 inflammatory diseases and 6 ectopias. The remaining 1025 were neoplastic diseases, including 334 thymomas, 194 neurogenic tumors, 182 carcinomas, 132 germ cell tumors, 115 hematopoietic and lymphoid tumors, 32 soft tissue tumors, 22 vascular tumors, and 14 mediastinal MLs. Mediastinal MLs accounted for 1.1% of all the mediastinal diseases diagnosed in this time period.

In the same interval, 252 MLs were diagnosed, most of which presented in the adrenal glands (228/252, 90.5%), with the remaining cases presenting in the mediastinum (14/252, 5.6%), liver (9), and lung (1).

Clinical manifestation

There were 6 male patients and 8 females, aged from 35 to 67 years(mean age 59.8 years, median age 63 years). Most patients (11/14) were diagnosed incidentally during a regular check-up, and the remaining three patients presented with cough, back pain and chest pain respectively. The clinical features of the 14 mediastinal ML/EMH patients are presented in **Table 1**.

After extensive systemic review, 5 patients were found to have hematologic system diseases: 2 patients had thalassemia, and 1 patient each with hemolytic jaundice, thrombopenia, or slight anemia, with two patients unaware of their hematologic condition until the preoperative examination. Two patients suffered from either hypertension alone (patient 12) or accompanied by diabetes and hyperthyroidism (patient 4). Patient 2 suffered from hepatocellular carcinoma. The left 4 patients were free of comorbidity.

Radiologic imaging

All patients underwent cross-sectional imaging: 4 had Computerized Tomography (CT) only, 1 had Magnetic Resonance Imaging (MRI) only and 9 had both. Most of the patients had only 1 mass in the posterior mediastinum (4 in the left side and 9 in the right), with only one patient presenting with two separate tumors in the bilateral posterior mediastinum (case 14).

The tumors in the CT images were encapsulated with well-defined borders and showed no infiltration of the neighboring tissue. The tumors showed mixed densities, ranging from soft tissue to fat-equivalent densities of approximately -80 Hounsfield units. Neither calcification nor active bleeding was found. Eight patients had intravenous injection of contrast media, and 7 showed slight to moderate heterogeneous enhancement. The CT diagnosis was neurogenic tumors (9 cases), angioleiomyolipoma (1

Table 1. Clinicopathologic features of 14 mediastinal myelolipomas/extramedullary hematopoiesis

Case	Sex	Age	Symptom	Accompanying disease	Location	CT diagnosis	MRI diagnosis	Size (cm)	Hematopoietic tissue percentage (%)	Treatment	Diagnosis
1	M	63	Back pain	Thrombopenia	LPM	Neurogenic tumor	NA	2.7	40	VATS	EMH
2	M	67	None	Hepatocellular carcinoma	RPM	Angiomyolipoma	Neurogenic tumor	5.7	40	Thoracotomy	ML
3	F	61	Cough	Thalassemia	RPM	Neurogenic tumor	Benign tumor	3.7	90	VATS	EMH
4	F	67	None	Hypertension, diabetes, hypothyroidism	RPM	Lipoma	NA	2.1	20	VATS	ML
5	M	54	None	Anemia, adrenal myelolipoma	LPM	Neurogenic tumor	Neurogenic tumor	8.0	65	Thoracotomy	EMH
6	F	66	None	None	RPM	Teratoma	Neurogenic tumor	6.5	30	VATS	ML
7	F	66	None	None	RPM	Neurogenic tumor	NA	5.0	30	VATS	ML
8	F	54	None	Thalassemia	RPM	NA	EMH	2.5	95	VATS	EMH
9	M	65	Chest pain	None	LPM	Liposarcoma	Liposarcoma	14.0	15	Thoracotomy	ML
10	F	57	None	None	RPM	Neurogenic tumor	Neurogenic tumor	5.6	70	VATS	ML
11	F	65	None	None	RPM	Neurogenic tumor	-	2.5	50	VATS	ML
12	F	63	None	Hypertension	RPM	Neurogenic tumor	Neurogenic tumor	3.8	60	VATS	ML
13	M	35	None	HBV, hemolytic jaundice	LPM	Neurogenic tumor	Lymphoma	2.9	60	Biopsy	EMH
14	M	54	None	None	Bilateral	Neurogenic tumor	Neurogenic tumor	2.9, 2.1	25	VATS	

CT, computed tomography; MRI, magnetic resonance imaging; M, male; F, female; LPM, left posterior mediastinum; RPM, right posterior mediastinum; NA, not available; VATS, video assisted thoracic surgery; EMH, extramedullary hyperplasia; ML, myelolipoma; HBV, hepatic B virus.

