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Chen Zhao · Taketo Yamada · Shigeru Kuramochi
Kazuto Yamazaki · Makio Mukai · Kaori Kameyama
Jun-ichi Hata

Two cases of ectopic hamartomatous thymoma

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Abstract Ectopic hamartomatous thymoma (EHT) is a rare benign neoplasm. Since it was named by Rosai et al. in 1984, 24 cases have been reported. We herein report two cases of EHT, one of which presented with massive myoid cells, and review the literature related to EHT. Both of our cases displayed the typical features of EHT: (1) nests of epithelial cells, including solid, cystic, or glandular epithelial islands; (2) spindle cells dominating the microscopic picture; and (3) adipose cells which intermingle haphazardly to impart a hamartomatous quality to the tumor. In this paper, we observed massive myoid cells and the transition from spindle epithelial cell to myoid cell in one of our cases. Immunohistochemical examinations showed that the main component of EHT, spindle cells, was positive for cytokeratin and epithelial membrane antigen (EMA). Intriguingly, the myoid cells simultaneously expressed cytokeratin, EMA, myoglobin, and creatine kinase-mm, suggesting that myoid cells may originate from epithelial cells and are an intermediate state between epithelial cells and muscular cells.

Keywords Ectopic hamartomatous thymoma · Immunohistochemistry · Myoid cell

Chen Zhao · Taketo Yamada (✉) · Shigeru Kuramochi
Jun-ichi Hata
Department of Pathology, Keio University School of Medicine,
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: taketo@mc.med.keio.ac.jp
Tel.: +81-3-5363-3764, Fax: +81-3-3353-3290

Chen Zhao · Taketo Yamada · Shigeru Kuramochi
Kazuto Yamazaki · Makio Mukai · Kaori Kameyama
Jun-ichi Hata
Department of Diagnostic Pathology, Keio University Hospital,
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Shigeru Kuramochi
Clinical Laboratories, National Tokyo Medical Center,
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Introduction

Ectopic hamartomatous thymoma (EHT) is a rare benign neoplasm that occurs exclusively in the supraclavicular, suprasternal, and presternal regions [7]. EHT was first described, almost simultaneously, as an "unusual subcutaneous mixed tumor exhibiting adipose, fibroblastic, and epithelial components" by Smith and McClure [20] and as a "spindle cell thymic anlage tumor" by Rosai et al. [17] in 1982. Rosai and his colleagues believed that these tumors represented a unique class of tumors and coined the term "ectopic hamartomatous thymoma" [18] in 1984. To date, 24 cases have been reported in the literature (Table 1). Among these cases, myoid cells have only appeared in two patients [1, 19].

We herein report two cases of typical EHT, one of which presented with massive myoid cells that expressed myoglobin and creatine kinase (CK)-mm, certain markers of skeletal muscle cells. We then discuss the clinical and histopathological findings of EHT. In addition, the origin of myoid cells is discussed. The importance of recognizing EHT in pathological diagnosis is emphasized.

Case report

Case 25

A 71-year-old man was referred to a local hospital with a tumor in the left supraclavicular region. The tumor had been first identified 40 years previously, but had begun to slowly enlarge over the last 10 years. No other abnormal clinical symptoms or laboratory data were found. The tumor was excised, and no signs of recurrence have been seen.

Case 26

A 52-year-old man was admitted to Keio University Hospital with a tumor in the right supraclavicular region. The tumor had been found 6 months previously and had shown signs of enlargement. No other abnormal laboratory data were found. A local excision was performed, and no signs of recurrence have been seen 3 years after resection.

