

Surgical Treatment of Budd-Chiari Syndrome Induced by Behcet's Disease

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Objective: Although Budd-Chiari syndrome in Japanese is usually chronic, and of unknown etiology and idiopathic, Behcet's disease is rare as an underlying disorder of Budd-Chiari syndrome in Japanese. To clarify the Behcet-induced Budd-Chiari syndrome, the clinical course and pathologic findings of patients with Behcet-induced Budd-Chiari syndrome were compared with those of patients with idiopathic Budd-Chiari syndrome.

Patients and Methods: We treated 45 patients (15 women and 30 men) with our devised surgical procedure. With normothermic partial bypass, the occluded vena cava and hepatic veins were reopened. The age of the patients ranged from 24 to 76 years (mean, 48.9 ± 13.0 years). In two patients, Budd-Chiari syndrome was induced by Behcet's disease (Behcet group). The other 43 patients (control group) had no distinct underlying disorder. The Behcet group was compared to the control group with regards to (1) onset of symptoms and duration of illness prior to medical treatment, (2) preoperative laboratory data including liver function, (3) intraoperative findings, (4) microscopic findings of liver tissue, and (5) postoperative course.

Results: (1) In the Behcet group, duration of illness from diagnosis to surgical treatment was markedly shorter ($P=0.027$, 8.5 months vs. 10.1 ± 10.6 years). (2) The preoperative laboratory data of liver function were similar in both groups with moderately impaired hepatic function. (3) The Behcet group had no patent hepatic vein ($P=0.025$ vs. 1.22 ± 0.57). (4) Microscopic examination of the liver tissue showed liver cirrhosis or liver fibrosis in the control group, and centrilobular marked congestion only in the Behcet group. (5) During hospitalization, one patient of the control group died due to preoperative severe hepatic failure. One patient with Behcet's disease underwent reoperation due to reocclusion by Behcet-induced vasculitis, and the other died of peritonitis by intestinal Behcet's disease.

Conclusion: In Budd-Chiari syndrome in Japanese, the Behcet-induced Budd-Chiari syndrome had an acute clinical course, and its postoperative prognosis depends on the prognosis of the Behcet's disease. (*Ann Thorac Cardiovasc Surg* 2002; 8: 374–80)

Key words: Budd-Chiari syndrome, Behcet's disease

Introduction

Budd-Chiari syndrome (BCS) is caused by total or partial obstruction of the hepatic veins (HVs) with or without inferior vena cava occlusion, and this syndrome may

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be a result of intravascular thrombus, polycythemia rubra vera, Behcet's disease, myeloproliferative disorders, contraceptive use, malignancy, pregnancy, postpartum state or trauma. In BCS in Japanese, the underlying cause is generally idiopathic, and long periods of illness including ascites, leg swelling, varicose veins, esophageal varices, and venous dilatation of the abdomen finally progress to liver cirrhosis. Behcet's disease is rare as an underlying disorder of BCS in Japanese, and Behcet-induced BCS shows a quite different clinical course compared to that of idiopathic BCS. We compare the clinical

course and pathologic findings of patients with Behcet-induced BCS with those of patients with idiopathic BCS to clarify the clinical feature of Behcet-induced BCS.

Patients and Methods

From December 1979 through May 2002, we operated on 45 patients with BCS with our devised surgical procedure.^{1,2)} With femorofemoral normothermic partial bypass, the obstructed lesion was directly repaired. The occluded vena cava was opened, and endovenectomy was performed. To widen the luminal space of the vena cava and reopen the ostia of the HVs, the thick caval wall involving the hepatic tissue was partially resected. We reopened as many of the obstructed HVs as possible. Finally, autopericardium was used for autologous patch graft to close the caval venotomy. The patients (15 women and 30 men) were aged 24 to 76 years (mean 48.9 ± 13.0 years). Etiologically, in two out of 45 patients (5.1%), BCS was induced by Behcet's disease (Behcet group). The other 43 patients (control group) had no distinct underlying disorder. To characterize the features of BCS induced by Behcet's disease, the Behcet group was compared to the control group with regards to (1) onset of symptoms and duration of illness prior to medical treatment, (2) preoperative laboratory data focusing liver function, (3) intraoperative findings, i.e., the number of patent HVs, (4) microscopic findings of liver tissue, and (5) postoperative course.

