主論文

THE MECHANISM OF DISCORDANT XENOGRAFT REJECTION

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*Abbreviations used in this paper: Complement components are identified according to World Health Organization recommendations (1981). CVF, cobra venom factor; CDC, complement dependent cytotoxicity; HA, hemagglutination; Egp, guinea pig erythrocyte; LEW, Lewis inbred rat; GGVB, glucose gelatine veronal buffer; RV, right ventricle; NRS, normal Lewis rat serum; RS, rat serum.

SUMMARY

The mechanism of discordant xenograft rejection using the guinea pig to rat heart graft model was studied . In this model, we found that: (A) Rejection occurred rapidly, in 17.5± 8.3 minutes (mean± SD) (n = 8). (B) The graft survived longer when the recipient rat was pretreated with cobra venom facter (CVF). (C) Complement hemolytic titers in serum showed significant reduction of C3 in rejection without consumption of C4 and C2, suggesting complement activation through the alternative pathway. (D) No natural antibodies were detected in this combination. Complement-dependent cytotoxicity (CDC) titer, and hemagglutination (HA) titer were lower than × 1. (E) Histological examination of the rejected heart xenograft revealed a large area of myocytolysis without interstitial cellular infiltration. (F) In vitro experiments showed that rat complement attacked guinea pig erythrocytes (Egp) via the alternative pathway. These findings indicate that rejection in this discordant xenograft model of guinea pig to rat was caused by primary activation of complement via the alternative pathway.

INTRODUCTION

Xenotransplantation is classified into concordant and discordant transplantation. Concordant grafts survive longer than discordant grafts. For example, when hamster hearts are transplanted to rats, rejection occurs in 3 to 4 days(1). In contrast, discordant grafts are rejected in an order of minutes : for example, when guinea pig hearts are transplanted to rats, the rejection time is 10 to 30 minutes (2-4). This rapid rejection has been termed hyperacute rejection. It has been generally accepted that discordant xenografts are rejected by the activity of natural or aquired antibodies and subsequent complement activation through the classical pathway (5,6).

However, no definitive evidence has been demonstrated that antibodies and classical complement components take part in this type of rejection. Furthermore, recent progress in complementology has shown that the complement system recognizes, and reacts with, foreign materials without the mediation of antibodies (7,8). This antibody-independent pathway of complement activation has been characterized as the alternative pathway. It has never been tested whether xenografts can be rejected by activation of the alternative pathway. In this work, we investigated the mechanism of hyperacute rejection using heart transplantation in two donor-recipient species combinations, guinea pigs to untreated rats and hamsters to presensitized rats.

MATERIALS AND METHODS

Animals. Female outbred guinea pigs weighing 180-205g, and female outbred hamsters weighing 120-155g were obtained from Nihon Dobutsu Co.. Male Lewis inbred rats (LEW) weighing 150-260g were obtained from Oriental

Yeast Co.. The pair of donor and recipient was selected according to the body weight ratio in 0.7-0.8.

Transplantation technique. Donor and recipients were anesthetized with ether. Heterotopic heart grafting was performed by a modified microvascular surgical technique as described by Ono and Lindsey (9). Rejection was considered to be completed when no heart contraction was revealed.

Experimental models. Four groups of animal pairs were selected to examine the discordant xenotransplantation immunology : group A = guinea pig to LEW rat (n = 8), group B = hamster to presensitized LEW rat (n = 8), group C (control) = LEW rat to LEW rat (n = 8), group D = guinea pig to C3-depleted LEW rat (n = 4).

Rat anti-hamster serum. Serum was obtained from LEW rats immunized twice with hamster spleen cells. 1.5 ml of this serum with high CDC titer ($\geqq 128$) was injected intravenously in group B rats to presensitize.

C3 depletion-effect test (3). CVF (200 u/kg) (Naja Naja Kaouthia, Sigma, lot no. 49c-0249) (10) was injected intraperitoneally 3 hours before transplantation in group D rats. The effect of CVF on graft survival time was studied by comparing group D with group A. (Rejection was judged manually through the abdominal wall every 12 hours in group D.)

Collection of sera (11). To study the change in serum complement during rejection, 0.2-0.3 ml of blood was collected from the recipient rats of groups A to C three times as follows: aortic blood before unclamping (before rejection), graft right ventricle (RV) blood about 5 minutes after release of clamp (during rejection), and aortic blood after rejection was completed (after rejection). In the control group, the aortic blood

was collected 20 minutes after the clamp was released. These blood samples were allowed to stand at room temperature for about 40 minutes and were centrifuged at 2500 rpm for 5 minutes to obtain the serum. The serum was stored at -70℃ and, in principle, the frozen serum was defrosted only once before the assay.

Assays of the hemolytic activities of complement. All hemolytic activities of complement were measured by the microtiter method. CH50 was determined according to the method of Mayer (12). ACH50 was assayed according to the method of Platts-Milles and Ishizaka (13) with slight modification, in which Egp was used as the target cell. The hemolytic activity of C4 and C2 in rat serum were determined as described previously (14,15) with some modifications. In brief, C4 activity was estimated by use of sensitized erythrocytes (EA) bearing guinea pig C1 (EAC1gp), C2 of guinea pig origin and normal rat serum diluted in EDTA buffer for the source of C3-C9 (Crat-EDTA). C2 activity was determined by use of EA bearing C1 and C4 of rat orign (EAC14rat), prepared from EA and rat serum by TTHA method (16), and Crat-EDTA. Hemolytic activities of C3 and C5 were estimated as described previously (17,18).

Assay for natural and aquired antibody in serum.

i) CDC assays. CDC titer was measured according to the methods described by Obata et al.(19), in which guinea pig serum diluted 1:15 in medium was used as a complement source. As a positive control, serum obtained from a rat sensitized twice with guinea pig spleen cells was used in group A, and serum obtained from a rat sensitized twice with hamster spleen cells was used in group B. Eagle with Earle's minimum essential medium was used as medium.

i) HA assays. HA titer was measured according to the

methods described by Tanaka et al.(20). The same serum used in CDC assays was utilized as a positive control.

Histological examination (4,21). After rejection was complete, the animals were sacrified to remove the graft for histological examination. Hematoxylin and eosin stain was used. The stained grafts were observed under the light microscope.

Sera for the in vitro study. For the study of cytolysis in vitro, sera were prepared from normal LEW rat serum (NRS) as follows. i) B-depleted rat serum (RS) : NRS was incubated at 48.0-48.5℃ for 30 minutes to deplete the activity of Factor B (22). In this serum, not the classical pathway but the alternative pathway of the complement system can be activated. ii) Aggre-Ig treated RS : NRS was allowed to react with aggregated human IgG to reduce the activity of early components (C4,C2) of the classical complement pathway (23). Only the alternative complement pathway can be activated in this serum. iii) Absorbed RS : Natural antibody to Egp in rat serum was depletede by repeated incubations of rat serum with packed Egp in the presence of EDTA.

In vitro assay to determine the complement pathway. Serial dilutions of the rat sera were incubated with Egp in glucose gelatine veronal buffer (GGVB) containing Ca^{2+} and Mg^{2+} or Mg-EGTA-GGVB (16,18) at 37℃ for 60 minutes. After centrifugation, each hemoglobin content in the supernatant was estimated and the degree of hemolysis of each serum was calculated and expressed in % hemolysis or CH50 value (16-18).

Statistical analysis. Quantitative data were analyzed by unpaired Student's t tests and considered significant at $P < 0.05$.

RESULTS

Two kinds of hyperacute rejection models (Table 1). Cardiac transplantation was carried out in two groups of experimental animals. As shown in Table 1, guinea pig hearts were rejected in 17.5 ± 8.3 minutes (n = 8) after transplantation in untreated rats (group A), and hamster hearts were rejected in 11.8 ± 4.9 minutes (n = 8) in the presensitized rat (group B). The difference in rejection times of these two groups was not statistically significant. In the control group, rat heart to rat (group C), all grafts showed normal pulsation as long as observed (n = 8). Thus, two kinds of hyperacute rejection models (guinea pig to rat and hamster to presensitized rat) were prepered. The following studies were carried out to investigate the mechanism of hyperacute rejection in these two groupes, especially the participation of the antibody and complement systems.

Effect of C3 depletion on the rejection time (Table 1). Guinea pig hearts were transplanteded rats pretreated with CVF to deplete C3 (group D). As shown in Table 1, the rejection time was greatly prolonged from 17.5 minutes to 2-3 days, indicating that the complement system, especialy C3, plays an important role in this discordant xenograft rejection.

Serum complement levels in rejection (Fig.1). To analyze complement participation in hyperacute rejection, we studied serum complement levels in these groups. Sera were obtained in groups A-C, and assayed for complement activity. The hemolytic titer of each serum sample was expressed as a percentage of the titer before transplantation. The results are summarized in Fig.1. As shown, in group A, C3 levels decreased significantly in the serum during and after rejection ,

but the CH50, ACH50, C4, C2 and C5 levels were not changed significantly. However, in group B, the CH50, C4, and C3 levels decreased significantly in the serum after rejection and the CH50, C4, C2, and C3 levels decreased in the serum during rejection. C4 activity during rejection was particularly low, 31.5± 19.6 % of that before transplantation. These findings indicate that, as expected, complement was activated through the classical pathway in group B. However, in group A, the complement profile is quite different from group B, indicating complement activation, not through the classical pathway but through the alternative pathway.

Natural antibody levels in rat serum (Table 2). The levels of natural antibody in rat serum against guinea pig tissue were measured to determine whether these antibodies participate in this complement-dependent xenograft rejection. CDC and HA were assayed in group A and B. As shown in Table 2, natural antibody against guinea pig tissue was not detected by CDC or HA assay in rat serum. But, in the sensitized rat, serum antibody against hamster cell was detected clearly, as expected. These findings indicate that, through the graft is rejected in an antibody-dependent fashion in group B, rejection may proceed without the perticipation of antibody in group A.

Histological study (Hematoxilin-eosin staining:Fig.2). The rejected grafts of group A were studied microscopically. Interstitial massive hemorrhage and myocytolysis were observed in a large area, but there was no interstitial cellular infiltration. These findings may be typical in the lesion of complement-dependent hyperacute rejection.

Thus, these in vivo studies suggest that the

hyperacute rejection of guinea pig grafts by rats is due to the complement activation through the alternative pathway without participation of antibody.

Lysis of Egp by rat serum as in vitro model of discordant xenotransplantation (Fig.3). In order to analyze the complement-dependent cytolysis of guinea pig tissue by the rat, an in vitro study was undertaken by using Egp as the target cell and four kinds of rat sera. Figure 3-A shows the complement activity (CH50 and ACH50) in each rat serum preparation. Hemolysis of Egp in GGVB or in Mg-EGTA-GGVB was estimated using these sera. As shown in Fig 3-B, the degree of lysis of Egp by untreated NRS in GGVB was similar to that in Mg-EGTA-GGVB, indicating that Egp lysis by rat serum in the presence of Ca^{2+} and Mg^{2+} proceeded not through the classical pathway but through the alternative pathway of the complement system. This was confirmed by further experiments using B-depleted RS and aggre-Ig treated RS, in which Egp was not lysed by B-depleted RS but lysed by aggre-Ig treated RS. Antibody-independent Egp lysis was indicated again by the effective Egp lysis by antibody-absorbed RS. The degree of Egp lysis by aggre-Ig treated RS or by absorbed RS in GGVB was similar to that in Mg-EGTA-GGVB. Thus, in vitro studies also indicated that guinea pig cells are lysed by complement in rat serum, not through the classical pathway, but through the alternative pathway of activation without participation of natural antibody.