Table 1 Cases of ectopic hamartomatous thymoma

Case no.	Gender/Age (years)	Site	Size (cm)	References
1	Female/55	Left supraclavicular	8×5×4	Smith et al. [20]
2	Male/35	Left supraclavicular	4×3×2	Rosai et al. [18]
3	Male/26	Left supraclavicular	6×3×3	Rosai et al. [18]
4	Male/40	Surprasternal	2	Rosai et al. [18]
5	Female/43	Right supraclavicular	5×4×3	Rosai et al. [18]
6	Male/79	Sternoclavicular	19	Fetch et al. [8]
7	Male/38	Right supraclavicular	5.5	Fetch et al. [8]
8	Male/37	Sternoclavicular	3.5	Fetch et al. [8]
9	Male/65	Sternoclavicular	10	Fetch et al. [8]
10[a]	Male/42	Surprasternal	5×4×4	Saeed et al. [19]
11	Male/66	Surprasternal	7×6×4	Chan et al. [2]
12	Male/58	Surprasternal	not available	Chan et al. [2]
13	Male/47	Left supraclavicular	3.8× 3.5×2.5	Chan et al. [2]
14	Male/adult	Supraclavicular	3×2.5×2	Chan et al. [2]
15	Male/68	Left sternoclavicular	3	Chan et al. [2]
16[a]	Male/47	Left supraclavicular	3.8×3.5×2	Armour et al. [1]
17	Female/49	Suprasternal	2.4×2×2 and 1.5×1×1	Doctor et al. [6]
18	Male/31	Right supraclavicular	6×3×3	Michal et al. [14]
19	Male/39	Right supraclavicular	5.5×4×4	Michal et al. [14]
20	Male/38	Suprasternal	3×3×3	Michal et al. [14]
21	Male/36	Suprasternal	1.5×1.5×1	Michal et al. [14]
22	Male/27	Presternal	3.5×2.5×1.5	Eulderink et al.[7]
23	Male/63	Suprasternal	3×3×3	Hirokawa et al.[10]
24	Male/39	Right sternoclavicular	1.4×1.0×0.8	Henderson et al.[9]
25	Male/71	Left supraclavicular	9×5×4.5	present report
26[a]	Male/52	Right supraclavicular	3.5×2.5×2and 0.8×0.8×0.8	present report

[a] Showed the presence of myoid cells

Materials and methods

The excised specimens were examined grossly, fixed in a solution of 10% formaldehyde, and then embedded in paraffin. Sections (4-μm thick) were prepared and stained with hematoxylin and eosin. Immunohistochemical stainings with antibodies against cytokeratin (1/200; AE1/AE3; Boehringer Mannheim; Germany), epithelial membrane antigen (1/100; Dako; Glostrup, Denmark), desmin (1/100; Bio-science; Chiho, Calif.), human muscle actin (1/100; HHF35, Dako), myoglobin (1/500; Dako), CK-mm (1/500; Pel-Freez Biologicals; rogers, Ark.), MyoD (1/100; Dako), CD34 (1/200; Novocastra; Newcastle, UK), CD20cy (1/200, L26; Novocasra), CD1a (1/2; Immunotech; Marseille, France), and CD99 (1/200; Signet; Peabody, Mass.) were performed using indirect reactions with horseradish peroxidase-conjugated secondary antibodies. Class-matched antibodies were used as negative controls.

Results

Gross and light microscopic findings

Grossly, the tumors were well circumscribed and had a firm, elastic consistency. The cut surface had a yellowish appearance in some fields (Fig. 1a–b). No relationship to the thymus or thyroid gland was found. Tumor sites and sizes are shown in Table 1.

The histopathological features of these two cases were similar to those of previous reports. The tumor contained epithelial cells, spindle cells, adipose cells, and a small amount of lymphocytes, as described previously [18]. The epithelial or squamous cell component consisted of solid round nests with branching strands, cystic structures, and glandular nests. Hassall's corpuscle-like structure was also observed in the epithelial component.