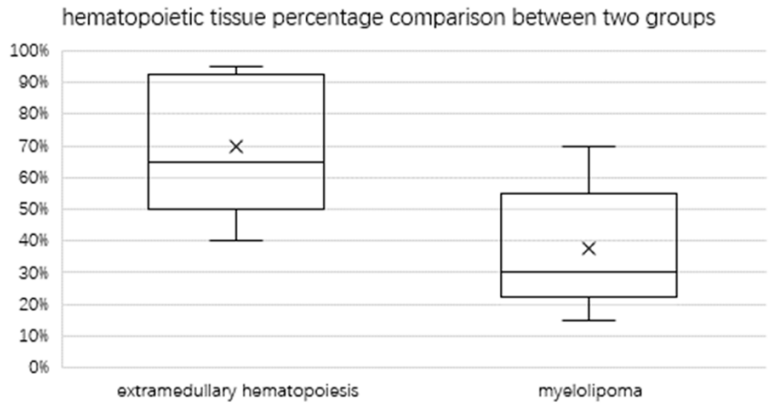

Figure 1. Boxplot for hematopoietic tissue percentage in two groups. The average hematopoietic tissue percentage in extramedullary hematopoiesis and myelolipoma is 70.0% and 37.8% retrospectively. An independent sample T test value is 2.872, and *P* value is 0.014.

case), lipoma (1 case), teratoma (1 case), and liposarcoma (1 case).

MRI imaging showed hyperintense T1 and T2 signal (3 patients) or isointense T1 and T2 signal (7 patients). Four patients underwent contrast scans, and all showed moderate to obvious inhomogeneous enhancement. Of the 10 cases undergoing an MRI scan, 6 were originally diagnosed with neurogenic tumor, and the remaining 4 were diagnosed with benign tumor, extramedullary hematopoiesis, liposarcoma and lymphoma.

Pathologic findings

The solid masses were well-circumscribed, oval to round, encapsulated, with yellow to grey cut surfaces. The diameter of the masses ranged from 2.1 cm to 14 cm, with a mean diameter of 4.7 cm. Histologically, the masses showed fat and hematopoietic elements, with the proportion of hematopoietic tissue varying substantially, from 15% to 95%. IHC staining was done in 1 case and illustrated that the cells were positive for glycophrin A (erythrocytes), CD20 (B cells)/CD3 (T cells), CD138 (plasma cells), and Myeloperoxidase (myelomonocytes), and negative for CD34, Cytokeratin, and S-100.

The pathological diagnosis was ML for 9 cases while the remaining 5 were diagnosed as EMH based on clinical manifestation.

Retrospective histologic review of the cases showed that the average hematopoietic tissue percentage in the EMH group was 70%, which was significantly higher than in the ML group (37.8%, *P*= 0.014, **Table 1**; **Figures 1**-**3**).

Treatment and follow-up

All but one patient underwent surgery, ten had video-assisted thoracic surgery (VATS) performed and 3 patients underwent thoracotomy. The remaining patient with hemolytic jaundice underwent video-assisted thoracic core biopsy only (patient 13).

All the patients underwent regular follow-up ranging from 4-64 months (median, 18 months). The patient with hepatocellular carcinoma died from progressive disease 5 months after the diagnosis of mediastinal ML, and the remaining 13 cases had no recurrence at the time of evaluation.

Case studies

Patient 5 came to the hospital after being troubled by backache for 2 weeks. Abdominal ultrasound showed a mass located near the right adrenal gland, and thoracic CT and MRI scan revealed a 7.0 cm × 5.5 cm mass in the left posterior mediastinum and enlarged spleen. Preoperative blood test showed the patient had 93 g/L hemoglobin. A diagnosis of mediastinal malignant neurogenic tumor with adrenal metastasis was made, and the patient underwent laparoscopy and thoracotomy. Postoperative pathologic examination showed ML and the hematopoietic tissue proportion was 65% for both the adrenal and mediastinal masses. Considering the patient's low hemoglobin, splenomegaly and low fat tissue proportion, the final diagnosis was EMH of two different sites.

