Photodynamic Association, a Board Certified Specialist of the Japan Gastroenterological Endoscopy Society and a Board Certified Specialist or Board Certified Instructor of the Japan Society of Laser Surgery and Medicine.

3. Adherence to the user's manuals and appendices and the safe keeping and management thereof.

All medical and paramedical personnel associated with the PDT procedure are required to have thoroughly read the manual and user's guide which come with the laser hardware (excimer dye laser PDT EDL-1, PDT EDL-2, YAG-OPO Laser 1000) and the medication (photofrin). The facility must keep the manual and user's guide in a safe location, ensure that it is constantly updated by the manufacturer, and have it available for reading at all times. The head of the medical facility must require the Laser Safety Manager (LSM) who is in charge of the manual and user's guide to ensure that all users adhere to the contents of the material. In the case of malfunction of the hardware or if any complications occur which are evidently due to any such malfunction, the LSM is required to report the event as an 'adverse incident' to the manufacturer and distributor, the facility management, and to the appropriate government agencies if necessary using the correct forms.

4. Superficial esophageal cancers and early stage superficial gastric cancers indicated for PDT

The first choice of treatment for superficial esophageal cancers where the tumor depth is limited to the mucous membrane layer and where there are no signs of lymph node metastasis, is endoscopic mucosal resection (EMR). [3] Since surgical removable of the esophagus is extremely invasive and associated with high morbidity, there may be cases where the patient does not wish to be operated on, or where the patient's general condition does not allow surgery and in these instances, EMR may be performed even though the tumor has spread to the submucosal layer. Also for esophageal squamous cell carcinoma,chemoradiation therapy is known to be efficacious. Therefore PDT for esophageal cancer is strictly limited to cases where complete resection by EMR is impossible and also where surgery andchemoradiation are contraindicated.

The first choice of treatment for superficial early stage gastric cancers less than 2 cm in diameter, is EMR. [4,5] For any superficial early stage gastric cancers divergent from this type, surgery is indicated. Therefore PDT is limited to cases where both EMR and surgery is either contraindicated or difficult.

1) If and when complete resection by EMR is possible, it should take precedence over PDT.

2) Superficial esophageal cancers suitable for treatment with PDT are tumors which have spread to less than 1/3 to 1/2 of the circumference and whose size is less than 2 cm x 2 cm and can be captured in a single visual field of the endoscope. The tumor must be diagnosed as non-resectable with EMR, its invasion depth limited to the submucosal layer and showing no evidence of lymph node metastasis.

3) Early stage superficial gastric cancers for which PDT is appropriate are those listed below, which have been diagnosed as non-resectable with EMR and show no signs of lymph node metastasis.
   a) Tumors without ulceration, the length of the longer axis are 1 to 3 cm and whose invasion depth is limited to the submucosal layer.
   b) Tumors with ulceration the length of the longer axis is less than 2cm and whose invasion depth is limited to the submucosal layer.

4) The endoscopic diagnosis criteria and endoscopic findings of superficial esophageal cancers and early stage superficial gastric cancers are listed in detail in the 9th edition of the Japanese Classification of Esophageal Cancer (revised February, 1999) [6] and in the 13th edition of the Japanese Classification of Gastric Cancer (revised September, 1999) [7] respectively.

5. Rules which should be observed to ensure safe PDT procedures

The rules which should be observed to ensure safe PDT procedures are listed below according following the chronicity of the procedure.

1) Pre-PDT examinations

Check and confirm that the indications listed in the user's manual are in concordance with the endoscopic findings which were observed according to the endoscopic diagnosis criteria for superficial esophageal cancers and early stage superficial gastric cancers, as previously mentioned. Histologic

evaluation of the tumor type is mandatory while ultrasonographic endoscope evaluation of the tumor invasion depth is desirable.

Peripheral blood counts, blood chemistry, blood coagulation and examination for any infectious diseases should be performed as in all endoscopic procedures. Since drugs used in the PDT procedure are excreted through the biliary system, close attention must be paid to hepatic function.

Confirm that there are no signs of lymph node or other metastasis by chest and abdominal X-ray imagery, ultrasonography and/or CT imaging.

2) Examination of the hardware prior to PDT

Preoperative examination of the hardware (visual examination, full scale operational check) including power check of the laser output at the laser emission tip and system calibration according to the manufacturer's instructions, must be performed prior to the infusion of the photosensitizer. If the tests reveal that the laser output at the emitting tip is extremely low, check all connections between the hardware, fiber and probe for poor connection and for any staining. Perform the power check again and if output is still low, check and contemplate gas or dye exchange (in the case of the use of an excimer dye laser).

A new probe should always use for the procedure and since intraprocedural damage to the probe resulting in decreased output of laser light is a possibility; a spare probe must be available at all times.

3) Preparation and infusion of the photosensitizer

In the case of Photofrin, 1 vial (75 mg) should be dissolved in 30 ml of 5% glucose solution creating a preparation of 2.5 mg/ml solution of Photofrin. Caution is advised to not create any bubbles or foaming of the solution and to make sure that the solution is well mixed and that no solute is left undissolved.

The preparation is infused slowly intravenously at a dose of 2 mg/kg. Care must be taken so that no extravasation occurs. The dosage of Photofrin must be checked and re-checked by multiple medical personnel.

4) Management of the patient after infusion (in order to avoid side effects due to photosensitivity)

Since drugs used for PDT are photosensitizers, the patient must avoid exposure to direct sunlight and must be placed in a room with adequate shading curtains where the illumination of the room is well controlled. In the case of Photofrin, it is dictated that the illuminance be kept between 100 and 300 lx.

Foods and supplements containing chlorella, *Houttuynia cordata* and celery are known to increase photosensitivity. The patient must be informed through written materials of such precautions and be given information and guidance concerning activities outdoors. The patient must keep these materials at hand at all times.

5) The PDT procedure

(1) Precautions concerning laser light emission

During the procedure the patient, doctor and medical personnel are required to wear adequate protective goggles. Laser irradiation must be performed according to the user's manual. Movements such as peristalsis, respiration and heartbeats should take into account, in order to evenly distribute laser light to the lesion and care should be taken to minimize laser irradiation of normal tissue.

In regular cases, the amount of laser light indicated is listed below

Superficial esophageal cancer: Energy Density of 60-150 J/cm^2

Early stage superficial gastric cancer: Energy Density of 60-200 J/cm^2

Equation to calculate irradiation time

$$\text{Irradiation time(secs)} = \frac{\text{Energy Density (J/cm}^2\text{) x Irradiation area (cm}^2\text{)}}{\text{Laser tip output (mJ/pulse) x Repetition Rate (Hz) x 1/000}}$$

(2) In an event where something irregular occurs adversely affecting patient's condition, make sure that the endoscope is removed from the patient only after the laser irradiation is terminated by pressing the "stop" button (in such case, the laser hardware has memory of the laser irradiation time and hence the procedure may be resumed by pressing the "start" button, as originally planned, after the recovery of the patient).