Control group (n=43)

The average age of the control group patients was 49.2 ± 12.6 years, and they were 29 men and 14 women. The average duration of illness was 10.1 ± 10.6 years, and the early symptoms from which diagnosis was made were slight liver function impairment and slight distention of the abdomen and legs. The patients of this group also underwent our devised radical operation.^{1,2)} There was one hospital death case who had suffered severe hepatic failure and underwent the serum exchange therapy prior to the surgery. The other patients were discharged in good condition. In intraoperative findings, 42 patients except one patient had at least one patent HV with the average being 1.22 ± 0.57 . Microscopic findings of the liver specimen obtained during surgery indicated liver cirrhosis in 29 patients and liver fibrosis in 14. During the postoperative long-term follow-up, obstruction of the reconstructed region occurred in two patients who underwent reoperation and PTA with successful results. During the

reoperation, the cause of occlusion was found to be compression from circumference tissue.

Behcet group (n=2)

Case 1

A 24-year-old man was diagnosed with Behcet's disease because he suffered intractable recurrent stomatitis and folliculitis, and he was treated with 5 to 20 mg Predonine for three years. In 1992, he suffered sudden abdominal distension with hepatomegaly, which progressed rapidly and was accompanied by swelling of both legs. Computed tomography (CT), magnet resonance imaging (MRI), and venography showed extensive occlusion of the inferior vena cava (IVC), excluding the suprahepatic IVC and a part of the IVC drained by bilateral renal veins. All three HV outflows were occluded by this IVC obstruction. The patient was referred to our hospital for surgical treatment 11 months after medical treatment involving three failed attempts to open the IVC with percutaneous transluminal angioplasty (PTA). Our procedure for radical surgical correction for BCS was performed.^{1,2)} The occluding tissue in the IVC and the liver parenchyma facing the retrohepatic IVC were resected to reopen the IVC and thereby restore flow to the HVs. The autopericardium was sutured in advance to a polytetrafluoroethylene (PTFE) graft (20-mm diameter) to make a long composite graft by which the subtotal occluded IVC was reconstructed. Microscopic examination of a liver specimen showed marked liver congestion without fibrosis, and the occluding tissue in the IVC was found to be granulomatous tissue that was microscopically shown to be rich in fibrous components. The postoperative course was uneventful. Postoperative venography showed good patency of the retrohepatic IVC and the three HVs. The portion of the infrahepatic IVC reconstructed with the PTFE graft was occluded (Fig. 1). After discharge, the patient was given Predonine for Behcet's disease and warfarin for anticoagulation. Five years after the surgery, he suffered a recurrence of sudden abdominal distension with hepatomegaly, high fever, and stomatitis. Enhanced CT of the liver showed circulation only in the quadrate lobe. This was due to obstruction of the HV outflows by a retrohepatic IVC occlusion. A reoperation was performed according to Senning's procedure³⁾ with cardiopulmonary bypass at a rectal temperature of 20°C. The retrohepatic and suprahepatic IVCs were occluded completely with a granulomatous mass that extended into the right atrium and occupied two-thirds of the right atrial space. To avoid the previous operative field because of its severe adhesions

