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EDITORIAL

Enigmatic thymus: Variations in anatomical localisation of thymic tissue as an easily misdiagnosed congenital anomaly in surgical practice

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Abstract

We point out the issue of differential diagnosis regarding the finding of ectopically localised thymic tissue (a thymic cyst) in the neck. Thymic tissue can be found anywhere along its developmental tract of descent, from the angle of the mandible to the upper mediastinum. Disruption of the thymic descent can result in ectopically/abnormally localised islets of accessory thymic tissue, which may undergo cystic changes, as described in a case report by Sun *et al*. This anatomical variation of the thymus may be clinically misinterpreted as a neoplasm or other congenital anomalies as a branchial cyst, lymphatic malformation or cystic hygroma. The present editorial focuses on the challenge of establishing a diagnosis of ectopically localised tissue of thymus often presented as a lateral cervical mass, especially in the case of cystic variation/degeneration of this thymic tissue. We summarise hypotheses on the origin of such congenital cervical thymic cysts from the point of view of evolutionary history and embryology. We also discuss lesser-known facts about the anatomy, histopathology and developmental biology of the thymus as one of the most enigmatic organs in the human body.

Key Words: Thymus; Thymic anomalies; Thymic ectopy; Congenital cervical thymic cyst; Embryonic development

Core Tip: In this editorial, we comment on a case report by Sun *et al*, entitled: Multilocular thymic cysts can be easily misdiagnosed as malignant tumor on computer tomography. We focus specifically on the pertinence of establishing a diagnosis in clinical practice of the ectopically localised tissue of thymus, especially in the case of cystic variation of this thymic tissue. We also summarise lesser-known facts about the anatomy, histopathology and developmental biology of the human thymus as one of the most enigmatic organs in the human body.

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INTRODUCTION

The thymus is a primary lymphatic organ with an important endocrine function. It is responsible for generating a self-tolerant T- lymphocyte repertoire, as the key cells of cellular immunity, capable of recognizing foreign antigens or cancer cells[1,2]. Additionally, thymic hormones play a crucial role in immune system regulation and are studied extensively due to their immunomodulatory effects[3]. Extracted and purified thymic tissue has been hypothesized to regulate immune functions in cancer patients, resulting in better elimination of cancerous cells. Such tissue extract can also protect against infection caused by opportunistic pathogens[4]. In this editorial, we comment on a case report by Sun *et al*[5]. In our editorial, we point out the issue of differential diagnosis regarding the finding of ectopic thymic tissue in the neck. Thymic tissue can be found anywhere along its developmental tract of descent, from the angle of the mandible to the upper mediastinum. Ectopically localised submandibular or intrathyroidal accessory thymic tissue may be misinterpreted as a neoplasm[6]. An excellent example of such a clinical finding and diagnostic challenges is the mentioned case study of Sun *et al*[5]. However, we want to give readers a brief summary of why we believe that the thymus is still considered an enigmatic organ, even from the point of view of contemporary clinical medicine and anatomy.

THYMUS AS THE MOST ENIGMATIC ORGAN OF THE HUMAN BODY

We have several reasons to confirm this bold statement. (1) The thymus was the last organ of our body to give away its importance; the function of the thymus was recognized only 60 years ago. It was not until 1961 when the function of the thymus was finally revealed in Jacques Miller's seminal article "Immunological function of the thymus" published in *The Lancet* journal[7]; (2) Before this discovery, in the 19th and beginning of 20th centuries, a thymus of normal size was considered to be the cause of various fictive pathological conditions. These conditions were based on a mythical mechanical compression on the airways by a "large" thymus as a cause of sudden unexpected death in infants (Kopp's thymic asthma or thymic death), and improper overdevelopment of the entire lymphatic system of obscure nature (Paltauf's *status thymolymphaticus*)[8-11]. Even today, possible relationships between sudden infant death syndrome and the thymus are emerging; changes of thymic anatomy are related to its microscopic structure and are probably associated with cellular as well as inflammatory events during stress-related thymic involution[12]. This may be due to the influence of an exogenous/environmental stressor as part of the triple-risk model for developing sudden infant death syndrome [13,14] or a combination of underlying immune dysregulation and infections[15,16]; (3) The thymus undergoes substantial changes in its size and composition during human ontogenesis. These changes include rapid prenatal development[17] and gradual age-related involution. The age-related involution starts very soon, sometimes even within the first year of age, and occurs throughout the whole life. It is estimated that around three to five percent cell reduction a year is a rate by which the thymic shrinkage progresses well into adulthood. Past the middle age, the rate decelerates to around one percent a year[18,19]. In children, the ultrasonographical echo-texture[20] and elasticity[21] of the normal thymus also changes with age; (4) In radiological practice, the thymic size in children is an early sensitive barometer of any type of chronic and acute stress[22,23] as well as nutrition[24,25]; (5) The gross anatomy of the thymus, as well as thymic shape and size varies not only between individuals in humans, but also varies substantially between individual species of mammals. In humans, ultrasound examination is safe, effective and suitable for simple assessment of thymic size as well as shape in children[26]. Cervical thymic extension is sonographically visible in ca. one-third[27] up to half [28] of children undergoing neck ultrasonography. Thus, radiologists and clinicians should be aware of this entity to avoid unnecessary imaging studies as well as interventional procedures. For the sake of completeness, in some mammals—such as sheep, cattle, pigs, horses and deer—the thymus normally consists of thoracic and cervical parts[29, 30]; in others—such as koalas (*Phascolarctos cinereus*)—only a cervical thymus is present[31], and in mice a functional additional second cervical thymus develops only after birth[32,33]; (6) The cellular composition of the thymus is also unique. The stroma of the thymus is formed by stellate-shaped thymic epithelial cells and other thymic-specific non-epithelial cells with the ability to support the maturation of phenotypically and functionally distinct T lymphocytes[34-36]. A poorly researched population of the thymic microenvironment is thymic myoid cells, which histologically resemble muscle elements. These myoid cells hypothetically may be a source for development of some uncommon neoplasms and are also implicated in the pathogenesis of myasthenia gravis[37]; and (7) The epithelial, non-epithelial stromal and