(3) When, during the PDT procedure, a malfunction of the laser hardware such as aberrant laser output occurs, first abort the procedure by stopping the emission of the laser. Record all pertinent parameters, and than remove the probe from the endoscope and inspect the laser hardware. After inspection, the procedure is resumed by pressing the "start" button if the pertinent parameters are memorized by the hardware (if the parameters are lost from memory, re-calculate the irradiation time and total energy and re-start the proce-

dure).

(4) If sedatives are required during the PDT procedure, the patient should be monitored by a pulse-oxymeter. If there is any concern on fluctuation of the blood pressure of the patient, monitoring with an automated sphygmomanometer is advised. One must be careful with the pulse-oxymeter, since there are reports of skin damage caused by prolonged application of the device. When oxygen is administered to the patient during the PDT procedure, the oxygen level should be that of normal atmospheric level and no higher.

(5) After the PDT procedure

After the PDT procedure, adequate measures must be taken such as administration of anti-ulcer agents to treat the ulcer created by laser irradiation. Periodic endoscopic and histologic examinations are required for the follow up of the lesion.

(6) Management of photosensitivity and exposure to sunlight

Immediately following the injection of Photofrin, the patient must avoid all exposure to sunlight for at least 30 days. After 30 days a challenge test for photosensitivity must be performed. If the patient tests negative for photosensitivity, than the patient may resume normal daily activities, but the patient should be advised to avoid direct exposure to sunlight exposure for a further period of time. If the patient tests positive for photosensitivity, the patient must remain under management until the patient tests negative. For those patients, who can manage shielding themselves from exposure to light at home, early discharge from the hospital, as early as 2 weeks, is possible. These patients must have a full understanding of photosensitivity, and have knowledge on what measures to take in case of a deleterious incident.

(7) Informed consent

Written consent forms signed by the patient and family members are required after they have been fully informed regarding he therapeutic effect, risks and complications associated with the procedure.

6. Rules and stipulations for the distributors and manufacturers of the PDT related drugs and laser hardware.

1) Obligation of the distributors to offer complete information of the products through user's manuals and appendices.

All distributors and manufacturers of drugs and laser hardware associated with PDT must provide ample and sufficient information to the institutions, medical and paramedical personnel through the user's manuals and appendices, for the proper and safe usage of the drugs and devices. [8,9,10] They must hold technical courses, such as showing actual video footage of PDT procedures, at meetings and congresses of relevant academic and medical societies with the cooperation of those societies. They are required to disseminate information for the safe and effective treatment with PDT.

The content and information that are required in the user's manual are dictated in the " Instructions for the use of laser surgical devices" appendix to " Concerning laser surgical devices" , release no. 524 Notice from the Division Head of the Evaluation and Licensing Division, Pharmaceutical Affairs Bureau of the Japanese Ministry of Health and Welfare, dated April 22nd , 1980. [11] The content concerning checking and maintenance of laser devices must include: (a) daily pre-operative checks involving both visual and operational checks; (b) intra-procedural checking (checking while the device is actually being used); and (c) postoperative checks at the end of the day, including checks to be performed on the day after the procedure, and cleaning up .

2) Items requiring written confirmation upon the delivery of the laser device.

Upon delivery of the laser device, the distributor and the medical facility must sign and seal a written confirmation concerning the items listed below, abiding by Appendix 2 of "Rules and Regulations of the Manufacturer and Distributor" from the business communication of the Division of Medical Device Development, Pharmaceutical Affairs Bureau of the Japanese Ministry of Health and Welfare, dated August 6th ,1991.[12] Two copies of this written confirmation must be made, each party keeping a single copy.

Subjects requiring confirmation upon delivery of the laser device

(1) That laser safety managers ((LSMs, chief and deputy, at least 2 people) are assigned and present.

(2) That a registered users' list has been made.

(3) That the manager has the right to appoint the user of the device.

(4) That the user is technically qualified and has attended courses for handling of the drug and laser device, laser safety management, risk and danger prevention.
(5) That the laser device is key controlled, and that the safe keeping of the key has been determined.
(6) That appropriate protective goggles for the wavelength of the laser device are supplied.
(7) That a protective earth terminal is made available.

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< Reference Notes >

1. Contrivances for laser irradiation during PDT

The images generated by generally used electronic fiberscopes during laser irradiation tend to be disrupted. In order to avoid this, an extracorporeal video camera is attached to the fiberscope and the procedure is watched on a video monitor. If a safety filter or film, with a major cut-off at the wavelength of 630nm [13], is taped to the video lens, a much sharper image can be gained. For esophageal lesions, oblique view endoscopes, and for gastric lesions side view endoscopes best fit the purpose. [13] In some cases of both esophageal and gastric lesions where direct view endoscopes are used for lesions that are tangent relative to the visual field, a transparent hood attached to the tip of the endoscope may be useful for laser irradiation. [14] For PDT of esophageal cancer lesions, iodine staining is useful in delineating the circumference of the lesion while for PDT for gastric cancer lesions, spraying of indigocarmine makes the lesion more visible and such marking of the lesion prior to laser irradiation should be performed. [15] In general, the lesion and the area 5 mm circumscribing the lesion are irradiated with the laser. [16] If the area of the lesion is extensive or the lesion is deep in the submucosal layer, repeated laser irradiation at 48 hours and 72 hours after the infusion of Photofrin is recommended. This is using the characteristics of Photofrin where the difference in the tissue concentration level of Photofrin between cancer cells and normal tissue is at the greatest at this respective times. [17]

2. Extending the indications for superficial esophageal cancers and early stage superficial gastric cancers.

Recent advances and development surrounding EMR has led to the expansion of indications for EMR. Surgery has become safer than before, even for the elderly. However there are still cases where a gross deterioration of the quality of life (QOL) of the patient can be anticipated following surgery, and in cases where PDT may be curative, PDT may be chosen and performed but only after the consent of the patient and family members. PDT may be chosen in cases for those who refuse surgery, even after a thorough explanation, and at the same time have lesions contraindicating EMR, such as submucosal invasion of the lesion. For such cases PDT following chemotherapy, EMR or polypectomy is more effective and recommended.

In general, it is thought that PDT is strongly indicated for remnant tumors or local recurrences following EMR of esophageal and gastric cancers. Efficacy of PDT of remnant esophageal cancer after chemoradiation has also been reported. [14,18]

3. Extending the indication of PDT beyond superficial esophageal cancers and early stage superficial gastric cancers.

There are reports depicting the efficacy of PDT with Photofrin for treatment of digestive tract lesions other than superficial esophageal cancers and early stage superficial gastric cancers. However, from the fact that PDT of such lesions have not yet been approved by the Japanese Social Healthcare System and that the number of patients in the reports are still limited, one should take into account that such indications of PDT are still in the clinical trial stage. Only in cases where there are no other treatment methods, and only when the patient strongly asserts their desire to undergo PDT should the attending physician thoroughly inform the patient of the benefits and risks associated with the procedure, and should refer the patient to physicians and to facilities which have experience of the procedure. Before any treatment commences, the issue should be discussed and approved by the Ethics Committee of that facility.