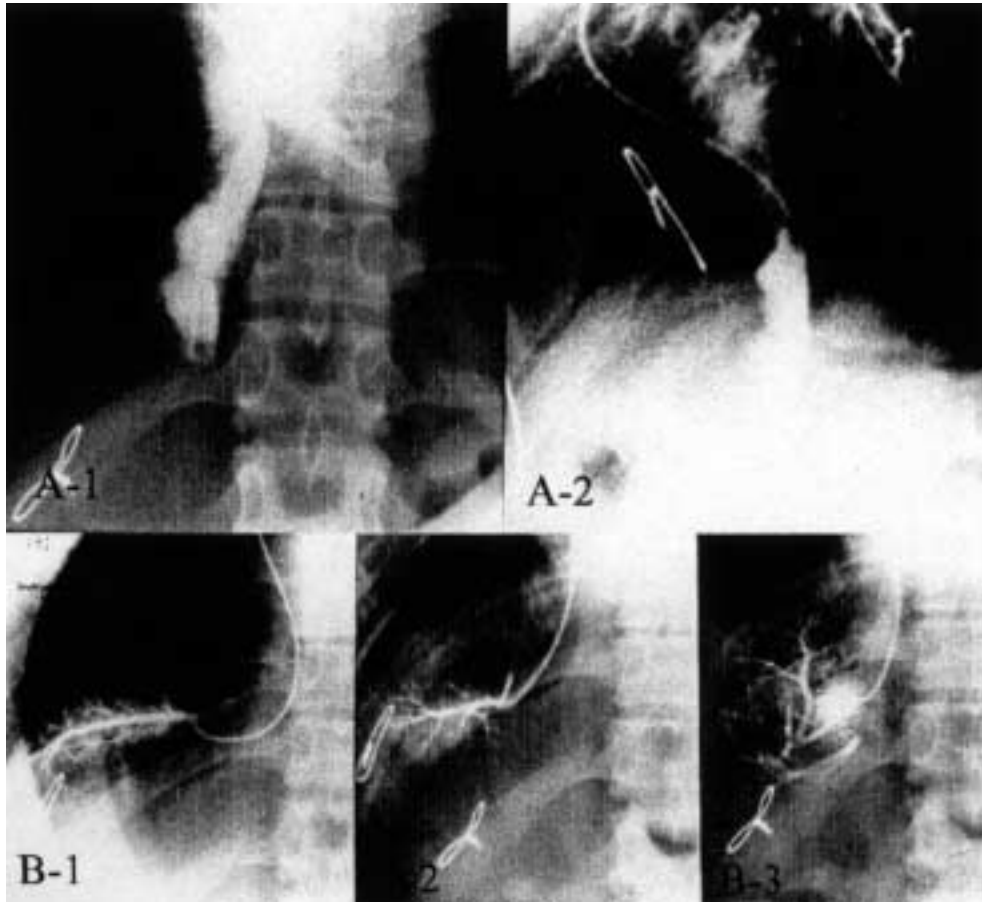


Fig. 1. The retrohepatic inferior vena cava reconstructed with autopericardium was opened (A-1, 2); however, the inferior vena cava reconstructed with PTFE was occluded. Three major hepatic veins are all patent (B-1, 2, 3).

and to reach the patent HVs from a new operative approach, the liver parenchyma was resected from the superior surface of the liver. The right atrial wall that was infiltrated with the granulomatous mass was extirpated. Xenograft was used to make a bypass pathway between the right atrium and the new HV outflow of the liver. The postoperative course was uneventful. Postoperative venography showed good patency of the HVs, and the constructed pathway between the liver and right atrium had no stenosis (Fig. 2). The microscopic findings of his liver specimen showed marked liver congestion, and the resected right atrial wall had considerable fibrosis.

Case 2

A 58-year-old woman was admitted to our hospital with a clinical history of sudden onset of abdominal disten-

sion with ascites and medical treatment six months earlier. Liver echography and CT findings suggested BCS. IVC venography showed severe stenosis at the junction of the retrohepatic IVC and suprahepatic IVC. There were no patent HVs, and BCS was diagnosed. Surgery was performed according to our operative procedure.^{1,2)} Intraoperatively, all three HVs were occluded with fibrous tissue. To reopen the HVs, the fibrous tissue at the IVC wall was extirpated, and the surrounding liver parenchyma was resected. There were a few small HVs. The microscopic findings of her liver specimen showed marked congestion. The postoperative course was uneventful, and the patient was discharged in good condition, however was readmitted for ileus with abdominal distension three months after surgery. No improvement of ileus occurred with conservative therapy; therefore, an emergency lap-