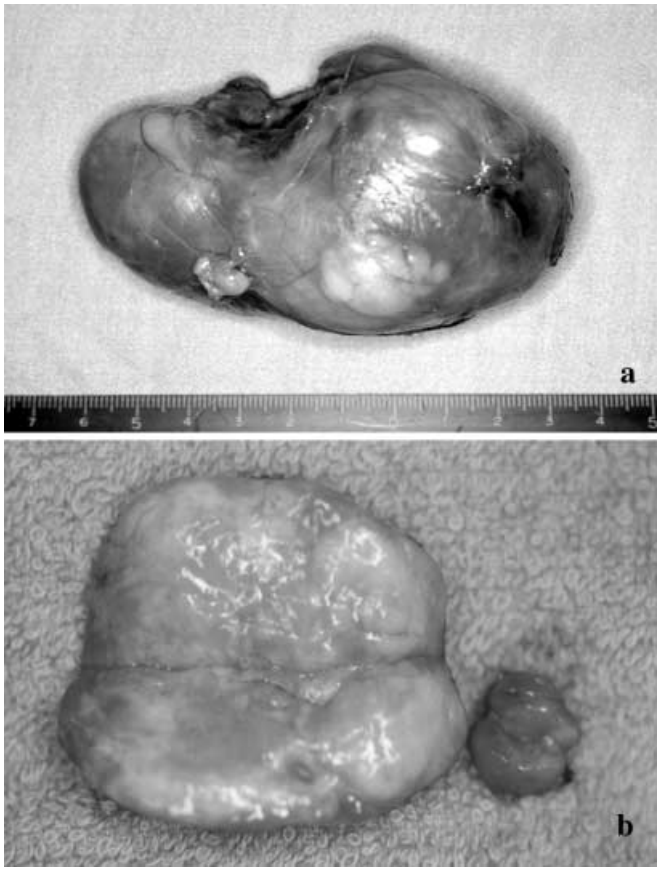

Fig. 1 Gross finding of ectopic hamartomatous thymomas. **a** Case 25: the tumor was well-circumscribed and elastic. The ruler was graduated in centimeters. **b** Case 26: the tumor consisted of two nodules. The surface of the cross section was bulgy and yellowish