(1) Prevention of cancer in Barrett's esophagus

In Western countries where the incidence of esophageal adenocarcinoma is high due to high incidence of reflux esophagitis and Barrett's esophagus, PDT for Barrett's esophagus is performed from the standpoint of preventive medicine. [19] Presently, in Japan the incidence of Barrett's esophagus-based adenocarcinomas is low and hence there are no facilities which have clinically attempted PDT for the condition. However this is a possibility for future consideration.

(2) Advanced esophageal cancers

In Western countries, PDT procedures are performed for inoperable, chemoradiotherapy-resistant advanced esophageal cancers. Such treatment is approved in these countries and PDT is routinely performed as a palliative measure. [20]

(3) Advanced gastric cancers

Treatment of advanced gastric cancers with PDT alone is only performed as a palliative measure to alleviate stenosis, for hemostasis and for debulking of tumor mass. For polypoid tumors whose invasion is limited to the layer of muscularis propria, polypectomy or EMR followed by PDT, there are cases reported where local control of the tumor has been achieved. [17]

(4) Advanced biliary tract cancers

There are reports that PDT and stent placement for inoperable biliary tract cancers have increased the longevity and prognosis in certain patients [21]. There are a number of institutions that are contemplating performing the procedure in Japan [22].

(5) Rectal cancer

There are reports that PDT is effective in certain cancers of the lower rectum, located at positions where no danger of perforation is present. [23]

(6) Others

While clinical trials of PDT for pharyngeal, duodenal, intestinal and colonic lesions are being attempted, the safety and treatment efficacy remain to be established.

4. Complications of PDT other than photosensitivity

So far in Japan, only a single case has been reported of post-operative hemorrhage following PDT for early stage superficial gastric cancer. To date there are no reports on any serious complications such as perforation.

For PDT of esophageal lesions using a direct view endoscope without using a transparent hood, the lesion presents at a tangent angle relative to the visual field. This and movements due to peristalsis and cardiac movement causes laser irradiation of large non-lesional areas. In cases of post- EMR or post-chemoradiotherapy, such laser irradiation may cause mediastinitis or stricture of the esophagus, and care must be taken. One must keep in mind that PDT for extended indications is more suscepti-

ble to complications such as stenosis and perforation.

5. Laser hardware used for PDT

When performing PDT using Photofrin as the photosensitizer, a laser device emitting laser light at the wavelength of 630 nm is required. The first laser device approved by Japan's social health care service was the excimer-dye laser. Recently, PDT using Photofrin and the YAG-OPO laser has also been approved due to similar treatment efficacy. [24,25] In most Western countries, smaller and less expensive diode lasers are used for PDT with Photofrin, but such a combination has not yet been approved in Japan. If photosensitizers other than Photofrin are to be used, laser devices emitting laser light of the wavelength appropriate for the respective agents are required.

6. PDT using agents other than Photofrin

There are other agents besides Photofrin that are fit for PDT. For some agents the safety and efficacy have already been proven. However, the use of those agents in PDT for gastrointestinal lesions has not been approved, and from the fact that the numbers of patients in the reports are still limited, one should take into account that such sensitizers are still in the clinical trial stage. Only in cases where there are no other treatment methods, and only when the patient strongly asserts their desire to undergo PDT, should the attending physician thoroughly inform the patient of the benefits and risks associated with the procedure, and should refer the patient to physicians and to facilities which have experience of the procedure. Before any treatment commences, the issue should be discussed and approved by the Ethics Committee of that facility.

(1) Laserphyrin (mono-L-aspartyl chlorine e6)

PDT for early stage lung cancer using intravenous infusion of 100 mg of this agent in combination with a specific diode laser (PD laser) has already been approved. [26] Comparable treatment efficacy with PDT using Photofrin for gastrointestinal lesions is anticipated and shorter periods of irradiation with laser energy are strongly awaited in the field of PDT for gastrointestinal lesions.

(2) 5-ALA (aminolevulinic acid)

This agent is used mostly in Western countries for the treatment and prevention of Barrett's esophageal adenocarcinomas. [27] This agent is highly acknowledged for its use in fluorescence diagnostics but use as an agent for PDT is limited to relatively superficial lesions. The hepatic toxicity of this agent should be considered when it is used.

(3) Foscan (mTHPC)

This is new photosensitizing agent that has been approved in Western countries. Therapeutic benefits for even deeply invasive lesions have been shown. [28]

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MEDIMOND

INTERNATIONAL PROCEEDINGS

Esophageal Capsule Endoscopy Versus Magnifying Endoscopy for Detecting Esophageal Lesions

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Summary

The aim of this study was to compare the diagnostic yield of esophageal capsule endoscopy (ECE) and high-resolution magnifying endoscopy (HME) in patients with known esophageal disease. Secondary aim was to assess tolerability of both methods. In total 10 patients were indicated. Just after ECE procedures, HME was performed one expert endoscopist. Evaluation of tolerability for both examinations was obtained by means of questionnaires. ECE images were interpreted by another trained endoscopist who was not known all patients. We compared these findings with HME images. Interpretations of ECE matched with diagnoses by HME, 9 as esophagitis, 10 as Barrett's esophagus and 9 as hiatus hernia. No adverse event was observed. Nine of 10 patients preferred ECE. In conclusions, despite small number of patients, ECE showed a high diagnostic yield and tolerability to the patients suffering from esophageal diseases.

Introduction

Capsule endoscopy has become the first line investigation of the small bowel since its introduction in 2000[1]. Because of its excellent tolerance, patients requested to extend of its indication to other gastrointestinal tract such as esophagus. Thus, esophageal capsule endoscopy (ECE: PillCam ESO, GIVEN imaging Ltd, Yoqneam, Israel) was developed and the first clinical trial of

ECE was reported in 2004[2]. The aim of this study was to compare the diagnostic yield of ECE and high-resolution magnifying endoscopy (HME: EG-490, Fujinon, Saitama, Japan) in patients with known esophageal disease. Secondary aim was to assess tolerability of both methods.