DISCUSSION

The goal of this study was to clarify the mechanism of rejection of xenografts within 30 min. Rapid rejection that occurs in such a hyperacute manner (so called hyperacute rejection) has been observed when recipients

are presensitized antibodies to their donors, or when discordant xenografts are transplanted. Participation of humoral factors such as antibodies, complement and factors of the coagulation system, as well as cellular immuinity has been described in this kind of rapid rejection (3,24). Successive reports, however, did not show an effect of anti-platelet or anti-clotting reagents on prolongation of graft survival. In addition, several reports suggested that pretreatment with CVF, but not with anti-platelets agents such as aspirin, prolonged discordant xenograft survival (3). Prolongation of graft survival by pretreatment with CVF was demonstrated in our hyperacute rejection model as well as in other models (25). These results indicate that antibodies and the complement system participate in the induction of hyperacute rejection, and the effect of platelets and, possibly, clotting is minimal, if any. We established two models of hyperacute rejection of heart xenotransplants (discordant model and presensitized concordant model) and changes in serum complement levels due to rejection in these models was studied to distinguish the complement activation pathways. We did not use a model of allograft hyperacute rejection in which cardiac grafts from ACI rats are transplanted to LEW rats (6), since rejection takes more than 10 hours, indicating an atypical hyperacute rejection (26). Complement levels of the recipient rats were determined in serum obtained immediately after rejection. A significant reduction of C4 and C3 was detected in the serum of presensitized rats receiving concordant heart xenografts. C3, C4, and C2 titers tended to decrease more in the graft RV blood than in aortic blood. Reduction of C4 and C2 indicated the activation of the classical complement pathway that occurs in an antibody-

dependent fashion. In contrast, only C3 was reduced in the unsensitized rats receiving discordant hearts. Decrease of C3 without consumption of C4 and C2, is a typical profile of activation of the alternative complement pathway that is independent to antibodies. These results, taken together with the fact that CVF depletes C3 without any effect on C4 and C2, indicats that hyperacute rejection of discordant heart xenografts is related mainly to activation of C3. In the discordant xenotransplantation model of guinea pig to rat, CDC and HA titers in rat serum were negligible, and thus the presence of natural antibodies to the grafts in the recipient rats was ruled out. Therefore, the activation of C3 is considered to have occurred primarily through the alternative pathway. The results from the presensitized concordant xenotransplantation model supported the concept that antibodies and secondary activation of the classical complement pathway induce hyperacute rejection. On contrast, the results from the discordant xenotransplantation model led to the conclusion that the activation of only the alternative complement pathway, without any participation of antibodies, induces graft rejection in hyperacute manner.

It has been reported that there is a correlation between natural antibodies and the alternative pathway (20,27). The alternative pathway can also be activated by some types of antibodies. However, it would be surprising if undetectable amounts of natural antibodies could induce a rapid reaction ocurring in the order of minutes. Furthermore, no depletion of C4 and C2 in the graft RV blood suggests a lack of antibodies. Reduction of C3 in the RV blood shows that the xenografts directly activate complement.

We also investigated whether some cellular immunity contributed to hyperacute rejection. Histological analysis of the rejected heart grafts revealed no celluar infiltration. It is unlikely that cellular infiltration occures within minutes. Moreover, according to results described by others, cyclosporine and aspirin did not effectively prolong xenograft survival (3). These results indicate that the influence of cellular immunity on this type of rejection may be minimal. Our results disagree with a current concept that ischemic changes in myocaldial tissue after transplantation resulting in infraction, may be responsible for hyperacute rejection (3,21), and suggest that ischemic changes do not occur within 20 minutes.

Using an in vitro system, we examined whether rat serum damaged guinea pig cells, and found that recipient complement attacked the transplanted xenografts. Rat serum easily lysed Egp, and the lysis ocurred only via the alternative pathway. These results are in agreement with our in vivo results. However, guinea pig nucleated cells such as spleen cells are resistant to rat complement. Failure of nucleated cells to be lysed by complement has been reported , but no definitive mechanism has been proposed (28). Some unknown process may underlie in the extensive damage of graft myocytes accomplished by the recipient complement system.

The mechanism of rejection by complement activation might occur as follows. Once the activated form of C3, C3b, is deposited on the target cells, the subsequent components are activated in turn to form a membrane attack complex resulting in cell lysis. If the cell is protected from complement attack, the deposited C3b must be rapidly inactivated by complement regulatory proteins that reside in plasma or on the cell-surface

(29-33). However, in the xenograft rejection, the deposited recipient C3b remains active on the graft cell-surface, because C3b is essential to activate the alternative pathway via which the rat C3 was consumed by the guinea pig grafts. If rat C3b were compatible with guinea pig regulatory proteins, the C3b deposited on the graft would have been effectively inactivated, and subsequent activation of the alternative pathway would not have ocurred. Therefore, one possible mechanism that causes comsumption of the C3 in the grafts is the incompatibility of rat C3b with guinea pig regulatory proteins. Further studies on species-specific reactions between complement and its regulatory proteins will be necessary to test the above hypothesis.

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TABLE 1. Outcome of graft survival

Group	Graft survival time
A; guinea pig→LEW rat	2,13,15,15,17,20,28,30 (17.5± 8.3)[a] min.
B; hamster→presensitized LEW rat[b]	5,7,7,10,14,15,17,19 (11.8± 4.9)[a] min.
C; LEW rat→LEW rat	All grafts showed normal pulsation.
D; guinea pig→C3 depleted LEW rat[c]	2, 2.5, 3, 3 days

[a]Mean ± SD.

[b]LEW rat which was given anti-hamster serum.

[c]LEW rat which was given CVF (200u/kg) 3 hours before transplantation.

TABLE 2. CDC and HA titers in A and B groups

CDC titer		HA titer	
A-1[a]: <1	B-1[b]: 16-32	A-1[a]: <1	B-2[b]: 128
2 : <1	3 : 32	2 : <1	4 : 64
3 : <1	5 : 16-32	3 : <1	6 : 64
4 : <1	7 : 16-32	4 : <1	8 : 128
5 : <1	C[d]: >128	5 : <1	C[d]: >256.
6 : <1		6 : <1	
7 : <1		7 : <1	
8 : <1		8 : <1	
C[c]: 32-64		C[c]: >256	

[a]Guinea pig to LEW rat group.

[b]Hamster to presensitized rat with the anti-hamster antibody group.

[c]Serum from a rat twice sensitized with guinea pig spleen cells was used as the positive control.

[d]Serum from a rat twice sensitized with hamster spleen cells was used as the positive control.

FIGURE 1. Change in hemolytic activities of complement in heart graft rejection. All titers (represent mean ± SD) based on the initial value (= 100); titers of aorta blood before release of clamp (n = 8). Comparison of titers was done using Student's t test.

A; complement titers in aorta blood after rejection, in control group (group C) 20 minutes after release of clamp.[○ = guinea pig to LEW rat (group A); □ = hamster to presensitized LEW rat (group B); ● = LEW rat to LEW rat, control group (group C).] In group A, C3 was significantly lower than the control ($p<0.01$). In group B, CH50, C4, C3 were reduced significantly ($p<0.05$).

B; complement titers of graft RV blood during rejection (graft perfution blood) about 5 minuts after release of clamp. In group A, C3 was significantly decreased ($p<0.05$). In group B, CH50, and C2 were significantly decreased ($p<0.05$). C3 was also decreased ($p<0.01$), and C4 was decreased greatly ($p<0.005$). All these changes of complement hemolytic activity imply that in group B the classical pathway activated but in group A the alternative pathway was activated.

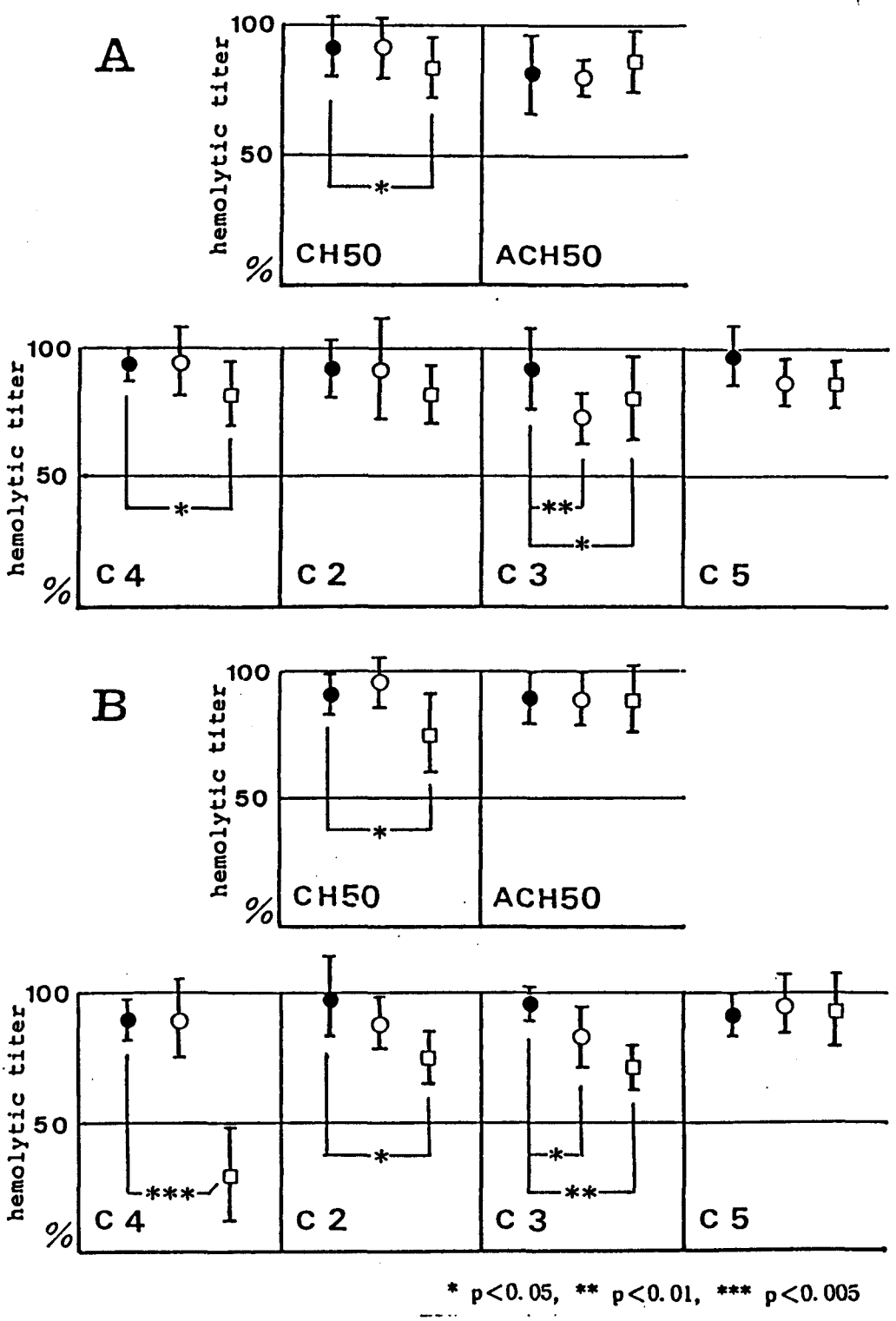
FIGURE 2. Guinea pig heart graft removed at the time of rejection. (A) Massive interstitial hemorrhage was seen (Hematoxylin and eosin, × 100). (B) Large area of myocytolysis appears but ischemic change of myocytes in about 20 minutes was not considerable (Hematoxylin and eosin, × 100). There was no interstitial cellular infiltration in any rejected heart grafts.

