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# Pancreatic Changes Associated with Cases of Thymic Dysplasia*

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## *Introduction*

In the last two decades, it has been recognized that the immunological competence in man, as in certain animal species, has two functionally separate compartments of lymphoid cells; each of these having separate immunological responses, namely a cellular and a humoral one.[1]

By now numerous immunological deficiency entities showing defects in each system separately and/or both, have been defined. Thymic dysplasia, represents the hereditary clinical counterpart of chickens, subjected to the extirpation of both the thymus and the bursa Fabricius at hatching. These patients exhibit combined humoral and cellular immunodeficiencies, show failure to thrive, have recurrent diarrhea, and present life-threatening bacterial, viral and fungal infections.[2]

Also in recent years, among patients suffering from thymic dysplasia, in addition to lymphoid tissue pathology, involvement of other systems and organs have been reported. Among these, congenital megacolon, pancreatic insufficiency, bone marrow dysfunction, dyschrondroplasia and cartilage-hair hypolasia can be cited.[3-7]

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In our survey of the literature, with the exception of a single report where thymic alymphoplasia and mucoviscidosis[6] were both present in two siblings, we have not encountered any studies concerning histopathological changes of the pancreas in association with thymic dysplasia. We have ohserved that in thymic dysplasia, histological changes resembling cystic fibrosis were occasionally seen.[7,8] The purpose of this study is to present the histopathological findings of the pancreas in 22 cases of thymic dysplasia diagnosed at post-mortem examination and to discuss, if any, the possible relation existing between the pancreas and the thymus.

## *Material and Methods*

Among the 1,000 necropies performed between 1966-1972 at the Dept. of Pediatric Pathology at the Hacettepe Children's Hospital, there were 22 cases showing thymic dysplasia (Figure 1,2). The general clinical pathological characteristics of these cases are summarized in Table I. Since systemic post-mortem examination was available it has been possible in all cases to carry out extensive histological examination of various organs and tissues. Paraffin block sections were prepared from the tissue samples obtained from the head, body and tail of the pancreas. Each block was then stained with hemotoxylen-eosin, silver stain, and PAS. A summary of the histological findings seen in the pancreas is shown in Table II.

## *Findings*

As seen in Table II, the microcytic dilatation of the acini which shower some degree of atrophy of their lining epithelium, was present in 16 of the 22 cases. In 12 of these the occurrencè was infrequent. In 14 of the cases there was also an inspissated eosinophilic material in the lumina of these acini, which gave positive PAS reaction and resisted to digestion with diastase (Figure 2-4). In of these 14 cases a mild degree of fibrosis was found in the interstitial tissue.

In the retrospective study of the clinical charts, there was only one case in which the electrolyte values of sweat were determined and which was found to be within normal limits. In 4 of these 14 babies, below 6 months of age, although products of full-term pregnancies, morphologic appearance of the pancreas suggested a delay in maturation of the gland. In addition, other findings showed the presence of inclusions in the

**Figure 1**

Thymus of an infant in our series with hereditary thymic dysplasia. There are no Hassal's corpuscles, or corticomedullary differentiation, lymphocytes are decreased.