Materials and Methods

In total 10 patients (4 men, 6 women, mean age 63.6 years) who had diagnosed esophageal disease such as gastroesophageal reflux disease (GERD), Barrett's esophagus and hiatus hernia were indicated. The study was approved by the institutional Review Boards at Dokkyo Medical University School of Medicine. Written informed consent was obtained from all patients. ECE was carried out according to the simplified ingestion procedure[3]. After that, HME was performed for 20 minutes by one expert endoscopist under conscious sedation using midazolam (0.05mg per kg) and capsule was retrieved endoscopically at the end of examination. At endoscopic observation of HME, the investigator captured more than 100 pictures including not only esophagus but also oral cavity, stomach and duodenum. The procedures were recorded by digital filing system and digital video tapes. After awakening of patients by injection of flumazenil (0.2 to 0.3mg per body), evaluation of tolerability for both examinations were obtained by means of the original questionnaires. ECE images were interpreted by another trained endoscopist who was not known all patients. We compared interpretations of ECE findings with diagnoses by HME. Concerning GERD, we divided into five grades as M (minimal change), A, B, C, D according to modified LA classification which was previously reported[4]. Barrett's esophagus was divided into short

Table 1 Interpretations of ECE findings

No.	Age	Sex	P-Time*	GERD	Barrett	Hernia	Other findings
1.	74	M	15'00"	M	LSBE	+	Two tumors
2.	64	F	0'04"	NC	SSBE	+	NC
3.	68	F	15'30"	M	SSBE	+	not significant
4.	63	M	12'39"	M	SSBE	+	Ectopic mucosa
5.	40	M	11'05"	A	SSBE	−	Caries
6.	48	F	NP	C	LSBE	+	Caries
7.	75	M	0'03"	A	SSBE	−	not significant
8.	76	F	NP	M	SSBE	NC	Ectopic mucosa
9.	66	F	NP	A	LSBE	+	not significant
10.	62	F	18'00"	M	SSBE	+	SMT**

*P-Time: Passing time through the esophagus, NP: not passed
NC: not clear, ** SMT: Submucosal tumor

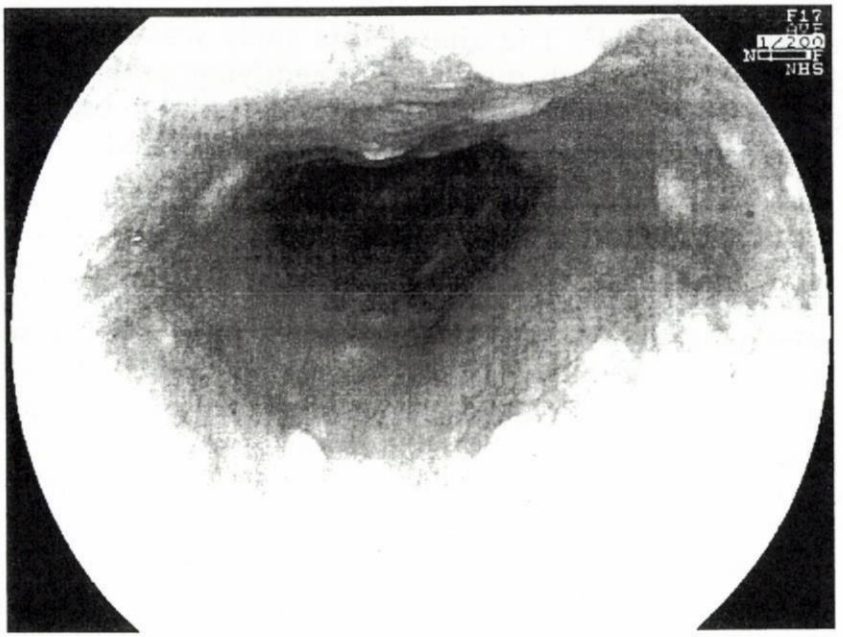

Figure 1 Upper esophagus (HME).

segment Barrett's esophagus (SSBE, less than 3cm lengths) and long segment Barrett's esophagus (LSBE, over 3cm lengths). Hiatus hernia was divided into two grades: negative (none to <2cm) and positive (more than 2cm).

Results

Interpretations of ECE findings matched with diagnoses by HME; 9 as GERD, 10 as Barrett's esophagus and 9 as hiatus hernia (Table 1). Quality of HME images (Figure 1, 2) were superior to that of ECE (Figure 3); however,

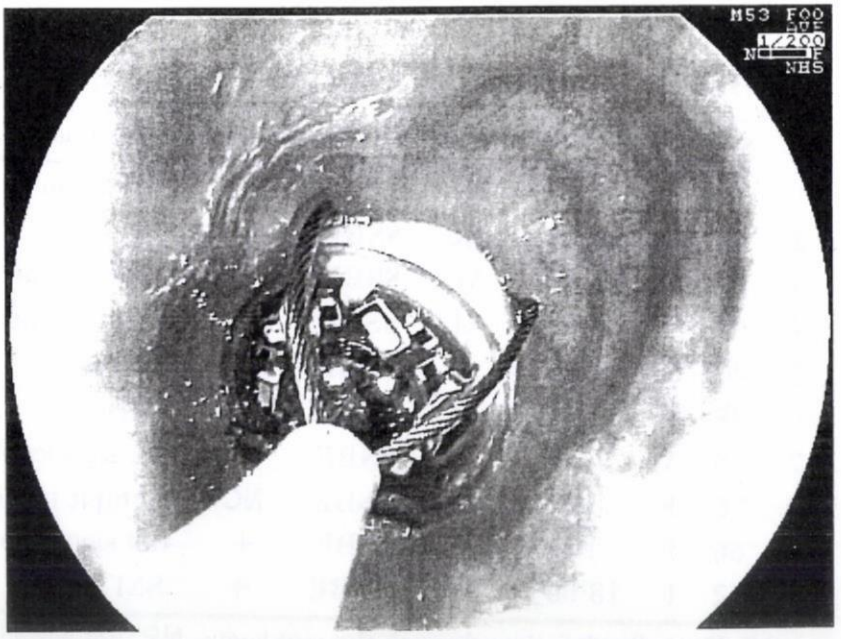

Figure 2 Retrieval of capsule by HME.

