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Ectopic cervical thymus: A clinicopathological study of consecutive, unselected infant autopsies

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ABSTRACT

Objectives: An ectopic cervical thymus (ECT) is regarded as a rare congenital anomaly; therefore, the optimal diagnostic and therapeutic strategy remains a debatable matter. We designed a study to elucidate the clinicopathological characteristics of ECTs in consecutive, unselected infant autopsies, to help guide case management.

Methods: We searched for ECTs in all of the 21 consecutive, unselected infant autopsy cases performed at our institution over a period of 3 years, and all ECT consensus diagnoses were confirmed by histological examination. The following clinical characteristics were evaluated in cases with ECTs: age, gender, birth week and weight, clinical symptoms due to the ECT(s), position on discovery of death, cause of death, ECT contribution to the cause of death, and concomitant congenital disorders. The anatomical features evaluated included the location, number, size, color, shape, and margins of the ECTs, and the presence of a mediastinal thymus. Histological findings of the ECT(s) and the mediastinal thymus were compared within each individual. Fusion of the parathyroid and the ECT was also investigated histologically. Spearman's rank correlation coefficient (ρ) and the corresponding P value were calculated to determine if there was an association between ECT diameter and age.

Results: We detected 10 ECT lesions in seven cases (33%) among the 21 infant autopsy cases. The ECT cases involved five boys and two girls, with ages ranging from 1 day to 4 months. There were no reports of a positive family history of sudden death or antemortem clinical symptoms due to ECT in any of the cases. The ECTs were considered incidental regarding the cause of death, with the exception of one case that was extremely rare. Most ECTs were localized to the inferior thyroid, ranging from 0.4 to 1.9 cm in size. Size demonstrated a significant negative correlation with age ($\rho = -0.75$ and $P = 0.034$).

Conclusions: This study revealed that ECT is an essentially benign anomaly that occurs frequently during the development of the thymus, and may disappear over the first few years of life. These results suggest a conservative approach to the management of ECTs would be appropriate.

1. Introduction

An ectopic cervical thymus (ECT), which can be located anywhere along the developmental pathway of thymic descent, represents a rare cause of pediatric neck masses [1–3]. The natural incidence and clinical course of ECTs are still unknown because nearly all of the previously reported cases have undergone surgical removal, and a prospective randomized study is not feasible because of the rarity of ECTs [4]. This lack of knowledge has led to controversy regarding the optimal diagnostic and therapeutic strategy for this lesion [4,5]. Some reports have recommended surgical excision based on the safety of this procedure, the necessity for a pathological diagnosis, and the potential for malignant transformation and severe clinical symptoms such as dyspnea and dysphagia without surgery [2,6,7]. Meanwhile, others have recommended conservative management, such as a "watch and wait" policy, for ECTs diagnosed before surgery because of concerns regarding the high morbidity associated with surgical excision; these proponents consider ECT to be an anomaly with a basically benign course and without convincing evidence to support an increased risk of malignant transformation [4,8].

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Advanced high-resolution ultrasonography (US) and magnetic resonance imaging (MRI) have recently been described as alternatives to histological evaluation for the diagnosis of an ECT [9–11]. Song et al. stated that the echo characteristics of ECT, such as multiple echogenic inner linear structures and foci surrounded by hypoechoic rims, are key to its diagnosis and that MRI facilitates diagnosis because the appearance of an ECT is identical to that of a mediastinal thymus on MRI [9]. In addition to these imaging methods, fine needle aspiration has been recommended as a diagnostic method in recent years because it is a less invasive procedure than surgical excision; the presence of fibrous septa, Hassall's corpuscles, and other characteristics of normal thymic architecture on cytology can provide clues to an accurate diagnosis of ECT [4,8,11,12].

If we could improve current diagnostic strategies by increasing available information regarding the natural incidence and clinical course of ECTs, it would help pediatricians to determine the appropriate strategy when they encounter a particular case that may require surgery. A prospective randomized study with healthy infants using radiological images such as US may seem to be a logical approach. However, the images do not provide a definitive diagnosis of ECT without pathological confirmation. Therefore, we decided to investigate the clinicopathological characteristics of ECTs by performing a survey of consecutive, unselected infant autopsies associated with histological examinations. To the best of our knowledge, this study is the first to clarify the features of this lesion in consecutive autopsies at a single institution.

