

—Original Article—

THYMUS ABNORMALITIES IN ULCERATIVE COLITIS
—COMPARATIVE STUDY WITH OTHER
AUTOIMMUNE DISEASES

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Summary

Since the thymus is thought to play an important role in the pathogenesis of ulcerative colitis, thymic abnormalities were studied on 18 cases of ulcerative colitis by using pneumomediastinography and histopathological examination. We have compared the thymic abnormality of ulcerative colitis with that of 104 cases of variety of autoimmune diseases.

The denser and larger thymic shadow was seen in ulcerative colitis and this finding was same as in other autoimmune diseases. But the thymic size in ulcerative colitis was the largest in all examined autoimmune diseases.

The incidence of thymic lymphoid follicle formations in ulcerative colitis was significantly higher than that of accidental death and this high incidence of lymphoid follicle formation is similar to other autoimmune diseases. We suggested that ulcerative colitis might be caused by the abnormal thymus dependent system.

Key Words: *ulcerative colitis, thymus, pneumomediastinography, autoimmune disease.*

Introduction

Ulcerative colitis is a chronic disease mainly affecting the large bowel. Autoimmune pathogenesis in this disease has been postulated by some investigators. Since the thymus is thought to be a central organ in the immune system of men and animals, a number of investigators have focused their efforts on the elucidation of thymic role in the pathogenesis of autoimmunopathy. In 1936, Condorelli¹⁾ first introduced the technique of pneumomediastinography showing its usefulness in visualization of persistent or hyperplastic thymus and otherwise undetectable tumor. In the present study, thymic abnormalities were studied on ulcerative colitis by using

pneumomediastinography. The purpose of the study is to evaluate the usefulness of pneumomediastinography in the detection of thymic abnormalities including occult thymoma and to correlate the pneumomediastinographic findings with histopathological changes of the thymus in ulcerative colitis in contrast with other autoimmune diseases.

Materials and Methods

Patients: Nineteen patients with ulcerative colitis were studied. Eleven patients were female and eight were male. The mean age of the patients was 31 years old. Thirteen patients were performed thymectomy. Ulcerative patients were compared with 104 patients

with other autoimmune diseases. Patients consist of 51 cases of myasthenia gravis, 31 cases of Behçet's diseases, 12 cases of systemic lupus erythematoses, 7 cases of Hashimoto's diseases and 3 cases of Sjögren's syndrome.

Pneumomediastinography²⁾: The approach through the supra-sternal fossa was used for pneumomediastinography. No special apparatus was necessary for this procedure except for a three-way stop-cock, a puncture needle, a 100 ml syringe, a small oxygen container and pieces of rubber tubing. Local anesthesia was applied to the supra-sternal region with the neck extended in a supine position. The puncture needle held at an angle of about 120 degrees was then inserted in the supra-sternal fossa toward the posterior surface of the manubrium of the sternum to a depth of 3-4 cm. Oxygen gas was then administered to the fossa through the syringe very slowly, at a rate of about 10 ml per minute up to 150-300 ml. At 10-15 minute intervals, the patient was asked to lie on his right and left sides alternatively before taking X-ray pictures,

so that the administered gas could be distributed diffusely around the area. In addition to anteroposterior, lateral, and oblique X-ray pictures, five lateral tomograms are obtained at a distance of 1 cm to the right and left of the midline respectively.

Diagnosis by pneumomediastinography³⁾: The thymic shadow was classified by the following criteria.

1) Shape and location

The thymic shadows were classified into ten types according to the shape and location (**Fig. 1**). Type I to III is located at the posterior part of the anterior mediastinum, type IV to VII is located at the middle part of the anterior mediastinum and type VIII to IX is located at the anterior part of the anterior mediastinum. Type X means the occult thymoma which is not shown by plain X-ray film and tomography.

2) Size

The size of the thymus on pneumomediastinograph was estimated by measuring the largest part on the lateral tomogram as follows.











Location of the thymus diseases (cases)	Posterior			Middle				Anterior		Occult Thymoma (X)
	I	II	III	IV	V	VI	VII	VIII	IX	
Ulcerative colitis (18)										
Myasthenia gravis (46)	18	11	5	0	45	5	11	5	0	0 Cases
Behçet's disease (31)	9	9	9	2	61	4	0	4	2	5
S L E (12)	25	16	7	0	45	0	0	7	0	0
Hashimoto's disease (7)	8	17	8	0	25	0	8	34	0	0
Sjögren syndrome (3)	14	0	29	0	57	0	0	0	0	0
Total (117)	0	0	0	0	67	0	33	0	0	0
	15	11	8	1	50	3	4	7	1	5 Cases

Fig. 1. Types of shape of the thymus and their incidence in various autoimmune diseases. (122 cases) (%).