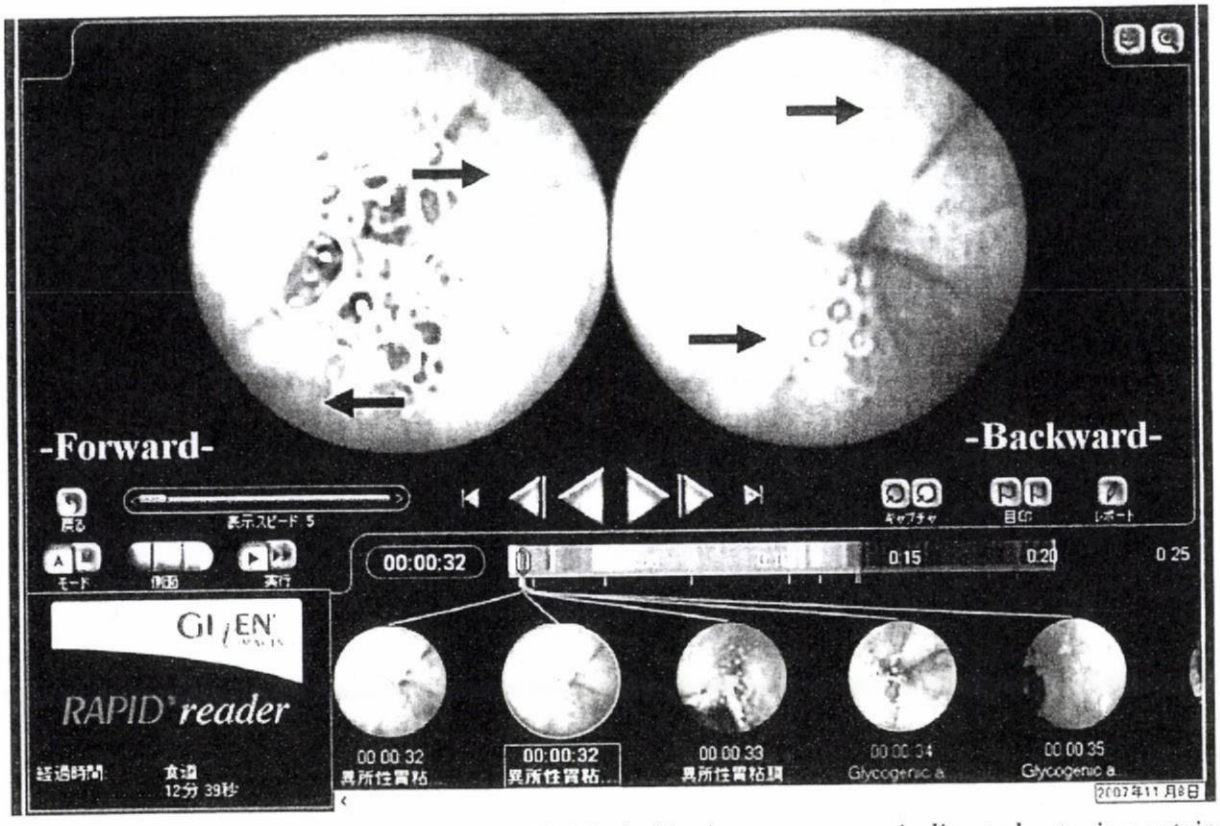

Figure 3 ECE images of No.4 patient in Table 1. Black arrows were indicated ectopic gastric mucosa that was missed by HME.

an ectopic gastric mucosa was only found by ECE in one patient (Table 1, No. 4, Figure 3). No adverse event was observed after either ECE or HME. According to the original questionnaires, 9 of 10 patients preferred ECE for the next endoscopic examination for esophagus.

Conclusions

The first generation of ECE (PillCam ESO) has dual-camera that acquires video images from both ends of the capsule at 14 frames per second during passage through the esophagus[2]. The quality of conventional endoscopies included HME is superior to that of ECE; however, ECE has advantage of dual side observations. It makes possible to observe the upper part of esophagus from anal side. In our experienced case, ECE captured the clear images of ectopic gastric mucosa that was missed by HME. Recently, second-generation of ECE (PillCam ESO 2, GIVEN imaging Ltd, Yoqneam, Israel) was developed and approved by the FDA (food and drug administration) of USA[5]. In the future, introduction of new-generation of ECE might be able to replace the conventional endoscopic examinations for the esophagus. In this study, despite small number of patients, ECE (PillCam ESO) showed a high diagnostic yield and tolerability to the patients in the detection of esophageal diseases.

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NSAIDs関連小腸病変の病理学的特徴

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NSAIDs関連小腸病変の病理学的特徴

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要旨　カプセル内視鏡とダブルバルーン内視鏡の普及により，NSAIDs関連小腸病変が多数見つかるようになってきた。NSAIDs関連病変の肉眼所見は，発赤・びらんの段階から，潰瘍や狭窄まで多彩である。確定診断には，内視鏡所見に加えて組織学的根拠がいるが，非特異的な炎症所見にとどまる。したがって，確定診断には小腸病変の存在とNSAIDsの投与歴および投与中止後の臨床経過も調べることが重要である。

key words：NSAIDs，小腸病変，病理学的所見

はじめに

非ステロイド性消炎鎮痛剤(non-steroidal anti-inflammatory drugs：NSAIDs)の長期投与が原因となり，小腸に多発性潰瘍や狭窄性病変が生じて消化管出血や低蛋白血症をきたすことは1980年代より知られており，その切除標本の肉眼的形態から“diaphragm disease”とよばれてきた[1,2](**図1**)[3]。

病理解剖714症例における病理学的検討では，死亡6カ月以上前よりNSAIDsを内服していた249症例中21例(8.4%)に非特異的な小腸潰瘍を認め，うち3症例は小腸潰瘍の穿孔が死因となっていた。

一方，NSAIDsを内服していなかった症例において，そのような小腸潰瘍を認めたのは，464例中3例(0.6%)にとどまり，有意に少なかった[4]。

ゾンデ式小腸内視鏡による検討では，NSAIDsを長期内服している貧血のある慢性リウマチ患者46症例中19例(41.3%)において，出血の原因となる小腸病変を認めた[5]。そのほか，手術によって確認された小腸の“diaphragm disease”の症例報告も散見される。しかし，小腸の内腔全域を比較的容易に観察することが可能な検査がなかったため，小腸は長い間「暗黒大陸」と言われ，NSAIDs関連小腸病変の詳細は不明であった。

2000年になってカプセル内視鏡[6]とダブルバルーン内視鏡[7]が相次いで開発され，それらが臨床現場に普及するとともに，NSAIDsによる小腸病変が予想以上に多数見つかるようになってきた。

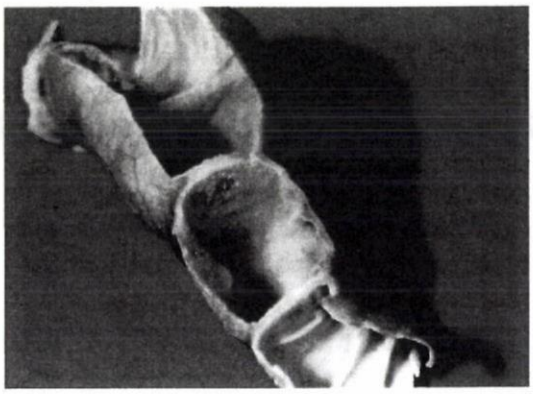

図1　NSAIDsの長期投与による小腸の狭窄病変“diaphragm disease”
(Martin K, Friedrich H, David EF: Atlas of Video Capsule Endoscopy. 146, Springer Medizin Verlag, Germany, 2006より引用)

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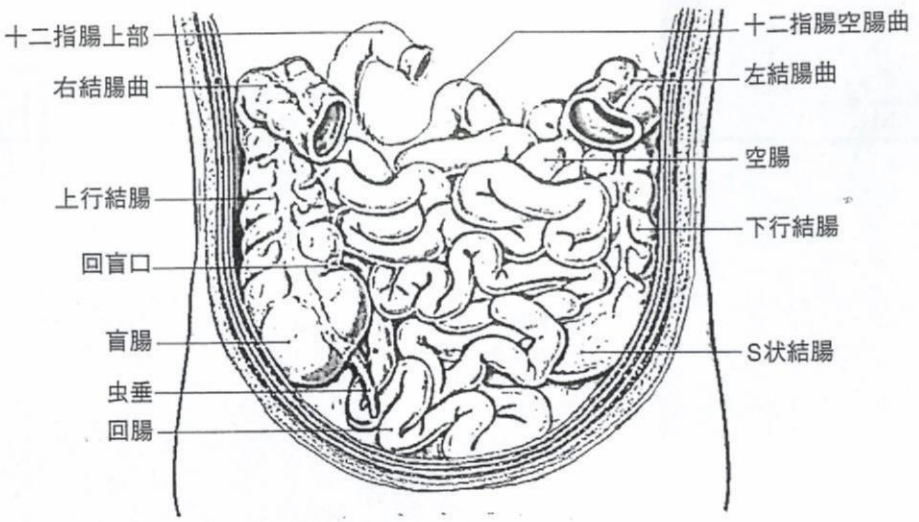