FIGURE 3. In vitro study to determine which complement pathway of rat serum is activated in Egp lysis.[NRS = nornal Lewis rat serum (●), B-depleted RS = rat serum which was heated to inactivate Factor B (□), Aggre-Ig treated RS = rat serum which was pretreated with aggregate IgG to deplete the classical pathway (○), Absorbed RS = rat serum subjected to antibody absorption(△).]

A; The CH50 and ACH50 titers of these sera are indicated (open bars = CH50, closed bars = ACH50). Bar indicats the mean value of titers and barbell shapes line reveal SD from three experiments.

B; The pattern of Egp lysis in each dilution of these sera is indicated. These sera were incubated with Egp in GGVB at 37° C for 60 minutes as a model of in vivo xenograft rejection (thick line). In comparison, patterns of ACH50 incubated with Egp in Mg-EGTA-GGVB at 37° C for 60 minutes were shown (thin line). The two curves in each serum were almost the same, indicating that rat complement attacked Egp only through the alternative pathway.

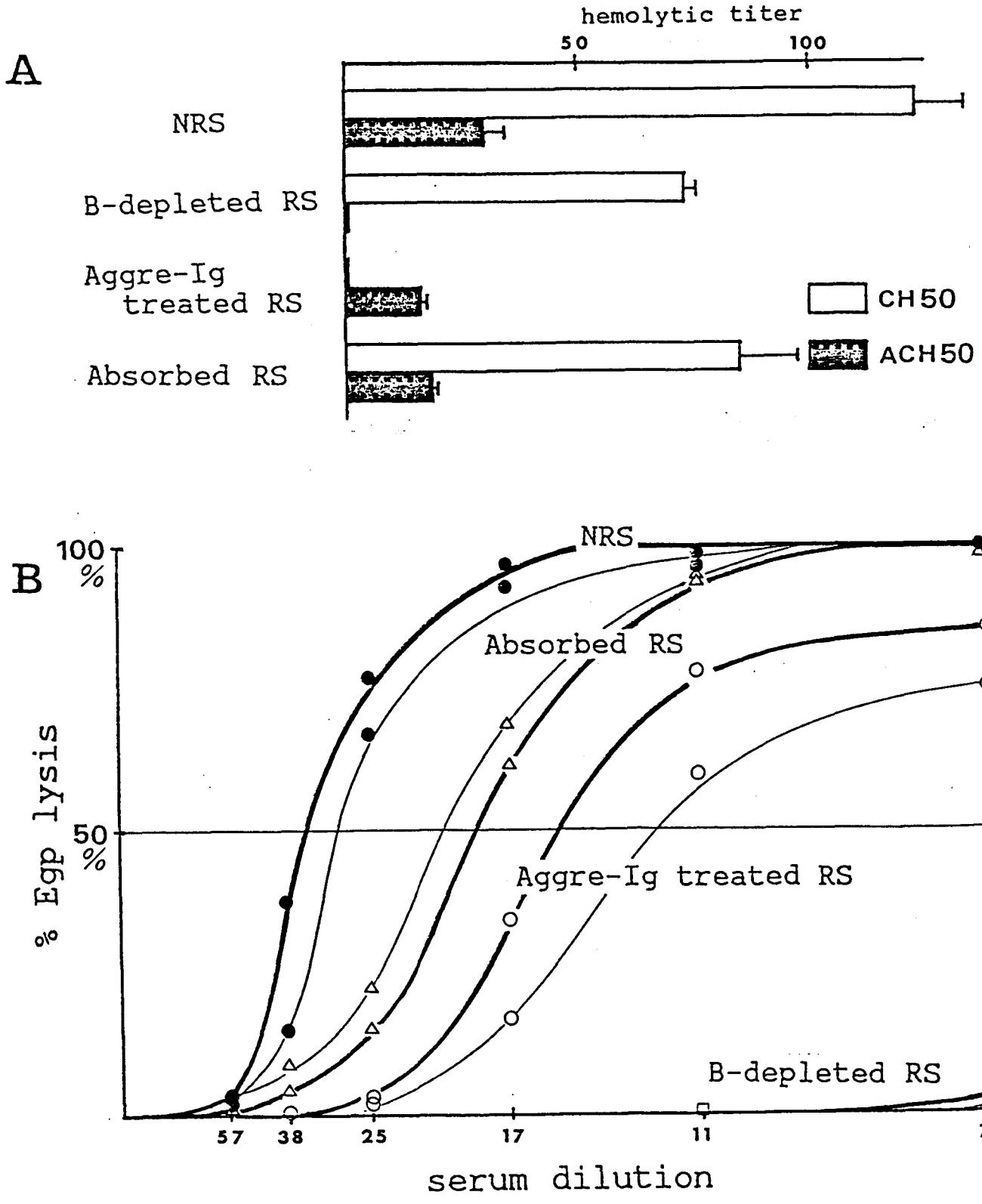
Fig 1



* $p<0.05$, ** $p<0.01$, *** $p<0.005$

Fig 2

Fig 3


A
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57
38
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Congenital Absence of Small Intestinal Musculature (One Case Report)

Angeborenes Fehlen der Dünndarmmuskulatur (Bericht über einen Fall)

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Summary

Intestinal obstruction due to congenital absence of the small intestinal musculature in a neonate is presented.

This report represents the seventh known case of this abnormality.

In addition, in our case ectopic oesophageal mucosa and ectopic gastric mucosa is detected.

The aetiology of this condition is unknown, and the diagnosis must simply depend on pathological examination of biopsy samples taken from appropriate regions.

Unfortunately the regions of this disease have no continuity. Therefore, course of treatment cannot be established as the extent of the region cannot be correctly identified.

To detect change of colour tone of the bowel may be helpful in the treatment of the disease.

Key words: Intestinal obstruction–Intestinal musculature–Small bowel

Zusammenfassung

Es wird ein Darmverschluß durch angeborenes Fehlen der Dünndarmmuskulatur bei einem Neugeborenen beschrieben.

Der vorliegende Bericht bezieht sich auf den 7. bekannten Fall dieser Anomalie. Bei dem vorliegenden Fall wurde überdies ektop Speiseröhren- und Magenschleimhaut gefunden. Die Ätiologie der Muskelagenesie ist unbekannt. Die Diagnose begründet sich ausschließlich auf eine histologische Untersuchung von Darmwandbiopsien. Eine Farbtonänderung der Darmwand kann jedoch auf die Fehlbildung hinweisen.

Schlüsselwörter: Darmverschluß – Darmwandmuskulatur – Dünndarm

Case report

On August 6th, 1981, a female baby was born, weighing 2,300 gm at 38 weeks of normal gestation. The Apgar score was 10 points. There was no evidence of hydramnion. Her brother was normal.

Her abdomen became distended, and she began to vomit repeatedly green, bile-like fluid 14 hours after birth. Her abdominal roentgenograms revealed abdominal gas retention in the small bowel.

A nelaton catheter was inserted 6 cm deep into the rectum and consequently there was discharge of a small quantity of meconium. Her subsequent barium enema revealed microcolon, but failed to visualise as far as the ileum. An obstruction of the small intestine was thus suspected. An emergency operation was performed.

The jejunum was rather dilated over a length of 50 cm from *Treitz*'s ligament, and shrinkage extended down to the anus from the dilation (Fig. 1). Here and there meconium colour was observed through the bowel walls, and the colour tone of some bowel sections mainly near *Treitz*'s ligament changed gradually reflecting the colour of the bile (Fig. 1, arrows). The small intestine had no obstruction, and there was no cyst in the pancreas. Therefore, we did not only suspect meconium plague syndrome, but we also suspected extensive aganglionosis.

An intestinal fistula was formed at the caliber charge-like portion between the dilated and shrunken regions, and frozen biopsy samples were collected from the ileum and descending colon. No remarkable change at the two frozen sections was detected, and the presence of ganglion cells was confirmed.

After the operation, the patient's bowel remained distended. There were weak bowel sounds and vomiting.

An upper gastrointestinal series showed poor mobility, and no evidence of obstruction. Anorectal manometric study showed positive reflex.

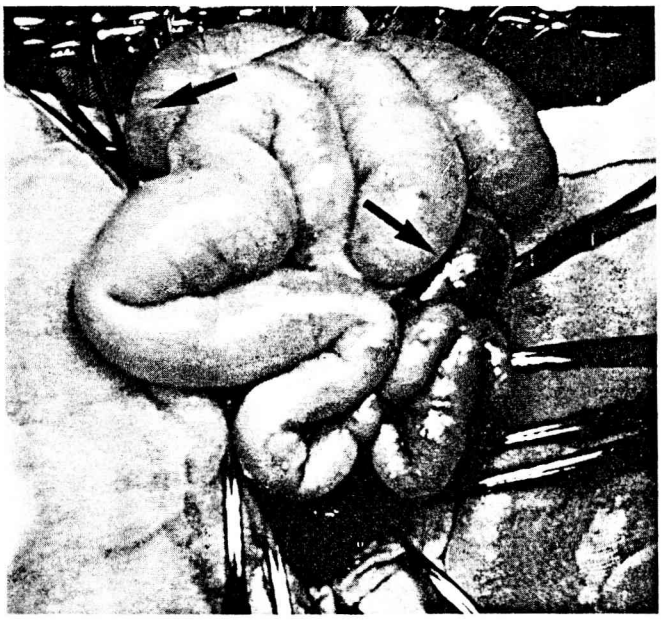

Fig. 1 The jejunum was rather dilated over a length of 50cm. As indicated by the arrows (↑), a change in colour tone was also observed