The thymic outline was traced onto paper of standard thickness and the weight of this template was correlated with the weight of 1 sq cm of the same paper to obtain the area. And we also measured the widest part of the thymic shadow on the lateral tomogram.

3) Density

Density of the thymic shadows were divided into three grades:

a; implies same density of that of the heart.

b; implies same density of that of the vertebra.

c; implies intermediate density of a and b.

Histopathological study³⁾: The thymuses were extirpated through the supra-sternal notch as previously described⁴⁾. The extirpated thymuses were fixed in 10% formalin and paraffin sections were stained with hematoxylin and eosin.

Results

Fig. 2 shows a pneumomediastinogram of 42 years old male patient. Right side is a simple lateral projection and left side is a tomogram in lateral projection of pneumomediastinography. We can see the denser

thymic shadow (type V, density "a") even in the patient aged over 40. **Fig. 3** shows lymphoid follicle formation found in the thymus extirpated from same patient.

1) Shape and location (**Fig. 1**)

In ulcerative colitis the most frequently encountered type (45%) was of tongue-like shape localized in the middle of the anterior mediastinum (type V) and this was followed by type I (18%). Type V was found in 61% of myasthenia gravis and 45% of Behçet's disease. Type I plus type V (type I and type V were of same shape but different in location and width.) was found in 63% of ulcerative colitis, 70% of myasthenia gravis and 70% of Behçet's disease. Type I was found more frequently in ulcerative colitis and Behçet's disease. Type VII was found in two cases of ulcerative colitis, a case of Sjögren's syndrome and a case of SLE. Type X (occult thymoma) was found in 5 cases of myasthenia gravis, but we could not find the occult thymoma in ulcerative colitis.

2) Size (**Fig. 4**)

In ulcerative colitis, thymic size on pneumomediastinograph was the largest in autoimmune

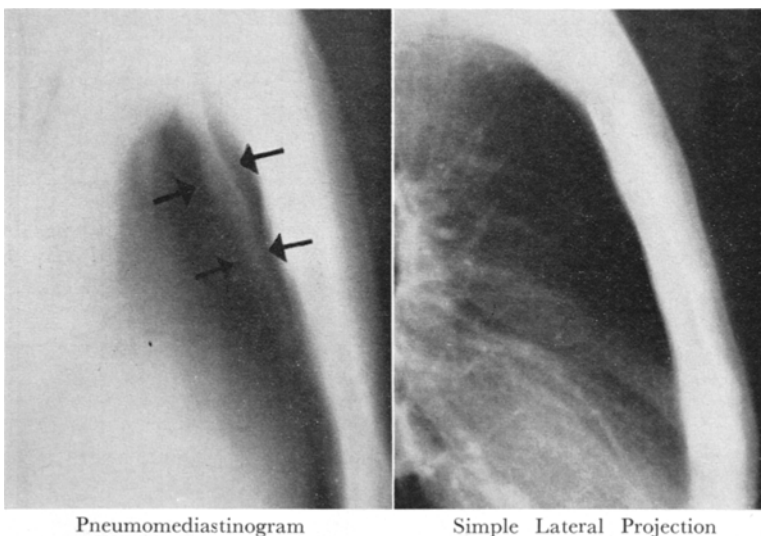


Fig. 2. Case H.K. 42 Y.O. Male, Ulcerative colitis.

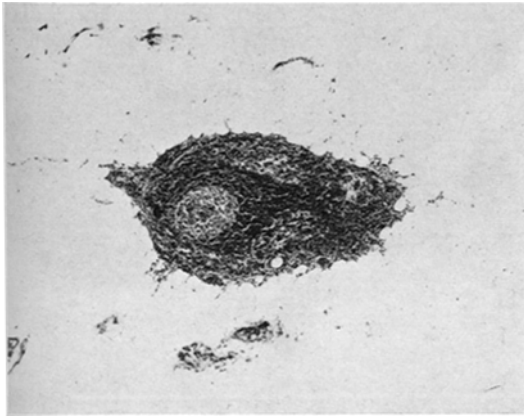


Fig. 3. Lymphoid follicle formation in the thymic medulla.

