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Abstract

Three patients with severe halothane-induced liver injury are described. All patients received halothane anesthesia twice within a short period. High fever and jaundice were noticed soon after the second operation. The prothrombin time was less than 40%, and eosinophilia was greater than 7% prior to these symptoms. Other causes of liver injury were excluded. Diagnostic criteria for halothane-induced liver injury are proposed.

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CLINICAL SIGNIFICANCE OF EOSINOPHILIA IN THE DIAGNOSIS OF HALOTHANE-INDUCED LIVER INJURY

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Abstract. Three patients with severe halothane-induced liver injury are described. All patients received halothane anesthesia twice within a short period. High fever and jaundice were noticed soon after the second operation. The prothrombin time was less than 40 %, and eosinophilia was greater than 7 % pior to these symptoms. Other causes of liver injury were excluded. Diagnostic criteria for halothane-induced liver injury are proposed.

Key words : halothane, liver injury, eosinophilia.

Diagnosis of halothane-induced liver injury is difficult. Several etiological factors such as posttransfusion hepatitis and drug-induced liver injury must be considered and evaluated. We have examined three patients with severe liver injury caused by halothane. All of them showed marked eosinophilia in the absence of liver injury after the first operation.

CASE REPORTS

Patient 1. A 46-year-old female received bilateral lumbar synpathectomies under halothane anesthesia twice within 18 days. The patient was suffering from Burger's disease, and was operated upon in March and April 1973. High fever arose immediately after the second operation, followed by eosinophilia, severe jaundice, and ascites. The patient was admitted to Okayama University Hospital in April 1973. The clinical course is shown in Fig. 1. The prothrombin time was 13 % at the time of admission, and total serum bilirubin rose to a maximum of 29.0 mg/dl. HBsAg was negative. Hepatic encephalopathy did not occur during the entire clinical course. A liver biopsy performed under peritoneoscopy six months later demonstrated the convalescent stage of submassive hepatic necrosis.

Patient 2. A 37-year-old male received a skin transplant under halothane anesthesia after extensive burns in December 1978. High fever, jaundice, eosinophilia, and liver dysfunction were seen on the 11th day after the operation.