2. Materials and methods

2.1. Cases

We searched for ECTs in all 21 of the consecutive, unselected infant cases autopsied at our institution for 3 years from the time we encountered the first ECT case, which we previously described [3]. The 21 cases were categorized into sudden unexpected death in infancy (SUDI) and ranged in age from 1 day to 10 months; 13 of the cases were boys. No cases required exclusion because of unavailability, e.g., because of a long postmortem interval or severe neck trauma. The Department of Forensic Medicine at Kyoto University Graduate School of Medicine, Japan, is one of two forensic autopsy institutions in the Kyoto prefecture (population of 2.8 million) and is assigned two-thirds of the out-of-hospital SUDI cases. The following clinical characteristics were evaluated in cases with ECTs: age, gender, birth week and weight, clinical symptoms due to the ECT(s), position on discovery of death, cause of death, ECT contribution to the cause of death, and concomitant congenital disorders. This study was conducted within the framework established by the Ethics Committee of Kyoto University.

2.2. Anatomical and histological features

In all cases, the cervical organs along with the tongue and thoracic organs were resected after removal of the heart. Two experienced forensic pathologists (H.K. and K.T.) sought ECTs throughout the cervical and thoracic organs, and all ECT consensus diagnoses were confirmed by histological examination. The anatomical features evaluated included the location, number, size, color, shape, and margins of the ECTs and the presence of a mediastinal thymus. Size was defined as the greatest diameter. Histological findings of the ECT(s) and mediastinal thymus were compared within each individual on H&E stained specimens and by immunohistochemical analysis of the lymphocytes. Fusion of the parathyroid and the ECT was also investigated histologically.

2.3. Statistical analyses

Spearman's rank correlation coefficient (ρ) and the corresponding P value were analyzed to determine if there was an association between diameter and age. P value less than 0.05 was considered statistically significant. All statistical analyses were performed using R software for Windows, version 2.14.1.

3. Results

3.1. Clinical characteristics of cases with ECT

We encountered seven cases with solid ECTs in 21 consecutive, unselected infant autopsies during the study period, an incidence of 33% within this population. The clinical characteristics of the seven cases are summarized in Table 1; the cases ranged in age from 1 day to 4 months, and five cases (71%) in this series were boys. All were born as mature full term infants except for one male infant with congenital heart disease born at a gestational age of 36 weeks. There were no reports of a positive family history of sudden death or antemortem clinical symptoms due to ECT in any of the cases. Five were found dead in a supine position, and two were found in a prone position. The cause of death was sudden infant death syndrome in three cases, pneumonia due to respiratory syncytial virus infection in two, and accidental asphyxia in one. The ECTs were considered to have been incidental to their deaths with the exception of a 4-month-old boy (case 6).

3.2. Anatomical features of the ECTs

Anatomical features of the ECTs are summarized in Table 2. The ECTs were found on both sides without laterality but were preferentially located at the inferior region of the thyroid gland except for one visually undetectable ECT. The detectable ECTs appeared as well-circumscribed soft and solid nodules with a spherical shape and a reddish gray-white color (Fig. 1a and b and Supplementary Fig. 1). The undetectable lesion was covered by the right lobe of the thyroid, and the thyroid isthmus was absent (Fig. 1b, case 7); the ECT was detected on histological examination (Figs. 1b and 2a). Three cases had two lesions each; the others had a single lesion. The mean lesion size was 1.0 cm (range, 0.4–1.9 cm). The size of the lesion demonstrated a significant negative correlation with age for all ECTs except the two lesions found in

Table 1
Clinical characteristics of cases with ectopic cervical thymuses.

Case no.	Age/gender	Birth wk/wt (g)	Position on discovery	Cause of death	ECT contribution to death	Congenital anomalies
1	1 day/M	36/2300	Supine	CCA	No	CCA
2	2 months/M	40/3250	Supine	SIDS	No	Absent
3	2 months/F	40/3210	Supine	SIDS	No	Absent
4	3 months/M	38/3310	Prone	Pneumonia	No	Absent
5	4 months/M	37/2410	Supine	SIDS	No	Absent
6	4 months/M	40/3472	Prone	Asphyxia	Yes	Absent
7	4 months/F	39/2888	Supine	Pneumonia	No	ATI

ATI, absent thyroid isthmus; CCA, congenital cardiac anomaly; ECT, ectopic cervical thymus; SIDS, sudden infant death syndrome.