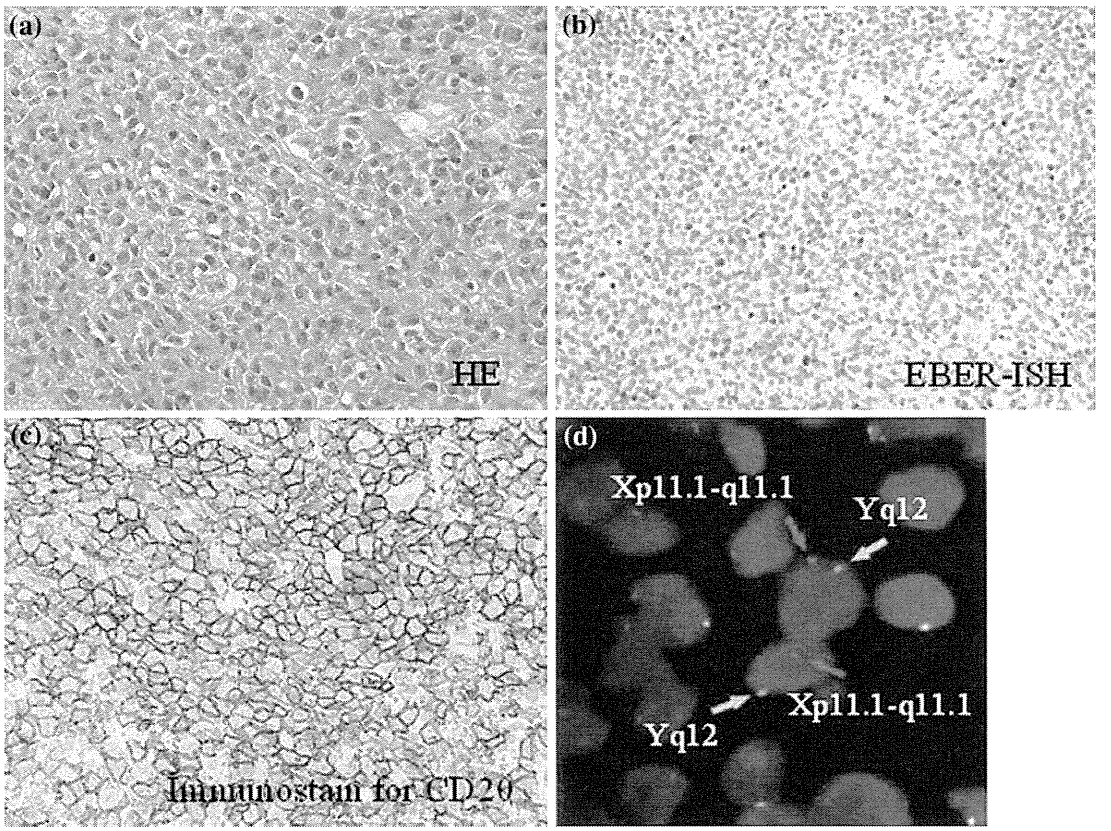

Fig. 2 Histology of a biopsy from patient 4 showed an EBV-related, CD20-positive, diffuse, large-B-cell lymphoma, which was of recipient origin, as confirmed by FISH. **a** Histology showed large-cell lymphoid proliferation [hematoxylin–eosin (*HE*) staining; ×400) **b** In situ hybridization of EBV-encoded small RNA (EBER) was performed. EBER was positive in several lymphoid cells (×400). **c** Immunostaining for CD20 revealed that these lymphoma cells were CD20 positive (×400). **d** Lymphoid cell showing an X–Y pattern on fluorescence in situ hybridization (FISH), indicating that post-transplantation lymphoproliferative disorder (PTLD) was of recipient origin because the donor was his mother. The *red signal* indicates chromosome Xp11.1–q11.1 and the *green signal* indicates chromosome Yq12

rejection developed after the treatment, he was still in complete remission at his 15-month follow-up.

The patient with large mediastinal and pulmonary masses was intubated and on a mechanical ventilator when he was transferred to our institution. Six cycles of rituximab and three cycles of cyclophosphamide and prednisolone chemotherapy every 3 weeks reduced the size of the tumors (Fig. 1b), and he was successfully extubated. His blood EBV load decreased quickly, but for the remaining mediastinal and pulmonary tumors, he received another two cycles of rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone (R-CHOP) chemotherapy. A CT scan after these treatments revealed residual mediastinal and pulmonary tumors (Fig. 1c). Fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) CT revealed abnormal uptake only in the mediastinal tumor (Fig. 3). We recognized viable tumor cells only in the mediastinal tumor, which was then removed surgically. Histological examination of the removed tumor revealed residual viable tumor cells (Fig. 4). After another two cycles of CHOP chemotherapy, the patient was in complete remission when last seen at the 12-month follow-up (Fig. 1d). None of the patients had immunosuppression completely withdrawn at their last follow-up.

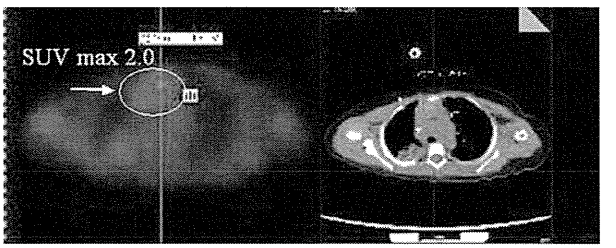

Fig. 3 FDG-PET CT revealed abnormal uptake (SUV-max 2.0) only in the mediastinal tumor (*arrow*) after two cycles of R-CHOP (patient 4). The residual lung mass showed no abnormal uptake, so the mediastinal tumor was resected

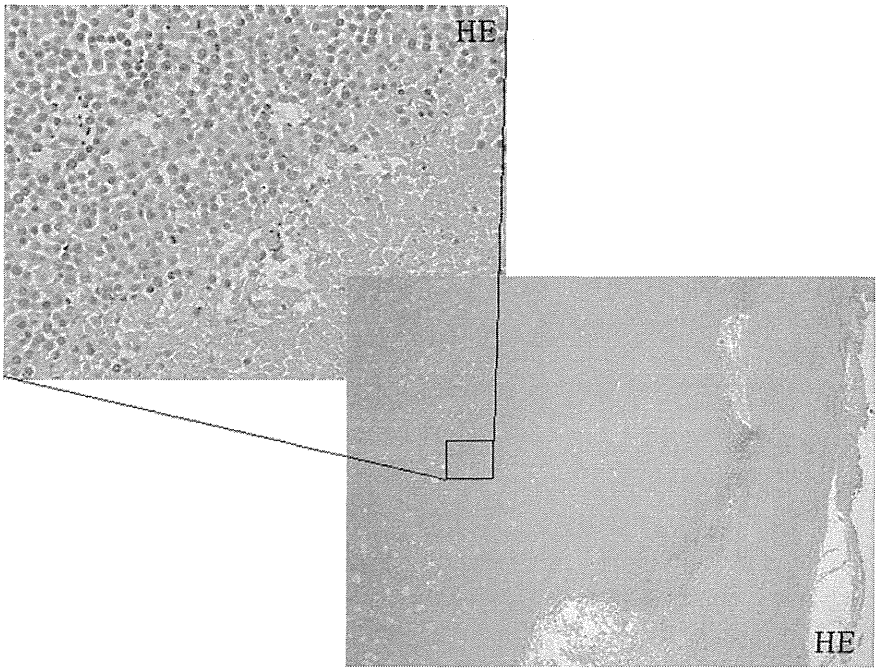

Fig. 4 Histology of the resected mediastinal tumor from patient 4 showed viable lymphoma cells surrounded by ghost cells and capsule (*HE* staining)

