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DEVELOPMENTAL HISTOLOGY OF HUMAN FOETAL THYMUSES AT DIFFERENT GESTATIONAL AGES

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ABSTRACT: Very few studies on developmental histology of thymuses at different gestational ages were reported in literature. In the present study the developmental histology of thymus in human fetuses of different gestational ages were observed. **MATERIALS AND METHODS:** A total of 30 thymuses of 6 weeks gestational age to full term collected from aborted fetuses, were processed for routine paraffin embedding, sectioning and staining with Haematoxylin & Eosin stains. The histological sections were observed under binocular research microscope for age related changes in microscopic structure of the human thymus and representative fields were photographed. **RESULTS:** The earliest specimen of 6 wks gestational age presented the thymus along with parathyroid as ventral primordium of 3rd pharyngeal pouch. Cortex-medulla differentiation and early stage of formation of Hassall's corpuscles were observed at 14 -16 wks. At 36 wks "starry-sky" appearance, an indication of emperipolesis was observed at the cortico-medullary junction. Hyalinization of Hassall's corpuscles, their keratinization and high endothelial venules were seen at full term. **CONCLUSION:** There is a delay of 5 weeks in cortico-medullary differentiation and a delay of 3wks in the time of appearance of Hassall' corpuscles in the present study when compared to the reported studies in literature.

KEYWORDS: Thymic Primordium, Cortico-Medullary Junction, Inter Lobular Septum, Hassall's Corpuscles, Emperipolesis.

INTRODUCTION: Thymus is a primary lymphoid organ playing an important role in the development of immune system by generation of "T- cells". It is a bilobed and encapsulated organ consisting of two pyramidal lobes. It is located in the mediastinum behind the sternum and in front of the pericardium and great vessels of the heart in the adult. The paired epithelial primordia of thymus develop from the ventral part of 3rd pharyngeal pouch along with inferior parathyroid primordia in the region of superior neck in early fetal life. It progressively descends caudally with the descent of heart and aortic sac to reach final destination in the superior mediastinum. Understanding age related changes in the macroscopic and microscopic appearance of the thymus is important in the evaluation of patients with diseases of thymus which are presented as a variety of immune system disorders. There are a few studies on the anatomy of thymus in Indian population.^{1,2} Both were on clinical and immunological aspects, but not on development. The present study is an initial step in illustrating the histological details of developing thymus gland in local population of Andhra Pradesh of South India. Therefore the present investigation was carried out on a sample of thymus glands collected from prenatal aborted embryos and foetuses of different gestational ages.

MATERIALS AND METHODS: A total of 30 thymuses of 6 weeks gestational age to full term were collected from aborted fetuses with normal obstetric history and normal external foetal morphology, received from Govt. Maternity Hospital, Tirupati as it was approved by the institutional ethical

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committee, Sri Venkateswara Medical College, Thirupati, A. P. The thymus glands were obtained by opening the thoracic cavity after observing their location, relations and external morphological features. Small bit of thymus removed from each specimen were processed for routine fixation, paraffin embedding and sectioning for histological examination. The sections were stained with haematoxyline and eosin. The histological sections were observed under binocular research microscope and representative fields were photographed.

RESULTS: In the present study a total of 30 thymuses of 6 weeks of gestational age to full term were collected from aborted fetuses with normal external features and obstetric history. After routine tissue processing the histological sections were observed for age related changes in microscopic structure of the human foetal thymuses of different gestational ages. Serial sections of cervical and thoracic segments of 6wks. and 9 wks. embryos available in the department, were observed for early stages in the development of thymic primordium. The earliest thymic primordium could be identified at 6 wks. (Fig. 1A). At this stage thymic and parathyroid primordia were seen as ventral and dorsal expansions from the ventral wall of 3rd pharyngeal pouch. Ventral thymic primordium was connected to the parathyroid primordium dorsally. At higher-level anastomosing cords of epithelial cells of 3rd pharyngeal pouch with intervening mesenchyme were observed (Fig. 1B). A section at a lower level presented flask shaped thymic primordium with narrow cranial and expanded caudal parts (Fig. 2). In this section darkly stained cords of endodermal cells surrounded by lightly stained mesenchyme were observed. Thymic tissue was not seen in thoracic segments of 6 weeks embryo.

In the serial sections of cervical region of 9 weeks old foetus the developing thymic tissue was observed on either side of trachea and in front of carotid sheath (Fig. 3). At the thoracic segment of 9 weeks foetus, thymus was observed lying adjacent to pericardium. At this stage the gland presented reticular arrangement (Fig. 4).

At 14 wks. gestation thin capsule covered thymic lobules with early differentiation of dense outer cortex, loose inner medulla could be seen (Fig. 5). At 16 weeks clear cortico-medullary differentiation, interlobular septa with blood vessels and aggregations of small eosin stained masses of epithelial reticular cells indicating early stage in the formation of Hassall's corpuscles were observed (Fig. 6, 7). At 20 wks. Thicker capsule and wider inter lobular septa with blood vessels and their branching at the cortico medullary junction was observed (Fig. 8). One Hassall's corpuscle of relatively larger size but still in early stages of formation with a single nucleus was seen (Fig. 9).