図 2　小腸の外観　（文献8より引用，一部改変）

本稿では，まず小腸の解剖学的，組織学的構造について解説し，NSAIDs関連小腸病変について，現時点で明らかになっているその病理学的特徴を，カプセル内視鏡による症例を中心に紹介したい。

Ⅰ．小腸とは

1．解剖学的な小腸

小腸の外観を**図2**に示す[8]。解剖学的な小腸とは，消化管のうち食道・胃に続く部分で，十二指腸，空腸，回腸に区分される。

十二指腸は，脊柱の右寄りをC字状に走る約25 cm（12本分の指の長さに相当）の腹膜後器官で，幽門に続く十二指腸上部（球部）からTreitz靱帯付近の十二指腸空腸曲までである。十二指腸下行部には大十二指腸乳頭（Vater乳頭）があり，合流した総胆管と主膵管が開口している[8]。

十二指腸に続く空腸と回腸は，腸間膜で吊り下げられているため腸間膜小腸とも言われ，左上腹部から右下腹部の回盲部にかけて存在する。空腸および回腸は生体では平滑筋の収縮のため全長3 m程度であるが，人為的に伸ばすと平均6.5 mになる。空腸と回腸は，およそ2:3で分けられる。両者の境界は不明瞭であるが，空腸は一般的に平滑筋が発達していて壁が厚く，そのために運動が活発であり内容物が速やかに移送され，内腔が空であることが多い。空腸の名は，これに由来する[8]。

2．臨床的な小腸

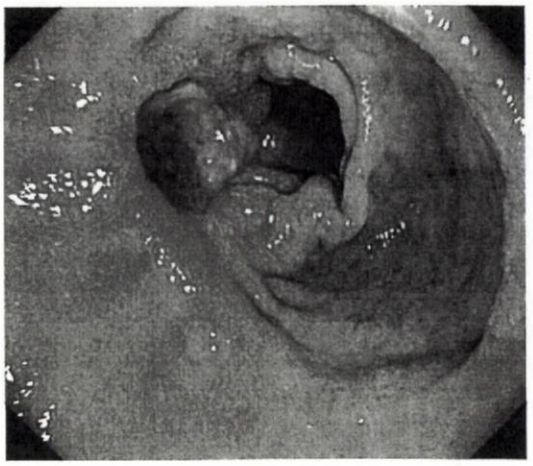
カプセル内視鏡とダブルバルーン内視鏡が臨床応用されるまで，消化管の内視鏡検査は主に上部消化管内視鏡と下部消化管（大腸）内視鏡が行われていた。消化管出血のうち，上部および下部消化管内視鏡検査で出血源が不明のものは，原因不明消化管出血（obscure gastrointestinal bleeding：OGIB）とよばれていた[9]。OGIBの大部分は小腸からの出血であり，カプセル内視鏡とダブルバルーン内視鏡の良い適応となる。これらの検査が普及し，多数の小腸病変が発見されるようになったため，これまで上部・下部の区別しかなかった消化管出血が，以下の3つに再分類された[10]。

1．上部消化管出血（upper GI bleeding）：上部消化管内視鏡で検査が可能な，食道・胃・十二指腸のVater乳頭までの出血。

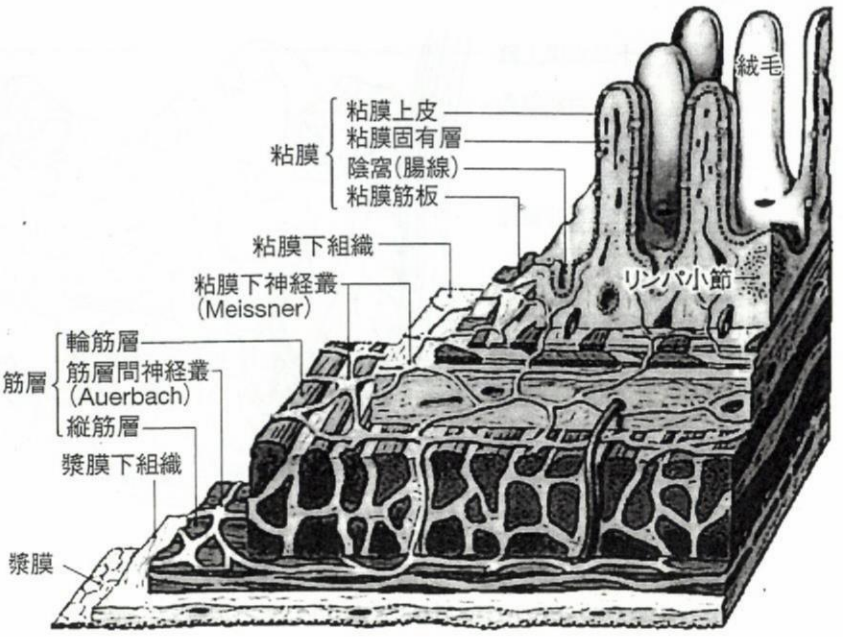
2．中部消化管出血（mid GI bleeding）：カプセル内視鏡やダブルバルーン内視鏡による検査が最適な，Vater乳頭から回腸末端までの小腸における出血。

3．下部消化管出血（lower GI bleeding）：大腸内視鏡により検査が行える，大腸からの出血。

一方，*Helicobacter pylori*の感染率が高く，除菌治療の認可が欧米に遅れたわが国では，胃・十二指腸に発生する消化性潰瘍が大きな問題であった。除菌治療が保険適用となって急速に普及したため，典型的な消化性潰瘍は減少し，NSAIDsによる胃・十二



▲図 3　胃潰瘍術後の吻合部潰瘍



▶図 4　小腸の組織構築
(文献8より引用，一部改変)

指腸潰瘍が問題となってきている。

図3に，胃潰瘍術後の吻合部潰瘍を示す。吻合部潰瘍とは，胃切除後の吻合部に起こる潰瘍で，しばしば小腸側に発生するが，臨床的な扱いは消化性潰瘍と同様である。つまり，胃酸の影響が及ぶ部分は，それ以外の小腸とは臨床的には別に扱われている。

以上，解剖学的な小腸と臨床的な小腸とは，区別して考える必要がある。

3．正常小腸の組織学的構築

小腸の組織構築を**図4**[8]に，正常小腸壁のHE染色標本ルーペ像を**図5**に示す。小腸が他の消化管(食道，胃，大腸)と大きく異なる点は，粘膜に絨毛(villi)という突起が無数に存在することである。さらに，絨毛の表面には微絨毛(microvilli)が存在し(図5)，小腸内腔の表面積はバレーボールのコートより広いとされている[8]。