The tumor in case 9 was the largest one in our collection. According to the patient, the mass was first found accidentally 5 years ago by a regular checkup, was approximately 1 cm × 1 cm and caused no symptoms; he did not ask for medical help until he developed chest pain and dyspnea a week before he came to our hospital. MRI showed a 14 cm × 12 cm × 10 cm mass located in the left posterior mediastinum

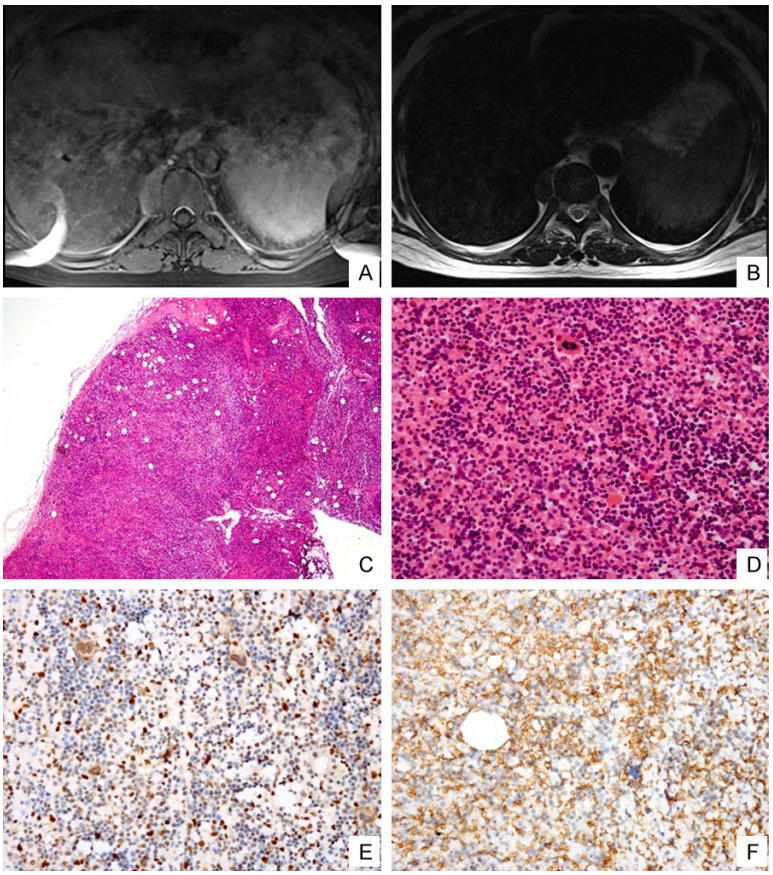

Figure 2. Magnetic resonance imaging and pathologic imaging of case 8. (A and B) were MRI T1 and T2 weighted imaging, respectively, showing a mass 3.7 cm × 2.8 cm × 1.1 cm located near the 8th thoracic vertebra. The mass was encapsulated with well-defined borders and no infiltration of the neighboring tissue. (C and D) hematoxylin and eosin stain of the tumor (at 40 X and 400 X, respectively, showed the adipose and hematopoietic element. (E) was factor VIII staining indicating the megakaryocyte, (F) highlighted erythroid cells by glycophorin A staining.

with fat tissue inside (**Figure 2**), and liposarcoma was suspected. The patient underwent thoracotomy after regular preoperative tests had been performed. The removed mass was approximately 14 cm in diameter, with a soft, yellow cut surface. The pathologic findings indicated no signs of malignancy, and the mass was diagnosed as mediastinal massive ML.

Discussion

Mediastinal ML/EMH is a rare differential diagnosis of mediastinal solid tumor, mostly located in the posterior mediastinum, affects patients in their 60 s and shows no sex predilection. In most cases, no clinical symptoms occur unless the mass is large enough to cause compression, in which case a productive cough, stiff neck, and dull back pain may be observed. In CT/MRI imaging, mediastinal ML/EMH is a well-circumscribed mass with a heterogeneous appearance. CT findings vary according to the elements inside: myeloid elements exhibit high attenuation values, while fat tissue has low attenuation values. By MRI imaging, isointensity or slight hyperintensity appears in T1 and T2-weighted imaging. After the application of contrast media, the myeloid elements show moderate enhancement and adipose tissue showsno enhancement, resulting in heterogeneous enhancement.