Discussion

The overall incidence of PTLD in this series at our institution was 3.8% overall, and 6.4% of the pediatric patients. PTLD did not develop in any of the adult patients. These incidences are similar to those reported in other studies that predominantly analyzed deceased-donor liver transplantation recipients [7, 11, [12]. The incidence in this series was slightly higher than that in other recent Japanese studies, in which LDLT patients were predominantly analyzed [13, 14]. This is probably because our series included early cases, treated in the 1990s. Two of our PTLD patients received liver grafts in the mid 1990s and one received their graft in 2001. The other two patients, who received liver grafts after 2005, were only 6 months old when they underwent liver transplantation, which suggests that younger age at transplantation is a risk factor for PTLD among pediatric patients, although we could not show that the age at transplantation was associated with the incidence of PTLD in this study. One Japanese report suggested younger age at transplantation as a risk factor for post-transplantation EBV infection among pediatric recipients [14].

An important risk factor for the development of PTLD is the intensity and amount of immunosuppression administered to the patient [26]. Although we found no significant difference, two patients suffered from biopsy-proven cellular rejection and one suffered from repeated episodes suggesting rejection. Consequently, their steroid therapy could not be discontinued within 12 months. Induction and rejection treatments with anti-T-cell antibody, especially OKT3, and anti-thymocyte globulin increase the risk of PTLD [9, 27, 28, 29]. Although three pediatric patients received OKT3 for allograft rejection in our series, PTLD did not develop in any of them. Interestingly, induction therapy with anti-IL2 receptor antibody does not seem to be associated with an increased risk of PTLD [9, 30, 31]. At our institution, 48 adult and 3 pediatric recipients who underwent transplantation after December 2002 received induction therapy with anti-IL2 receptor antibody, and none of them suffered PTLD, which supports the safety of induction therapy with this antibody. Although some studies have compared the effects of tacrolimus with those of cyclosporine A as risk factors for PTLD [9, 27, 32, 33], there were no differences between the pediatric patients with and those without PTLD in terms of the calcineurin inhibitor in our series.

In general, PTLD is characterized by the transformation of lymphocytes by EBV; therefore, patients who are EBV-seronegative patients receiving allografts from EBV-seropositive donors, resulting in primary EBV infection, are at 10 to 50-fold risk of PTLD development [26, 34, 35, 36],. This also accounts for the high incidence of PTLD in the early post-transplantation period in pediatric patients, who are more often still EBV seronegative at the time of transplantation. In the present study, four of five cases of PTLD occurred during the first 2 years after transplantation. Furthermore, two patients who received liver grafts at 6 months of age suffered PTLD in the first year after transplantation. Four PTLD patients were EBV seronegative and received liver grafts from EBV-seropositive donors, although one gastrointestinal PTLD patient was

EBV-seropositive before transplantation. The measurement of peripheral-blood EBV levels is helpful for the diagnosis and monitoring of PTLD, and some studies have also shown promising results of measuring peripheral-blood PCR [37, 38, 39, 40, 41]. In our series, all five patients had high EBV loads when PTLD was diagnosed and their EBV loads decreased to undetectable or normal control levels after treatment.

Because PTLD often presents in a nonspecific way if it is not suspected clinically, it is a major challenge to diagnose at an early stage. PTLD often presents at extranodal sites, including in the allograft and gastrointestinal tract [15, 16]. Because the gastrointestinal tract is frequently involved, gastrointestinal signs and symptoms, such as diarrhea and bleeding, may lead to a diagnosis of gastrointestinal PTLD. In the present study, two patients suffered gastrointestinal PTLD with severe diarrhea, high fever, and high blood EBV loads. In patients with respiratory symptoms, CT of the thoracic cavity may be helpful. Pulmonary masses in patients with high blood EBV loads indicate lung involvement in PTLD, as in our patient with pulmonary and mediastinal masses. FDG-PET scanning is becoming an important tool in the visualization of malignant lymphomas, especially for detection in extranodal locations and in post-treatment evaluations [42, 43]. Some studies have found FDG-PET scanning to be superior to conventional imaging for the staging of PTLD and evaluation of treatments [44, 45, 46]. In our patient treated with R-CHOP therapy, FDG-PET clearly differentiated between the residual masses of the vital tumor and scar tissue. As FDG-PET is also thought to be useful for the early detection of recurrent PTLD, it was performed as part of the post-treatment surveillance of this patient.

Two different sources of the lymphocytes involved in PTLD have been suggested: the recipient and the donor. Lymphocytes of donor origin are those EBV-positive cells that have escaped the immune system of the recipient. Lymphoid cells of donor origin transplanted within the allograft may undergo proliferation in the tolerant environment produced by immunosuppression. PTLD of donor origin is reportedly localized to the transplanted organ, whereas PTLD of recipient origin has an extra-allograft location [47]. It has been suggested that PTLD is usually of recipient origin in solid organ transplantation recipients [3]. Because it is difficult to biopsy abdominal lymphadenopathies and perform digestive endoscopies in young children, we could only perform pathological examination in one patient. This patient was male and received an allograft from his mother. Histology showed an EBV-related, CD20-positive, diffuse, large-B-cell lymphoma and FISH analysis showed an XY pattern; thus confirming that his PTLD of recipient origin.

Because of its inherent association with immunosuppression, a key feature of PTLD treatment includes the restoration of a functional immune system in the recipient. Therefore, initial therapy is aimed at reducing immunosuppression in most of the patients. The response rates vary with some patients achieving complete remission with a reduction in immunosuppression alone or in combination with localized therapy, such as radiation or surgery, whereas others experience progressive disease [20, 48]. Factors that predict failure of reduced immunosuppression as a single treatment modality include elevated lactate dehydrogenase levels, organ dysfunction, and multi-organ involvement [20]. A previous study undertaken at our institution demonstrated that a reduction in the blood level of tacrolimus was associated with a reduction in the EBV load after liver transplantation, and that EBV infection could be kept asymptomatic when the tacrolimus trough level was under 3.0 ng/mL [21]. Rituximab is a chimeric anti-CD20 antibody that has recently been used to treat lymphoma. Rituximab also displays activity against PTLD after solid organ transplantation, and response rates of 44–100% have been reported in several studies [49, 50, 51, 52]. A recent phase 2 clinical trial of rituximab for the treatment of PTLD revealed a response rate of 44% on day 80. This trial included patients whose only previous therapy was the reduction of immunosuppression, but excluded patients with central nervous system PTLD [23]. Chemotherapy with regimens used in lymphoma therapies, such as CHOP, remains a therapeutic option for patients who do not respond to immune manipulation or rituximab. PTLD generally remains chemotherapy-sensitive after progression or failure to respond to rituximab, when used as the first-line therapy, and CHOP salvage therapy can achieve an overall response rate of up to 70% in these patients [53]. To reduce the toxicity of chemotherapy, lower-dose chemotherapy with cyclophosphamide and prednisone was evaluated in 36 pediatric patients who had failed to respond to the first-line therapy, with an excellent overall response rate of 83% [54]. When PTLD is confined to one site, radiation and/or surgery can effectively control the local disease [5]. Surgery and radiation also play roles in managing the local complications of PTLD. Our current treatment algorithm is outlined in Fig. 5. In our series, the reduction of immunosuppression alone sufficiently controlled PTLD in three patients. This might mean that the patients received over immunosuppression at the onset of the disease. Indeed, two of these three patients had suffered from repeated biopsy-proven rejection, and another patient was still undergoing steroid therapy at the onset of PTLD because of repeated episodes suggesting rejection. The method of reducing immunosuppression improved with time. We had no criteria upon which to base the appropriate immunosuppression doses for our initial two