小腸粘膜は，絨毛，陰窩(intestinal crypt)，粘膜固有層，粘膜筋板よりなる。粘膜固有層は粘膜筋板によって粘膜下組織から隔絶され，絨毛の芯になっている。粘膜固有層には血管，神経，リンパ管，形質細胞，好酸球，マクロファージをはじめとする自由細胞が存在する[8]。また，リンパ小節(lymph follicle)がよく発達し，特に回腸ではリンパ小節が数個集まって集合リンパ小節を作るが，これはパイエル板

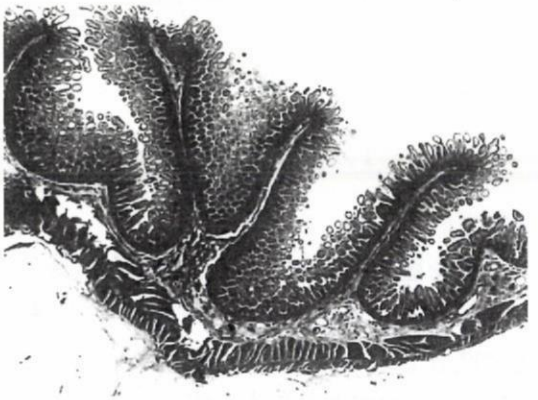


図 5　正常小腸壁のHE染色標本ルーペ像

(Pyer's patches)と言われ，カプセル内視鏡やダブルバルーン内視鏡で観察が可能である。

Ⅱ．NSAIDs関連小腸病変の特徴

1．肉眼所見

NSAIDsの長期投与による小腸の狭窄病変は，古くから“diaphragm disease”とよばれ，手術後固定標本の割面像を見ると，狭窄部が隔膜に類似していることが特徴である(図1)。このような小腸病変をカプセル内視鏡で発見したという最初の報告は，2004年と比較的最近である[11]。松本らによれば，このような狭窄はNSAIDs関連小腸病変の終末像と考えられ，NSAIDs長期投与による小腸病変の基本は，小

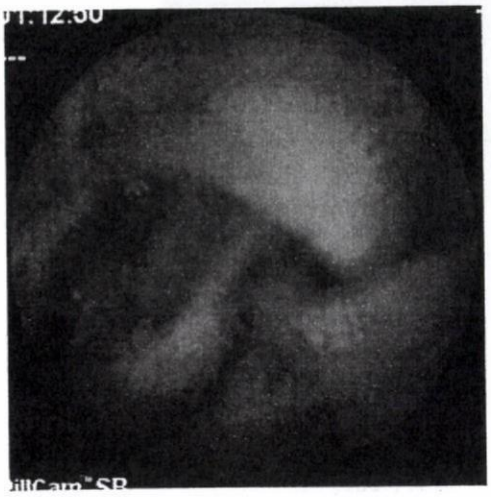


図 6　症例1(71歳女性)
カプセル内視鏡像：多発性の発赤びらんを認める。

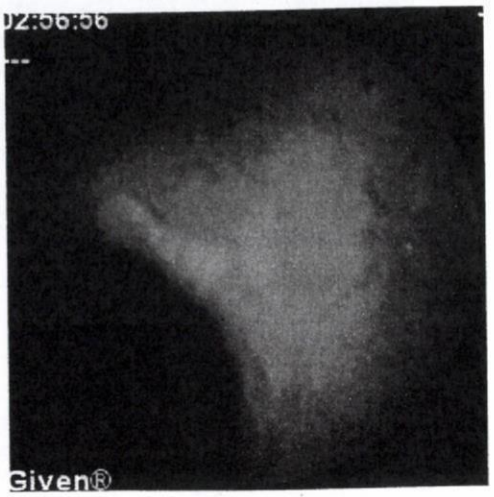


図 7　症例2(73歳女性)
カプセル内視鏡像：小腸潰瘍を認め，軽度の狭窄を伴う。

腸皺襞上のUl-Ⅰないし Ul-Ⅱの幅の狭い輪状潰瘍であるとしている[12]。また，NSAIDs短期投与後にも，小腸に辺縁明瞭な開放性潰瘍や大腸炎に付随した終末回腸のびまん性病変が発生するとしている[12]。

NSAIDs関連小腸病変の好発部位は上部・中部病変であるが，ジクロフェナク徐放剤の場合には下部回腸に発生することがあるとする報告[12]や，空腸よりも回腸に偏在するとの報告[13]があり，まだ確定していない。

現時点で確からしいことは，NSAIDsの種類や投与期間，患者側因子(食物内容や免疫力，二次感染の有無など)，その他が複雑に関係するため，発赤・びらんの段階から潰瘍や狭窄まで多彩な肉眼形態を示しうることであり，今後の症例の集積と臨床病理学的な検討が期待される。

以下では，筆者らがカプセル内視鏡で診断したNSAIDs関連小腸病変の症例を呈示する。

〔**症例1**〕71歳，女性

下血および体重減少のため近医を受診したところ，鉄欠乏性貧血を指摘された。上部・下部消化管内視鏡，腹部超音波検査，腹部CT，小腸造影を行うも，出血源不明で，経口および経肛門的にダブルバルーン内視鏡を行ったが，小腸に明らかな病変を認めなかった。精査目的で当院を受診し，カプセル内視鏡を施行したところ，小腸に多発性の発赤びらんを認め(**図6**)，特に上部小腸に所見が多く，一部は潰瘍に近いものもみられた。

詳細な問診を行ったところ，頭痛のため毎晩服用していた処方にメフェナム酸が含まれていた。内服を中止して3カ月後にカプセル内視鏡を再検したところ，小腸病変はすべて消失し，貧血も治癒，NSAIDs関連小腸病変と確定診断した。

〔**症例2**〕73歳，女性

ふらつきのため近医を受診したところ鉄欠乏性貧血を指摘され，上部・下部消化管内視鏡，腹部CTなどの検査が行われたが，出血源不明であった。その後も便潜血陽性が続くため当院を紹介され，カプセル内視鏡を施行した。小腸に多発性の潰瘍(**図7**)やびらんを認め，空腸下部付近の大きな潰瘍には露出血管様の所見もみられた。回腸にも大きな潰瘍を認め，カプセルはこの部分でRTA(regional transit abnormality:ある部分で60分以上カプセルの動きが鈍くなること)[14]を示したが，検査3日目にカプセルは排出された。