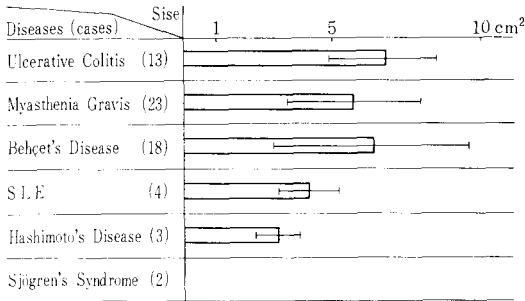


Fig. 4. Size of the thymus in various autoimmune diseases.

diseases and its size was 6.30 ± 1.77 sq cm (Mean \pm SEM). In other autoimmune diseases the thymic size was 5.7 ± 2.19 sq cm in myasthenia gravis, 6.26 ± 3.24 sq cm in Behçet's disease, 3.15 ± 0.73 sq cm in Hashimoto's disease, 4.25 ± 1.13 sq cm in SLE, and 5.76 and 4.36 sq cm in Sjögren's syndrome.

3) Density of the thymic shadows (**Fig. 5**)

Density of the thymic shadows was divided into three grades by previously described criteria. Density "a" occupied 78% of 18 cases of ulcerative colitis. But in other autoimmune diseases density "a" occupied from 93 to 100% except Hashimoto's disease.

4) Relationship between normal and abnormal thymus on age involution

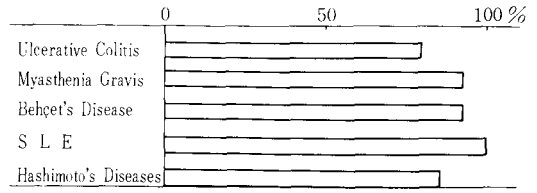


Fig. 5. Incidence of the density "a" in various autoimmune diseases.

Fig. 6 is a diagram to illustrate the relationship between age and age involution of normal thymus modified from Hammar and Boyd⁵⁾. The solid triangle means the extirpated thymus of ulcerative colitis. The solid circle means the extirpated thymus of myasthenia gravis. The open square and circle mean the extirpated thymus of Behçet's disease and the open square indicates the cases under treatment with prednisolone (PSL) and the open circle indicates the cases under treatment without PSL. The solid line indicates normal age involution curve. As shown in this diagram, 64% of ulcerative colitis, 93% of myasthenia gravis and 63% of Behçet's disease were below the solid line. This finding suggests that the thymic involution is delayed in ulcerative colitis, myasthenia gravis and Behçet's disease.

5) Histopathological examination of extirpated thymus (**Fig. 7**)

In ulcerative colitis, thymic lymphoid follicle formation was found in 8 cases out of 13 patients (61%). This incidence is significantly higher than that of accidental death ($p < 0.001$). And this high incidence of lymphoid follicle formation is similar to other autoimmune diseases such as myasthenia gravis (71 out of the 92 cases, 77%), Behçet's disease (20 out of the 43 cases, 46%), SLE (5 out of the 9 cases, 56%) and autoimmune hemolytic anemia (3 out of the 3 cases, 100%). There was no significant relationship between the thymic shadows and histopathological findings in ulcerative colitis.

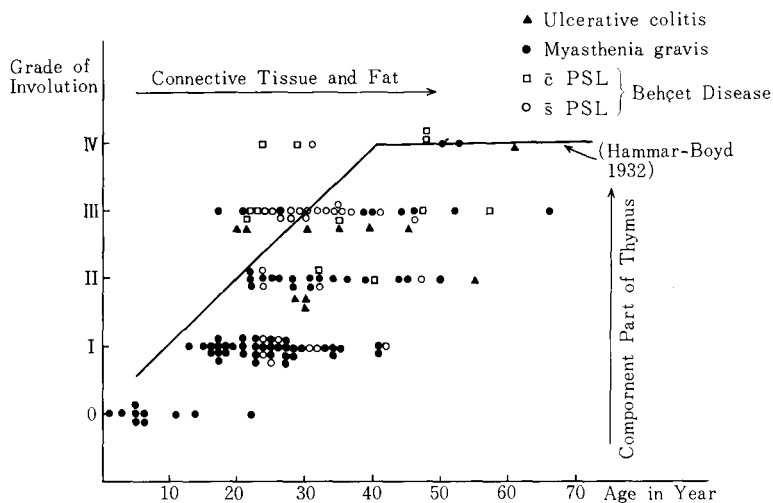


Fig. 6. Relationship between age and age involution of the thymus in ulcerative colitis myasthenia gravis and Behçet's syndrome.

Fig. 7. Number of subjects and incidence of thymic lymphoid follicles in thymectomized cases.

	No. cases studied	No. cases with lymphoid follicles	% positive
Ulcerative colitis	13	8	61.5*
Behçet's disease	43	20	46.5
Myasthenia gravis	92	71	77.5
Hashimoto's thyroiditis	15	6	40.0
SLE	9	5	55.6
AIHA	3	3	100.0
Sjögren's syndrome	2	2	100.0
Total	177	115	64.9
Accidental death	71	12	16.9

*P<0.001, X- = 12.1.