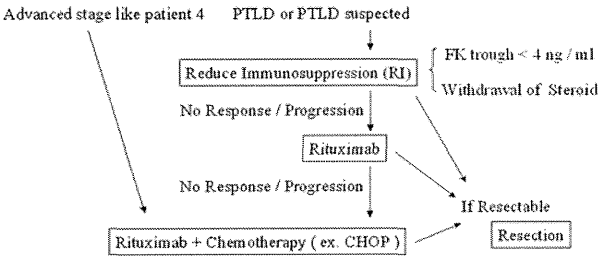

Fig. 5 Our therapeutic strategy for post-transplantation lymphoproliferative disorder (PTLD). In patients with early or suspected disease, the initial therapy is reduction of immunosuppression. In patients who fail to respond or whose PTLD progresses, the addition of rituximab may sufficiently control the disease. For extensive high-grade disease or further progression after the initial therapy, chemotherapy, such as R-CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone, and rituximab) therapy, is commenced. Surgery is performed when the disease is localized

patients. Now, reducing the dose of tacrolimus to a level that maintains the trough below 3.0 ng/mL and withdrawing steroids is our treatment approach for PTLD, although rituximab was necessary for one patient with gastrointestinal PTLD. Because there was no safely accessible lymph node for biopsy in this patient, it was possible that his PTLD was a T-cell lymphoma; however, his symptoms improved and his EBV DNA load decreased rapidly after the initiation of rituximab. This outcome suggests that his PTLD was a B-cell lymphoma. Because rituximab is not very dangerous, its use has been suggested when there is no safely accessible site for a pathological diagnosis, especially in pediatric patients. We used chemotherapy with rituximab followed by surgical resection to treat our patient with aggressive lung and mediastinal masses. Complete remission was achieved in all five patients, with no recurrence to this point.

In summary, we treated five pediatric cases of PTLD after LDLT. Each case manifested differently and required different therapeutic approaches, including cytotoxic chemotherapy. Although PTLD is a life-threatening complication after liver transplantation, prompt and appropriate treatment with rituximab and chemotherapy, as deemed appropriate, can contribute to a good outcome.

Conflict of interest None of the authors have any conflict of interest.

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ORIGINAL ARTICLE

Noninvasive acoustic radiation force impulse (ARFI) elastography for assessing the severity of fibrosis in the post-operative patients with biliary atresia

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Abstract
Purpose Liver biopsy (LB) is still considered the "gold standard" for hepatological evaluation, but recently noninvasive methods have attempted to replace this invasive procedure. Recently, acoustic radiation force impulse (ARFI) imaging has been developed as a noninvasive modality to evaluate the stiffness of tissues. ARFI imaging theoretically measures liver stiffness of all the segments independently. The aim of this study was to determine whether ARFI elastography is a reliable method for predicting the severity of fibrosis in the post-operative patients with biliary atresia.
Methods ARFI elastography was performed 21 times in eight patients with biliary atresia over the last 2 years. At the same time, we measured serum hyaluronic acid (*H* value), which is one of the serum elastic makers, to compare ARFI versus values in these patients. We obtained ARFI versus values as the median of S2 to S8 by three consecutive measurements acquired with a Siemens Acuson S2000 (Siemens Medical Systems, Germany).
Results Histological evaluation of fibrosis is graded from F0 (normal) to F4. The normal *H* value is under 50 mg/dl. One patient had F0 (*H* value 29.2 mg/dl), four had F1 (*H* value 11.5–18.1 mg/dl), one had F3 (*H* value 61.3 mg/dl), two had F4 (*H* value 29.2, 112 mg/dl). One patient with F4 whose ARFI versus value (3.56 m/s) was the highest, needed liver transplantation and her liver was cirrhotic.
Conclusion These findings suggest that ARFI measurement may be a reliable method for predicting the severity of fibrosis after a Kasai operation.

Keywords Acoustic radiation force impulse (ARFI) · Biliary atresia · Hepatic fibrosis · Serum hyaluronic acid

Introduction

Progressive hepatic fibrosis (HF) is a hallmark feature of biliary atresia (BA), the most common indication for liver transplantation (LT) in patients after a Kasai operation. However, assessment of HF has not yet been incorporated into routine post-operative patient care, mostly due to a lack of reliable noninvasive markers for assessing liver fibrosis.

Liver biopsy (LB) is still considered the "gold standard" for hepatological evaluation [1]. However, attempts are being made to develop reliable noninvasive methods to replace this invasive procedure. The reason for this is that LB is usually a stressful procedure for many patients and on many occasions, insufficient histological material is obtained. Recently, several noninvasive methods for the evaluation of liver fibrosis using ultrasound waves such as transient elastography (TE, FibroScan) [2–4], sono elastography (real-time tissue elastography) [5–7], and acoustic radiation force impulse (ARFI) [8–12] have been developed.

ARFI elastography is the newest of these noninvasive procedures used for the assessment of liver fibrosis [8–12], offered by Siemens and integrated into an ACUSON S2000 ultrasound system. Our recent report by Igarashi et al. [13] has shown that the fibrosis staging significantly correlates

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with whole liver stiffness as assessed by ARFI, which enables us to quantitatively estimate the stiffness of liver in adult patients. ARFI imaging theoretically measures liver stiffness in each of the segments independently.

There are no reports of attempts to diagnose liver fibrosis in patients with BA by ARFI imaging. The aim of this study was to determine whether ARFI elastography is a reliable method for predicting the severity of fibrosis in patients with biliary atresia after a Kasai operation.

Materials and methods

ARFI elastography was performed 21 times in eight patients with biliary atresia over the last 2 years. There were two boys and six girls. The average age in these patients was 8.8 years (ranging from 1 to 31, median 4 years old). ARFI was performed, when they all had a Kasai's procedure, but had not received a liver transplantion.

ARFI versus values were acquired with a Siemens Acuson S2000 (Siemens Medical Systems, Germany), which has been modified to obtain ARFI images. We obtained ARFI versus values from S2 to S8 (Cuinaud's segmentation system) with three consecutive measurements. We chose the median value of these three measurements to represent ARFI versus values of each segment. The average of ARFI versus value of all segments was calculated as the ARFI versus value for the whole liver. Staging of liver fibrosis by ARFI in each patient was decided on the basis of our previous results in adult patients with chronic hepatitis [13]. Our co-authors Igarashi et al. [13] mention that the histological evaluation of fibrosis is graded from F0 (normal) to F4 due to new Inuyama classification. In their previous study median ARFI versus value is 1.22 m/s on F0, 1.56 m/s on F1, 1.92 m/s on F2, 2.20 m/s on F3, 2.56 m/s on F4. We have evaluted our patients with BA using ARFI versus values on basis of their histological classification.

At the same time, we measured serum hyaluronic acid (*H*) value, which is one of the high correlations with a pathological findings to serum elastic makers, to compare against ARFI versus values in these patients.