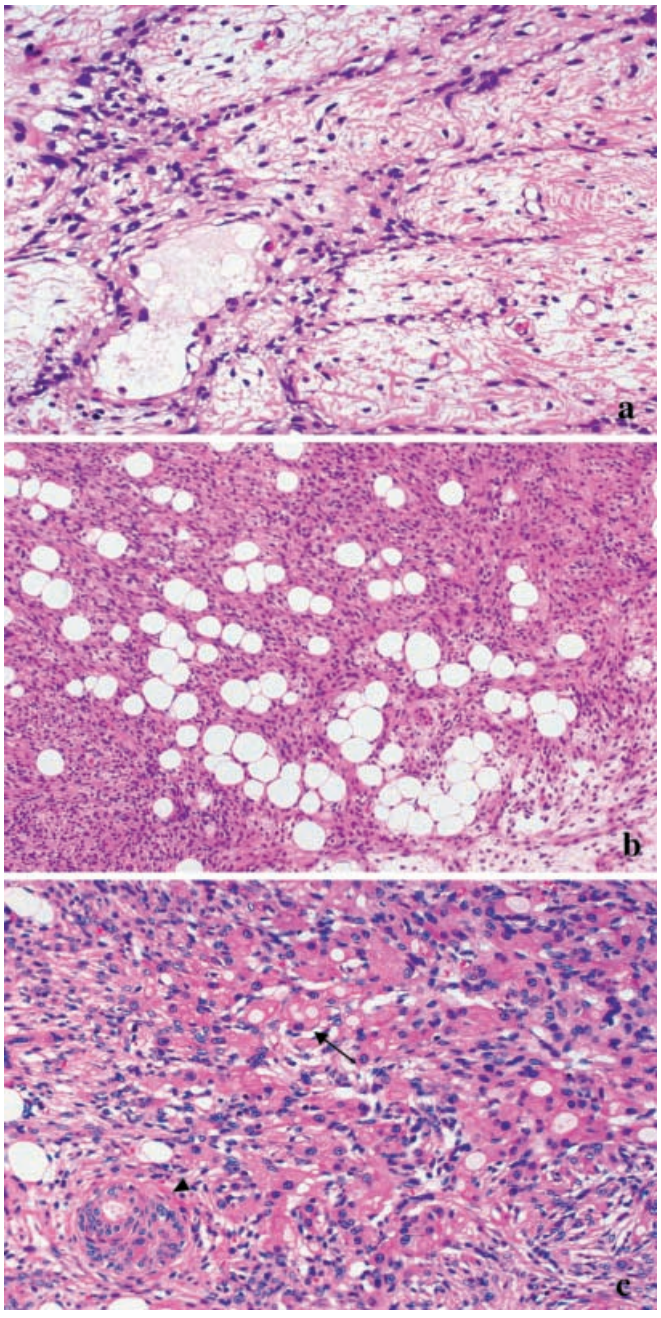

Fig. 2 Histological findings of ectopic hamartomatous thymomas (EHTs). **a** Case 25: the tumor consisted of spindle cells, predominantly lattice-like. **b** Case 25: adipocytes were diffusely distributed between the spindle cells and the epithelial cells in EHT. **c** Case 26: a lot of myoid cells were present in EHT. The transitional focus between spindle and myoid cells was often found

The spindle cell component, which dominated the tumors, was arranged in fascicles with a lattice-like pattern (Fig. 2a) or sometimes a storiform-like pattern. Adipocytes were distributed haphazardly in the form of islands bound by the epithelial and spindle cell components described above (Fig. 2b). The diffuse infiltration of lymphocytes, which is an inconspicuous but characteristic feature of EHT, was also seen diffusely.

Large numbers of myoid cells were seen among the spindle cells in case 26. The myoid cells were oval or spindle-shaped with copious brightly eosinophilic cytoplasm and vesicular nuclei. No striations were found. The distribution of myoid cells among the spindle cells was irregular and patternless. Furthermore, intracytoplasmic vesicular formation was observed in some myoid cells. The transition from spindle cells to myoid cells was also seen (Fig. 2c).

Immunohistochemical and histochemical findings

Both epithelial and spindle cell components were strongly positive for cytokeratin, as previously reported. The spindle cell component was also positive for CD34 but negative for CD20cy (L26). It has been reported that CD20cy (L26) antigens are present in spindle epithelial cells of thymoma [4]. Interestingly, the massive myoid cells of case 26 were simultaneously positive for cytokeratin, epithelial membrane antigen (EMA), myoglobin, and CK-mm (Fig. 3a–d, which are same step sections as Fig. 2c). However, they were negative for desmin, as reported previously in EHTs [1, 19]. Other muscular markers, MyoD and muscle actin, were also negative (data not shown).

The lymphocytes scattered throughout the tumors were CD45RO-positive T cells. However, both CD99 and CD1a antigens were not expressed on these T lymphocytes. CD99 expression was shown in a large number of spindle cells but not in either epithelial cells or myoid cells (data not shown). Cystic spaces and intracytoplamic cysts were positive when stained with periodic acid Schiff (PAS) and alcian blue stains (data not shown).

Discussion

EHT is a very rare benign tumor that only occurs in the supraclavicular, suprasternal, and presternal [7] areas. Since it was first named by Rosai et al. [18], 24 cases have been reported (Table 1).

The clinical and pathological features of the two cases presented in this report were identical to those of previous reports. The patient age at the time of occurrence ranged from 26 years to 79 years (mean 52.5 years). Male cases were dominant (male to female ratio was 23:3). The tumor size varied from 8 mm to 19 cm in diameter. The EHT was solitary in 24 cases of the 26 reported cases (including ours), but multiple tumors were seen in the remaining two cases. None of these cases showed any relationship with either the thyroid gland or the proximal bones.