詳細な問診を行ったところ，別の整形外科にてNSAIDs(詳細不明)が処方されていた。このため，このNSAIDsを中止して4カ月後にカプセル内視鏡を再検したところ，所々に軽度のびらんが残るものの潰瘍は瘢痕治癒し，また貧血も改善，NSAIDs潰瘍と確定診断した[15]。

a|b

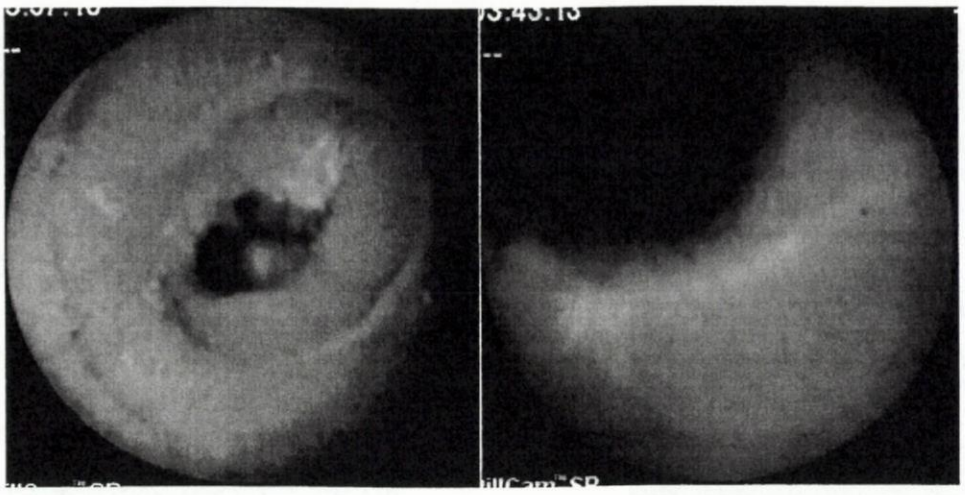


図 8　症例3（76歳女性）
a．NSAIDs中止直後のカプセル内視鏡像：全周性の狭窄を伴う輪状潰瘍を認める。
b．NSAIDs中止10カ月後のカプセル内視鏡像：軽度の内腔の狭窄を伴うものの，瘢痕治癒していた。

〔**症例3**〕76歳，女性

10年前発症の狭心症でインターベンションを行い，バイアスピリン®を内服していた。2年前頃から易疲労感が出現し，高度の鉄欠乏性貧血を指摘され，輸血後，上部・下部消化管内視鏡，骨髄穿刺などが行われたが原因不明であった。バイアスピリン®を中止しても貧血が続くため，精査目的で当院を紹介された。詳細な問診を行ったところ，脳梗塞後遺症のため27年前からジクロフェナクを内服していたが，胃潰瘍を指摘されたため，2年前からメロキシカムに変更していた。メロキシカムが原因のNSAIDs関連小腸病変が疑われたため，直ちに内服を中止してカプセル内視鏡を施行した。十二指腸に粘膜の発赤や浮腫を認め，空腸下部から回腸上部あたりには多発性の潰瘍を認めた。カプセルは，全周性の輪状潰瘍（**図8a**）の口側でとどまったまま検査は終了したが，その後自然に排出された。

NSAIDsの内服はすべて中止し，外用薬や漢方薬に変更して10カ月後にカプセル内視鏡を再検したところ，全周性の輪状潰瘍は瘢痕治癒し（図8b），そのほかに明らかな小腸病変は認めず，また貧血も改善し，NSAIDs潰瘍と確定診断した。

2．組織学的所見

NSAIDs関連小腸病変の終末像と考えられる小腸の狭窄病変（diaphragm disease，図1）における組織所見は，著明な粘膜筋板の肥厚と，粘膜下層の高度の線維化（fibromuscular hyperplasia）が特徴である[12]（**図9**）[16]。狭窄を伴わない潰瘍やびらんにおいては，軽度から中等度の非特異的な炎症細胞浸潤にとどまる。その際，しばしば腺窩のアポトーシスを認め，NSAIDs短期投与後にみられる大腸炎に付随した終末回腸のびまん性病変では，著明な好酸球浸潤を認めるとの報告もある[17]。

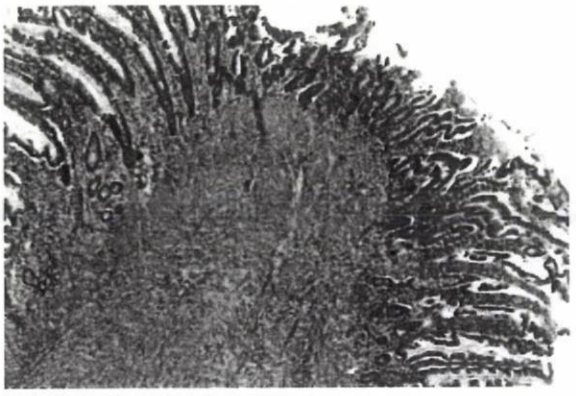


図 9　狭窄をきたしたNSAIDs関連小腸病変の組織像
（Cave DR: Iatrogenic Disease. Halpern M, Jacob H (ed), Atlas of Capsule Endoscopy, First (ed), 68, Given Imaging, Haifa, 2002より引用）

NSAIDs関連小腸病変に特異的な組織学的所見は，狭窄をきたすような病変以外では認められないものと考えられる。

表　NSAIDs起因性小腸炎の確定診断に必要な項目

1．小腸病変の確認
2．NSAIDs使用歴
3．慢性炎症性腸疾患の除外
4．感染性腸炎および他の薬剤性腸炎の除外
5．NSAIDs中止後の病変治癒の確認
6．特異的組織所見の否定

（文献18より引用，改変）

3．診断基準

NSAIDs関連小腸病変における診断基準は，まだ確定していないが，松本らの提唱する「NSAIDs起因性小腸炎」の確定診断に必要な項目が最も参考となる（**表**）[18]。

最近，ダブルバルーン内視鏡による小腸の所見を基にして，1）内視鏡的に小腸の潰瘍性病変，もしくは膜様狭窄を認める，2）発症時にNSAIDsが投与されており，かつNSAIDsの使用中止で症状もしくは症状の改善が認められる。潰瘍瘢痕のみの膜様狭窄の場合はNSAIDsの明らかな服用歴があり，観察時にはNSAIDsの使用が中止されている，3）特異的炎症性腸疾患や病原細菌の感染など，他の原因が否定されている，という診断基準も提唱されている[19]。

いずれにしてもNSAIDs関連小腸病変の確定診断には，小腸病変の存在とNSAIDsの投与歴および投与中止後の病変治癒が必須であると考えられる。

おわりに

カプセル内視鏡とダブルバルーン内視鏡の普及により，NSAIDs関連小腸病変が多数見つかるようになってきた。現時点で明らかと考えられるのは，NSAIDsの種類や投与期間，患者側因子（食物内容や免疫力，二次感染の有無など），その他により，発赤・びらんの段階から潰瘍や狭窄まで，多彩な肉眼形態を示しうることと，狭窄をきたすような病変以外では組織学的に非特異的な炎症所見にとどまることである。NSAIDs中止後に病変が治癒する点も特異的であり，カプセル内視鏡のみによる経過観察だけで確定診断できる可能性も示唆される。

一方，高齢化社会が到来したわが国では，NSAIDsの内服患者は今後ますます増加すると考えられる。今後の症例の集積と臨床病理学的な検討により，小腸に傷害をきたさないような新しいNSAIDsの創薬も期待される。

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