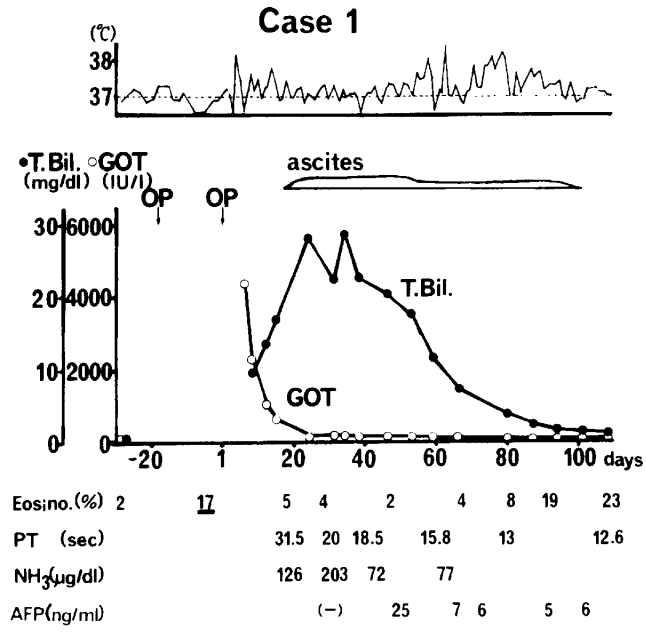

Fig. 1. Clinical course of Case 1

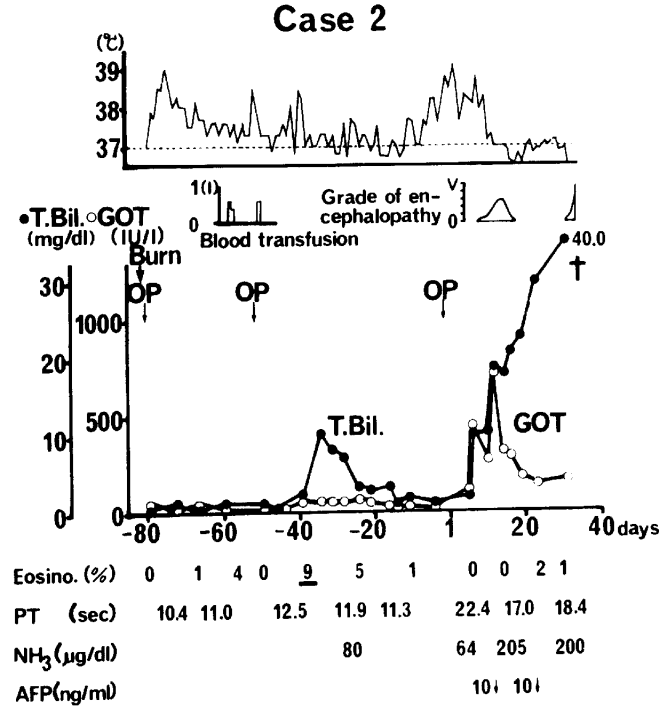

Fig. 2. Clinical course of Case 2

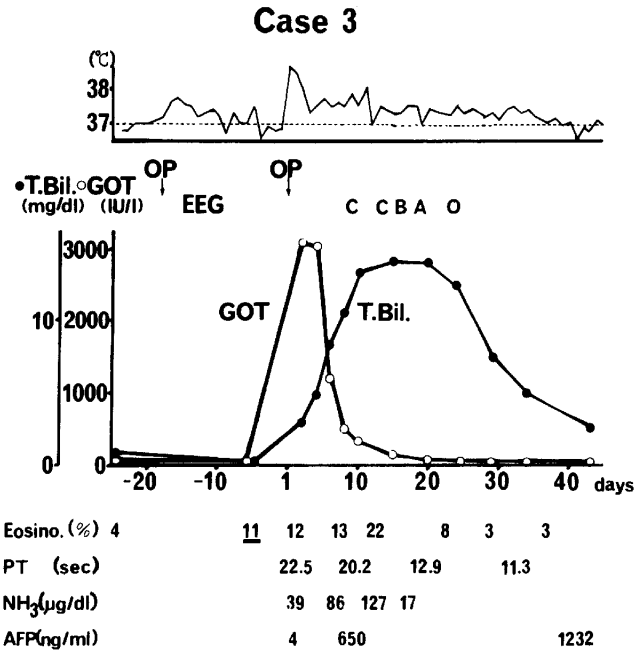

Fig. 3. Clinical course of Case 3

These signs improved shortly thereafter. A second skin transplant under halothane anesthesia was performed 51 days after the first operation. The next day the patient vomited, and had high fever, loss of appetite, jaundice, hepatic encephalopathy and severe liver dysfunction. He was admitted to Okayama University Hospital in a stuporous state. The clinical course is shown in Fig. 2. The prothrombin time was 25 %, and HBsAg was positive. At the time of admission the patient had severe jaundice and marked ascites. His condition deteriorated gradually, and the patient presented clinical symptoms identical to hepatic insufficiency. The patient died 34 days after the onset of symptoms.

Patient 3. A 36-year-old female was operated upon under halothane anesthesia in May 1982 to remove a benign thymoma. Eighteen days later a mammary adenoma was removed, also under halothane anesthesia. High fever, vomiting and jaundice were noted immediately after the second operation. The patient presented eosinophilia and severe liver dysfunction. She was admitted to Okayama University Hospital. The clinical course is shown in Fig. 3. The prothrombin time was 25 %, and HBsAg was negative. The immunological tests, antinuclear factor, antimitochondrial antibody and leukocyte migration inhibition, were all negative. The patient recovered from liver dysfunction and did not exhibit hepatic encephalopathy during the entire course. Nevertheless electroencephalography was grade C according to Persons-Smith's classification (1).