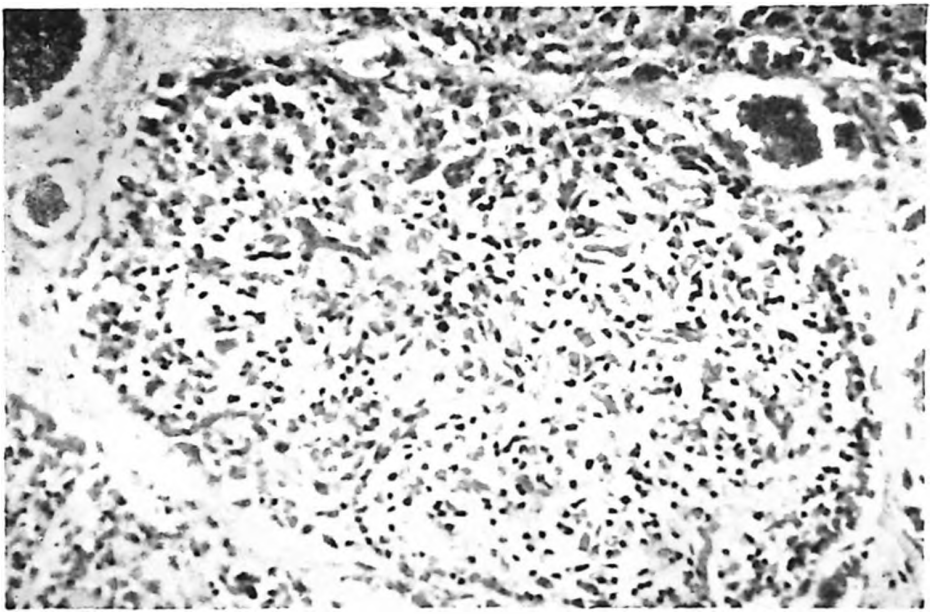

**Figure 2**

Thymus of another case showing, no Hassal's corpuscles or lymphocytes. (Hematoxylin eosin x 75)

## TABLE I

CLINICO-PATHOLOGICAL FINDINGS IN 22 CASES OF THYMIC DYSPLASIA

| | No. of Cases | Associated Diseases | | No. of Cases |
|---|---|---|---|---|
| Family History Complaints | 14 | I. Infections | a) Viral ..... (CMY** Giant cell pneumonia) | 9 |
| 1. Fever ..... | 10 | | b) Fungal ..... (Moniliasis, Cryptococcosis) | 4 |
| 2. Cough ..... | 7 | | | |
| 3. Diarrhea ..... | 12 | | c) Bacterial ..... | 14 |
| 4. Failure to thrive ..... | 10 | | d) Parasitic ..... (Toxoplasmosis) | 1 |
| Blood Findings | | II. Leukemia ..... | | 1 |
| Anemia ..... | 12 | III. Cerebro-Hepato-renal syndrome ..... | | 1 |
| Lymphopenia ..... | 10 | IV. Dyschondroplasia ..... | | 1 |
| Neutropenia ..... | 1 | | | |
| GVH* Reaction ..... | 3 | | | |

* Graft-versus-host.

** Cytomegalovirus

pancreatic acinar cells in two cases; however evidence of viral infection were found in other organs. The only case which revealed leukemic infiltration of its pancreas, was that of a 3 and half year-old boy, whose growth was severely retarded and diagnosis of leukemia was based, at postmortem examination on the bone marrow and visseral infiltration. In our series one other case was clinically diagnosed as periodic neutropenia and malabsorption syndrome; in addition to pancreatic changes resembling cystic fibrosis, the postmortem examination, even though performed 48 hours after death, revealed well preserved intestinal villie and mucosal glands. No evidence of autolysis of the mucosa could be found, although a few crypt ulcers were present.

## TABLE II

### THYMIC DYSPLASIA AND ASSOCIATED PANCREATIC HISTOPATHOLOGICAL FINDINGS IN 22 AUTOPSIED CASES AT HACETTEPE CHILDREN'S MEDICAL CENTER

| | | No. of Cases |
|---|---|---|
| I. | Exocrine Pancreas | |
| | 1. Microcytic dilatation of acini with atrophic changes of epithium | |
| | a) Occasional | 12 |
| | b) Mild | 4 |
| | 2. Inspissation of eosinophilic material, in the lumina of cystic acini | 14 |
| II. | Interstitial Tissue | |
| | 1. Fibrosis, mild | 4 |
| | 2. Interstitial pancreatitis | 4 |
| | 3. Leukemic infiltration | 1 |
| III. | Others | |
| | 1. Immaturity of glandular pancreas as compared with the age | 4 |
| | 2. Cytoplasmic inclusion of acini cells | 2 |
| IV. | No pathology | 2 |