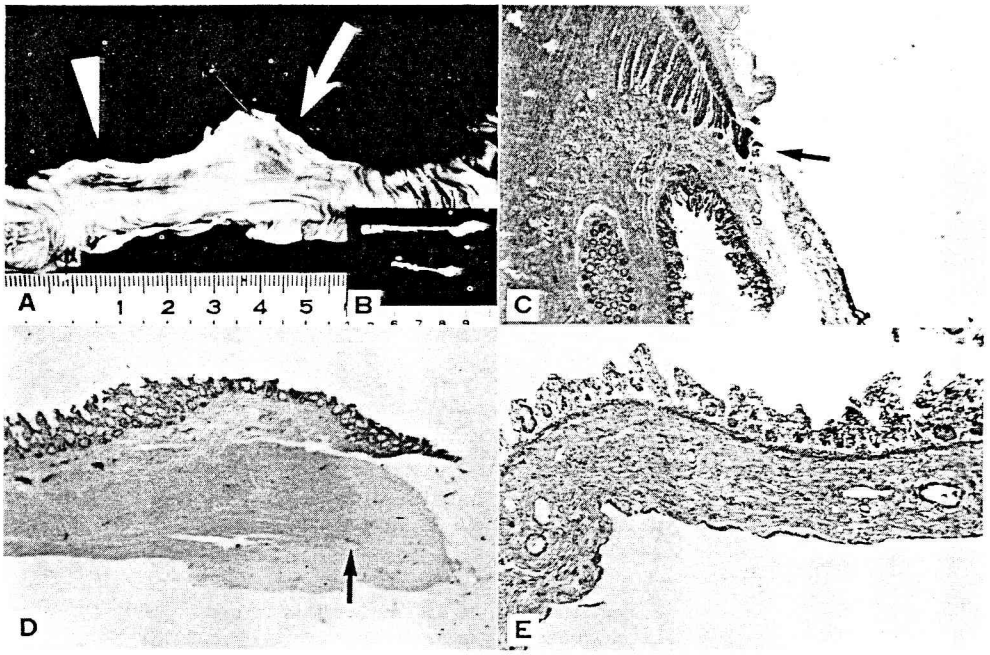

Fig. 2 A) Gross specimen (after fixing in formalin). *B)* Fragments. *C), D)* Photomicrographs showing junction of the normal and abnormal bowel wall, by the arrows (↑). (H & E, x40). *E)* This section showing only mucosa and serosa. (H & E, x40).

However, the state of the ileus persisted. Her condition gradually degenerated due to unknown causes, and she died of sepsis on Oct. 7th after 72 days of her life. Permission was granted for autopsy.

Pathology

Macroscopically skipped paper-like thin regions were revealed mainly at the dilated jejunum.

Histologically those parts were lacking completely in musculature (Fig. 2, E). In addition, ectopic oesophageal mucosa and ectopic gastric mucosa were seen in the other sections of the dilated jejunum (Fig. 3, A and B). The nerve plexus was present, although it looked rather atrophic. No remarkable change in the colon was detected.

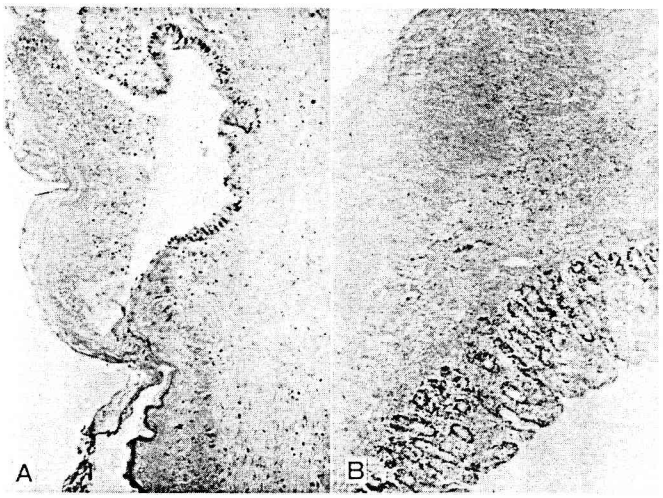

Fig. 3 A) Ectopic oesophageal mucosa was observed near *Treitz*'s ligament. (H & E, x.100). *B)* Ectopic gastric mucosa was seen in the section, 40–50 cm from *Treitz*'s ligament. (H & E, x40)

Comments

The case of the absence of the small intestine musculature presented here has brought the total of such cases to seven since the first case reported by *Emanuel* et al (3) in 1967. Details of individuals are summarised in Table I. Our case also presented mucosal abnormalities. However, no mucosal changes were described at all in the other cases.

Case 4 developed from a right inguinal hernia, strangulated for 48 hours. Case 6 developed at the 12th month because of incomplete muscular deficiency. All the other cases developed the disease with symptoms of obstruction at the small intestine in the neonatal stage. Microcolon was detected in this case by barium enema, but not in cases 1, 2 and 3.

Obstruction of the small intestine usually requires an emergency operation. Therefore, it is highly probable that the disease may be treated by laparotomy under the diagnosis of suspected stricture or obstruction of the small intestine.

By means of laparotomy the possibility of stricture of obstruction of the small intestine can be definitively discounted. Except for case 1 whose outward appearance indicated abnormality, the diagnosis must simply depend on pathological examination of biopsy samples taken from appropriate regions. Appropriate regions would be the parts of stricture and dilatation just above the affected section.

Unfortunately the regions of the disease have no continuity. Therefore, course of treatment cannot be established as the extent of the region cannot be correctly identified.

Steiner et al (6) state that transillumination of the bowel provides some insight. In our case, change of colour tone could also be detected in the photograms after the operation (Fig. 1, arrows). This may be helpful for treatment of the disease in future.

Table I Summary of the reported cases

Case	1[1]	2[2]	3[3]	4[4]	5[5]	6[6]	Our case
Gestation	37 wk	Full	Full	?	Full	?	38 wk
Family history	+	–	?	?	?	?	–
Physical exam.							
Birth wt.	2523 g	2740 g	1930 g	?	?	?	2300 g
Early abd. distension	+	+	+	?	?	?	+
Meconium	–	–	–	?	?	?	+
Abd. mass	–	+(RLQ)	–	?	–	?	–
Radiologic findings							
Small bowel obstruction	+	+	+	–	+	–	+
Ba-enema	Normal	Normal	Normal	?	?	?	Microcolon
Operation	Small bowel resection	Ileocol-ectomy	R-hemicol-ectomy	End-to-end anastomosis	End-to-end anastomosis	End-to-end anastomosis	Jejuno-stomy
Pathology gross							
Small int.	Sausage link	Dilated	Dilated	Dilated	Dilated	Dilated	Dilated
Colon	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Microscopic absence of musculature	Complete	Complete	Complete	Complete	Complete	Circular muscle	Complete
Extent of region	Entire small int.	Distal ileum	Distal ileum	Mid. ileum	Distal ileum	Mid. ileum	Entire small int.
Colon	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Age at death	62 hr	40 days	124 days	–	–	–	72 days
Autopsy	+	+	+	–	–	–	+

RLQ: Right Lower Quadrant

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参考論文

転移性肝腫瘍に対する肝動脈塞栓術により生じた気管支胆管瘻の1例

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CASE OF BRONCHOBILIARY FISTULA FOLLOWING HEPATIC ARTERY EMBOLIZATION FOR METASTATIC LIVER TUMOR

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症　例

転移性肝腫瘍に対する肝動脈塞栓術により生じた気管支胆管瘻の1例

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症例は43歳男性で，Gastorinomaの肝転移巣に対して，肝動脈塞栓術を施行した．その結果，すでに横隔膜に浸潤していたと考えられる腫瘍が壊死に陥り，術後19日目に右肝下葉気管支との間に気管支胆管瘻を形成した．経皮経肝ドレナージを施行したが，塞栓術後29日目に呼吸不全のため死亡した．

気管支胆管瘻は，本邦ではすでに48例の報告をみている．本例を加えて，その成因，発生機序，診断法，治療法，等につき文献的検討を加えて報告した．特に，治療に関しては，急性期は膿瘍腔のドレナージを主とし，瘻孔そのものより，むしろ原疾患に対する加療が重要であると考えられた．

索引用語：気管支胆管瘻，肝動脈塞栓術

はじめに

我々は，転移性肝腫瘍に対し，肝動脈塞栓術を施行した．その結果，すでに横隔膜に浸潤していたと考えられる腫瘍が壊死に陥り，右肺下葉，気管支との間に気管支胆管瘻を形成するに至った極めて稀な1症例を経験したので報告する．

症　例

患者：43歳，男，会社員．

主訴：全身倦怠感，背部痛．

家族歴：父に十二指腸潰瘍の既往がある．

既往歴：昭和49年（37歳時）尿路結石と診断されるも自然流出する．

現病歴：昭和49年より空腹時の心窩部痛あり，十二指腸第2部に巨大な十二指腸潰瘍を指摘されていた．昭和52年10月，大量吐血にて，某医に緊急入院し，幽門側広範胃切除術（Billroth II 法）をうけた．しかしながら，術直後より心窩部痛を覚え，時に下血がみられた．そのため，内科医を転々としていた．昭和54年8月某内科にて難治性吻合部潰瘍と診断され，手術目的のため当科を紹介された．その後の精査により，胃液過分泌，空腹時血漿ガストリンの異常高値（4,800 pg/ml），セクレチン負荷試験陽性，ならびに膵頭部腫瘍などが判明し，Zollinger-Ellison 症候群と診断した．

昭和54年10月30日，開腹手術を施行した．既に肝両葉に，径1cmまでの多数の転移巣が認められた．門脈合併切除を伴う膵頭十二指腸切除，ならびに残胃全摘，腫瘍直接浸潤部の肝右葉部分切除術を施行した．術後，膵腸吻合部の縫合不全を生じ，一時敗血症に陥ったが，全身状態は徐々に改善した．昭和55年1月に退院し，社会復帰した．

外来にて5-FUの投与を続け，経過を観察していた．CT像上残存肝転移巣の増大はなく，血中ガストリン値も約800pg/ml前後を持続し，上昇がみられなかった．昭和56年1月突然肝腫大が著明となり，血中ガストリン値も，2,300pg/mlと急激に上昇した．CT像上肝転移巣の増大がみられ，全身倦怠感，背部痛が著明となった．昭和56年4月7日，肝転移巣に対する補助療法のため入院した．

入院時理学的所見：身長170cm，体重48kg，栄養状態は不良であった．眼瞼結膜は貧血様，眼球結膜には黄疸は認められなかった．表在性のリンパ節は触知されなかった．呼吸音は清であったが右上肺野では減弱していた．心音は純であった．胸部打診にて肺肝境界は右第5肋間に認められた．腹部は著明に膨隆し，肝は右鎖骨線上，約15cm触知され，弾性硬であり，表面は凹凸不整な大小多数の結節が触知された．腹水は認

められず，直腸内指診においてもダグラス窩に異常は認められなかった．

入院時検査所見(表1)：検血にて軽度の貧血が認められた．生化学検査にて，血清中のカルシウム，γ-GTP，アルカリフォスファターゼの高値が認められた．また，空腹時血漿ガストリン値は137,000pg/mlと異常高値であった．胸部レ線にて右横隔膜は著しく上昇していたが，辺縁は明瞭であった．肺野には異常陰影を認めなかった（図1 A）．腹部CTにて肝両葉にわたり多数のlow density areaを認めた．周囲肝組織との境界は明瞭で，内部は比較的均一であった（図2 A）．