Results

Histological evaluation of fibrosis by ARFI is graded from F0 (normal) to F4 on the basis of our previous findings. The normal *H* value is under 50 mg/dl. These data are shown in Fig. 1. One patient had F0 (*H* value 29.2 mg/dl), four had F1 (*H* value 11.5–18.1 mg/dl), one had F3 (*H* value 61.3 mg/dl), two had F4 (*H* value 29.2 and 112.0 mg/dl). She is the youngest girl in the present study. ARFI versus value has not changed in any patient over the past 2 years. The data of all patitents shown in Fig. 1 were the initial evaluation in each case. Clinical information is shown in Table 1. Case 8 whose ARFI versus value (3.56 m/s) was the highest, needed liver transplantation in the transplanted hospital later and her liver was histologically cirrhotic.

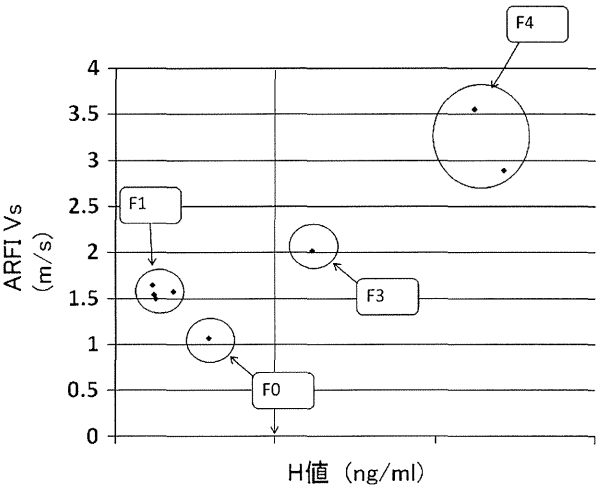

Fig. 1 The correlation between ARFI versus value and *H* value. We have classified our data using the histological classification, where fibrosis is graded from F0 to F4 due to new Inuyama classification in our previous paper. In that study,the median ARFI versus value is 1.22 m/s on F0, 1.56 m/s on F1, 1.92 m/s on F2, 2.20 m/s on F3, 2.56 m/s on F4. One patient had F0, four had F1, one had F3, two had F4

Discussion

Liver biopsy is the current reference examination for the assessment of liver fibrosis. Needle liver biopsy removes only about 1/50,000 of the liver and carries substantial interpreter errors [14]. Liver biopsy is an invasive procedure with certain unavoidable risks and complications. This procedure cannot be repeated easily and is not ideal for following the condition of the liver over the long term. Therefore, the development of noninvasive tests to assess hepatic fibrosis has been an active area of research. Several noninvasive methods have been proposed to stage liver fibrosis, including biochemical tests and imaging techniques. Among the imaging methods, TE is one of the new techniques that rapidly and noninvasively measures mean tissue stiffness. It is largely accepted that hepatic stiffness is related to the degree of fibrosis. Most clinical studies have been performed with Fibroscan, which had been used clinically since 2002 [2, 3]. But, hepatic elastometry with fibroscan is unsuccessful in the cases with ascites, a narrow intercostal space, morbid obesity, and progressive hepatic atrophy [15, 16].

Table 1 Summary of ARFI versus value and *H* value in each case

Case	Histology at Kasai	Initial evaluation				Recent evaluation				Present symptom		
		Age	*H* value (mg/dl)	ARFI (m/s)	Stage	Age	*H* value (mg/dl)	ARFI (m/s)	Stage	Icteric	Ascites	Varix
1	Uncertain	8	29.2	1.07	F0	9	24	1.25	F0	–	–	–
2	F3	3	12.5	1.5	F1	4	11.5	1.33	F1	–	–	–
3	F3	3	12.1	1.54	F1	4	–	1.5	F1	–	–	–
4	F3	4	18.1	1.58	F1	5	30.3	1.43	F1	–	–	–
5	Uncertain	31	11.5	1.65	F1	32	37	1.56	F1	–	–	–
6	Uncertain	17	–	2.02	F3	18	61.3	2.05	F3	–	–	–
7	F2	3	121	2.9	F4	4	133	2.47	F4	–	–	+
8	F3	0.8	112	3.56	F4	1.2	–	3.62	F4	++	–	–

Stage is evaluated using ARFI versus value on the basis of our previous results

Recently, ARFI imaging sono elastography has been proposed as an alternative method to assess liver elasticity. ARFI imaging technology involves the mechanical excitation of tissue using short-duration acoustic pulses (push pulses) in a region of interest chosen by the examiner, producing shear waves that spread away from the region of interest, generating localized, micron-scale displacements in the tissue [14, 17]. Simultaneously, detection waves of lower intensity than that of the push pulse are generated. The push pulse uses a few hundred cycles and different voltage compared to the short cycle B-mode pulse. The moment of interaction between the shear waves and detection waves marks the period of time elapsed between the generating of shear waves and their entire crossing of the entire region of interest. By recording the shear wave front at several locations and correlating these measurements with the elapsed time, the shear wave velocity can be quantified. Generally, the stiffer a region in the tissue, the greater the shear wave velocity as it travels through this region [2, 14, 17]. Although needle biopsy evaluates only 1/50,000 of the total volume of the liver, due to the small volume of the tissue sample, ARFI can evaluate the degree of hepatic fibrosis in any part of liver.

There are a few reports that have attempted to diagnose liver fibrosis in post-operative patients with BA using noninvasive methods to determine the optimal timing of liver transplantation. Noninvasive methods such as FibroScan and ARFI are basically stress free for pediatric patients. We have used ARFI in adult patients with chronic hepatitis since 2009 [13]. To determine the usefulness of ARFI in adult chronic hepatitis patients, this previous study has examined the correlation between biochemical elastic makers including prothrombin time international normalized ratio (PT-INR), indocyanine green (ICG) R15, hyaluronic acid, platelet, type III procollagen N side peptide (PIIINP), type collagen, α2-macroglobulin (α2-M), zinc sulfate turbidity test (ZTT), total bilirubin (T-Bil), aspartate amino transferase (AST), alanine transaminase (ALT), albumen, thymol turbidity test (TTT),and haptoglobin [13]. Igarashi et al. [13] have reported the correlation between liver fibrosis and serum hyaluronic acid as well as ARFI versus value. ARFI versus value is the most high correlative with their histological findings in these adult patients.

In the present study, we also described the correlation between ARFI versus value and serum hyaluronic acid, which is one of the biochemical elastic makers in the patients with BA. These findings suggest that ARFI measurement may be a reliable method for predicting the severity of fibrosis after a Kasai operation.

Evaluation of the timing of liver transplantation after Kasai procedure is important, but difficult to estimate. Serum hyaluronic acid is one marker used to detect liver fibrosis noninvasively. Although pediatric liver transplantation is not indicated due to the degree of liver fibrosis, the symptom of hepatic cirrhosis decreases the quality of life and leads to liver transuplantation. In our recent series of ARFI measurement, we suggest that ARFI measurement may reliably predict the severity of fibrosis after a Kasai operation without liver biopsy.