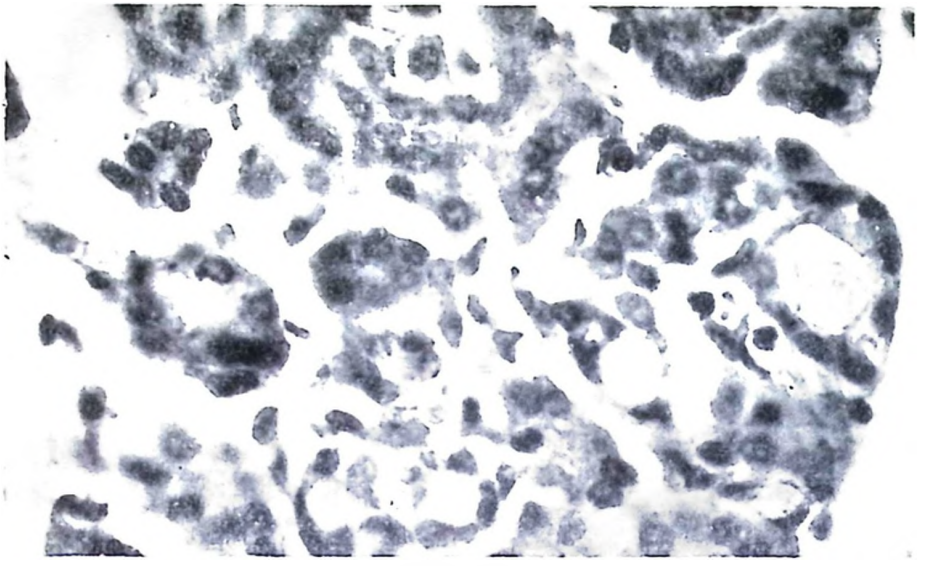

**Figure 3**

Pancreas showing dilatation of acini with minimal inspissated material in their lumina. (Hematoxylin eosin x 75)

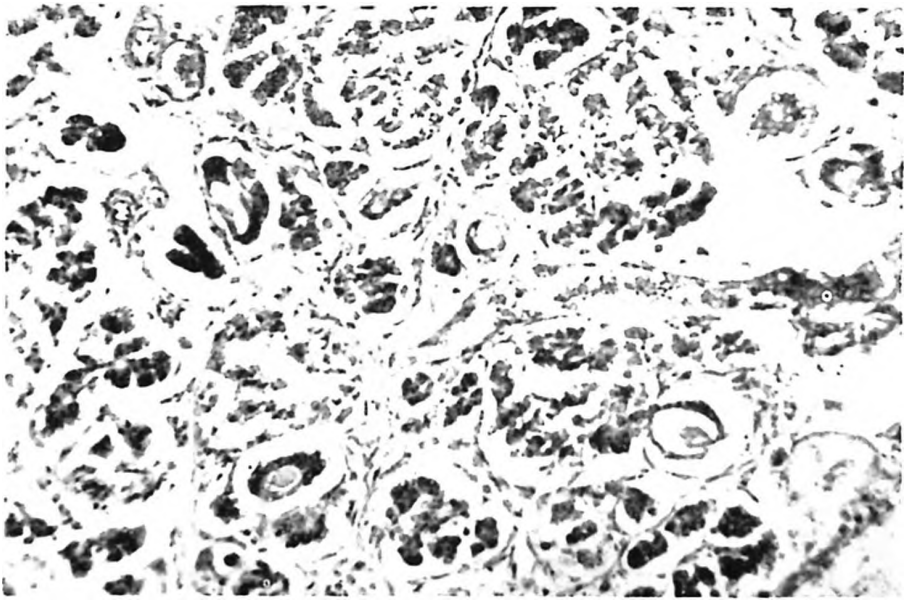

**Figure 4**

Pancreas showing dilatation of acini with inspissated material and fine interstitial fibrosis.

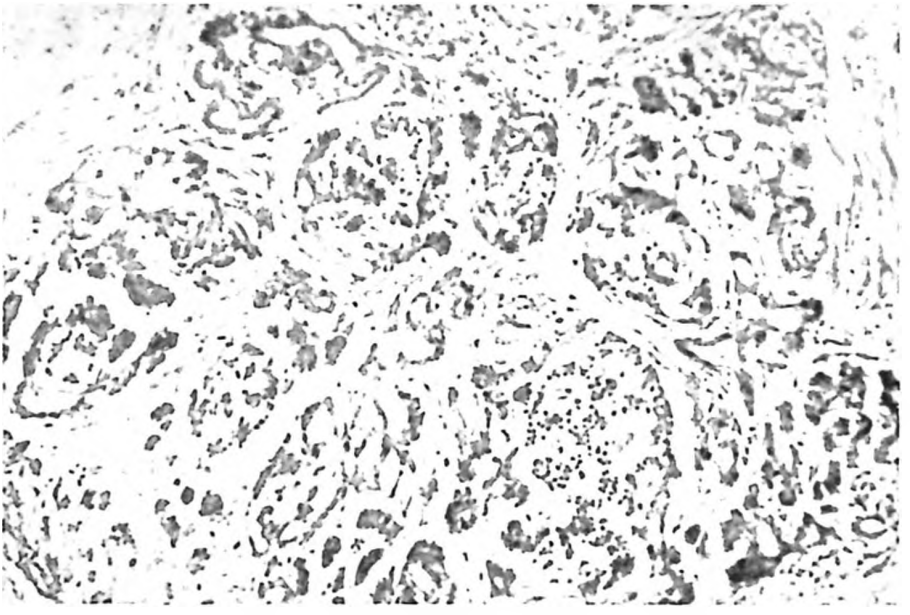

**Figure 5**

Pancreas showing dilatation of acini with atrophy of the epithelial lining cells and moderate interstitial fibrosis. (Hematoxylin eosin x 75)