入院後，Gastrinomaの肝転移巣に対し，4月13日よりStreptozotocinの投与を開始した．1回/週，1.0～1.5gを5週にわたり計6.5g静脈内に投与した．しかし，投与終了後3日目（5月14日）のCT像上において肝転移はさらに増大しており，血漿ガストリン値も290,000pg/mlと増加し，腹囲も，入院時70cmであったものが，約40日間に79cmにまで増大していた．Streptozotocinにては抗腫瘍効果は得られないと判断し，5月18日肝動脈内抗癌剤投与ならびに塞栓術を

表1　入院時検査

末梢血液像	RBC 327×10⁴/mm³, WBC 6600/mm³, Hb 8.9g/dl, Ht 26.6%
肝機能	T.P. 6.8g/dl, Alb. 3.8g/dl, A/G 1.3, T.Bil 0.6mg/dl, GOT 50u/dl, GPT 34u/dl, γ-GTP 239u/dl, LDH 171u/dl, ALP 1233u/dl
血清電解質	Na 133mEq/l, K 5.2mEq/l, Cl 98mEq/l, Ca 8.0mg/dl, P 3.1mEq/l, BUN 32mEq/l, Cr. 1.2mEq/l
新鮮尿	異常を認めず
血中腫瘍マーカー	AFP 3ng/dl, Gastrin 137,000pg/ml

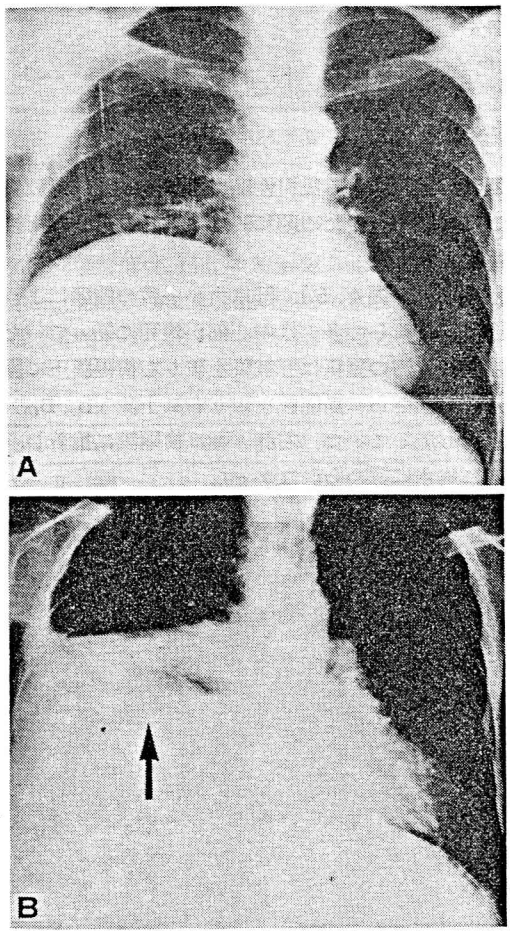

図1　(A) 入院時胸部単純レ線像：右横隔膜の著明な挙上を認める．
(B) 塞栓術後16日目の胸部レ線像：肝内にfree airが認められる(↑)．また，胸水の貯溜が示唆される．

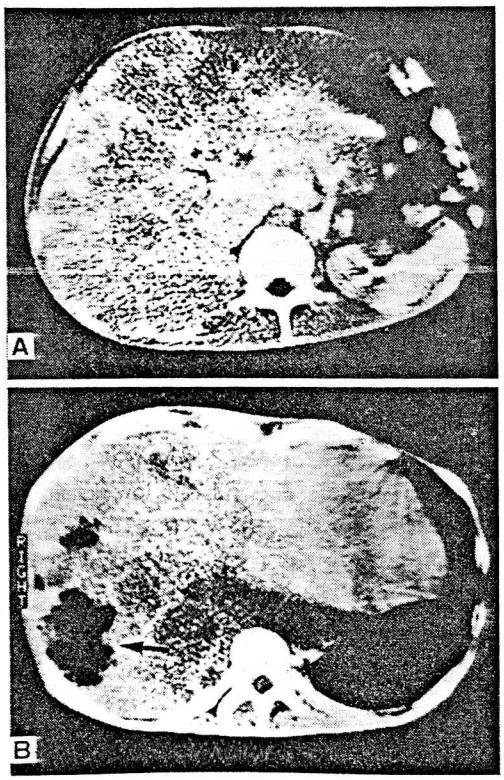

図2　(A) 入院時CT像：肝両葉にわたり，境界明瞭な多数のlow density areaを認める．
(B) 塞栓術後17日目のCT像：肝上部のlow density area中にairによると思われるareaが認められる（←）．

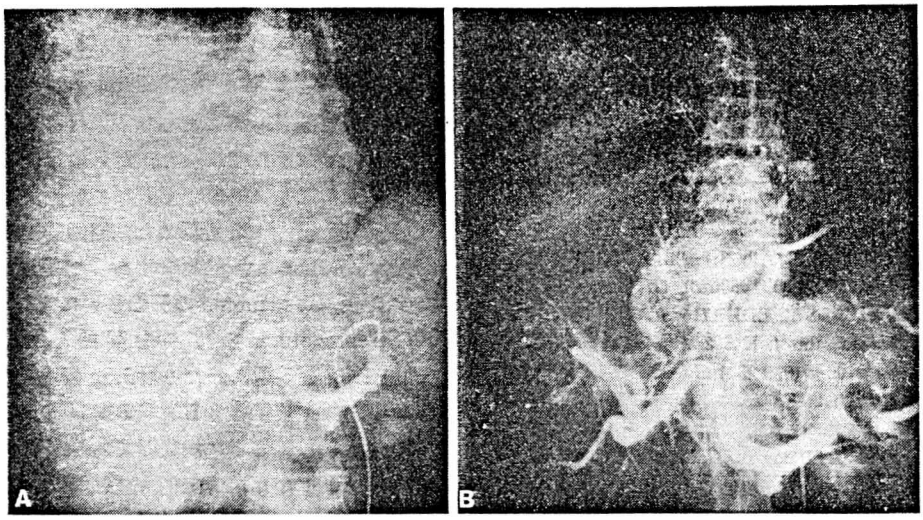

図3　腹腔動脈造影
(A) 塞栓術前：腫大した肝内に多数の血管に富んだ結節を認める．
(B) 塞栓術後：右肝動脈は閉塞していることが判る．また，多数の結節像は造影されない．

施行した．固有肝動脈より，Adreamycin 30mg, Mytomycin 10mg を注入後，同じく固有肝動脈よりゲルフォームにて塞栓術を施行した（図3）．

塞栓術後，腹囲は減少（肝表面の結節は縮小し，軟化した．血漿ガストリン値も術後1日目より121,000 pg/ml と著明な低下がみられた．しかし塞栓術後6日目，突然38.8℃の発熱をきたし，動脈血細菌培養の結果，Streptococus fecalis が検出された．強力な化学療法にもかかわらず，その後も発熱は持続し，全身倦怠感，食欲不振，背部痛が増強した．右横隔膜はさらに上昇し右胸水の貯溜を認めた（図1 B）．さらに右横隔膜下ならびに肝内に多数のガス像を認めた．術後17日目に行った CT にて，肝右葉上部の low density area の辺縁は不明瞭となり，内にガス像を認めた(図2 B)ため，肝腫瘍壊死と診断した．

術後19日目，突然，咳嗽発作が生じ患者は呼吸困難を訴えた．気管内挿管後，気道内吸引を行ったところ，胆汁を混じた膿様の分泌物が多量に得られた．このため肝転移巣と肺との瘻孔形成を疑い，気管支鏡検査を施行した．肝右葉上部の転移巣を経皮的に穿刺し，Evans Blue を注入すると，右肺下葉気管支（B_9, B_{10}）の末梢より色素の流出が確認された．肝転移巣より右肺への瘻孔形式と診断し肝右葉の転移巣に経皮的にドレナージチューブを挿入し，持続吸引を開始した．しかし腹水貯溜，肝腫大に伴う呼吸抑制に加え，両側肺に胆汁，膿汁による吸引性肺炎を併発した．悪液質ならびに呼吸不全のため昭和56年6月16日，塞栓術後29日目に死亡した．

解剖所見（図4，5）：肝は大小多数の腫瘍により占められ，これらの多くは中心部が壊死に陥っていた．肝右葉後側方の腫瘍は肝被膜を破り右横隔膜下に膿瘍を形成し，さらに横隔膜を破り右肺下葉（B_9, B_{10}）に瘻孔を形成していた．右肺下葉は横隔膜に癒着し，胸腔内に胸水は認められなかった．

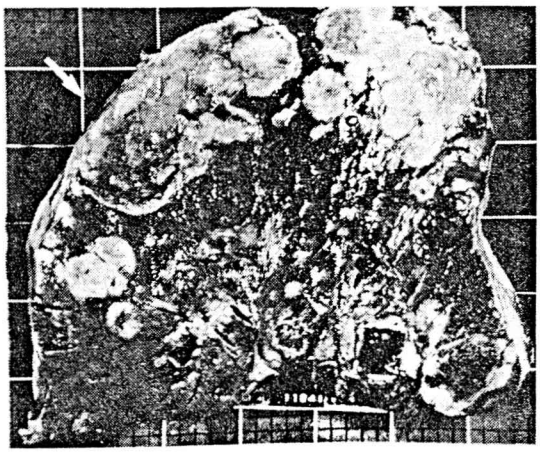

図4　解剖所見（肝臓）　肝は大小多数の転移巣で占められ，多くは中心部が壊死に陥っている．右肝上部より気管支への瘻孔形成を認める（⇩）．

図5　解剖所見（肺）　右肺下葉（B_9, B_{10}）に瘻孔形成を認める（↑）.

考　案

気管支胆管瘻は，1837年 Kunde らによる報告が最初とされ，1928年には Morton[1]がすでに50例を集計している．本邦では，我々が抄猟した範囲では，1896年田中による報告が最初で，現在までに48例の報告をみている（表2）[2)~40)].