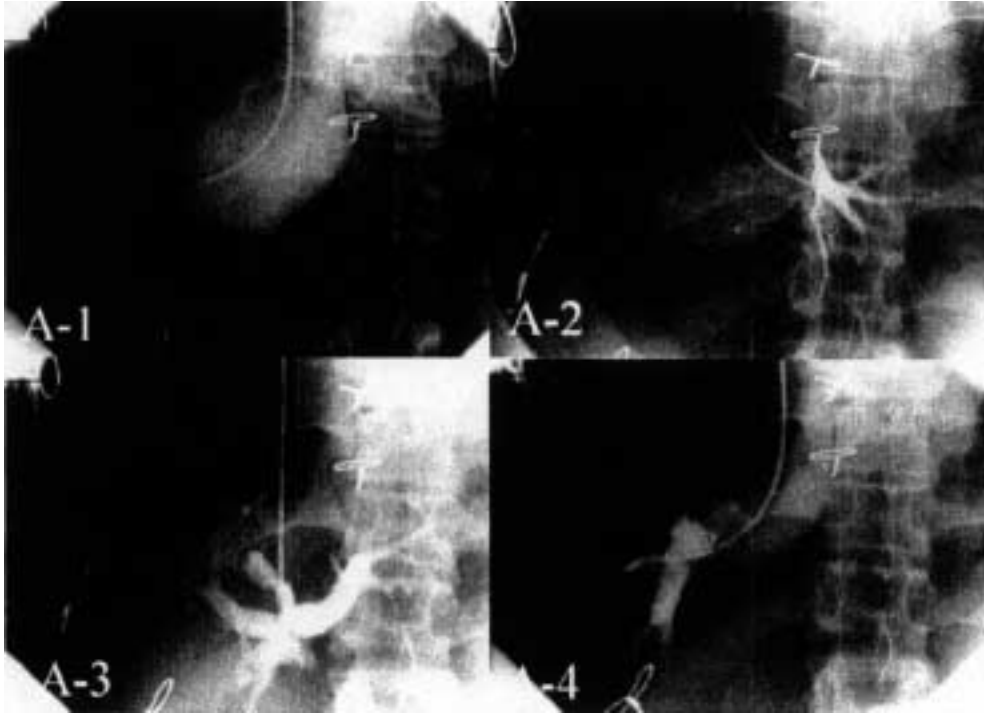


Fig. 2. Venography shows the chamber that formed from liver extirpation to reopen the three major hepatic veins (A-1). Through this chamber, the three hepatic veins were observed to be patent (A-2, 3, 4).

arotomy was performed. The peritoneal cavity was occupied by a high volume of ascites without signs of infection. A reddish, swollen section of the ileum, located about 100 cm from the end of the ileum, contained two deep ulcers that could be seen through the serosal surface and were in impending danger of perforating the opposite side of the mesentery. In the specimen of resected ileum, linear ulcerations were found associated with the two ulcers parallel to and along the long axis of ileum (Fig. 3). No lymph nodes in the mesentery were swollen. Microscopic examination showed that the ulcers were deep and surrounded by well-developed, granulomatous tissue and an infiltration of inflammatory cells. Behcet's disease had not been diagnosed by the time of the surgery for ileus. Examination of the resected small intestine led to a diagnosis of Behcet's disease accompanied by neurological abnormality involving stupor, which suggested neuro-Behcet's disease. This patient had no history of treatment directly for Behcet's disease. The patient had slight improvement after the laparotomy but died from multiorgan failure secondary to disseminated intravascular coagulopathy 10 days later, which was five

months after her initial surgery.

Statistical analysis

Data were analyzed by the Stat View 5.0 (SAS institute, Cary, NC) statistical software packages. Data are expressed as mean \pm standard deviation (SD). Differences of variables in results were compared by Mann-Whitney's test.

Results

(1) Duration of illness from diagnosis to surgical treatment

In the control group, duration of illness from diagnosis to surgical treatment ranged from 0.3 to 41 years (mean, 10.1 \pm 10.6 years), and in the two patients of the Behcet group the duration 11 months in one and six months in the other. The period in the Behcet group is significantly shorter ($P=0.027$).

(2) Preoperative laboratory data including liver function (Table 1)