## *Discussion*

In some cases of immunological deficiency disease combinations of congenital megacolon, pancreatic insufficiency, bone marrow dysfunction and dyschondroplasia have been reported in individual patients. Mc Kusick earlier reported that an intestinal malabsorption and congenital megacolon, as well as the consistent finding of neutropenia, were seen in some patients with cartilage-hair hypoplasia.[3] The cause of malabsorption was not investigated in these patients. The pancreatic and bone marrow deficiency syndromes have been defined by Schwachman et al,[9] in which a combination of malabsorption and neutropenia is present. The chloride level in sweat is within normal limits, and in these patients, infections such as pneumonia, meningitis and osteomyelitis are observed more frequently than expected. In this syndrome, the information pertaining to the histopathological changes in the pancreas is confined to a couple of other cases and has been interpreted as congenital lipomatosis and congenital atrophy of the exocrine pancreas.[10] If there is any relationship between pancreatic insufficiency and the bone marrow noted in these patients, the mechanism of the relationship is still to be elucidated. In normal individuals whose pancreas has been extirpated

either because of a cyst or traumatic injuries, bone marrow deficiency due to a resictic pancreas is not observed. As shown in Table I, one patient in our series had periodic neutropenia. The retrospective evaluation of conspicious morphological changes in the pancreas and the small intestines of this case, which also showed clinical findings of malabsorption, have suggested the presence of pancreatic achilia.

Similar changes of the exocrine pancreas have also been observed in patients on cortisone therapy and in chronic uremia cases.[11, 12] In the cortisone treated cases it was reasoned that the cortisone had thickened the pancreatic secretions. In the cases of our series, an incidence of chronic uremia has been observed.

Atrophy of the acini of the pancreas can also be seen in chronic protein malnutrition, especially in Kwashiorkor.[13] Although Kwashiorkor which yields typical clinical and laboratory findings was not present in any of our cases, chronic malnutrition was not altogether eliminated. The pancreatic changes observed in our cases resemble the changes seen in the cases of mucovisidosis in early infancy, although in general our cases revealed no extra-pancreatic morphological findings to establish mucovisidosis. Therefore we did not think that our cases of thymic dysplasia were associated with cystic fibrosis. It is interesting to note that Beltaos and McCreadie[6] have previously reported two siblings with thymic dysplasia, both of whom were diagnosed as having mucovicidosis in the light of pancreatic histopathological findings. However they also recorded that in one sibling a sweat test resulting in normal chloride levels on two occasions (15.5 and 8.2 mEq/lt), and this sibling also showed strongly positive triptic activity in the stool. These findings contradict a diagnosis of cystic fibrosis.

The fact that these pancreastic changes were not rare in our cases of thymic dysplasia, suggests the possibility that besides secondary changes, these may be associated with the thymus also. Such a frequent association of combined immunodeficiency with malabsorption and pancreatic insufficiency, cannot be explained by coincidence alone. On the other hand, if these pathological manifestations were due to the absence of an intact thymus during intrauterine life, (in other words, if the thymus were dysplastic), it would be expected that similar pancreatic changes be encountered in patients with the DiGeorge Syndrome in which the thymus is either absent or hypoplastic. DiGeorge himself mentioned the existence of pancreatic changes suggesting cystic fibrosis in one of this four cases of DiGeorge Syndrome; but the sweat chloride level was normal in this particular patient.[14]

At present we have an explanation for this association. One may speculate that pancreatic pathology may just be one of the components due to maldevelopment of mesenchymal tissue which results in a common gene or genes, causing thymic pathology. We consider that in our study we have for the first time drawn attention to the relationship between the pancreas and the thymus in cases of thymic dysplasia.

*Summary*

Morphological changes of the pancreas were investigated in 22 necropsy cases of thymic dysplasia. In the majority of cases exocrine pancreas showed cystic acinar dilatation with epithelial atrophy and precipitation of eosinophilic material in their lumina and additional mild interstitial fibrosis. The relation of these pathological findings resembling cystic fibrosis and the absence of an intact thymus has been discussed.

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