EHTs consist of epithelial cells, spindle cells, adipocytes, and a small amount of lymphocytes. Rosai et al. postulated that this type of tumor originates from the thymic anlage or branchial arch [18], because it shows an irregular blend of these components. Recently, Michal et al. suggested that EHT was a manifestation of salivary gland differentiation [14]. However, the histopathologic

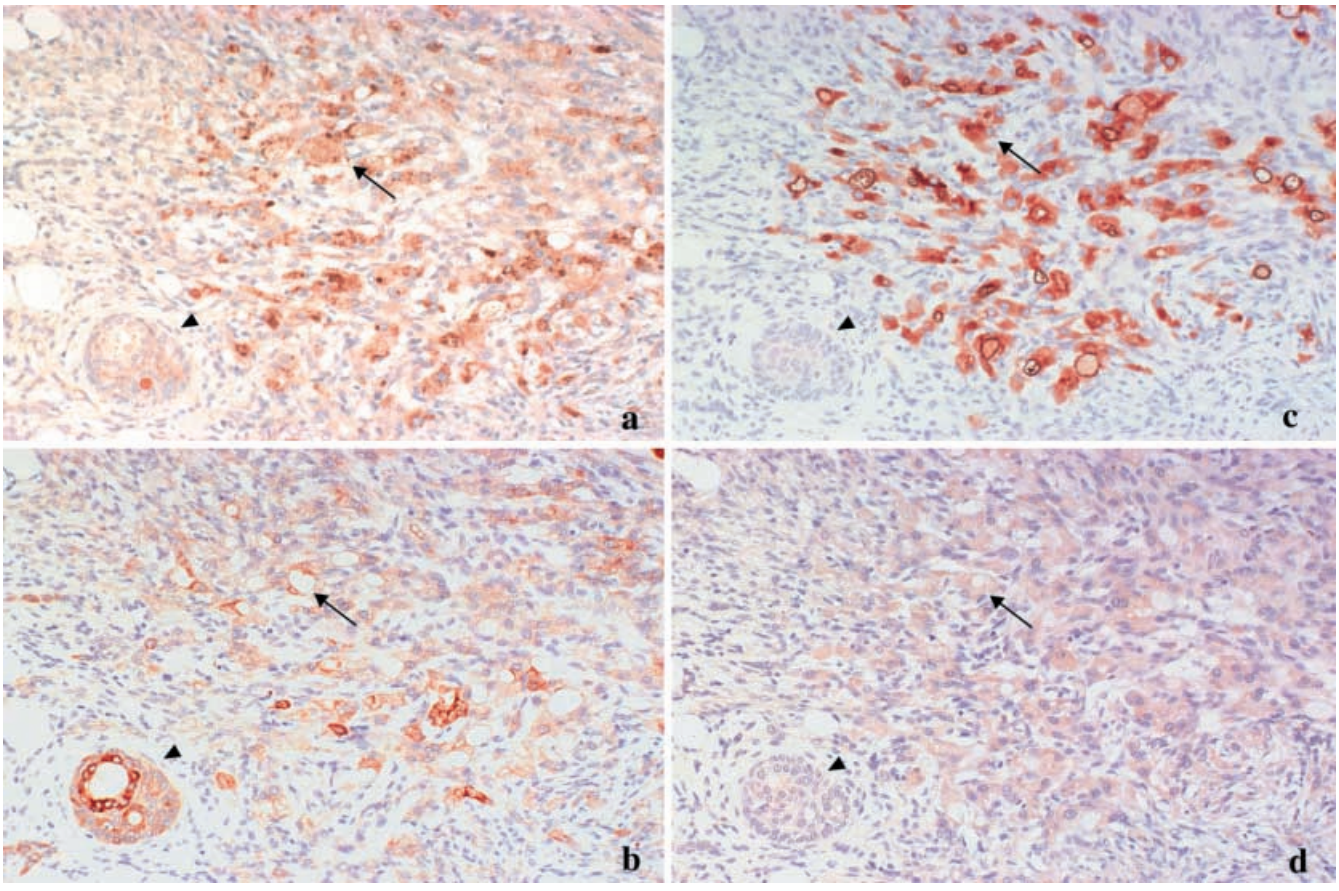

Fig. 3 Immunohistochemical features of myoid cells in case 26 (same step sections as Fig. 2c). In Case 26, myoid cells revealed the expressions of cytokeratin (**a**), epithelial membrane antigen (**b**), myoglobin (**c**) and creatine kinase-mm (**d**) upon immunohistochemical examination. The same field was shown in Fig. 2c as here in **a**–**d** by step sections. *Arrow* and *arrowhead* showed myoid cells and epithelial cells, respectively

appearance of spindle epithelial cells, Hassall's corpuscle-like structures, lattice-like structures, and various other components, including myoid cells, seem to support the interpretation of Rosai et al [18]. CD1a and CD99 are available for the confirmation of a diagnosis of thymoma, ectopic thymoma, or metastatic thymoma, because both of CD99 and CD1a have been thought as useful markers of immature thymocytes [3]. We could not find CD1a- or CD99-positive lymphocytes in our EHTs. However, the previous report also showed that CD99-positive lymphocytes were not present in two cases of EHT [3]. These results may show that the T lymphocytes in EHTs are not developing T lymphocytes specific for the thymic organ.

Myoid cells were observed in 3 of the 26 reported cases (Table 1). Although these cells have also been found in the medulla of the human thymus, the origin of myoid cells is still unclear. Myoid cells exhibit similar features to those of skeletal muscle cells [16]. In the two previous EHT cases in which myoid cells were observed, the myoid cells stained positive for myoglobin. In one of these cases, the myoid cells also stained positive for human muscle actin [1, 19]. In this paper, we found that when using immunostaining on step sections of the tumor specimen, the myoid cells stained positive for not only myoglobin and CK-mm but also for cytokeratin and EMA. Myoid cells in EHT have not been previously reported to possess