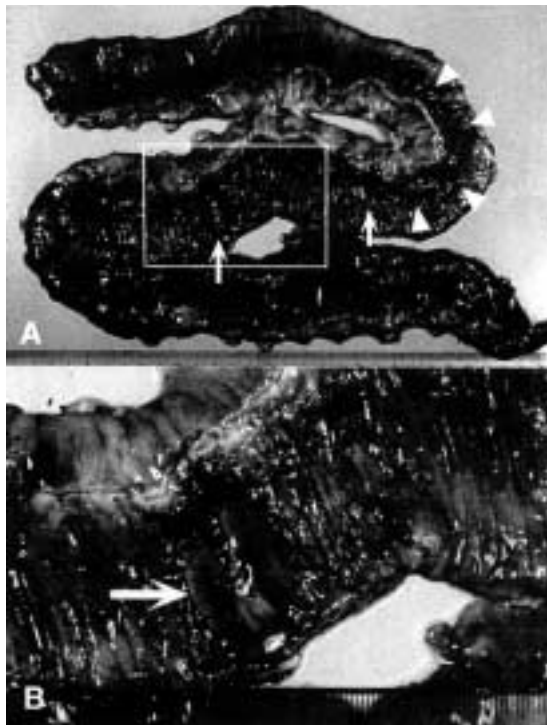


Fig. 3. The two deep intestinal ulcers (arrows), and linear ulcers (arrowheads) along the long axis are found in the resected specimen of the ileum (A). The ulceration (arrow) is so deep that intestinal perforation is imminent (B).

The preoperative laboratory data for 19 parameters related to liver function were similar between the two groups.

(3) Intraoperative findings, i.e., the number of preoperative patent HVs

The patency of the control group HVs ranged from 0 to 3 with an average of 1.22 ± 0.57 per patient. The Behcet group had no patent HVs. In case 1, the HVs were occluded by a granulomatous mass at both operations. In case 2, the ostia of the HVs were all occluded with thick fibrous tissue. The patency of both groups showed significantly difference ($P=0.025$).

(4) Microscopic findings of liver tissue

Microscopic examination of the liver tissue showed liver cirrhosis in 29 patients, liver fibrosis in 14 patients, and centrilobular marked congestion only in the two Behcet's disease patients. In the case of the 24-year-old man, microscopic examination showed severe congestion even

at the reoperation.

(5) Postoperative course

There was only one hospital death in all patients. Seven patients died during the follow-up period: two from hepatoma, one from pneumonia, one from suicide, one from cerebral infarction, one from arrhythmia, and one from peritonitis (patient 2 in the Behcet group). Three patients with restenosis were treated successfully with PTA in one patient and with reoperation in the other two including patient 1 of the Behcet group. All other survivors of the control group have remained well for two months to 22.2 years with an average of 8.8 ± 6.0 years and with considerable improvement of symptoms related to portal hypertension and caval stagnation. The cumulative survival rates were 95.5% at one year, 87.8% at five years, 81.2% at 10 years, 75.8% at 15 years, and 75.8% at 20 years (Fig. 4). One of the two patients with Behcet's disease underwent reoperation due to reocclusion of the reconstructed region five years after surgery, and the other died of peritonitis five months after surgery.

Discussion

The clinical course of BCS caused by Behcet's disease is rapid and is quite different from that of idiopathic BCS. Among our 45 patients, only the two patients with BCS induced by Behcet's disease had a clear underlying disease. The incidence of Behcet's disease as a cause of BCS is reported at 2 to 5.8%³⁻⁵⁾ which is almost the same rate as that in our series. In Turkey, the prevalence of Behcet's disease is markedly high at 42.4%.⁶⁾ The cause of Behcet's disease remains unknown, and the reported regional differences in its occurrence obviously imply that unknown regional factors may be involved or that the cause may vary between populations.⁴⁾ Since there are no specific diagnostic laboratory clues for Behcet's disease, its diagnosis relies on history taking and clinical manifestations and is made according to diagnostic criteria.⁷⁾ Behcet's disease is known to be a multi-system disorder in which vasculitis plays a major role. The potential mechanism of Behcet's disease as a cause of BCS is venous thrombosis induced by thrombophlebitis, which is characterized by a relapse and disease progression.

The cause of reobstruction of the reconstructed IVC in our series was quite different between the patients with Behcet's disease and patients with idiopathic BCS. In the patients with idiopathic BCS, the cause of reocclusion was compression by circumference tissue. In the Behcet's

Table 1. Liver function and its related laboratory data (preoperative data) (n=45)