成因としては，エヒノコックスあるいはアメーバ性肝腫瘍による場合が多いとされ[1]，前者はオーストラリア・イランなど，後者は南アフリカ・メキシコ・インドなどで，現在でも報告が見られ，地方性伝染性色彩が強い．又，前者では2％[41]，後者では3.3％[42]に気管支胆管瘻の発生を見ると報告されている．

一方，本邦においては，戦前は，胆道結石に原因する症例が多かったが，戦後は細菌性肝膿瘍が原因と考えられる症例が多くなっている．本症例においては，後述のごとく，転移性肝腫瘍の壊死が主因をなしていた特殊症例である．

原疾患が肝膿瘍の場合の発生機序としては，肝表面の近くに発生した腫瘍が肝外に破れ，横隔膜下膿瘍を形成し，炎症性変化が横隔膜に波及し，引続いて，肺底部がその横隔膜の炎症部位に癒着し，膿瘍が肺に穿孔して気管支瘻を形成することになる．また，肺底部が横隔膜に癒着しない場合には，胸膜胆管瘻になる[43]．胆道結石及び化膿性胆管炎による場合も，二次的に肝膿瘍の形態をとるのが一般的である．また，この場合は肝外胆道系より肝外に直接破れて，横隔膜下膿瘍を形成，さらに気管支瘻となることもある．本症例では，病理所見上腫瘍浸潤は肝表面まで確認し得たのみで，

表2　気管支胆管瘻報告例（その1）

	報告者	報告年度	症例	原疾患	部位	治療	転帰
1	田　中[2]	1896	43歳♀	胆　石	右　肺	保存的	治
2	井戸・保田[3]	1911	20歳♀	胆　石	右　肺	保存的	死
3	尾　見[4]	1916	52歳♂	肝膿瘍	右　肺	開胸排膿	死
4	〃	〃	32歳♂	肝膿瘍	右　肺	開胸排膿	治
5	〃	〃	39歳♂	肝膿瘍	右　肺	開胸排膿	—
6	〃	〃	30歳♂	肝膿瘍	右下肺	開胸排膿	死
7	〃	〃	41歳♂	肝膿瘍	右下肺	保存的	死
8	高　村	1918	—	肝膿瘍	—	—	治
9	吉村・山崎[5]	1918	28歳♂	胆　石	右下肺	保存的	死
10	新　海[6]	1920	51歳♂	胆　石	右下肺	保存的	死
11	志　村[7]	1923	66歳♂	—	—	保存的	死
12	栁　[8]	1923	61歳♀	肝　石	右下肺	保存的	死
13	谷　[9]	1927	60歳♂	肝膿瘍	右　肺	保存的	死
14	永　山[10]	1931	47歳♂	胆　石	右下肺	保存的	死
15	沼　田	1934	—	横隔膜下膿瘍	—	—	治
16	杉　村[11]	1935	48歳♂	胆　石	右下肺	横隔膜下切開排膿	治

表 2　気管支胆管瘻報告例（その 2）

	報告者	報告年度	症例	原疾患	部位	治療	転帰
17	後藤	1935	—	自然穿孔発生	—	試験開胸	—
18	宮城[12]	1937	44歳♂	胆石	右肺	胆石摘出＋膿瘍腔ドレナージ	治
19	板津・宮地[13]	1938	25歳♂	胆石	右下肺	保存的	治
20	大城[14]	1943	41歳♂	アメーバ性肝膿瘍	右肺	右胸下部切開排膿	死
21	志田・石田[15]	1947	27歳♂	肝膿瘍	右肺	保存的	死
22	代田[16]	1948	29歳♂	肝膿瘍	右下肺	経皮的膿瘍腔ドレナージ	治
23	橋本[17]	1949	—	横隔膜下膿瘍	右肺	保存的	治
24	砂田[18]	1949	37歳♂	肝膿瘍	右下肺	開胸瘻孔ドレナージ	治
25	上山[19]	1951	31歳♂	肝膿瘍	—	保存的	治
26	乾[20]	1953	64歳♀	アメーバ性肝膿瘍	—	保存的	治
27	渡辺[21]	1954	—	アメーバ性肝膿瘍	—	—	—
28	吉村[22]	1954	38歳♂	横隔膜下膿瘍	右下肺	瘻孔閉鎖＋膿瘍腔掻爬	治
29	吉浦[23]	1955	33歳♂	胆石	右下肺	経肋膜横隔膜間膿瘍腔ドレナージ	治
30	入江[24]	1956	—	肝膿瘍	—	保存的	治
31	伊藤[25]	1957	30歳♂	外傷	右下肺	肺右下葉部分切除＋瘻孔閉鎖＋肝内破裂腔ドレナージ	治
32	中村[26]	1958	27歳♂	エヒノコックス	右肺	肺右葉切除	死

表 2　気管支胆管瘻報告例（その 3）

	報告者	報告年度	症例	原疾患	部位	治療	転帰
33	中村[26]	1958	42歳♂	—	右下肺	肺右下葉切除＋瘻孔掻爬＋肋間腔ドレナージ	治
34	Enjoji[27]	1963	7カ月♂	先天性	気管分岐部	胆嚢空腸吻合＋試験開胸	死
35	矢毛[28]	1963	42歳♂	アメーバ性肝膿瘍	右下肺	瘻孔・肺右下葉部分切除	治
36	土井[29]	1965	45歳♂	肝膿瘍	右下肺	肺部分切除＋瘻孔閉鎖＋腹膜胸腔ドレナージ	死
37	Furusawa[30]	1972	59歳♀	胆石	右中肺	肺右中葉・胆嚢切除＋胸腔ドレナージ	治
38	和田[31]	1972	34歳♂	肝膿瘍	右肺（B_9, B_{10}）	経皮的胸腔穿刺	治
39	槻・佐藤[32]	1972	—	肝膿瘍	—	—	治
40	中村[33]	1973	7カ月♀	先天性	気管分岐部	胆嚢空腸吻合＋試験開胸	死
41	山下[34]	1976	58歳♀	肝膿瘍	右肺（B_9）	経皮的胆管ドレナージ（PTCD）	治
42	岡部[35]	1978	35歳♂	アメーバ性肝膿瘍	右下肺	経皮的膿瘍腔ドレナージ	治
43	近藤[36]	1978	46歳♂	肝石	—	内視鏡的乳頭切開	治
44	安田[37]	1980	—	肝膿瘍	—	—	—
45	山崎[38]	1980	45歳♂	肝・胆道系形成異常	左肺（B_9）	肺縫縮＋瘻孔閉鎖＋肝左葉切除＋肝空腸吻合	治
46	城之内[39]	1980	1歳9カ月♀	先天性	気管分岐部	胸腔内瘻孔切除	治
47	井内[40]	1983	67歳♀	肝・胆道系形成異常	右中肺	開胸肺側瘻孔閉鎖＋横隔膜側瘻孔ドレナージ	死
48	（自験例）	1985	43歳♂	転移性肝腫瘍	右肺（B_9, B_{10}）	経皮的膿瘍腔ドレナージ	死

横隔膜への浸潤は確認し得なかった．従って，塞栓術とは関係なく，直接腫瘍塊が横隔膜下に破れ，横隔膜下膿瘍を形成し，二次的に気管支胆管瘻を形成した可能性も考えられる．しかし，塞栓術施行前に横隔膜下膿瘍を疑わしめる所見はなく，また，剖検時，瘻孔形成部位の転移巣以外の大小の転移巣においても，一様に中心部は壊死に陥っており，しかも腹腔内への腫瘍の波及は認められなかった．従って腫瘍浸潤はすでに肝表面に及び，肺底部も反応性に癒着していたと考えられる．この様な状態のもとで塞栓術により，腫瘍が壊死に陥り，一挙に穿孔したと考えられる．

本症例の如く，肝腫瘍に対する肝動脈塞栓術の合併症としての気管支胆管瘻の発生は，検索した限りにおいて報告はない．しかし，類似例として Jochimsen ら[44]が，64例の肝動肝結紮術に際し6例に肝膿瘍を合併し，うち乳房切断術後，肝転移をきたした乳癌症例で，気管支胆管瘻の発生をみた症例を報告している．

気管支胆管瘻の主症状としては，胆汁を混じた喀痰の排出である．多く感染性胆汁である為，気管支炎症状を示すことになる．そして原疾患の特徴がこれに加わる．本症例においては，発熱，白血球の増多，血沈の亢進など，肝膿瘍による場合とほぼ同様の症状が出現した．本症例において特徴的であったのは背部痛で，塞栓術施行後は，ペンタゾシン15mg，ヒドロキシジン25mg の筋注を1日3～4回必要とした．この背部痛は，胆道結石や肝膿瘍の際も出現するが，本症例では，瘻孔形成過程での肋膜刺激によるものではないかと考えられる．

診断は肝膿瘍による場合，その所見と吸引性肺炎の所見が合わされば，瘻孔が示唆されるが，瘻孔そのものの証明には，やはり経皮胆管造影が有力である．城ノ内ら[39]は，肝胆道シンチグラム(^{99m}Tc-PI)で，また，井内ら[40]は^{99m}Tc-HIDA にて，瘻孔造影に成功している．また，ICG 静注による気管支内吸引物の検索も一法である．我々は腫瘍を穿刺して色素を注入し，気管支鏡下に，気管枝への色素の流入を認めた．この方法では，膿瘍との交通気管支をも確認する事が可能であり，今後試みられて良い方法と考えている．

治療としては，急性期は膿瘍腔のドレナージを主体とし，原疾患に対する加療が重要視されている[45][46]．本邦において，直接瘻孔の閉鎖を行った報告が9例あるが，うち3例は死亡しており，やはり侵襲の面より急性期はドレナージを第1撰択とし，全身状態の改善を計るべきで，しかる後に，瘻孔に対する治療を加えるべきと考える．本症例においては，腫瘍壊死巣にドレナージを加える一方，気管内挿管し，気管内吸引及び洗浄を繰り返した．しかし，原疾患である転移性肝腫瘍に対する，積極的な治療方法はもはやなく，しかも，すでに悪液質に陥り，加えて肺炎を併発したため，全身状態が急速に悪化し死亡した．

本症の予後について，1938年の Ochsner and Debakey ら[47]の報告では死亡率50%で，1933年杉村[11]の報告では，世界的には43%，本邦では83%の死亡率であった．近年では，Ibarra ら[48]は5.2%の死亡率と報告し，Adams ら[42]の報告もこれに近い．本邦においては，1972年以後の死亡率は23%で，以前に比らべ，やはり激減している．これらは，診断技術の向上と，化学療法の発達によるところが大きいと思われる．

総　括

転移性肝腫瘍に対し，肝動脈塞栓術を施行した．その結果，腫瘍縮小効果は得られたが，気管支胆管瘻の発生をみ，呼吸不全のため施行後29日目に死亡した．

気管支胆管瘻の成因としては，塞栓術施行時すでに肝表面へ腫瘍浸潤および，腫瘍部分が壊死に陥ることにより，一挙に穿孔したと考えられた．

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CASE OF BRONCHOBILIARY FISTULA FOLLOWING HEPATIC ARTERY EMBOLIZATION FOR METASTATIC LIVER TUMOR

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Hepatic artery embolization was performed for metastatic liver lesions in a 43-year-old man with gastrinoma. The tumor invading the diaphragm necrotized. Subsequently, a bronchobiliary fistula was formed between the tumor and the lower lobe bronchus of the right lung. The patient died of respiratory failure. Forty-Eight cases of bronchobiliary fistula reported in Japan were reviewed.