lymphoid compartments of the thymus can give rise to a wide variety of tumours; including thymomas, thymic carcinomas, lymphoreticular proliferations, germ cell tumours and sarcomas[38]. Thymomas and thymic carcinomas are thymic epithelial tumours, which are characterized by their extreme rarity and variable clinical presentation. These neoplasms, particularly thymomas, have peculiar features. Most notably, their pathogenesis involves severe paraneoplastic conditions such as the autoimmune disorder myasthenia gravis[39]. Managing patients with thymic epithelial tumours requires continuous multidisciplinary expertise at all stages of the disease; including radiologists, histopathologists, experienced surgeons and oncologists (radiotherapy, chemotherapy or possibly immunotherapy)[40].

THYMIC ANATOMY – ANATOMICAL VARIATIONS OR ECTOPY?

In humans, the paired thymic primordia are derived together with the inferior parathyroid glands from the third pharyngeal pouches, as lateral parts of the wall of the embryonic pharynx. Evolutionary, this pharyngeal region was the place, where the gills of aquatic vertebrates developed[41]. In the 7th week, thymic primordia start to descend and separate from the pharyngeal wall, progressing towards their ultimate destination, the thoracic region located anteriorly to the pericardial cavity. Despite the third pharyngeal pouches being the typical origin sites of thymic primordia, fourth pharyngeal pouches have also been described to partially contribute to thymus formation, although this occurrence is rare. Nevertheless, after the descent, the thymus organogenesis proceeds by the bilateral fusion of both thymic primordia, giving rise to a V-shaped mediastinal thymus consisting of two lobes[42]. However, the thymus can also be unilobed, trilobed or shaped as a letter X or an inverted letter V[43]. Disrupting the thymic descent can result in a completely ectopically/abnormally localised thymus or ectopically/abnormally localised islets of accessory thymic tissue; which may undergo cystic changes, as described in the mentioned case report of Sun *et al*[5].

The presence of ectopically localised accessory thymic tissue is not rare. Unencapsulated lobules of thymus and microscopic foci of the thymus may be widely and invisibly distributed in the pretracheal and anterior mediastinal adipose tissue from the level of the thyroid to the diaphragm, and bilaterally from beyond each phrenic nerve. Occasionally, microscopic foci of thymus have also been found in subcarinal adipose tissue[44]. This anatomical knowledge is especially important for thoracic surgeons who perform extended surgical thymectomy of patients with myasthenia gravis[45]. The presence of ectopic thymic tissue has been considered one of the most pertinent predictors of poor outcome after thymectomy for myasthenia gravis[46]. In more than 40% of patients, ectopic thymic tissue is found; new methods of ectopic thymectomy, for the purpose of adipose tissue clearance, are implemented in surgical practice[47]. Even on the basis of such a frequent occurrence, we rather terminologically term it as a "variation" of the localisation of thymic tissue, and not of a real "ectopy"[48].

VARIATIONS IN THE LOCALISATION OF THYMIC TISSUE – DIAGNOSTIC CHALLENGE IN SURGERY

The clinical presentation of the anatomically variant accessory thymic tissue (sometimes termed ineptly as aberrant cervical thymus[49]) reflects the thymic descent occurring during its organogenesis. Most typically, a patient reports a neck mass without additional signs or symptoms, which is found anywhere along its descent path from the angle of the mandible to the superior thoracic aperture/to the superior mediastinum. It is clear that the ability to consider the exceptional way in which the thymus develops helps in differential diagnosis and mitigates the risk of gratuitous invasive measures. However, in scientific manuscripts we often come across terms that are not even mentioned in the internationally recognized nomenclature, the *Terminologia Embryologica*[50] (Table 1), as a non-existent "thyropharyngeal duct"[51].