Discussion

Pneumomediastinography was first described in 1936 by Condorelli¹⁾ and soon became an important diagnostic tool among the European countries. Although it is very useful for the demonstration of the thymus, this technique has not gained wide acceptance in Japan until when Tsuchiya²⁾ first introduced this technique in 1958. Although there are several ways of insufflation of gas into the mediastinum as described by Simecek⁶⁾, the retrosternal

method appears most useful to demonstrate the thymus, because we can see not only the anterior mediastinum but also the posterior mediastinum by changing the position of the patient. No special apparatus is necessary for this technique. We recommend to use the oxygen for visualization, because the oxygen was absorbed quickly within 4-6 hours. The patient might complain of slight sensation of compression in the epigastric and diaphragmatic regions at short time and

usually no dangerous side effect occurs. However some authors described other complications such as air embolism, pneumothorax, mild fever and myasthenic crisis^{6,7}.

Hare et al.⁸) and Benendo-Kapuścińska et al.⁷) described about location of the thymic shadows. According to Benendo-Kapuścińska et al., the thymic shadows were divided into six types and most frequent type (61%) was a "tongue-like" one, long and flat in myasthenia gravis. This thymic shadow corresponds to type V of our classification. They also described that the second most frequent shape was "band-like" form which corresponds to our classification type VII. We observed that type in 4 cases of ulcerative colitis, SLE and Sjögren's syndrome. These 4 patients are over 40 years old and were not treated with PSL. So we suggest that these thymus contained large amount of fatty tissue comparable to age involution, but remaining several narrow bands were abnormal findings according to histopathological examination. It is suggested from the present study that type V is a characteristic shadow in autoimmune diseases including ulcerative colitis, however type I was relatively frequently found in ulcerative colitis and Behçet's disease. Since these two diseases were very similar in clinical findings, we suggest that these two diseases have similar thymic abnormalities.

There were several reports concerning the thymic size on pneumomediastinography⁹⁻¹². Nakata et al.¹²) reported that the largest size was seen in Hashimoto's disease and the second in ulcerative colitis and the third in myasthenia gravis. However, the present study showed that ulcerative colitis had the largest thymic shadow. We have thought that the thymic size of SLE would be small because the patients with SLE are almost invariably placed on PSL which is known to have thymolytic action and produce thymic

involution. Hare et al.¹¹) reported that the thymus of SLE was small and its size did not depend on the treatment with PSL. Then the question arises whether PSL affects the thymic size. The present study suggests that PSL does not affect the thymic size when judged by pneumomediastinography. Thus it appears that the various diseases have their own thymic size irrespective of the treatment. This is further supported by the fact that the thymic size of hypoplastic anemia¹³) or Behçet's disease¹⁴) which is often placed on PSL was larger than that of myasthenia gravis which is usually not treated with PSL. In contrast to the pneumomediastinographic findings, the PSL seems to affect involution of the thymus when examined histopathologically because the patients of Behçet's disease with PSL have more involuted thymus than the patients without PSL (**Fig. 6**).

A formation of lymphoid follicles in thymus of ulcerative colitis was observed in 61%. This high incidence of lymphoid follicle formation is similar to other autoimmune diseases. The presence or absence of lymphoid follicle formation is an important factor for establishing diagnosis of thymic abnormality in autoimmunopathy, because in non-autoimmunopathy, lymphoid follicle formation was noted in 12 out of the 71 cases (17%) of accidental death. An extremely frequent detection of the lymphoid follicle formation in autoimmunopathy may be the evidence to indicate positive intrathymic proliferation of auto-antibody producing cells.

As for relationship between thymus and ulcerative colitis, Schmid¹⁵) described that 8 severe chronic ulcerative colitis patients were performed thymectomy and he found thymic lymphoid follicle formations in 3 cases out of 8 ulcerative colitis patients. So he considered that this finding is a sign of increased activity of the thymus as well as supporting sign for

the assumption of an autoimmunological process within the ulcerative colitis. Nokita et al.¹⁶⁾ also performed thymectomy for three ulcerative colitis patients who have no effects for medical treatment and described that they have a good clinical course and thymectomy should be considered as a choice of treatment for ulcerative colitis.

Concerning the occult thymoma we found 5 cases of occult thymoma by using pneumomediastinography and 3 out of 5 patients were found less than one year duration of disease. But we could not find the occult thymoma in ulcerative colitis. Therefore this method is a very useful tool to find the occult thymoma even when thymoma is not shown by X-ray film and tomography^{17,18)}. We strongly recommend to apply the pneumomediastinography in ulcerative colitis and also in other autoimmune diseases so that we are able to find the occult thymoma associated with the autoimmune diseases.

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