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症例

Extended descending thoracic aneurysmに対する血栓嚢置化術の1治験例

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(〒737 呉市青山町 3-1)

§ 抄録

動悸および全身倦怠感を主訴とする70歳男性に，血管造影，CTscan等を施行し，extended descending thoracic aneurysmと診断した．また昭和56年度の集団検診時に比し，入院時の胸部X線像に，明らかなる大動脈陰影の拡大を認めたため，手術適応と判断した．患者は高齢，かつ低肺機能であるためCarpentierのaortic clampを用いて，大動脈瘤の末梢側にもclampを加える方法で，血栓嚢置化術を施行した．術後経過は順調であるが，末梢側clampよりの嚢置腔内へのleakageが判明した．そのためか，術後8カ月目のCTscanにおいて，嚢置腔内の血栓化は，中枢側の一部を除き，ほとんど進行していないことが確認された．

(心臓 17：901～906，1985.)

A case of thromboexclusion thchnique for extended descending thoracic aneurysm

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extended discending thoracic aneurysm
Carpentier's permanent aortic clamp

1979年Carpentier[1]により，解離性大動脈瘤に対する新しい手術方法として，いわゆる血栓嚢置化術が発表された．以来，本邦でも類似の術式の報告をみるようになった．

今回われわれは，extended descending thoracic aneurysmに対し，Carpentierのpermanent aortic clampを用いて血栓嚢置化術を施行した．その結果，末梢側clampより嚢置腔内へのleakageを生じた1症例を経験したので，若干の文献的考察を加えて報告する．

§ 症例

患者：70歳，男性．

主訴：動悸および全身倦怠感．

既往歴：昭和38年腹部外傷，聴力不能．

家族歴：特記すべきことなし．

現病歴：昭和56年7月の集団検診にて，胸部X線上，異常陰影を指摘された(図1左)．昭和58年に入り自覚症状の出現および異常陰影の拡大が指摘され，諸検査の結果，同年11月8日当科入院となった．

入院時現症：身長164 cm．体重53 kg．栄養状態は良好．呼吸音は清で，心音は純．血圧128/74 mmHg．脈拍80回/分．末梢動脈はすべて触知良好であった．腹部は平担かつ軟で，特に異常を認めなかった．また神経学的にも，聴力不能以外，特に異常は認めなかった．

入院時検査：表1に示すごとく，血沈の亢進と，CRP 3＋，RPR＋，TPHA＋を認め，また肺機能で1秒率の低下を認めた．

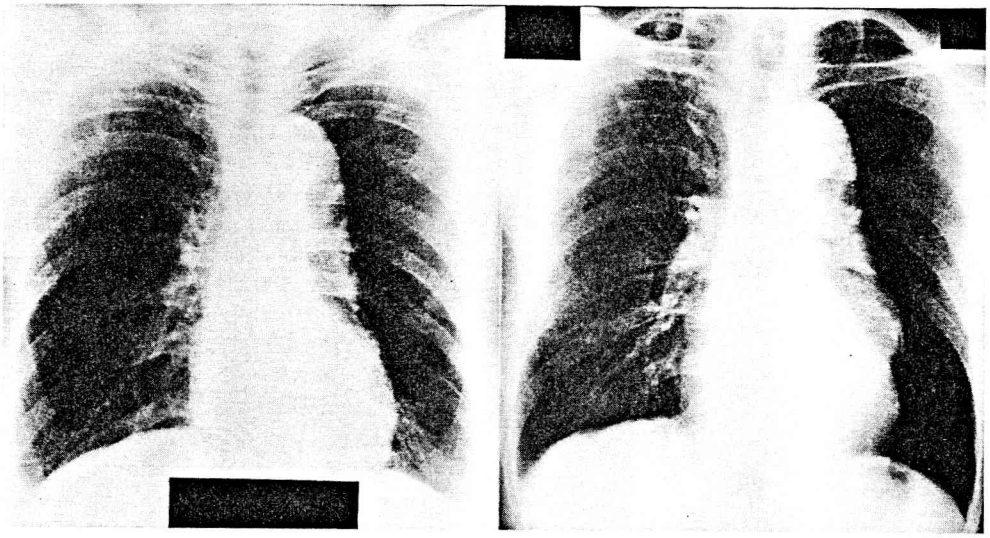

図 1　左：昭和 56 年 7 月の集団検診時の胸部X線.
右：昭和 58 年 11 月の入院時の胸部X線で，明らかに大動脈の陰影に変化が認められる.

胸部X線像(図 1 右)：心臓の陰影に重なる大動脈の陰影と，気管の右方への圧排が認められた．また昭和 56 年の集検時の胸部X線 (図 1 左) に比し，大動脈の陰影は明らかに拡大しているのが確認された.

血管造影(図 2)：大動脈は，左腕頭動脈分岐部あたりより径を増し，胸部下行大動脈で，瘤を形成していた．また横隔膜下でも，大動脈はその径を増しているように思われた.

CTscan (図 3)：上は下行動脈部で瘤のほぼ最大径の部位での断層像である．61 mm であった．下は，肝横隔膜面より末梢側の，腹腔内での断層像である．大動脈はやはり腹腔内においてもその径を増しているのが確認できた.

以上の所見より extended descending thoracic aneurysm と診断した．また昭和 56 年の集団検診時の胸部X線像および入院時の胸部X線像の変化より，手術適応であると考えた.

胸腹部におよぶ大動脈瘤であり，高年齢でかつ肺機能にも異常を認めることにより，昭和 58 年 11 月 22 日血栓嚢置化術を施行した.

手術所見 (図 4) および経過：胸骨正中切開および腹部正中切開し，胸部は大動脈基部より弓部を露出した．次に，腹部は，まず横隔膜を前方より下大静脈に向って切開し，肝左葉を剝離，右方へ圧排した．さらに，胃小彎側より胃の後面，膵十二指腸後面を指で鈍的に剝離し，後腹膜にトンネルを作成した．一方，腹部大動脈は前面より到達し，腎動脈の末梢部，下腸間膜動脈との間で露出した.

表 1　入院時検査

検血：RBC 433×10³/mm³, WBC 5,600/mm³, Hb 14.0 g/d*l*, Ht 42.7 %, p*l*. 16.9×10⁴/mm³
血沈：1 時間値 45 mm, 2 時間値 85 mm
血清電解質：Na 145 mEq/*l*, K 4.5 mEq/*l*, Cl 105 mEq/*l*
肝機能：GOT 18 IU/*l*, GPT 12 IU/*l*, Alp 213 IU/*l*, γ-GTP 17 IU/*l*, T-Bil 0.4 mg/d*l*, ZTT 5.7 K-U, TP 6.8 g/d*l*, Alb 3.8 g/d*l*
腎機能：BUN 16.8 mg/d*l*, クレアチニン 0.8 mg/d*l*
血清反応：CRP(3+), RPR(+), TPHA(+), RAHA 40↓, ASLO 128, ASK 1,280
動脈血ガス：pH 7.37, $Paco_2$ 41 mmHg, Pao_2 83 mmHg, HCO_3^- 24 mEq/*l*, BE-1 mEq/*l*, SaO_2 96 %
肺機能：% VC 91.0 %, $FEV_{1.0}$ 65.6 %
検尿：特に異常なし
検便：特に異常なし

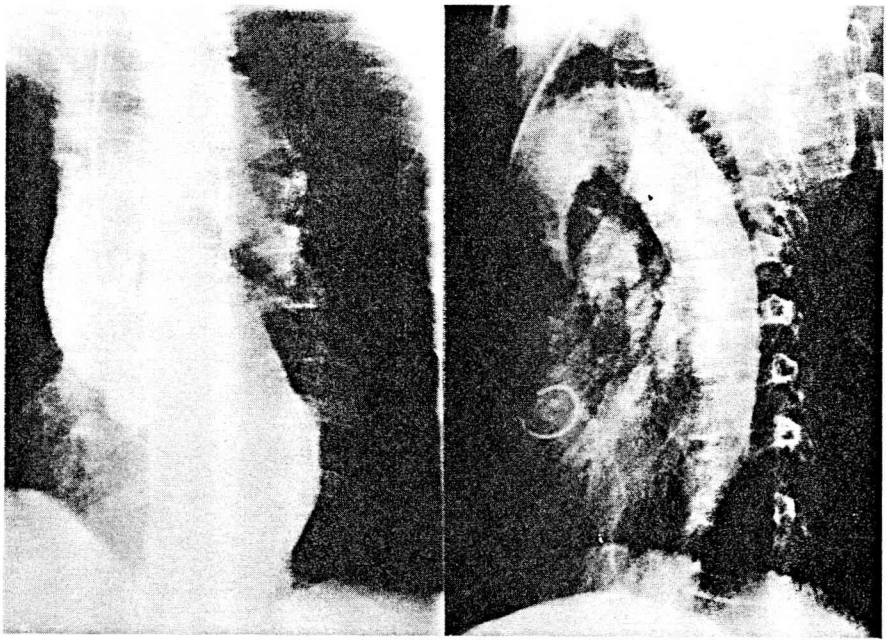

図 2 術前の血管造影：やや不鮮明でわかりにくいが，胸部下行大動脈で瘤を形成し，横隔膜下でも，大動脈はその径を増している様に思われた．

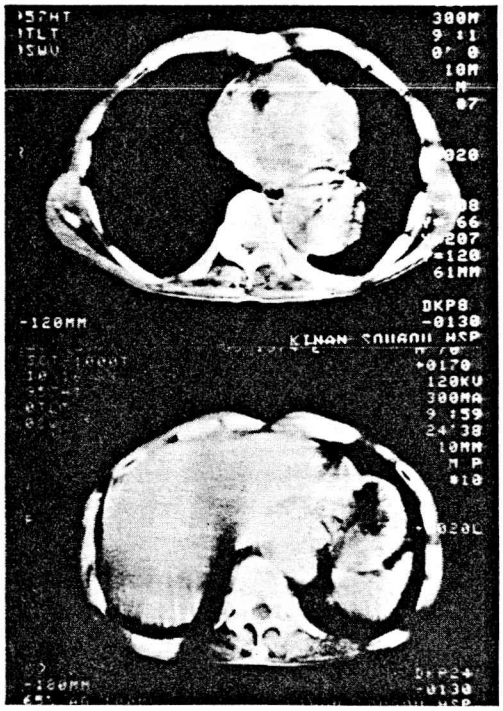

図 3 上：ほぼ最大径の部位である．61 mm であった．下：肝横隔膜面より末梢側である．やはりその径を増している．

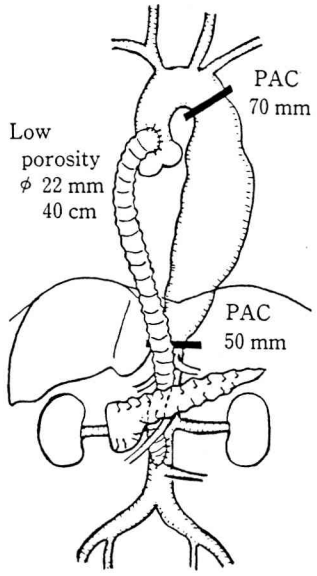

図 4 手術術式
PAC：permanent aortic clamp

ヘパリン静注後，腹部大動脈および上行大動脈には side clamp をかけ φ 22 mm の人工血管（low porosity woven Dacron）を end to side に吻合した．人工血管は上行大動脈より右心房，下

