Histogenesis of human fetal thymus in different gestational age groups
Prabavathy G
Assistant Professor of Anatomy, Mahatma Gandhi Medical College Hospital and Research Institute, Puducherry

Abstract

Background & Aim: The present study is aimed to document the histological changes of thymus gland during different weeks of gestation in human fetuses.

Materials & methods: Fifty-three human fetuses (30 males and 23 females) of different age groups ranging from 9th to 40th gestational week were procured from the Department of Obstetrics and Gynaecology, Sree Balaji Medical College and Hospital, Chennai and from Mahatma Gandhi Medical College, Puducherry. The fetuses were dissected. The thymic tissues thus obtained were immersed in 10% formalin for one week. After proper fixation, the tissue was subjected to routine processing and then the sections were stained with Haematoxylin and Eosin for microscopic examination.

Results: Formation of lobules had started at 9th week and distinct formation of lobules was observed during the 12th week. The differentiation of the cortex and the medulla became well distinguished from the 14th week onwards. Presence of Hassal’s Corpuscles was observed from 14th week and was found in all sections from 15th week onwards. Hassal’s Corpuscles increased in number, size and maturity with the increase in the gestational age. Conclusion: Familiarity with the embryology, anatomy, and dynamic physiology of the thymus is essential for clinicians to avoid unnecessary imaging or invasive procedures.

Key words: Lobulation, Hassall’s corpuscles, Human fetuses

Introduction

The thymus is a primary central lymphoid organ and a key regulator of the immune system. The lymphocytes of the thymus are called T-lymphocytes, and they are responsible for the cell mediated immunity of the body. The main bulk of the human thymus is situated in the anterior mediastinum. The thymus grows rapidly during the embryonic life and the childhood, reaches its maximum absolute size by the time of puberty. Thereafter the growth ceases and it involutes gradually until the old age, when the gland is often smaller than at birth. This however, may be disrupted in children living with HIV and other severe illnesses where the thymus may involute at an early stage. This age involution is shown by a decrease in the overall weight of the organ associated with lymphoid tissue atrophy and replacement by adipose tissue.

The growth hormone of the pars anterior and the thyroid hormone, both stimulate the growth of the thymus gland. Most of the steroid hormones on the other hand, if present in sufficient quantities in the blood stream, tend to bring about the involution of the gland. The growth curve suggests that the organ is of primary importance in the early life, and most studies of its structure have concentrated on this period of its development. There is, however, no certainty that these findings are the true representative of the normal structure of the thymus among the living individuals since ‘stress involution’ may occur rapidly in any terminal illness, although it is generally assumed that involution is minimal when the terminal illness lasts less than 24 hours.

The thymic components along with the microenvironment of the thymus gland are responsible for terminal T-cell differentiation and the development and maintenance of cellular immunity. So there is a specific and characteristic histological alteration of the thymus gland in the acquired immune deficiency syndrome (AIDS). Knowledge of anatomical and histological features of the normal thymus is of helpful in analysing the pathology of thymic neoplasia. This study is aimed to document the histological changes of thymus gland at different weeks of gestation in human fetuses.
Materials and methods

Fifty-three human fetuses (30 males and 23 females) of different age groups ranging from 9th to 40th gestational week were procured from the Department of Obstetrics and Gynaecology, Sree Balaji Medical College and Hospital, Chennai and from Mahatma Gandhi Medical College, Puducherry with informed and written consent from the parents.

These fetuses were obtained by termination of pregnancies under the Medical Termination of Pregnancy Act of India 1971, spontaneous expulsions & Stillbirths, without any congenital anomalies. Crown-Rump Length and body weight of the fetuses were measured to assess the Gestational age. Thereafter all fetuses were fixed in 10% formalin for 10 days. Then the fetuses were dissected. The thymic tissues thus obtained were immersed in 10% formalin for one week. After proper fixation, the tissue was subjected to routine processing and then the sections were stained with Haematoxylin and Eosin.

The specimens of the human fetuses utilized in the present study were categorized into the following three groups according to gestational age:

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (weeks)</th>
<th>No. of fetuses</th>
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<tbody>
<tr>
<td>Group I</td>
<td>9-12 wks</td>
<td>12</td>
</tr>
<tr>
<td>Group II</td>
<td>13-24 wks</td>
<td>18</td>
</tr>
<tr>
<td>Group III</td>
<td>25-40 wks</td>
<td>23</td>
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</table>

Results

Using Haematoxylin and Eosin stain, the observations at different gestational weeks were as follows:

Group I (9-12 wks)

The gland was seen to be made up of lymphocytes with a fine capsule. Lobulation of the gland had started at this stage (Fig 1). The trabeculae associated with blood vessels were observed from the 10th week onwards. There was no distinct differentiation of cortex and medulla. Hassall’s corpuscles were not observed at this stage.

Group II (13-24 wks)

The gland was seen to be surrounded by the connective tissue capsule. The lobulation of the thymus gland was still advancing at this stage. The connective tissue trabeculae started developing between the lobules (Fig 2). The number of lobules increased with the increase of gestational age. Presence of blood vessels in between the lobules which became more extensive beyond 18 wks. Cortex and medulla were recognizable from 14th week onwards (Fig 3). The peripheral part of each lobule heavily infiltrated with lymphocytes is its cortex and the more central part of the lobule which is lightly stained, that does not contain so many lymphocytes is its medulla.