No		Control group (n=43)		Behcet group (n=2)		P value
		Avg±SD	Case 1	Case 1	Avg±SD	
1	Total protein (g/dl)	7.3±0.7	7.7	6.6	7.15±0.78	ns
2	Albumin (g/dl)	3.8±0.5	3.9	2.8	3.35±0.78	ns
3	Albumin/Globulin ratio	1.1±0.2	1.03	0.74	0.89±0.21	ns
4	Total bilirubin (mg/dl)	1.7±0.8	0.5	1.5	1±0.71	ns
5	GOT (IU/L)	37.2±13.4	30	37	33.5±4.95	ns
6	GPT (IU/L)	31 ±13.6	74	21	47.5±37.5	ns
7	LDH (IU/L)	406.2±163.4	368	607	487.5±169	ns
8	LAP (IU/L)	238.2±73.4	349	179	264±120	ns
9	ChE (IU/L)	326.3±100.1	427	229	328±140	ns
10	γ-GTP (IU/L)	70.4±49.4	195	34	114.5±113	ns
11	TTT(KU)	8.7±6.4	11.5	11.2	11.35±0.21	ns
12	ZTT (KU)	13.9±5.0	15.7	17.5	16.6±1.27	ns
13	ICG test (15') preoperation (%)	32.4±17.4	17.1	63.1	40.1±32.5	ns
14	ICG test (15') postoperation (%)	29.4±17.5	13	30	21.5±12.0	ns
15	Platelet counts (×10 ⁴ /μl)	10.8±4.8	24.6	26.6	25.6±1.41	ns
16	Thrombo test (%)	63.6±18.1	65	67	66.0±1.41	ns
17	Partial thromboplastine test (sec)	44.8±11.2	53.9	41.7	47.8±8.63	ns
18	Fibrinogen (mg/dl)	257.6±82.8	517	262	390±180	ns
19	FDP (μg/dl)	6.9±7.5	3	4	3.5±0.71	ns

The liver function related laboratory data show moderately impaired liver dysfunction in the patients with BCS (n=43). The patients with BCS induced Behcet's disease had no characteristic laboratory data compared with the control group. All value is shown as mean±SD.

ICG test (15'): indocyanine green excretion ratio at 15 minutes, GOT: glutamic oxaloacetic transaminase

GPT: glutamic pyruvic transaminase, LDH: lactate dehydrogenase, LAP: leucine aminopeptidase, ChE: cholinesterase

γGTP: γ-glutamyl transpeptidase, TTT: thymol turbidity test, ZTT: zinc sulfate test, FDP: fibrin degradation products

disease patients, granulomatous tissue occupied and occluded the IVC and HVs. The granulomatous tissue was formed as a result of fibrosis. A thrombus formed, extended into the right atrium, and was organized progressively like a malignant proliferative tumor. Macdonald et al.⁸⁾ and Davies⁹⁾ described organized thrombus extending into the right atrium and a lymphocytic infiltration in

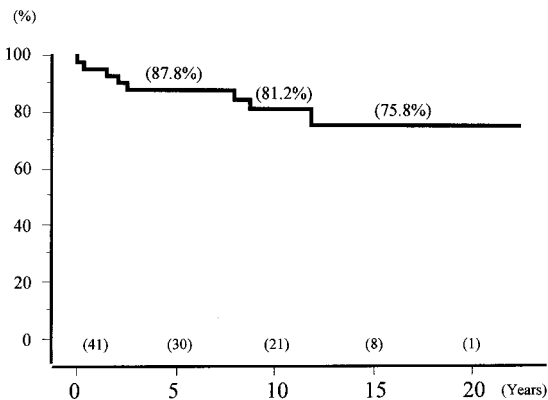


Fig. 4. Cumulative survival curve of all patients including hospital death patient.

the IVC wall and liver tissue in BCS patients with Behcet's disease. An intracaval thrombus is formed by vasculitis induced by Behcet's disease, and cannot currently be controlled well. Therefore, anticoagulation therapy was not effective and did not prevent relapse of the thrombus in one of our patients with Behcet-induced BCS. Since we anticipated that a repeat of the original procedure might lead to recurrence of the obstruction, we used Senning's procedure for the reoperation. Although the patient has shown no signs of reocclusion during the four years since the reoperation, the possibility of recurrence is high due to occlusion of the right atrium. The inhibition of vasculitis induced by Behcet's disease is important for prevention of reocclusion of the reconstructed part. In our second case, the diagnosis of Behcet's disease was established by laparotomy after a radical BCS operation. Ileal ulceration was deep and ran in a linear configuration along the ileal long axis. Intestinal ulceration with such characteristics is rare and is also found in tuberculosis or other inflammatory diseases. Takada et al.¹⁰⁾ reported on seven cases of intestinal Behcet's disease with inflammatory ulceration that was invariably located opposite the attachment site of the intestinal mesentery. However, they

did not mention the mechanisms of occurrence of intestinal ulcers in Behcet disease.