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4．母子健康手帳に便色見本が掲載された意義

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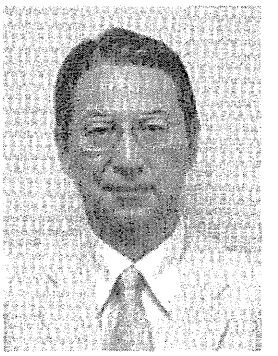
KEY WORDS
胆道閉鎖症
スクリーニング
便色カード
ビタミンK欠乏性出血症
葛西手術



Akira Matsui

はじめに

胆道閉鎖症は，新生児および乳児の肝外胆管が，原因不明の炎症のために閉塞する，破壊される，あるいは消失するために，肝から腸へ胆汁を排出できない疾患である（**図1**）。出生児約10,000人に1人が罹患する稀な疾患だが，同年齢の肝・胆道系疾患の中では死亡率が最も高い。予後不良の理由の一つとして発見の遅れがあげられ，早期発見のためのスクリーニングの必要性が強調されてきた。私どもはその方法として患者および生後1カ月の健常乳児の便を写真撮影してカラースケールとした便色カードを考案し，これを9つの自治体で使用してきた。厚生労働省は平成24年度からこの便色カードを，母子保健法施行規則の一部を改正する省令（平成23年12月28

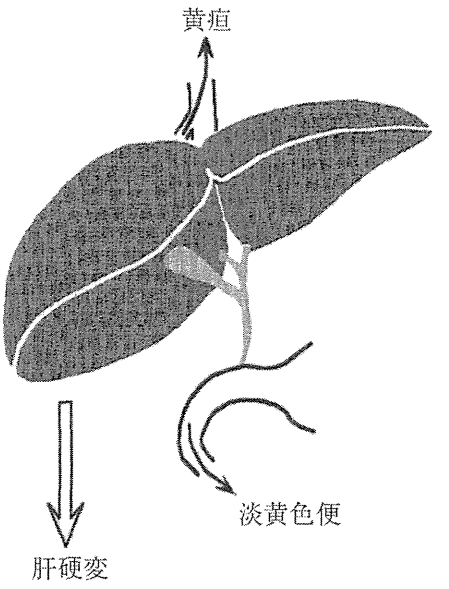


図1　胆道閉鎖症の病態
胆管が閉塞している．

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日厚生労働省令第158号）により，わが国で配布されるすべての母子健康手帳に掲載することを全自治体に義務付けた。本稿では母子健康手帳に掲載される便色カードの意義，使用法について概説する。なお医療機関，各市区町村関係の方は，詳細に関して国立成育医療研究センターのホームページ[1]を参照されたい。

Ⅰ．胆道閉鎖症の症候

胆道閉鎖症の３主徴は遷延性黄疸，淡黄色便，濃黄色尿である。

新生児の90％に見られる生理的黄疸は生後14日までに肉眼上消失する。これに対して生後14日を超えても認められる黄疸を遷延性黄疸という。この遷延性黄疸の大部分は，母乳性黄疸である。母乳栄養児の約15％は遷延性黄疸を呈する。母乳性黄疸は黄色調が明るく，生後２，３カ月までに自然軽快し，無害である。その診断は血清直接型ビリルビン値が総ビリルビン値の20％以下で，ほかの診断が除外でき，かつ消失して初めて確定する。

胆道閉鎖症の黄疸も遷延性黄疸を呈する。その黄疸は消失せずに持続する，あるいはいったん消失した黄疸が再び現れてくる。非水溶性のビリルビンは肝細胞でグルクロン抱合されて水溶性になるが，胆管が閉鎖しているため胆道系に排泄されずに，肝細胞から末梢血中に逆流し，脂肪組織に沈着して皮膚や眼球結膜を黄染する。生後１カ月ごろの胆道閉鎖症の患児の黄疸はそれほど強くないことが多く，色調もくすんだ黄色なので見逃されやすい。

淡黄色便はもっとも特異的な症状のひとつである。淡黄色便とは黄色みがうすい色の便という意味だが，生後１カ月ごろの胆道閉鎖症患児の便色は，しいて言うならうすいベージュ色に近い。胆道閉鎖症患児の70～80％は生後４週までに便の黄色調がうすくなって淡黄色になり，残りの20～30％も多くは生後２カ月までに淡黄色便を発症する。

濃黄色尿は胆汁色素であるビリルビンが尿中に出ることによるもので，生直後からしばしば認められる症状である。黄疸が著明な時には尿が暗褐色になる。オムツに尿だけがしみている時には注意して見るとよい。これに対して母乳性黄疸で増加するのは非抱合型ビリルビンで尿中には出ないため，尿が強く黄染することはない。

胆道閉鎖症では，頭蓋内や消化管，臍などにビタミンＫ欠乏による出血を起こすことがある。ビタミンＫは胆汁中の胆汁酸によりミセルとなって腸で吸収される。しかし胆道閉鎖症では胆汁が腸に排泄されないため，ビタミンＫの吸収が不良になる。ビタミンＫは血液の凝固を助けるので，これが不足すると出血を起こす。頭蓋内出血では突然の哺乳力低下，意識レベルの低下等の重い神経症状を認めることがある。胆道閉鎖症では肝脾腫を認めることが多いが，それ以外には生後１カ月ごろの本症患児は一般に全身状態良好である。

Ⅱ．淡黄色便の臨床的意義

淡黄色便を認める疾患は胆道閉鎖症だけではない。先天性胆道拡張症のように胆管が狭窄する外科的疾患でも認められ，放置すると肝硬変を来すので早期手術が必要である。内科的疾患でも敗血症や尿路感染症，梅毒は，抗菌剤投与により胆汁うっ滞が軽快するので早期に除外すべきである。その他の内科的疾患は肝内胆汁うっ滞を来すものとして，鑑別診断の対象になる（**表**）。

またこれらすべての疾患において，胆汁酸排泄が減少する結果，ビタミンＫ欠乏性出血症の危険がある。この場合，半減期の短いビタミン K_2 の経口投与では効果が不十分である。淡黄色便を認める児は，ただちに入院・

表　新生児・乳幼児胆汁うっ滞の分類（Mowat を改編）

非閉塞性胆汁うっ滞		
新生児肝炎（特発性）		
二次性肝内胆汁うっ滞		
感染性（新生児肝炎症候群）		
	ウイルス	サイトメガロウイルス，B型肝炎ウイルス，風疹ウイルス，単純ヘルペスウイルス，水痘・帯状疱疹ウイルス，コクサッキーウイルス，エコーウイルス，ヒトパピローマウイルスなど
	細菌	大腸菌（尿路感染症，敗血症），梅毒，結核，リステリアなど
	原虫	トキソプラズマ
遺伝性・奇形症候群		Alagille 症候群
		α1-アンチトリプシン欠損症
		（膵）嚢胞性線維症
		進行性家族性肝内胆汁うっ滞（良性反復性肝内胆汁うっ滞を含む）
		シトリン欠損による新生児肝内胆汁うっ滞
		Aagenaes 症候群
		Donahue 症候群
代謝異常		
	アミノ酸	高チロシン血性
	脂質	Wolman 病
		Niemann-Pick 病3型
		Gaucher 病
		acyl-CoA 脱水素酵素欠損症
	炭水化物	ガラクトース血症
		フルクトース血症
		糖原病　Ⅲ/Ⅳ
		phosphoenolpyruvate carboxykinase deficiency
	胆汁酸	トリヒドロキシコプロスタン酸血症
		Δ4-3-Oxysteroid -5β-reductase deficiency
		3β-Hydroxy -Δ5-ステロイド脱水素酵素イソメラーゼ欠損症
		Zellweger 症候群（他のペルオキシゾーム異常を含む）
	金属	新生児鉄貯蔵症
		銅過剰症
解剖学的異常		先天性肝線維症／乳児多発性嚢胞性腎疾患
		Caroli 病
		非症候性肝内胆管減少症
		ミクロフィラメント機能障害
染色体異常		21トリソミー
		18トリソミー
中毒性		完全静脈栄養
内分泌学的異常		下垂体機能低下症（Septo-optic dysplasia を含む）
		尿崩症
		甲状腺機能低下症
		副甲状腺機能低下症
		副腎機能低下症
血液学的異常		血球貪食症候群
そ血症		新生児肝壊死
自己免疫性		原発性硬化症胆管炎
		自己免疫性肝炎
閉塞性胆汁うっ滞		
肝外・肝内胆管閉塞		胆道閉鎖症
肝外胆管閉塞		先天性胆道拡張症（特発性胆管穿孔を含む）
胆石		
悪性腫瘍		