Accessory thymic tissue localised in the neck may contain smaller or larger cysts filled with fluid. In general, cystic neck masses in adolescents pose a diagnostic challenge as they may be neoplastic or non-neoplastic, congenital, inflammatory or infectious. Cervical thymic cysts in children contribute to less than 1% cystic lesions in the neck[52]. Despite the obscurity of precise incidence figures, these cysts, occurring most commonly within the left anterior triangle of the neck, are undoubtedly rare. Males are affected more frequently, usually between five and seven years of age[53]. In adults, cervical thymic cysts are extremely rare; in the scientific literature less than 60 cases of adult thymus cysts had been reported[54]. However, in recent years, the number of reports of thymic cyst cases have increased, one possible cause being the heightened awareness of thymic cysts among pathologists[55].

The "enigmatic" cervical thymic cysts as well as accessory thymic tissue without cysts are usually present as a painless, latero-cervical swelling that progressively increases[56], sometimes with clinical features in keeping with malignant characteristics[57]. Sometimes this asymptomatic mediastinal thymic cyst is visible in the neck whenever the patient is asked to perform the Valsalva manoeuvre[58] or during phonation[59]. Cervical thymic cysts may be a cause of numerous misdiagnoses in children and adults as they may be: Mimicking a cystic hygroma[60], Mimicking a congenital branchial cleft cyst or a lymphangioma[61], In the case of subglottic localisation, mimicking a subglottic haemangioma or mucous retention cysts[62], Causing aural fullness and otalgia[63], Mimicking a laryngocele[64,65], Mimicking thyroid malignancy[66-68], Causing respiratory difficulties and airway deviation[69-71], Causing dysphagia[72].

The typical workup of neck masses in children includes imaging (*e.g.*, MRI, CT scan) and possibly cytopathology following fine-needle aspiration. Some features may help distinguish thymic masses from other aetiologies. An MRI can be used to confirm the presence of a mediastinal thymus and compare soft tissue densities between the suspect neck mass and the existing mediastinal thymus[73]. The densities of thymic components in the neck and mediastinum in CT scans are variable. Nevertheless, the neck density is lower[74]. In accordance with Atalay *et al*[75], preoperative diagnosis is

Table 1 Embryological anomalies of thymus in accordance with the *Terminologia Embryologica*[50]

Latin term	English equivalent
Aplasia thymi	Aplasia of thymus
Aplasia thymoparathyroidea	Thymoparathyroid aplasia (DiGeorge syndrome)
Ectopia thymi	Ectopic thymus
Hypoplasia thymi	Hypoplasia of thymus (Shprintzen syndrome)
Textus thymicus accessorius	Accessory thymic tissue

almost impossible. Surgical excision is often mandatory for treatment and final histological confirmation[54]. However, a conservative management might be appropriate in cases of asymptomatic lesions, especially in young children. The rationale for this includes the fact that the ectopically localised thymus could be the only active thymus in the body[76].

HISTOLOGICAL PICTURE AND POSSIBLE ORIGIN OF CERVICAL THYMIC CYSTS

A cystic form of accessory thymic tissue located in the neck is termed a congenital cervical thymic cyst. The exact origin of cystic spaces filled with fluid inside thymic tissue is unknown. These cysts are lined by thymic epithelial cells; inside, cholesterol crystals and multinucleated giant macrophages are often present[42,77]. The accessory thymic tissue anatomically localised in the neck has the same lymphopoietic function and microscopic structure, including thymic epithelial cells, prominent Hassall's corpuscles or myoid cells, as the normal thymus[78]. Rarely, ectopically localised thymic tissue may contain parathyroid tissue as well[79]; what can easily be explained by their common embryonic origin from the third pharyngeal pouches. Due to all these aspects in the description of possible misdiagnoses, a definitive diagnosis depends on imaging findings as well as intraoperative findings and mostly on histopathological examination.

In our previous report[78] we summarised several hypotheses about the developmental origin of cysts inside the cervical thymic tissue: (1) Cysts are huge, cystic variants of thymic Hassall's corpuscles normally present in smaller form in the mediastinal thymus; (2) Cysts are evolutionary atavisms of our animal ancestors, due to the fact that cysts are present in thymuses of amphibians or thymic ducts (which may be cysts) and are present in some species of cartilaginous fish, where the thymus has an excretory function; and (3) The persistence of embryonic "thymic or thymopharyngeal duct," a remnant of the lumen of third pharyngeal pouch, during separation of the thymic primordia from the lateral wall of the embryonic pharynx, less-probable hypotheses regarding formation of cysts within thymic tissue are associated with impaired immune functions or infections, the result of radiation or malignancy.

CONCLUSION

Cervical thymic cysts, described recently in the case report by Sun *et al*[5], are among the rarest cysts found in the neck. Being uncommon, they are rarely included in a clinical diagnosis of lateral neck masses and are commonly misdiagnosed as branchial cysts, lymphatic malformations, epidermoid cysts, dermoid cysts, lymphadenitis or neoplastic masses[80]. In this Editorial, we point out the difficulty of establishing a diagnosis in the case of ectopically localised tissue of the thymus, and the clinical aspect of this anatomical variation. We also introduce readers to lesser-known knowledge regarding the anatomy and developmental biology of the human thymus.

FOOTNOTES

Author contributions: Varga I conceived the idea; Mayer A and Voller J conducted a literature search; Mayer A wrote the preliminary draft; Varga I and Voller J critically reviewed as well as improved the manuscript; all authors contributed equally to preparing this manuscript;

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