No Hassall’s Corpuscles could be seen till the 13th week. By 14th week, the Hassall’s Corpuscles were clearly seen in the medulla in some of the sections. The Hassall’s corpuscles were visible in all sections from the 15th week onwards and it increased in number and size with the increase of gestational age. Monocytes and Macrophages were also seen at this stage.

Group III (25-40 wks)

Each lobe was surrounded by connective tissue capsule which is clearly evident. This extends into the substance of each lobe to form septa and dividing the lobes into lobules (Fig 4). Each lobule has an outer darkly stained Cortex and an inner lightly stained Medulla. The thymic tissue of each lobule is continuous in the more central part of each lobe with that of other lobules. The trabeculae were seen to be extending up to the cortex, leaving the medulla remain undivided. The blood vessels also had become distinct.

The parenchyma of the cortex seen to be consisting of dense population of lymphocytes of all sizes, closely and uniformly packed. These cells occupy the spaces in the cyto-reticulum and obscure it. Medulla is clearly demarcated from the cortex. The lymphocytes are less in number and hence the cyto-reticulum is seen well. The medulla of the adjoining lobules is continuous. The central core of the medulla extends into each lobule.
Fig. 1: Human Fetal Thymus (11 wks) showing the Capsule and red arrow indicates the lobule formation (H&E stain 10x)

Fig. 2: Human Fetal Thymus (14 wks) showing the capsule with trabeculae (red arrow) extending into the gland (H&E stain 10x)

Fig. 3: Human Fetal Thymus (14 wks) showing the lobule with the cortex (C) & medulla (M) (H&E stain 10x)

Fig. 4: Human Fetal Thymus (36 wks) showing the Capsule with the well developed inter lobular trabeculae (red arrow) (H&E stain 10x)

Fig. 5: Human Fetal Thymus (38 wks) showing the well developed cortex (C) & medulla (M). Red arrow indicates the Hassall's Corpuscle. (H&E stain 4x)

Fig. 6: Human Fetal Thymus (36 wks) showing the Hassall's Corpuscles (Red arrow) of different sizes & maturity (H&E stain 10x)
There is a sharp demarcation between the cortex and the medulla forming a clear cortico-medullary junction (Fig 5).

**Hassall's corpuscles**

Hassall's corpuscles were seen as epithelial pears of various sizes and shapes. Various shapes of the Hassall's corpuscles were observed, i.e. round, oval and irregular. Some Hassall's corpuscles were observed to be cystic i.e. filled with degenerated material. Compound type of Hassall's Corpuscles (fusion of two corpuscles) was also noted. The size of the corpuscle was also highly variable (Fig 6). Majority of the Hassall's Corpuscle were found in the medulla. They are also seen in other sites such as cortex, septa and cortico-medullary junction. Some of them were seen close to blood vessels. Some Hassall's Corpuscles in formative stage were also noted. The number of corpuscles increased with the increase in the gestational age of the fetus.

**Discussion**

The authors have reported different findings in relation to the structure of the thymus.

Williams et al. have reported the time of appearance of lymphocytes during the 8th week, and at 9th week by Hamilton & Mossman, VonGaudecker and Ajita et al. In the present study, the authors observed the presence of the lymphocytes from the 9th week onwards. Ghali et al. and Harr reported regarding the lobulation of thymus gland during the 10th and 12th week respectively. Ajita et al. reported that the Lobulation was observed at 9th week and completed by the 12th week. Whereas, in the present study, lobules had started forming during the 9th week and the formation of lobules become clearly evident after 12 wks.

Differentiation of the cortex and medulla of the thymus was reported at 11th week by Ghali et al., at 12th week by Hayward at 14th week by Harr and Lobach & Haynes. Whereas the differentiation of the cortex and medulla became well distinguished from the 14th week onwards in the present study. Metcal measured the width of cortex in relation to width of the medulla, and assessed that the ratio of the cortex to the medulla is 9:1. In the present study, it was found that the cortex occupied 80% of the lobule and medulla occupied the remaining 20%.

The time of appearance of Hassall's Corpuscles were reported as early as 8th week by Fawcett, from the 9th week by Gilhus et al., during the 10th week by Williams et al., at 11th week Ghali et al., between 15th and 16th week by Lobach & Haynes. In the present study, the presence of Hassall's Corpuscles was observed from 14th week onwards and was present in all sections from 15th week onwards. Liberti et al. reported that the mean areas of the Hassall's Corpuscles increased with the fetal age, with the greatest difference observed between 16th-19th week and 20th-23rd week fetal age groups. Whereas, the Hassall's Corpuscles increased in number, size and maturity with the increase in the gestational age in the present study.

**Conclusion**

Familiarity with the embryology, anatomy, and dynamic physiology of the thymus is essential for clinicians to avoid unnecessary imaging or invasive procedures. With the advent of intensive chemotherapy regimens for a variety of cancer syndromes, and the discovery that the infection with HIV leads to severe loss of T lymphocytes, has brought the need to understand the role of the human thymus in reconstitution of the immune system among the adults. Thymic tumours are of considerable interest to the clinicians and to the pathologists, because of their association with other conditions.

**References**

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Histogenesis of human fetal thymus – Prabavathy


Address for Communication
Dr. Prabavathy, G.
Assistant Professor of Anatomy, Mahatma Gandhi Medical College Hospital and Research Institute, Puducherry - 607 402.
Mobile : 09003833409
e-mail ID : prabajai1986@yahoo.com