精査・治療の必要がある。ビタミンK欠乏性出血症も胆道閉鎖症およびそれ以外の胆汁うっ滞性疾患をスクリーニングにより検出すべき根拠の一つである。

Ⅲ. 胆道閉鎖症の診断・治療

血液では血清総ビリルビン値の上昇，直接型ビリルビン値の上昇（1.5 mg/dL 以上），直接型対総ビリルビン比（D/T比）20%以上，AST および ALT 値の上昇，リポプロテイン-X陽性等，臨床検査値の異常を認める。さらに腹部超音波検査，十二指腸液検査などを実施する。これらの結果から胆道閉鎖症を否定できない場合に，開腹手術を行い，肉眼所見および，胆嚢に内腔がある場合には手術的胆道造影によって診断を確定する。

診断確定に引き続いて，肝門部空腸吻合術（以降，葛西手術と略す）を行う。これは東北大学小児外科の葛西が1959年に考案した手術で，現在は Kasai procedure と呼ばれて，世界中の先進国で実施されている。胆道閉鎖症において閉塞した索状胆管組織を一塊として切除し，肝門部に小腸を Roux-Y 吻合する（**図2a，b**）。この手術の第一の目標は黄疸を消失させること，第二の目標は黄疸が消失したら，自分の肝臓で長期生存することにある。

Ⅳ. 胆道閉鎖症の予後

葛西手術1年後の転帰は，黄疸なく生存が約57%，黄疸有生存が約11%，移植生存が約25%，死亡が約4%である[2]。黄疸の持続する患児はやがて胆汁性肝硬変，慢性肝不全となって，肝臓移植をしなければ死亡する。葛西手術によって黄疸が消失する患児には上行性胆管炎や，食道・胃静脈瘤破裂等による消化管出血を繰り返す場合と，そうした合併症の少ない場合がある。後者の場合には健常児と変わらない生活の質を得て，20歳以上に達する患者もいる。

葛西手術後，自分の肝臓で生存する確率を自己肝生存率という。Nio ら[3]によれば20年自己肝生存率は手術時日齢と負の相関があり，生後60日内であれば43%，61～90日では33%，91～120日では25%，121～150日では7%，151日以降では0になる。にもかかわらず生後60日以内に手術を受ける患児は，今日でも全体の約40%にすぎない。大部分の患児が生後60日以内に葛西手術を受けることができれば，自己肝生存率が上昇するであろう。しかし20年生存した場合にも，その患者には肝硬変があって，いずれ肝移植を必要と

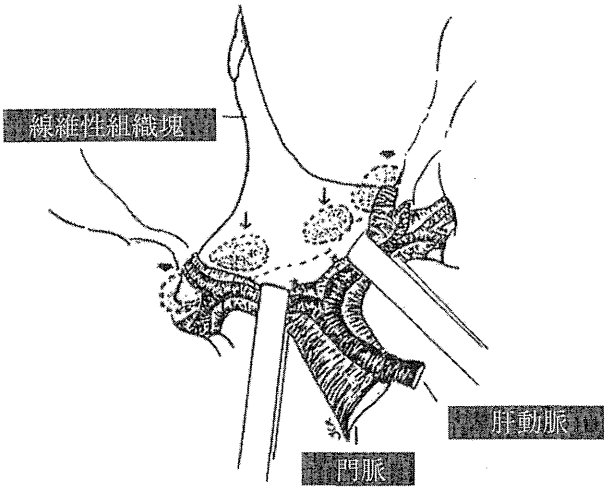


図2a　葛西手術（線維性組織塊を破線に沿って切除）

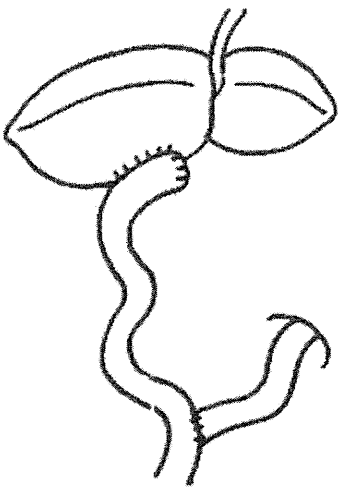


図2b　葛西手術（肝門部空腸吻合術）

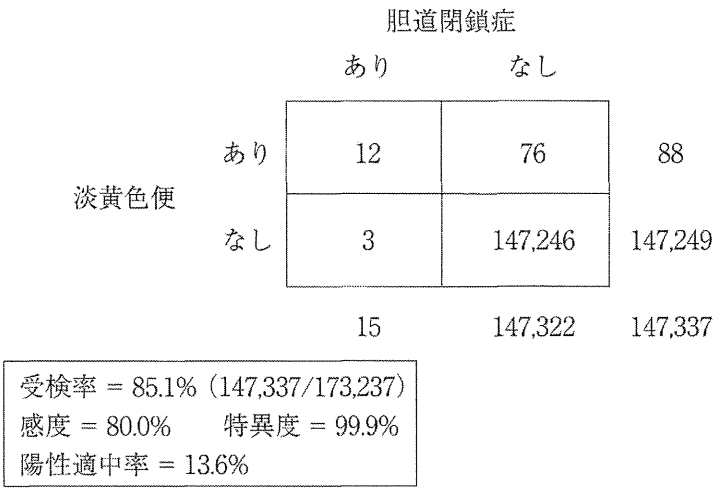


図3　精度の評価（栃木県，Aug. '94 ～ Jul. '03）[8]

することは否定できない[4]。しかしSerinetら[5]は，葛西手術を生後45日以内と46日以降に行った場合では，15年自己肝生存率に12.1%の有意差があることを明らかにした。そして，このことは小児期に肝移植をする必要性を減らすという理由で，胆道閉鎖症のスクリーニングを採用すべきという理論的根拠を与えるとした。

V．胆道閉鎖症のスクリーニング法

胆道閉鎖症のスクリーニング法としてこれまでに提唱された方法を大別すると，選択的スクリーニングと非選択的スクリーニングがある。前者は，生後3週で黄疸のある児から毛細管採血をして，血清直接型ビリルビンを測定する方法で，英国の一部で実施されている[6]が，その効果についての報告はない。1994年，私どもが開発して実施した便色カード法[7]は，生後1カ月乳児の便色を，同時期の乳児の便を写真撮影し，カラー印刷して作成した便色スケールの7種類の便色と比べて，その便色番号を保護者に答えさせるものである。