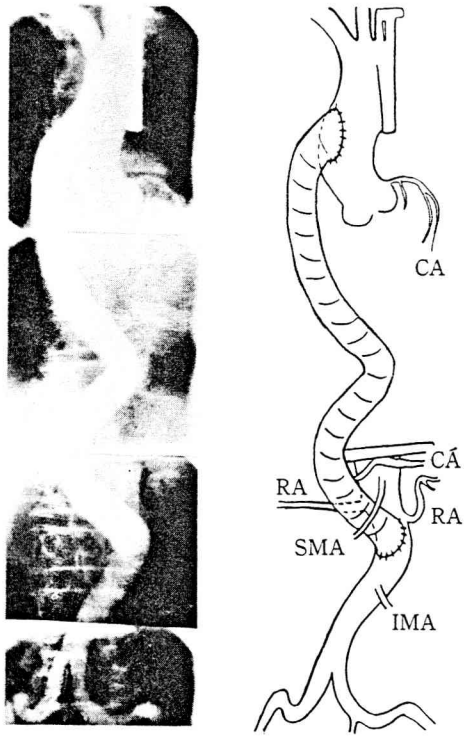

図 5　術後血管造影（その 1）：人工血管中の良好な血流を認める．
CA：冠動脈，RA：腎動脈
SMA：上腸間膜動脈
IMA：下腸間膜動脈
CÁ：腹腔動脈

大静脈の前面を下り，横隔膜を貫通し，胃膵十二指腸後面を後腹膜トンネル経由で腹部大動脈に到達することとなった．

人工血管縫着後，70 mm の Carpentier の clamp を左腕頭動脈分岐部の末梢胸部大動脈にかけ，最後に 50 mm の clamp を腹腔動脈の中枢側腹部大動脈にかけて，瘤内部の圧の減弱を触診による拍動の消失により確認して手術を終えた．術中出血量は 2,450 m*l* であった．

術後経過は，順調であった．また術直後より，Ht は 40％前後，PT も 100％前後の値を示していた．しかし，術後 16 日目の CTscan では，嚢置腔内は血栓化されていないことが判明した．そこで，術後 30 日目に血管造影を施行した．

まず左上腕よりカテーテルを挿入し造影した（図 5）．大動脈瘤の中枢側にかけた clamp により，嚢置腔内は完全に遮断されており，人工血管

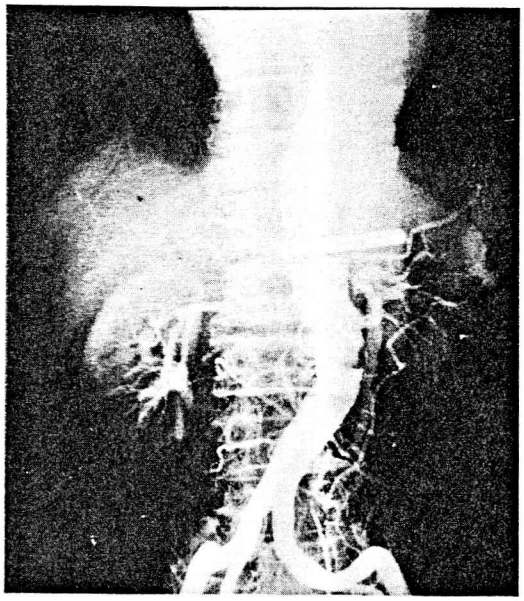

図 6　術後血管造影（その 2）：末梢側の clamp より，嚢置腔内へのリークが認められる．

中の良好な血液の流れが認められた．次に，腹腔内の動脈は，人工血管吻合部よりの逆向きの血流をうけ，はっきりと造影された．しかし，同時に末梢側 clamp よりの嚢置腔内への leakage を認めた（図 6）．

このあと退院とし，外来にて経過観察を続けた．外来では，大動脈の変化を CTscan にて追跡した．図 7 に，術後 8 カ月目の CTscan を示す．嚢置化腔の中枢側では（図 7 上段），血管径の半分近くまで血栓化されており，中枢側では血栓化が進んできているのが確認された．しかし，嚢置化腔のほぼ中央でもある瘤の最大径の部位（図 7 下段）および，末梢側では血栓化はごく一部に認めるにすぎないことが確認された．

患者は，現在，元気に日常生活を送っており，外来での follow を続けている．

§　考按

大動脈瘤に対する外科治療は，近年分離体外循環，一時バイパス法などの方法により，著しく進歩してきている．

① 手術方法について

1979 年 Carpentier[1] が新しい手術方法を提唱した．それは大動脈瘤の中枢側を clamp により永

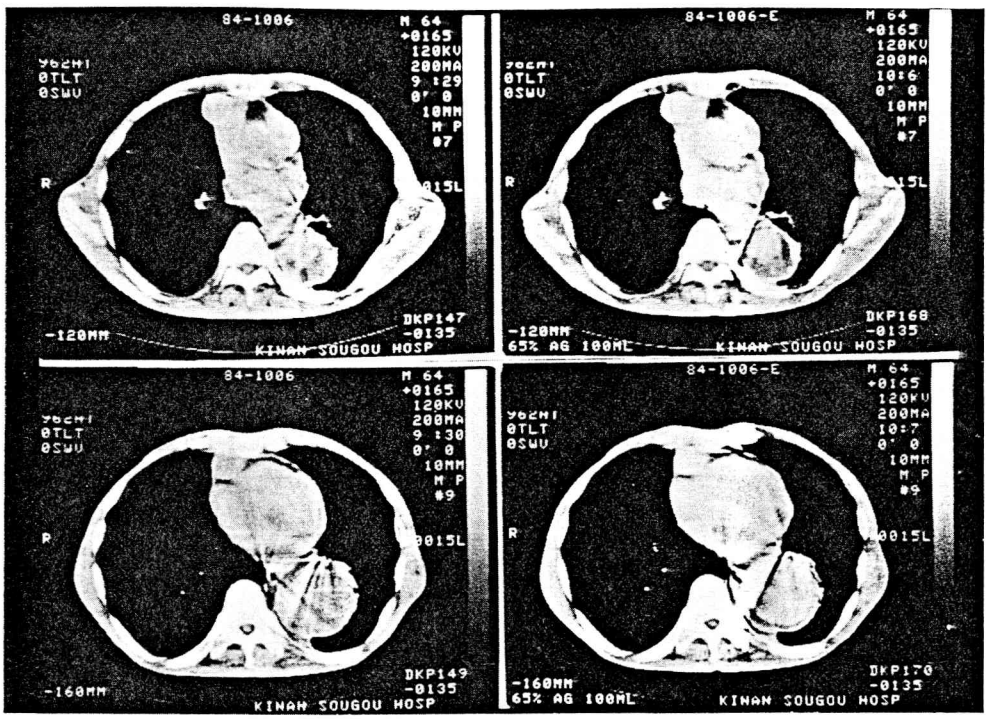

図 7 術後8カ月目の CTscan：右側は，エンハンスした像である．瘤の最大径の部位では血栓化はごく一部にとどまり，血栓化が進行していないことがわかる．

久的遮断し，さらにその中枢側の上行大動脈と大動脈瘤の末梢側である腹部大動脈に extra-anatomical に bypass する方法である．これにより，瘤内部は腹部大動脈から逆向きの血流を受けるが，主要動脈の流域を残し，次第に血栓腔になるというものである．

この血栓嚢置化術は，現在，主に解離性大動脈瘤において施行，研究されており，手術手技的に容易であること，また出血量，合併症が少ないことが諸家により報ぜられている[2)~4)]．

本症例の場合，昭和56年の集団検診時の胸部X線像で異常陰影を指摘された頃より，当院で follow されていた．昭和58年に入り，自覚症状の出現に加えて，瘤の拡大を認めたため，手術が必要であると考えた．しかし，従来の人工血管置換術では，高齢および低肺機能を有する当患者にとって，手術侵襲が過大であるため，血栓嚢置化術が適応であると考えた．血栓嚢置化術の手術適応に関しては川田ら[3)]によりすでに提唱されているが，われわれも，真性大動脈瘤の場合，A. 高齢者，B. poor risk の患者（特に，肺機能の低下，炎症を伴う場合），C. 大動脈瘤が広範囲におよぶものを適応と考えている．

② 末梢側にも clamp を加えるかどうかについて

嚢置化の方法については，Carpentier の原法のごとく，中枢側のみに clamp をおく方法と，大動脈瘤の末梢側にも clamp を加える方法とが行われている．末梢側にも clamp を加える方法を指示する報告としては，橋本，島津[5)]，岩[6)]の報告がある．橋本，島津の報告によると，末梢側 clamp 群では術後3～4日嚢置部は主として内胸動脈を介する側副血行が保たれ，その後血栓により埋まる．これは Carpentier 法より有利であり，これによる脊髄麻痺はおこらなかったとしている．また実際，解離性大動脈瘤において Carpentier の原法では早期に圧が減弱できないため，術後解離腔の拡大や破裂がおこったとの報告[7)]もみうけられる．したがって，本症例においては，あくまで圧の減弱が必要と判断して末梢側 clamp を加えた．

しかし，血栓嚢置化という意味では，結果的に末梢側 clamp よりの leakage が残り，術後8カ月

にしてなお，血栓化は中枢側 clamp の部位でしか進んでおらず，瘤の最大径より末梢側では，ほとんど血栓化されていないことが判明した．一方，完全な末梢側 clamp 症例においても，術後血栓化されていないことが判明したとの報告[8]もあるが，本症例においては，末梢側の leakage が血栓化をおくらせる要因となっていることは，確実であると考えられる．

血栓嚢置化術の合併症として脊髄麻痺が問題とされている．実際，対麻痺がおこったとの報告[9]もあるが，解剖学的に，内胸動脈から脊髄動脈へ行く経路が，動脈の解離等で損傷されないかぎり脊髄損傷の可能性は少ないと考えている．本症例の場合，末梢側 clamp からの leakage が原因となり，血栓化がおくれていると考えられるが，脊髄動脈の閉塞という観点からは，逆に leakage が好結果をもたらしていると考えられる．

③ Carpentier の aortic clamp の器具について

Carpentier の clamp は，特に深部での操作には構造上困難を必要とする．不安定であり，硬くしめにくくできており，逆にしめすぎると，深部ではゆるめることは非常に困難を必要とする．またしめすぎると，形としては三角形に近い形となり，血管の一方は損傷するほどしまっても，反対側は leakage が残る可能性があると考えられる．このため，本症例では，中枢側は比較的問題なくかけ得たが，末梢側においては深部操作となり，leakage が残る結果となった．一方，橋本，島津らの clamp にも多少の問題があると報告[10]されており，新たなる clamp の出現が望まれる．

§ まとめ

Extended descending thoracic aneurysm に対し Carpentier の permanent aortic clamp を用いて血栓嚢置化術を施行し，その結果，末梢側 clamp よりの leakage を生じた1例を経験したので報告した．

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