Liver congestion by occlusion of HVs produces liver fibrosis and finally progresses to liver cirrhosis. Consequently, the grade of liver fibrosis correlates with the duration of liver congestion, which may be almost equal to the duration of illness. Orloff et al.⁵⁾ reported that six months of HV occlusion caused liver fibrosis. In our Behcet group, liver microscopic findings showed a marked centrilobular congestion. The differences of onset and subsequent clinical course between the Behcet group and the control group were reflected in rapidity of occlusion and the number of HVs that became occluded. Because the onset and course of BCS with Behcet's disease is acute and all three HVs are occluded, the microscopic features of the liver involve centrilobular congestion. The prognosis of our Behcet patients was poor because one patient underwent reoperation due to progression of organized thrombosis caused by Behcet's disease and the other patient died from intestinal Behcet's disease. In our idiopathic BCS group, seven BCS patients died, but the causes of death were unrelated to their BCS disease. The association of Behcet's disease with BCS appears to be a detrimental one in terms of long-term outcome for patients with BCS induced by Behcet's disease. Orloff et al.⁵⁾ reported long-term results of BCS in which one patient with BCS induced by Behcet's disease died from a colon infarction associated with diffuse vasculitis. Because Behcet's disease is a multisystem, chronic, relapsing vasculitis of unknown origin that is resistant to both medical and surgical treatment, its prognosis is worse than that of BCS alone.¹¹⁾ When Behcet disease causes BCS, patients can suffer from multiple recurring symptoms that further deteriorate their condition with a high risk of death. Comprehensive aggressive treatment including immunosuppressive therapy for Behcet's disease will hopefully improve the prognosis of BCS associated with Behcet's disease.

Conclusion

In BCS in Japanese, the clinical course was chronic. However, Behcet's disease-induced BCS had an acute clinical course, and its prognosis was determined by severity of Behcet's disease.

References

1. Kojima K, Kusaba A, Kuniyoshi Y, Iha K, Akasaki M, Miyagi K. Radical open endovenectomy with autologous pericardial patch graft for correction of Budd-Chiari syndrome. *Cardiovasc Surg* 1996; **4**: 500–4.
2. Kuniyoshi Y, Kojima K, Akasaki M, Miyagi K, Kudaka M, Uezu T. Improvement in esophageal varices and liver histology postoperatively in Budd-Chiari syndrome. *Ann Thorac Surg* 1998; **65**: 1711–4.
3. Pasic M, Senning A, von Segesser L, Carrel T, Turina M. Transcaval liver resection with hepatoatrial anastomosis for treatment of patients with Budd-Chiari syndrome. *J Thorac Cardiovasc Surg* 1993; **106**: 275–82.
4. Wang ZG, Zhu Y, Wang SH, et al. Recognition and management of Budd-Chiari syndrome: report of one hundred cases. *J Vasc Surg* 1989; **10**: 149–56.
5. Orloff MJ, Orloff MS, Daily PO. Long-term results of treatment of Budd-Chiari syndrome with portal decompression. *Arch Surg* 1992; **127**: 1182–8.
6. Bayraktar Y, Balkanci F, Bayraktar M, Calguneri M. Budd-Chiari syndrome: a common complication of Behcet's disease. *Am J Gastroenterol* 1997; **92**: 858–62.
7. International Study Group for Behcet's disease. Criteria for diagnosis of Behcet's disease. *Lancet* 1990; **335**: 1078–80.
8. McDonald GS, Gad-Al-Rab J. Behcet's disease with endocarditis and the Budd-Chiari syndrome. *J Clin Pathol* 1980; **33**: 660–9.
9. Davies JD. Behcet's syndrome with hemoptysis and pulmonary lesions. *J Pathol* 1973; **109**: 351–6.
10. Takada Y, Fujita Y, Igarashi M, et al. Intestinal Behcet's disease—pathognomonic changes in intramucosal lymphoid tissues and effect of a "rest cure" on intestinal lesions. *J Gastroenterol* 1997; **32**: 598–604.
11. Orloff LA, Orloff MJ. Budd-Chiari syndrome caused by Behcet's disease: treatment by side-to-side porta-caval shunt. *J Am Coll Surg* 1999; **188**: 396–407.