characteristics of both muscle and epithelial cells. Furthermore, a transitional stage between myoid cells and spindle cells was evident. We interpreted these findings as suggesting that myoid cells are an intermediate state between epithelial cells and muscular cells. Although the neural crest [15], perithymic mesenchymal cells [23], transformed thymic epithelial cells [22], and thymic stromal elements of postcapillary venules [25] have also been suggested as possible origins of myoid cells, our immunohistochemical results seem to strongly support our thymic epithelial transformation theory [22]. Thymomatous epithelial cells have also been reported to share a common epitope with skeletal muscle [5], providing further support for our theory. However, we cannot exclude an alternative possibility that myoid cells may result from a metaplastic process [24].

Yoneda et al. suggested that both myoid cells and spindle cells might arise from the same multipotent "stem" cell [24]. In addition to normal thymus and EHT, myoid cells have also been found in thymic hyperplasia [12], thymolipoma [11], variant thymomas, thymic carcinoma [21], and thymic tissue in cases of myasthenia gravis. In the cases of myasthenia gravis, myoid cells are

believed to supply the triggering antigen, the acetylcholine receptor, that leads to pathogenesis of myasthenia gravis [16]. Myoid cells in various developmental stages have been observed in these diseases. These observations coincide with our view that the morphology of myoid cells differs according to their developmental stage.

Only one case of a carcinoma developing from an EHT has been reported [13]. Nearly all of the other cases showed benign clinicopathological features. To our knowledge, a recurrence after the surgical excision of an EHT has never occurred. In the case that developed into a carcinoma, the tumor did not metastasize. No deaths from EHT have ever been reported. EHT is easy for pathologists and clinicians to diagnose if they are aware of the EHT category.

The ability to recognize EHT is especially important for diagnoses involving biopsies. Biphasic synovial sarcoma, malignant peripheral nerve tumors, skin adnexal tumors, thymolipoma, and spindle cell thymoma are differential diagnoses for EHT.

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