栃木県における9年間のスクリーニング施行の結果，受検率は85%，感度は80%，陽性適中率は13.6%であった（**図3**）[8]。スクリーニングを県レベルで導入した栃木県とそれ以外の地域（日本胆道閉鎖症研究会の全国集計による）とを比較すると，前者において葛西手術時の平均日齢が小さく（54.8±19.9 vs 66.1±29.7），生後60日以内の手術を受けた患児の比率が高い（75.0% vs 48.8%）と推定された（統計学的有意差未検定）。またこのスクリーニングの費用—効用比は34万円/QALY（Quality Adjusted Life Year「生活の質を調整した生存年」）で，1人の患者の1QALYを延長するためにこの検査にかかる費用が34万円であった。ちなみにカナダの研究者の提案では，この値が200万円以下であればこの検査を利用するための強い根拠になる[9]という。その後，初版便色カードによる胆道閉鎖症のスクリーニングは茨城県，札幌市，岩手県，岐阜県，石川県，秋田県，北海道，新潟県，富山市の計9自治体で採用された。

VI．初版便色カードの長所と短所

初版便色カード法の長所は以下のとおりである。すなわち，①大多数の乳児が受診する1カ月健診の機会を利用できること，②便色に番号を付けて色彩名称による表現の個人差を排除し，母親が淡黄色便の異常性を知らなくても医師に異常を伝えられること，③児の便色調を日常的に観察している母親の情報源

としての信頼性を利用したこと，④判定に特別の技術や機器を必要としないので安価で医療経済学的に有効なこと，⑤ビタミンK欠乏性出血性疾患の予防に役立ちうること，⑥胆道閉鎖症以外に先天性胆道拡張症，新生児肝炎，アラジール症候群などの胆汁うっ滞性疾患の早期発見およびビタミンK欠乏性出血症の予防も可能であること，⑦胆道閉鎖症の手術成績の良い小児外科医の紹介が可能であること，⑧便色カードを配ること自体が胆道閉鎖症という稀少疾患のキャンペーン手段であることだった。

一方，短所は，①便色スケールの色の品質保持を印刷工の勘と経験に依存すること，②便色3番と4番の色調差が大きいのでそれらの中間の便色が必要であること，③1カ月健診受診後に発症する淡黄色便への対処が遅れる可能性があること，④便色カードを妊娠届提出時に母子健康手帳に挟んで渡すので，1カ月健診受診時にはカードをなくすなどインパクトが低下すること，⑤医師といえども胆道閉鎖症の患児を診たことのない場合もあって，便色カードを配るだけでは十分な効果は得られず，地道な啓発活動が必要なことであった。

Ⅶ．新版便色カード法の開発

便色カードに印刷される便色の品質管理は，胆道閉鎖症等の早期発見のうえで非常に重要である。私どもは2010年，第二版の便色カードを作成するにあたって，新しく撮影した胆道閉鎖症患児および生後1カ月の健常乳児の便をコンピューター処理し，色調を定量化した。またPDFファイルの一種であるPDF/X-1aファイルをデータフォーマットして印刷会社が指定すべき印刷用データを添付し，Japan Color 2001 Coated印刷規準で所定の用紙を使用した。これにより，便色スケールを最小限の誤差範囲で印刷することを可能にし，色調の標準化を図った。さらに初版便色カードの3番と4番の中間色が新版の4番に相当するようにした（**図4**）。

Ⅷ．新版便色カードの使用法

以下に，保護者（母親）への説明法を述べる。

1．使用方法

日中の明るい部屋で，オムツについた児の便に便色カードを近づけて色を見比べてください。カードの右側の部分をキリトリ線で切り取ると比べやすくなります。夜間でも昼光色の明るい照明の部屋で比べるなら大丈夫です。いずれの場合にもオムツの周囲に，色彩感覚に影響を与えるような派手な色のものを置かないでください。そしてオムツを交換する時などに，必ず便に便色カードを近づけて色を見比べて，もっとも近いと思う便色番号を記録してください。

便色カードには便色を見比べた結果の記録欄が3つあり，生後2週，生後1カ月，生後1～4カ月に，便色にもっとも近いと思う便色番号を，必ず3回ともカードに記入してください。生後1～4カ月と幅を持たせてありますが，生後2カ月がお勧めです。胆道閉鎖症の大部分の患児が生後2カ月までに淡黄色便を出すからです。

2．便色の判定後の対応

便と便色カードの色を見比べて，もっとも近いと思う便色番号を判定するとき，重要なのは以下の場合です。

① 1番～3番のうちのどれかに近い場合→1日も早く，その便を持参して，1カ月健診を担当する予定の医師を受診して，便と便色カードの色を見比べてもらいましょう。すでに1カ月健診が終わっている場合には，健診を担当した医師または小児科専門医が常勤する病院の小児科を受診してください。