Pathologically, MLs/EMHs are round masses with membranes, whose cut surfaces are yellow (fat dominant) or gray (hematopoietic predominant), ranging in size from 1.5 cm to 25 cm. Histologically, the tumors manifest the same features as MLs at other sites: fat and hematopoietic elements can both be seen. Histologically, EMH tends to have a higher hematopoietic tissue proportion which maybe a clue for clinician to look for evidence of EMH.

According to our finding, ML/EMH comprises only 1% of the mediastinal masses, making the diagnosis a challenge. Nine of our 14 cases were misdiagnosed as neurogenic tumors by cross-sectional imaging; even if the adipose element in the ML can help, the final diagnosis relies on pathologic examination. One case in our collection was misdiagnosed as liposarcoma before surgery, which may be excluded by the noninvasive growth pattern of the mass. Teratoma is another differential diagnosis, but it has components other than adipose tissue, such as cysts and calcification. To distinguish angioleiomyolipoma and ML based on radiological imaging alone is quite difficult and the main affected organs may help: the former tends to affect the kidney and liver, while the latter involves the adrenal gland mostly.

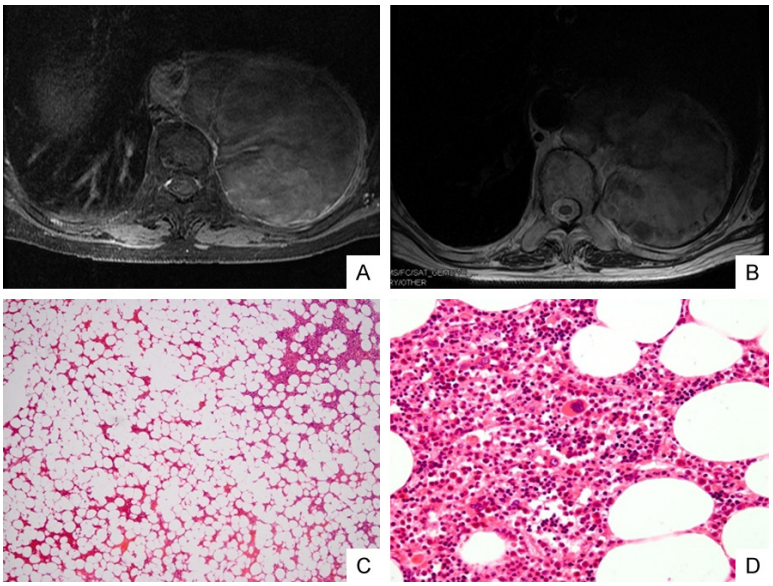

Figure 3. MRI imaging and HE imaging of case 9. (A and B) revealed a heterogeneous massive mass from the level thoracic vertebra 9 to 12 with hyperintensity on T1 and T2-weighted image. (C and D) showed the hematoxylin and eosin staining of the tumor (at 40 X and 400 X).

For patients with chronic hematologic systemic diseases whose diagnosis of EMH may be made through cross-sectional imaging [17], the recommended treatment includes close monitoring, with surgery only in the case of compression. In our series, patient 5 may have avoided two surgeries if his hematologic condition were considered in the diagnosis. For patients without hematologic conditions, there is no agreement on how to manage this diagnosis. Most MLs are surgically removed [18, 19], considering the potential progressive enlargement of the lesion to cause spinal compression and the uncertain preoperative diagnosis. Although CT-guided fine needle biopsy is recommended for some cases [20, 21], posterior mediastinal biopsy is dangerous, and small biopsy tissue may not give a correct diagnosis due to the heterogeneity of this tumor.

The prognosis of mediastinal EMH mainly depends on the hematologic condition and rupture/bleed of the EMH mass [22]. Most mediastinal MLs are believed to exhibit benign behavior and have a favorable outcome [23].

Conclusion

Mediastinal ML/EMH can present as a mass on cross-imaging and be misdiagnosed as a malignant tumor. The main difference between ML and EMH is the presence of a chronic hematologic condition. The fat element inside the mass can assist in the correct diagnosis using imaging. Treatment for mediastinal ML is VATS, while for EMH, the treatment is watchful waiting if no complication is suspected.

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Disclosure of conflict of interest

None.

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