At 24 wks. marked increase in the size of lobule and plenty of mature Hassall's corpuscles with whorl like appearance were observed. While cortex showed dense aggregations of lymphocytes medulla exhibited wide distribution of lymphocytes in between epithelial reticular cells (Fig. 10).

From 26 wks. to term the number of Hassall's corpuscles increased continuously (Fig. 11). At 36 weeks of gestation "starry-sky" appearance - an indication of emperiopolesis was observed at the cortico-medullary junction (Fig. 12). Some of Hassall's corpuscles were undergoing hyalinization and keratinization at full term (Fig. 13). High endothelial venules could also be identified (Fig. 14) at full term.

DISCUSSION: The thymic primordium along with parathyroid primordium was observed as an expansion in 6 weeks old embryo, the youngest available in the present study. Although 3rd pharyngeal pouch was not visible in this section, the location of thymus and para thyroid primordia approximated to that of 3rd pharyngeal pouch. While most of the authors reported the first

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appearance of thymus in 6 wks. of gestation,^{3,4,5,6} some indicated that thymic primordium appeared around 4th week.^{7,8,9} According to Varga et. Al,¹⁰ it begins in the 5th week. In the present study the earliest embryo studied was 6 weeks old. Therefore it is not possible to controverse regarding the first appearance of thymic primordia. Cortex-medulla differentiation and early stage of formation of Hassall's corpuscles were observed at 14 -16 wks. gestation in the present study. Varga et. al., (2011) reported cortico-medullary differentiation at 13th week. In the preset study it was observed at 14 weeks. When compared to the studies in west Bengal region of India by Ajita et. al.¹¹ who reported cortico-medullary differentiation at 9-11 weeks there is a delay of 5 weeks in the present study. Varga et. al. (2011), reported noticeably wide interlobular septa at 14-16 weeks which was observed at 16 weeks in the present study.

The first developing Hassall's corpuscle was reported at 13th week by Varga et. al., and 15th week by Ajita et. al., but in the present study it was observed at 16th week which is in agreement with that of Liberti et. al.¹² According to Bodey et. al.¹³ Hassall's corpuscles appear after establishment of lymphopoiesis. They are seen as epithelial pearls of different sizes and shapes as reported by Saradha Kadiresan.¹⁴ The cortex, medulla and cortico-medullary junction are capable of conducting the selection of T-lymphocytes undergoing maturation.^{13,14}

Good number of relatively large Hassall's corpuscles, branching blood vessels at cotico-medullary junction and thicker capsule with wider inter lobular septae were observed in the present study in thymic glands of 20-24 weeks old fetuses. In the literature there are varying reports on the time of appearance of Hassall's corpuscle - as early as 8th week,¹⁵ 9th week,¹⁶ at 10th week,¹⁷ at 11th week,¹⁸ between 15th and 16th week.¹⁹ Liberti et. al., and Varga et. al., reported these findings at 16-18 weeks. There were also published reports on their presence between 17 -30 weeks of gestation.^{4,9} According to Bodey and Kaiser (1997),²⁰ they develop in the second part of 3rd lunar month in human fetuses with greatest development between 6th to 10th lunar month.²¹ In the present study, the presence of Hassall's Corpuscles were observed only from 15th week of gestation that is during late part of 4th lunar month with a delay of 3 wks. When compared to that reported in literature.

Liberti et al (1994) reported that the mean areas of the Hassall's Corpuscles increased with the foetal age, with the greatest observable difference between 16th to 19th and 20th to 23rd weeks. In the present study Hassall's Corpuscles increased in number and size during 17th to 24th week. Between 26th weeks to full term the hyalinization and keratinization of Hassall's corpuscles and "Starry sky appearance" at cortico-medullary junction were observed in the present study. Similar observations were reported earlier for the fetuses of corresponding age.^{4,9,22}

CONCLUSION: In the present study we could present the microphotographic appearance of developing thymus in fetuses of 6th week to full term gestation. There is a delay of 5 weeks in cortico-medullary differentiation in the present study on south Indian fetuses when compared to those of west Bengal region of India. There is a delay of 3wks. in the time of appearance of Hassall' corpuscles in the present study when compared to the reported study in literature. These differences can be due to the difference in ethnicity, nutritional and environmental factors.

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Fig. 1A

Fig. 1B

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8

Fig. 9

Fig. 10

Fig. 11

Fig. 12 Thymus 36 weeks – wide lobules, clear interlobular septa, clear cortico medullary demarcation, starry sky appearance (arrow) at the corticomedullary junction X 40.

Fig. 12

Fig. 13 Thymus Full term - Multinucleated and keratinized Hassall's corpuscles X 200.

Fig. 13

Fig. 14 :Thymus - full term - – A single multi lamellated Hassall's corpuscle, two epithelial reticular cells (arrows) Two high endothelial venules (HV)- X 400-interference contrast

Fig. 14

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