② 4～7番に近い場合→4番以上ならば

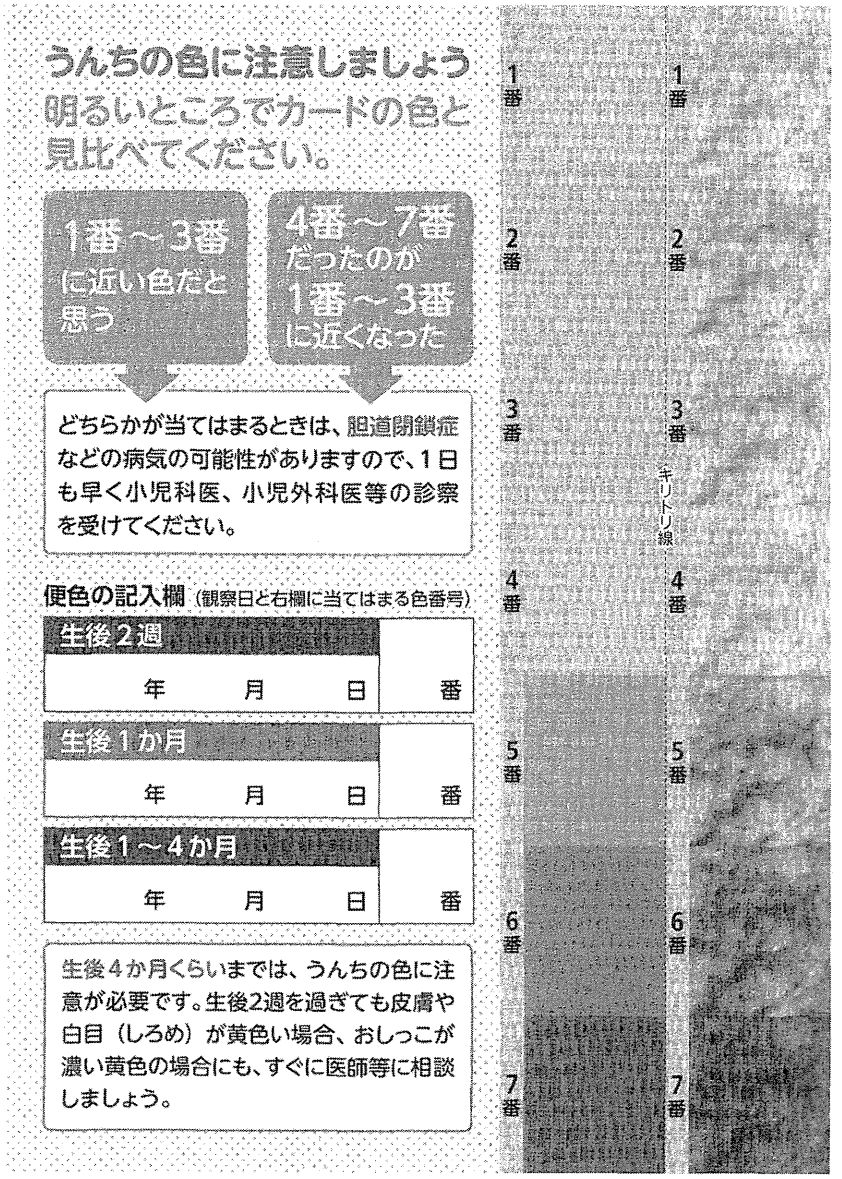


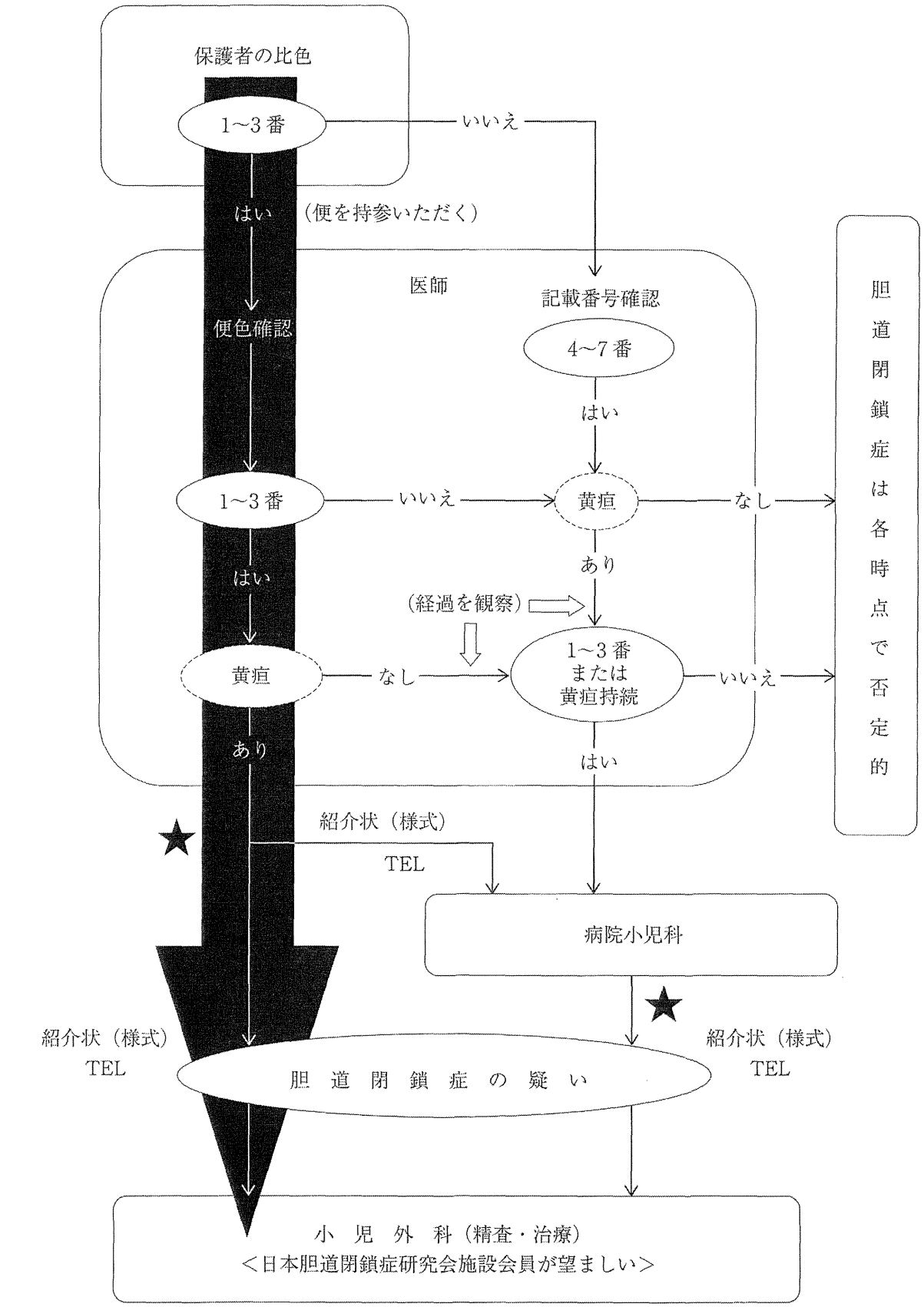
図4　全国的スクリーニングで使用される便色カード 無断転載禁止
（実物を添付する）

安心というわけではありません。その後，便色がうすくなって1～3番に近づくかどうかに注目してください。1～3番に近づいてきたと思ったら，その便を持参して，医師に見てもらいましょう。反対に4番から5～7番に近づく場合は，その時点で胆道閉鎖症の可能性はまずありませんが，生後5カ月になるまでは便色チェックを続けてください。

③　医師を受診する場合

医師や看護師と便色について話す時には，必ず便色番号をお伝えください。例えば「うちの子のうんちが3番なんです」というように伝えてください。同じ黄色といってもイメージする色は人によって異なるからです。それからできる限り，便のついたオムツを持っていき，医師に便と便色カードの色とを見比べてもらいましょう。時間が経過すると便色が変化するので，なるべく新しい便を持っていきましょう。

以上のスクリーニングのフローチャートを図示する（**図5**）。



★濃い黄色尿があればより確実！

図5　スクリーニングのフローチャート

おわりに

私ども小児科医，小児肝臓内科医は，長年にわたって胆道閉鎖症患児の早期発見に努めてきた。私が便色カードのアイデアを思いついたのは約20年前，１カ月健診で乳児の黄疸を推定するのに，イクテロメーターを使っていた時だった。便色を色の名前で表現すれば人が思い浮かべる色は十人十色である。母子健康手帳に便色を記入するアイデアは失敗だった。そこで便色スケールに番号を付けることを考えた。便色カードは栃木県をはじめ９つの自治体に普及して行った。やがて10年に一度の母子健康手帳の大改訂が平成24年度から行われたこと，改訂班の先生方，厚生労働省母子保健課の皆様をはじめ多くの方々のご理解を得て，母子健康手帳への便色カードの綴じ込みが実現した。母子健康手帳はわが国で生まれるほとんどすべての児に配布される。そして出生児の大部分が１カ月健診を受ける。これは胆道閉鎖症の全国的スクリーニングの開始を意味していた。しかし問題はすべて解決したわけではない。４番の便を出す児の取り扱いは簡単ではない。また便色カードの印刷は各自治体に任されており，その色の品質保持は容易ではない。啓発活動の必要性は消えたわけではないなど今後の検証が必要である。

これまでにご理解とお力添えをいただいた方々にこの場を借りて深謝申し上げるとともに，今後ともよろしくご指導をお願いいたします。

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☆　☆　☆　☆　☆　☆

うんちの色に注意しましょう
明るいところでカードの色と見比べてください。

1番～3番に近い色だと思う

4番～7番だったのが1番～3番に近くなった

どちらかが当てはまるときは、**胆道閉鎖症**などの病気の可能性がありますので、1日も早く小児科医、小児外科医等の診察を受けてください。

便色の記入欄（観察日と右欄に当てはまる色番号）

生後2週	
年　月　日	番
生後1か月	
年　月　日	番
生後1～4か月	
年　月　日	番

生後4か月くらいまでは、うんちの色に注意が必要です。生後2週を過ぎても皮膚や白目（しろめ）が黄色い場合、おしっこが濃い黄色の場合にも、すぐに医師等に相談しましょう。