DISCUSSION

Diagnosis of halothane-induced liver injury can be made by the presence of fever of unknown origin, eosinophilia occurring soon after an operation and history of multianesthesia of halothane within a short period (2). Obesity, age, surgical procedures, previous liver disease, and allergic constitution are considered causative factors of the condition (3). We found 3 cases of severe halothane-induced liver injury out of approximately 2000 patients with liver injury, who were admitted to Okayama University Hospital between 1973 and 1982. They were diagnosed by the following criteria : 1) Holothane anesthesia was given twice within a short period ; 2) high fever and jaundice were noted soon after the operation ; 3) severe liver injury was established by a prothrombin time of less than 40 % ; 4) eosinophilia was more than 7 %, and 5) other possibilities were eliminated as causes of liver injury.

It has been shown that 95 % of patients suffering from halothane-induced liver injury received halothane on more than two occasions (4). Fever appeared 8 to 14 days after halothane anesthesia, and jaundice 10 to 28 days following operations (5). However, these periods overlap the incubation period of post-transfusion hepatitis (non-A and non-B types). In the assessment of liver injury in the early postoperative period, it is very important to exclude posttransfusion hepatitis. The severity of halothane-induced liver injury correlated with the number of halothane administrations (3). Severe liver injury was determined by a prothrombin time of less than 40 % (6). Eosinophilia (>7 %) in halothane-induced liver injury has been reported in 9 cases out of 19 (5), 24 out of 72 (4) and 3 out of 5 (2). Although halothane hepatitis may occur in the absence of eosinophilia, eosinophilia does seem to be charactaristic of halothane-induced liver injury. Known etiologies of liver injury such as liver resection, shock, and massive bleeding, were excluded as possible causes.

According to strict criteria, 3 patients were diagnosed as having halothane-induced liver injury in our clinic over the past ten years. However, diagnosis of halothane-induced liver injury is still difficult in spite of these strict criteria. Patient No. 2 received a blood transfusion and was positive for HBsAg. Moreover, all the patients received antibiotics and many other drugs which may induce liver injury. In spite of this situation, it seemed likely that the severe liver injury observed was due to halothane anesthesia since each case satisfied all of the diagnostic criteria.

Biochemical and immunological assays have been unsuccessfully sought for the accurate diagnosis of halothane-induced liver injury. However, eosinophilia is the only characteristic finding. Antimitochondrial antibodies have been reported in 7 out of 9 cases with halothane hepatitis, although the titers were low and transient (7). Yamaguchi *et al.* (8) have suggested that the lymphocyte stimulation test is a useful parameter for establishing halothane-induced liver injury. In order to predict halothane-induced liver injury, several inciting factors may be

TABLE 1. PERIPHERAL EOSINOPHIL COUNTS BEFORE AND AFTER THE OPERATIONS.

	Case No.		
	1	2	3
Eosinophil counts (%)			
Prior to operation	2	4	4
After the first operation	17	9	11
After the second operation	23	0	22

considered. The three cases reported herein presented consistent features (Table 1). All three patients had less than 4 % eosinophils before the initial operation, and transient eosinophilia, more than 9 %, appeared shortly after the operation in the absence of liver injury. Eosinophilia was not observed consistently after the second operation : a normal eosinophil count was presented in Patient No. 2 who died. This case may support the findings of Lindendaum *et al.* (9) of a decreased number of eosinophils in severe halothane-induced hepatitis.

If a second operation is necessary shortly after the use of halothane, eosinophilia after the first operation may denote susceptibility to halothane hepatitis. Though eosinophilia was noted in less than 20 % of 30 patients having had operations under halothane anesthesia, this still means that many cases present eosinophilia. Nevertheless, if eosinophilia is observed after the first operation, it would seem wise to avoid halothane anesthesia or postpone the second operation. It is very important to establish criteria for the accurate diagnosis and prediction of halothane-induced hepatitis in patients undergoing surgery.

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